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HENRY FORD HEALTH

Henry Ford Health Publication List – November 2023

This bibliography aims to recognize the scholarly activity and provide ease of access to journal articles, meeting abstracts, book chapters, books and other works published by Henry Ford Health personnel. Searches were conducted in PubMed, Embase, and Web of Science during the month, and then imported into EndNote for formatting. There are 235 unique citations listed this month, including 107 articles, 112 conference abstracts, and 16 books or book chapters.

Articles are listed first, followed by conference abstracts and books and book chapters. Because of various limitations, this does not represent an exhaustive list of all published works by Henry Ford Health authors.

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Articles

Administration
Allergy and Immunology
Anesthesiology
Behavioral Health Services/Psychiatry/Neuropsychology
Cardiology/Cardiovascular Research
Center for Health Policy and Health Services Research
Center for Individualized and Genomic Medicine Research
Dermatology
Diagnostic Radiology
Emergency Medicine
Endocrinology and Metabolism
Gastroenterology
Global Health Initiative
Hematology-Oncology
Henry Ford Health + Michigan State University Health Sciences
Hospital Medicine
Infectious Diseases
Internal Medicine
Nephrology
Neurology
Neurosurgery
Obstetrics, Gynecology and Women's Health Services
Orthopedics/Bone and Joint Center
Otolaryngology – Head and Neck Surgery
Pathology and Laboratory Medicine
Pharmacy
Public Health Sciences
Pulmonary and Critical Care Medicine
Radiation Oncology
Research Administration
Sleep Medicine
Surgery
Urology

Conference Abstracts

Administration
Anesthesiology
Behavioral Health Services/Psychiatry/Neuropsychology
Cardiology/Cardiovascular Research
Center for Health Policy and Health Services Research
Dermatology
Diagnostic Radiology
Emergency Medicine
Endocrinology and Metabolism
Family Medicine
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Graduate Medical Education
Hematology-Oncology
Hypertension and Vascular Research
Infectious Diseases
Internal Medicine
Nephrology
Neurology
Neurosurgery
Nursing
Obstetrics, Gynecology and Women's Health Services
Ophthalmology and Eye Care Services
Orthopedics/Bone and Joint Center
Otolaryngology – Head and Neck Surgery
Pharmacy
Public Health Sciences
Radiation Oncology
Sleep Medicine
Surgery
Urology

Books and Book Chapters

Surgery

Articles

Administration
Luzum JA, Campos-Staffico AM, **Li J**, **She R**, **Gui H**, **Peterson EL**, **Liu B**, **Sabbah HN**, Donahue MP, Kraus WE, **Williams LK**, and **Lanfear DE**. Genome-Wide Association Study of Beta-Blocker Survival Benefit in Black and White Patients with Heart Failure with Reduced Ejection Fraction. *Genes (Basel)* 2023; 14(11). PMID: 38002962. Full Text

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In patients with heart failure with reduced ejection fraction (HFrEF), individual responses to beta-blockers vary. Candidate gene pharmacogenetic studies yielded significant but inconsistent results, and they may have missed important associations. Our objective was to use an unbiased genome-wide association study (GWAS) to identify loci influencing beta-blocker survival benefit in HFrEF patients. Genetic variant × beta-blocker exposure interactions were tested in Cox proportional hazards models for all-cause mortality stratified by self-identified race. The models were adjusted for clinical risk factors and propensity scores. A prospective HFrEF registry (469 black and 459 white patients) was used for discovery, and linkage disequilibrium (LD) clumped variants with a beta-blocker interaction of $p < 5 \times 10(-5)$, were tested for Bonferroni-corrected validation in a multicenter HFrEF clinical trial (288 black and 579 white patients). A total of 229 and 18 variants in black and white HFrEF patients, respectively, had interactions with beta-blocker exposure at $p < 5 \times 10(-5)$ upon discovery. After LD-clumping, 100 variants and 4 variants in the black and white patients, respectively, remained for validation but none reached statistical significance. In conclusion, genetic variants of potential interest were identified in a discovery-based GWAS of beta-blocker survival benefit in HFrEF patients, but none were validated in an independent dataset. Larger cohorts or alternative approaches, such as polygenic scores, are needed.

Administration
Shallal A, Jarrah J, **Prentiss T**, **Suleyman G**, **Veve MP**, Banat A, **Zervos J**, Mousa AB, Msadeh L, Zerriouh Thneibat FM, **Zervos M**, Al-Raiby J, Alsawalha L, and Zayed B. Lessons from the field: Supporting infection prevention and control and antimicrobial stewardship in Amman, Jordan. *J Infect Public Health* 2023; 16 Suppl 1:78-81. PMID: 37945495. Full Text

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Ministry of Health, ALhashimi Alshamaly, P.O.Box 86, Amman 11118, Jordan.
WHO Jordan Country Office, Ministry of Interior Circle, Mohammad Jamjoum Street, PO Box 811547, Amman 11181, Jordan.

BACKGROUND: To reduce antimicrobial resistance (AMR), appropriate antimicrobial prescribing is critical. In conjunction with Infection Prevention & Control (IPC) programs, Antimicrobial Stewardship Programs (ASP) have been shown to improve prescribing practices and patient outcomes. Low- and middle-income countries (LMIC) face challenges related to inadequate ASP policies and guidelines at both the national and healthcare facility (HCF) levels. METHODS: To address this challenge, the World

Health Organization (WHO) created a policy guidance and practical toolkit for implementation of ASPs in LMIC. We utilized this document to support a situational analysis and two-day ASP-focused workshop. In follow-up, we invited these attendees, additional HCF and hospital directors to attend a workshop focused on the benefits of supporting these programs. RESULTS: Over the course of a total three days, we recruited hospital directors, ASP team members, and IPC officers from fifteen different healthcare facilities in Jordan. We describe the courses and coordination, feedback from participants, and lessons learned for future implementation. CONCLUSIONS: Future efforts will include more time for panel-type discussion. which will assist in further delineating enablers and barriers. Also planned is a total three-day workshop; with the first two days being with ASP/IPC teams, and the final third day being with hospital directors and leadership. The WHO policy guidance and toolkit are useful tools to address overuse of antimicrobial agents. Strong leadership support is needed for successful implementation of ASP and IPC. Discussions on quality/safety, as well as cost analyses, are important to generate interest of stakeholders.

Allergy and Immunology

Clay S, Alladina J, Smith NP, Visness CM, Wood RA, O'Connor GT, Cohen RT, Khurana Hershey GK, Kercsmar CM, Gruchalla RS, Gill MA, Liu AH, **Kim H**, Kattan M, Bacharier LB, Rastogi D, Rivera-Spoljaric K, Robison RG, Gergen PJ, Busse WW, Villani AC, Cho JL, Medoff BD, Gern JE, Jackson DJ, Ober CC, and Dapas M. Gene-based association study of rare variants in children of diverse ancestries implicates TNFRSF21 in the development of allergic asthma. *J Allergy Clin Immunol* 2023; Epub ahead of print. PMID: 37944567. Full Text

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Division of Asthma Research, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.
Division of Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.
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Allergy and Immunology, Henry Ford Health, Detroit, MI, USA.
Department of Pediatrics, Columbia University Medical Center, New York, NY, USA.
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BACKGROUND: Most genetic studies of asthma and allergy have focused on common variation in individuals primarily of European ancestry. Studying the role of rare variation in quantitative phenotypes and in asthma phenotypes in populations of diverse ancestries can provide additional, important insights

into the development of these traits. OBJECTIVE: The goal of this study was to examine the contribution of rare variants to different asthma- or allergy-associated quantitative traits in children with diverse ancestries and explore their role in asthma phenotypes. METHODS: We examined whole-genome sequencing (WGS) data from children participants in longitudinal studies of asthma (n=1,035; parent-identified as 67% Black and 25% Hispanic) to identify rare variants (minor allele frequency < 0.01). We assigned variants to genes and tested for associations using an omnibus variant-set test between each of 24,902 genes and eight asthma-associated quantitative traits. Combining our results with external data on predicted gene expression in humans and mouse knockout studies, three candidate genes were identified. A burden of rare variants in each gene and in a combined 3-gene score was tested for its associations with clinical phenotypes of asthma. Finally, published single cell gene expression data in lower airway mucosal cells after allergen challenge was used to assess transcriptional responses to allergen. RESULTS: Rare variants in USF1 were significantly associated with blood neutrophil count (p=2.18x10(-7)); rare variants in TNFRSF21 with total IgE (p=6.47x10(-6)) and PIK3R6 with eosinophil count (p=4.10x10(-5)) reached suggestive significance. These three findings were supported by independent data from human and mouse studies. A burden of rare variants in TNFRSF21 and in a 3-gene score were associated with allergy-related phenotypes in cohorts of children with mild and severe asthma. Furthermore, TNFRSF21 was significantly upregulated in bronchial basal epithelial cells from adults with allergic asthma but not in adults with allergies (but not asthma) after allergen challenge. CONCLUSION: We report novel associations between rare variants in genes and allergic and inflammatory phenotypes in children with diverse ancestries, highlighting TNFRSF21 as contributing to the development of allergic asthma.

Anesthesiology

Alhamar M, **Uzuni A**, **Mehrotra H**, **Elbashir J**, **Galusca D**, **Nagai S**, **Yoshida A**, **Abouljoud MS**, and Otrock ZK. Predictors of intraoperative massive transfusion in orthotopic liver transplantation. *Transfusion* 2023; Epub ahead of print. PMID: 37961982. Full Text

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BACKGROUND: Although transfusion management has improved during the last decade, orthotopic liver transplantation (OLT) has been associated with considerable blood transfusion requirements which poses some challenges in securing blood bank inventories. Defining the predictors of massive blood transfusion before surgery will allow the blood bank to better manage patients' needs without delays. We evaluated the predictors of intraoperative massive transfusion in OLT. STUDY DESIGN AND METHODS: Data were collected on patients who underwent OLT between 2007 and 2017. Repeat OLTs were excluded. Analyzed variables included recipients' demographic and pretransplant laboratory variables, donors' data, and intraoperative variables. Massive transfusion was defined as intraoperative transfusion of ≥10 units of packed red blood cells (RBCs). Statistical analysis was performed using SPSS version 17.0. RESULTS: The study included 970 OLT patients. The median age of patients was 57 (range: 16-74) years; 609 (62.7%) were male. RBCs, thawed plasma, and platelets were transfused intraoperatively to 782 (80.6%) patients, 831 (85.7%) patients, and 422 (43.5%) patients, respectively. Massive transfusion was documented in 119 (12.3%) patients. In multivariate analysis, previous right abdominal surgery, the recipient's hemoglobin, Model for End Stage Liver Disease (MELD) score, cold ischemia time, warm ischemia time, and operation time were predictive of massive transfusion. There was a direct significant correlation between the number of RBC units transfused and plasma (Pearson correlation coefficient r = .794) and platelets (r = .65). DISCUSSION: Previous abdominal surgery, the recipient's hemoglobin, MELD score, cold ischemia time, warm ischemia time, and operation time were predictive of intraoperative massive transfusion in OLT.

Behavioral Health Services/Psychiatry/Neuropsychology

Sablaban IM, **Stodolak D**, and Stallworth B. Apathy in Anoxic Brain Injury Treated With Bupropion. *Am J Ther* 2023; 30(6):e554-e555. PMID: 37921682. Full Text

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Cardiology/Cardiovascular Research

Allana SS, Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, Alexandrou M, Choi JW, **Alaswad K**, Krestyaninov O, Khelimskii D, Gorgulu S, Davies R, Benton S, Karmpaliotis D, Jaffer FA, Khatri JJ, Poommipanit P, Azzalini L, Kearney K, Chandwaney R, Nicholson W, Jaber W, Rinfret S, Frizzell J, Patel T, Jefferson B, Aygul N, Rangan BV, and Brilakis ES. The Retrograde Approach to Chronic Total Occlusion Percutaneous Coronary Interventions: Technical Analysis and Procedural Outcomes. *JACC Cardiovasc Interv* 2023; 16(22):2748-2762. PMID: 38030360. Full Text

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BACKGROUND: Retrograde chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is associated with lower success and higher complication rates when compared with the antegrade approach. OBJECTIVES: This study sought to assess contemporary techniques and outcomes of retrograde CTO PCI. METHODS: We examined the baseline characteristics, procedural techniques and outcomes of 4,058 retrograde CTO PCIs performed at 44 centers between 2012 and 2023. Major adverse cardiac events (MACE) included any of the following in-hospital events: death, myocardial infarction, repeat target vessel revascularization, pericardiocentesis, cardiac surgery, and stroke. RESULTS: The average J-CTO (Multicenter CTO Registry in Japan) score was 3.1 ± 1.1. Retrograde crossing was successful in 60.5% and lesion crossing in 81.6% of cases. The collaterals pathways successfully used were septals in 62.0%, saphenous vein grafts in 17.4%, and epicardials in 19.1%. The technical and procedural success rates were 78.7% and 76.6%, respectively. When retrograde crossing failed, technical success was achieved in 50.3% of cases using the antegrade approach. In-hospital MACE was 3.5%. The clinical coronary perforation rate was 5.8%. The incidence of in-hospital MACE with retrograde true lumen crossing, just marker antegrade crossing, conventional reverse controlled antegrade and retrograde tracking (CART), contemporary reverse CART, extended reverse CART, guide-extension reverse CART, and CART was 2.1%, 0.8%, 5.5%, 3.0%, 2.1%, 3.2%, and 4.1%, respectively; P = 0.01). CONCLUSIONS: Retrograde CTO PCI is utilized in highly complex cases and yields moderate success rates with 5.8% perforation and 3.5% periprocedural MACE rates. Among retrograde crossing strategies, retrograde true lumen puncture was the safest. There is need for improvement of the efficacy and safety of retrograde CTO PCI.

Cardiology/Cardiovascular Research

Basir MB, Lemor A, **Gorgis S**, Patel KC, Kolski BC, Bharadwaj AS, Todd JW, Tehrani BN, Truesdell AG, Lasorda DM, Lalonde TA, Kaki A, Schrieber TL, Patel NC, Senter SR, Gelormini JL, Marso SP, Rahman AM, Federici RE, Wilkins CE, Thomas McRae A, 3rd, Nsair A, Caputo CP, Khuddus MA, Chahin JJ, Dupont AG, Goldsweig AM, Lim MJ, Kapur NK, Wohns DHW, **Zhou Y**, **Hacala MJ**, and **O'Neill WW**. Early Utilization of Mechanical Circulatory Support in Acute Myocardial Infarction Complicated by Cardiogenic Shock: The National Cardiogenic Shock Initiative. *J Am Heart Assoc* 2023; 12(23):e031401. PMID: 38014676. Full Text

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Inova Fairfax Hospital Fairfax VA.
Allegheny General Hospital Pittsburg PA.
Ascension St. John Hospital Detroit MI.
Lehigh Valley Hospital Allentown PA.
Washington Regional Medical Center Washington AK.
Mercy Hospital Buffalo NY.
Overland Park Regional Medical Center Overland Park KS.
Parkwest Medical Center Knoxville TN.
Presbyterian Hospital Albuquerque NM.
San Juan Regional Medical Center San Juan NM.
TriStar Centennial Medical Center Nashville TN.
Ronald Reagan UCLA Medical Center Los Angeles CA.
North Florida Regional Medical Center Gainesville FL.
Excela Health Westmoreland Hospital Greensburg PA.
Northside Cardiovascular Institute Atlanta GA.
Baystate Medical Center Springfield MA.
Hackensack Medical Center Hackensack NJ.
Tufts Medical Center Boston MA.
Spectrum Health Butterworth Hospital Grand Rapids MI.

BACKGROUND: Acute myocardial infarction complicated by cardiogenic shock (AMI-CS) is associated with significant morbidity and mortality. Mechanical circulatory support (MCS) devices increase systemic blood pressure and end organ perfusion while reducing cardiac filling pressures. METHODS AND RESULTS: The National Cardiogenic Shock Initiative (NCT03677180) is a single-arm, multicenter study. The purpose of this study was to assess the feasibility and effectiveness of utilizing early MCS with Impella in patients presenting with AMI-CS. The primary end point was in-hospital mortality. A total of 406 patients were enrolled at 80 sites between 2016 and 2020. Average age was 64±12 years, 24% were female, 17% had a witnessed out-of-hospital cardiac arrest, 27% had in-hospital cardiac arrest, and 9% were under active cardiopulmonary resuscitation during MCS implantation. Patients presented with a mean systolic blood pressure of 77.2±19.2 mm Hg, 85% of patients were on vasopressors or inotropes, mean lactate was 4.8±3.9 mmol/L and cardiac power output was 0.67±0.29 watts. At 24 hours, mean systolic blood pressure improved to 103.9±17.8 mm Hg, lactate to 2.7±2.8 mmol/L, and cardiac power output to 1.0±1.3 watts. Procedural survival, survival to discharge, survival to 30 days, and survival to 1 year were 99%, 71%, 68%, and 53%, respectively. CONCLUSIONS: Early use of MCS in AMI-CS is feasible across varying health care settings and resulted in improvements to early hemodynamics and perfusion. Survival rates to hospital discharge were high. Given the encouraging results from our analysis, randomized clinical trials are warranted to assess the role of utilizing early MCS, using a standardized, multidisciplinary approach.

Cardiology/Cardiovascular Research

Chamogeorgakis T, Toumpoulis I, Bonios MJ, **Lanfear D**, **Williams C**, Koliopoulou A, and **Cowger J**. Treatment Strategies and Outcomes of Right Ventricular Failure Post Left Ventricular Assist Device Implantation: An INTERMACS Analysis. *Asaio j* 2023; Epub ahead of print. PMID: 38029763. Full Text

From the Henry Ford, Transplant Institute, Detroit, Michigan.
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Right heart failure (RHF) management after left ventricular assist device (LVAD) implantation includes inotropes, right ventricular mechanical support, and heart transplantation. The purpose of this study is to compare different RHF treatment strategies in patients with a magnetically levitated centrifugal LVAD. A total of 6,632 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patients from 2013 to 2020 were included. Of which, 769 (69.6%) patients (group 1) were supported with inotropes (≥14 days post-LVAD implantation), 233 (21.1%) patients (group 2) were supported with temporary right ventricular assist device (RVAD) that was implanted during LVAD implant, 77 (7.0%) patients (group 3) with durable centrifugal RVAD implanted during the LVAD implant, and 26 (2.4%) patients (group 4) were supported with RVAD (temporary or permanent), which was implanted at a later stage. Groups 1 and 4 had higher survival rates in comparison with group 2 (hazard ratio [HR] = 0.513, 95% confidence intervals [CIs] = 0.402-0.655, $p < 0.001$, versus group 1) and group 3 (HR = 0.461, 95% CIs = 0.320-0.666, $p < 0.001$, versus group 1). Patients in group 3 showed higher heart transplantation rates at 12 and 36 months as compared with group 1 (40.4% and 46.6% vs. 21.9% and 37.4%, respectively), group 2 (40.4% and 46.6% vs. 25.8% and 39.3%, respectively), and group 4 (40.4% and 46.6% vs. 3.8% and 12.0%, respectively). Severe RHF post-LVAD is associated with poor survival. Patients with LVAD who during the perioperative period are in need of right ventricular temporary or durable mechanical circulatory support constitute a group at particular risk. Improvement of devices tailored for right ventricular support is mandatory for further evolution of the field.

Cardiology/Cardiovascular Research

Chaudry HA, and **Maskoun W**. An intuitive method to reduce the defibrillation threshold: a case report. *Eur Heart J Case Rep* 2023; 7(12):ytad577. PMID: 38046647. Full Text

Division of Electrophysiology, Department of Cardiovascular Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA.

BACKGROUND: Defibrillation threshold (DFT) testing is done to assess whether proper sensing of ventricular fibrillation and adequate safety margin for defibrillation are present in an implantable cardioverter defibrillator (ICD). This case report presents an intuitive method for lowering the DFT. It may be used on a larger scale in other patients with high DFTs when other methods for lowering the DFT (changing medications, adjusting the device, and adding coils) are not feasible or preferable to use. CASE SUMMARY: A 64-year-old male presented to the emergency room with failed appropriate shocks from his ICD. Device interrogation revealed that he failed his first maximum output shock before subsequent shock at the same polarity and output succeeded, suggesting a high DFT. Therefore, the DFT needs to be lowered in our patient. After considering the potential efficacy and risk of a number of traditional options, we used an intuitive method whereby the right ventricular (RV) coils of two separate leads were combined via a y-adapter. This method successfully lowered the patient's DFT, and he received successful shocks from his ICD over the next 9 months before reaching end-stage heart failure. He received a transplant, and the device and transvenous leads, except for the superior vena cava coil, were successfully removed. DISCUSSION: Combining two RV coils from different locations may lower the DFT. This method may be considered in the larger population in cases where using traditional methods are not safe or possible for certain patients. This method may work by lowering shock impedance and increasing the shock tissue surface area.

Cardiology/Cardiovascular Research

Gupta K, Hinkamp C, **Andrews T**, Meloche C, Minhas AMK, Slipczuk L, Vaughan E, Habib FZ, Sheikh S, Kalra D, and Virani SS. Highlights of Cardiovascular Disease Prevention Studies Presented at the 2023 European Society of Cardiology Congress. *Curr Atheroscler Rep* 2023; Epub ahead of print. PMID: 37975955. Full Text

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PURPOSE OF REVIEW: To summarize selected late-breaking science on cardiovascular (CV) disease prevention presented at the 2023 European Society of Cardiology (ESC) congress. RECENT FINDINGS: The NATURE-PARADOX was a naturally randomized trial that used genetic data from the UK Biobank registry to create "cumulative exposure to low-density lipoprotein-cholesterol (LDL-C)" biomarker and evaluate its association with major CV events regardless of plasma LDL-C levels or age. Safety and efficacy data of inclisiran, a PCSK9-interfering mRNA (PCSK9i) administered subcutaneously twice annually, were presented. Data on two new PCSK9is were presented, recaticimab, an oral drug, and lerodalcibep, a subcutaneous drug with a slightly different architecture than currently available PSCK9is. A phase 1 trial on muvalaplin, an oral lipoprotein (a) inhibitor, was presented. An atherosclerotic CV disease (ASCVD) risk prediction algorithm for the Asian population using SCORE2 data was presented. Long-term follow-up of patients enrolled in the CLEAR outcomes trial showed sustained and more significant ASCVD risk reduction with bempedoic acid in high-risk patients. The late-breaking clinical science at the 2023 congress of the ESC extends the known safety and efficacy data of a PCSK9i with the introduction of new drugs in this class. Using cumulative exposure to LDL-C rather than a single value will help clinicians tailor the LDL-C reduction strategy to individual risk and is an important step towards personalized medicine.

Cardiology/Cardiovascular Research

Kostantinis S, Rempakos A, Simsek B, Karacsonyi J, Allana SS, **Alaswad K**, **Basir MB**, Davies RE, Benton SM, Jr., Krestyaninov O, Khelimskii D, Jaber WA, Rinfret S, Nicholson W, Frizzell J, Jaffer FA, Khatri JJ, Poommipanit P, Choi JW, Chandwaney R, Jefferson BK, Patel TN, Al-Azizi KM, Potluri S, Aygul N, ElGuindy AM, Abi Rafeh N, Goktekin O, Alexandrou M, Mastrodemos OC, Rangan BV, Sandoval Y, Burke MN, Brilakis ES, and Gorgulu S. Impact of target vessel on the procedural techniques and outcomes of chronic total occlusion percutaneous coronary intervention. *J Invasive Cardiol* 2023; 35(9). PMID: 37983108. Request Article

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Texas Health Presbyterian Hospital, Dallas, TX, USA.
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Tristar Centennial Medical Center, Nashville, TN, USA.
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BACKGROUND: There is limited information on the impact of the target vessel on the procedural techniques and outcomes of chronic total occlusion (CTO) percutaneous coronary intervention (PCI). METHODS: We analyzed the baseline clinical and angiographic characteristics and procedural outcomes of 11,580 CTO PCIs performed between 2012 and 2022 at 44 centers. RESULTS: The most common CTO target vessel was the right coronary artery (RCA) (53.1%) followed by the left anterior descending artery (LAD) (26.0%) and the left circumflex artery (LCX) (19.8%). RCA CTOs were longer and more complex, with a higher Japanese CTO score compared with LAD or LCX CTOs. Technical success was higher among LAD (88.8%) lesions when compared with RCA (85.7%) or LCX (85.8%) lesions (P less than .001). The incidence of major adverse cardiovascular events (MACE) was overall 1.9% (n = 220) and was similar among target vessels (P=.916). There was a tendency toward more frequent utilization of the retrograde approach for more proximal occlusions in all 3 target vessels. When compared with all other RCA lesions combined, distal RCA lesions had higher technical success (87.7% vs 85.3%; P=.048). Technical success was similar between various locations of LAD CTOs (P=.704). First/second/third obtuse marginal branch had lower technical success when compared with all other LCX lesion locations (82.7% vs 86.8%; P=.014). There was no association between MACE and CTO location in all 3 target vessels. CONCLUSIONS: LAD CTO PCIs had higher technical and procedural success rates among target vessels. The incidence of MACE was similar among target vessels and among various locations within the target vessel.

Cardiology/Cardiovascular Research

Krzowski B, Kutyifa V, Vloka M, Huang DT, Attari M, Aktas M, Shah AH, Musat D, Rosenthal L, McNitt S, Polonsky B, **Schuger C**, Natale A, Ziv O, Beck C, Daubert JP, Goldenberg I, and Zareba W. Sex-Related Differences in Ventricular Tachyarrhythmia Events in Patients With Implantable Cardioverter-Defibrillator and Prior Ventricular Tachyarrhythmias. *JACC Clin Electrophysiol* 2023; Epub ahead of print. PMID: 38032582. Full Text

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BACKGROUND: Data on the risk of ventricular tachycardia (VT), ventricular fibrillation (VF), and death by sex in patients with prior VT/VF are limited. OBJECTIVES: This study aimed to assess sex-related differences in implantable cardioverter-defibrillator (ICD)-treated VT/VF events and death in patients implanted for secondary prevention or primary prevention ICD indications who experienced VT/VF before enrollment in the RAID (Ranolazine Implantable Cardioverter-Defibrillator) trial. METHODS: Sex-related differences in the first and recurrent VT/VF requiring antitachycardia pacing or ICD shock and death were evaluated in 714 patients. RESULTS: There were 124 women (17%) and 590 men observed during a mean follow-up of 26.81 ± 14.52 months. Compared to men, women were at a significantly lower risk of VT/VF/death (HR: 0.67; P = 0.029), VT/VF (HR: 0.68; P = 0.049), VT/VF treated with antitachycardia pacing (HR: 0.59; P = 0.019), and VT/VF treated with ICD shock (HR: 0.54; P = 0.035). The risk of recurrent VT/VF was also significantly lower in women (HR: 0.35; P < 0.001). HR for death was similar to the other endpoints (HR: 0.61; P = 0.162). In comparison to men, women presented with faster VT rates (196 ± 32 beats/min vs 177 ± 30 beats/min, respectively; P = 0.002), and faster shock-requiring VT/VF rates (258 ± 56 beats/min vs 227 ± 57 beats/min, respectively; P = 0.30). There was a significant interaction for the risk of VT/VF by race (P = 0.013) with White women having significantly lower risk than White men (HR: 0.36; P < 0.001), whereas Black women had a similar risk to Black men (HR: 1.06; P = 0.851). CONCLUSIONS: Women with a history of prior VT/VF experienced a lower risk recurrent VT/VF requiring ICD therapy when compared to men. Black Women had a risk similar to men, whereas the lower risk for VT/VF in women was observed primarily in White women. (Ranolazine Implantable Cardioverter-Defibrillator Trial; NCT01215253).

Cardiology/Cardiovascular Research

Luzum JA, Campos-Staffico AM, **Li J**, **She R**, **Gui H**, **Peterson EL**, **Liu B**, **Sabbah HN**, Donahue MP, Kraus WE, **Williams LK**, and **Lanfear DE**. Genome-Wide Association Study of Beta-Blocker Survival Benefit in Black and White Patients with Heart Failure with Reduced Ejection Fraction. *Genes (Basel)* 2023; 14(11). PMID: 38002962. Full Text

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In patients with heart failure with reduced ejection fraction (HFrEF), individual responses to beta-blockers vary. Candidate gene pharmacogenetic studies yielded significant but inconsistent results, and they may have missed important associations. Our objective was to use an unbiased genome-wide association study (GWAS) to identify loci influencing beta-blocker survival benefit in HFrEF patients. Genetic variant × beta-blocker exposure interactions were tested in Cox proportional hazards models for all-cause mortality stratified by self-identified race. The models were adjusted for clinical risk factors and propensity scores. A prospective HFrEF registry (469 black and 459 white patients) was used for discovery, and linkage disequilibrium (LD) clumped variants with a beta-blocker interaction of $p < 5 \times 10(-5)$, were tested for Bonferroni-corrected validation in a multicenter HFrEF clinical trial (288 black and 579 white patients). A total of 229 and 18 variants in black and white HFrEF patients, respectively, had interactions with beta-blocker exposure at $p < 5 \times 10(-5)$ upon discovery. After LD-clumping, 100 variants and 4 variants in the black and white patients, respectively, remained for validation but none reached statistical significance. In conclusion, genetic variants of potential interest were identified in a discovery-based GWAS of beta-blocker survival benefit in HFrEF patients, but none were validated in an independent dataset. Larger cohorts or alternative approaches, such as polygenic scores, are needed.

Cardiology/Cardiovascular Research

Mehra MR, Netuka I, Uriel N, Katz JN, Pagani FD, Jorde UP, Gustafsson F, Connors JM, Ivak P, **Cowger J**, Ransom J, Bansal A, Takeda K, Agarwal R, Byku M, Givertz MM, Bitar A, Hall S, Zimpfer D, Vega JD, Kanwar MK, Saeed O, Goldstein DJ, Cogswell R, Sheikh FH, Danter M, Pya Y, Phancao A, Henderson J, Crandall DL, Sundareswaran K, Soltesz E, and Estep JD. Aspirin and Hemocompatibility Events With a

Left Ventricular Assist Device in Advanced Heart Failure: The ARIES-HM3 Randomized Clinical Trial. *Jama* 2023; Epub ahead of print. PMID: 37950897. Full Text

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Ochsner Medical Center, New Orleans, Louisiana.
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Emory University Hospital, Atlanta, Georgia.
Allegheny Health Network, Pittsburgh, Pennsylvania.
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Medstar Washington Hospital Center, Washington, DC.
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IMPORTANCE: Left ventricular assist devices (LVADs) enhance quality and duration of life in advanced heart failure. The burden of nonsurgical bleeding events is a leading morbidity. Aspirin as an antiplatelet agent is mandated along with vitamin K antagonists (VKAs) with continuous-flow LVADs without conclusive evidence of efficacy and safety. OBJECTIVE: To determine whether excluding aspirin as part of the antithrombotic regimen with a fully magnetically levitated LVAD is safe and decreases bleeding. DESIGN, SETTING, AND PARTICIPANTS: This international, randomized, double-blind, placebo-controlled study of aspirin (100 mg/d) vs placebo with VKA therapy in patients with advanced heart failure with an LVAD was conducted across 51 centers with expertise in treating patients with advanced heart failure across 9 countries. The randomized population included 628 patients with advanced heart failure implanted with a fully magnetically levitated LVAD (314 in the placebo group and 314 in the aspirin group), of whom 296 patients in the placebo group and 293 in the aspirin group were in the primary analysis population, which informed the primary end point analysis. The study enrolled patients from July 2020 to September 2022; median follow-up was 14 months. INTERVENTION: Patients were randomized in a 1:1 ratio to receive aspirin (100 mg/d) or placebo in addition to an antithrombotic regimen. MAIN OUTCOMES AND MEASURES: The composite primary end point, assessed for noninferiority (-10% margin) of placebo, was survival free of a major nonsurgical (>14 days after implant) hemocompatibility-related adverse events (including stroke, pump thrombosis, major bleeding, or arterial peripheral thromboembolism) at 12 months. The principal secondary end point was nonsurgical bleeding events. RESULTS: Of the 589 analyzed patients, 77% were men; one-third were Black and 61% were White. More patients were alive and free of hemocompatibility events at 12 months in the placebo group (68%) vs those taking aspirin (74%). Noninferiority of placebo was demonstrated (absolute between-group difference, 6.0% improvement in event-free survival with placebo [lower 1-sided 97.5% CI, -1.6%]; $P < .001$). Aspirin avoidance was associated with reduced nonsurgical bleeding events (relative risk, 0.66 [95% confidence limit, 0.51-0.85]; $P = .002$) with no increase in stroke or other thromboembolic events, a finding consistent among diverse subgroups of patient characteristics. CONCLUSIONS AND RELEVANCE: In patients with advanced heart failure treated with a fully magnetically levitated LVAD, avoidance of aspirin as part of an antithrombotic regimen, which includes VKA, is not inferior to a regimen containing aspirin, does not increase thromboembolism risk, and is associated with a reduction in bleeding events. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT04069156.

Cardiology/Cardiovascular Research

Mesnier J, Simard T, Jung RG, Lehenbauer KR, Piayda K, Pracon R, Jackson GG, Flores-Umanzor E, Faroux L, Korsholm K, Chun JKR, Chen S, Maarse M, Montrella K, Chaker Z, Spoon JN, Pastormerlo LE, Meincke F, Sawant AC, Moldovan CM, **Qintar M**, Aktas MK, Branca L, Radinovic A, Ram P, El-Zein RS, Flautt T, Ding WY, Sayegh B, Benito-González T, Lee OH, Badejoko SO, Paitazoglou C, Karim N, Zaghloul AM, Agarwal H, Kaplan RM, Alli O, Ahmed A, Suradi HS, Knight BP, Alla VM, Panaich SS, Wong T, Bergmann MW, Chothia R, Kim JS, Pérez de Prado A, Bazaz R, Gupta D, Valderrábano M, Sanchez CE, El Chami MF, Mazzone P, Adamo M, Ling F, **Wang DD**, **O'Neill W**, Wojakowski W, Pershad A, Berti S, Spoon DB, Kawsara A, Jabbour G, Boersma LVA, Schmidt B, Nielsen-Kudsk JE, Freixa X, Ellis CR, Fauchier L, Demkow M, Sievert H, Main ML, Hibbert B, Holmes DR, Jr., Alkhouli M, and Rodés-Cabau J. Persistent and Recurrent Device-Related Thrombus After Left Atrial Appendage Closure: Incidence, Predictors, and Outcomes. *JACC Cardiovasc Interv* 2023; 16(22):2722-2732. PMID: 38030358. Full Text

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BACKGROUND: Scarce data exist on the evolution of device-related thrombus (DRT) after left atrial appendage closure (LAAC). OBJECTIVES: This study sought to assess the incidence, predictors, and clinical impact of persistent and recurrent DRT in LAAC recipients. METHODS: Data were obtained from an international multicenter registry including 237 patients diagnosed with DRT after LAAC. Of these, 214 patients with a subsequent imaging examination after the initial diagnosis of DRT were included. Unfavorable evolution of DRT was defined as either persisting or recurrent DRT. RESULTS: DRT resolved in 153 (71.5%) cases and persisted in 61 (28.5%) cases. Larger DRT size (OR per 1-mm increase: 1.08; 95% CI: 1.02-1.15; P = 0.009) and female (OR: 2.44; 95% CI: 1.12-5.26; P = 0.02) were independently associated with persistent DRT. After DRT resolution, 82 (53.6%) of 153 patients had repeated device imaging, with 14 (17.1%) cases diagnosed with recurrent DRT. Overall, 75 (35.0%) patients had unfavorable evolution of DRT, and the sole predictor was average thrombus size at initial diagnosis (OR per 1-mm increase: 1.09; 95% CI: 1.03-1.16; P = 0.003), with an optimal cutoff size of 7 mm (OR: 2.51; 95% CI: 1.39-4.52; P = 0.002). Unfavorable evolution of DRT was associated with a higher rate of thromboembolic events compared with resolved DRT (26.7% vs 15.1%; HR: 2.13; 95% CI: 1.15-3.94; P = 0.02). CONCLUSIONS: About one-third of DRT events had an unfavorable evolution (either persisting or recurring), with a larger initial thrombus size (particularly >7 mm) portending an increased risk. Unfavorable evolution of DRT was associated with a 2-fold higher risk of thromboembolic events compared with resolved DRT.

Cardiology/Cardiovascular Research

Nulty S, **Fore J**, **Madison J**, and **Day CS**. Revenue Generation and Follow-up for a Hand Trauma Program for Emergency Department Patients in an Inner-City Metropolitan Area. *J Am Acad Orthop Surg Glob Res Rev* 2023; 7(11). PMID: 37976438. Full Text

From Henry Ford Health, Detroit, MI.

BACKGROUND: Although hand trauma care has proved to be profitable, loss of trauma patients from a system may lead to revenue loss. Our study aimed to (1) elucidate the economic effect of hand trauma programs, (2) quantify the potential fiscal effect of loss of follow-up, and (3) determine factors contributing to leakage of patients from the healthcare system. METHODS: Revenue data were retrospectively extracted for all adult hand trauma patients within a multicenter healthcare system from 2014 to 2018. Demographic and encounter factors were analyzed using Wilcoxon rank-sum test for differences in continuous variables, Pearson chi square test for categorical variables, and odds ratios. A follow-up model was created using logistic regression. RESULTS: A total of 56,995 (31% new, 69% established) hand trauma encounters were recorded. Follow-up was markedly affected by many factors, including new

vs. established patients. Of the 17,748 new patients, 8638 (48.6%) returned for subsequent care, generating $34M. The patients who did not return may have lost $176M for the system. CONCLUSIONS: Many factors lead to loss of follow-up. Understanding these factors can help target efforts to minimize leakage of hand trauma patients. Hand trauma introduces new patients to hospitals, generating notable revenue. Leakage of hand trauma patients has substantial revenue losses.

Cardiology/Cardiovascular Research
Rawlley B, Sanchez AC, **Gupta K**, Ramm M, and Chaudhuri D. Angiotensin Receptor/Neprilysin Inhibitor Versus Angiotensin-Converting Enzyme Inhibitor Use in Patients With a Left Ventricular Assist Device: A Propensity Score Matched Analysis. *Am J Cardiol* 2023; 211:180-182. PMID: 37866448. Full Text

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Cardiology/Cardiovascular Research
Simonato M, Whisenant BK, Unbehaun A, Kempfert J, Ribeiro HB, Kornowski R, Erlebach M, Bleiziffer S, Windecker S, Pilgrim T, Tomii D, Guerrero M, Ahmad Y, Forrest JK, Montorfano M, Ancona M, Adam M, Wienemann H, Finkelstein A, **Villablanca P**, Codner P, Hildick-Smith D, Ferrari E, Petronio AS, Shamekhi J, Presbitero P, Bruschi G, Rudolph T, Cerillo A, Attias D, Nejjari M, Abizaid A, Felippi de Sá Marchi M, Horlick E, Wijeysundera H, Andreas M, Thukkani A, Agrifoglio M, Iadanza A, Baer LM, Nanna MG, and Dvir D. Clinical and Hemodynamic Outcomes of Balloon-Expandable Mitral Valve-in-Valve Positioning and Asymmetric Deployment: The VIVID Registry. *JACC Cardiovasc Interv* 2023; 16(21):2615-2627. PMID: 37968032. Full Text

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BACKGROUND: Mitral valve-in-valve (ViV) is associated with suboptimal hemodynamics and rare left ventricular outflow tract (LVOT) obstruction. OBJECTIVES: This study aimed to determine whether device position and asymmetry are associated with these outcomes. METHODS: Patients undergoing SAPIEN 3 (Edwards Lifesciences) mitral ViV included in the VIVID (Valve-in-Valve International Data) Registry were studied. Clinical endpoints are reported according to Mitral Valve Academic Research Consortium definitions. Residual mitral valve stenosis was defined as mean gradient ≥5 mm Hg. Depth of implantation (percentage of transcatheter heart valve [THV] atrial to the bioprosthesis ring) and asymmetry (ratio of 2 measures of THV height) were evaluated. RESULTS: A total of 222 patients meeting the criteria for optimal core lab evaluation were studied (age 74 ± 11.6 years; 61.9% female; STS score = 8.3 ± 7.1). Mean asymmetry was 6.2% ± 4.4%. Mean depth of implantation was 19.0% ± 10.3% atrial. Residual stenosis was common (50%; mean gradient 5.0 ± 2.6 mm Hg). LVOT obstruction occurred in 7 cases (3.2%). Implantation depth was not a predictor of residual stenosis (OR: 1.19 [95% CI: 0.92-1.55]; P = 0.184), but more atrial implantation was protective against LVOT obstruction (0.7% vs 7.1%; P = 0.009; per 10% atrial, OR: 0.48 [95% CI: 0.24-0.98]; P = 0.044). Asymmetry was found to be an independent predictor of residual stenosis (per 10% increase, OR: 2.30 [95% CI: 1.10-4.82]; P = 0.027). CONCLUSIONS: Valve stenosis is common after mitral ViV. Asymmetry was associated with residual stenosis. Depth of implantation on its own was not associated with residual stenosis but was associated with LVOT obstruction. Technical considerations to reduce postdeployment THV asymmetry should be considered.

Cardiology/Cardiovascular Research

Simsek B, Rempakos A, Kostantinis S, Alexandrou M, Karacsonyi J, Rangan BV, Mastrodemos OC, Mutlu D, Abi Rafeh N, **Alaswad K**, Avran A, Azzalini L, ElGuindy A, Egred M, Goktekin O, Gorgulu S, Jaber W, Kearney KE, Kirtane AJ, Lombardi WL, Mashayekhi K, McEntegart M, Nicholson W, Rinfret S, Allana SS, Sandoval Y, Nicholas Burke M, and Brilakis ES. International survey of chronic total occlusion percutaneous coronary intervention operators. *Catheter Cardiovasc Interv* 2023; Epub ahead of print. PMID: 37983649. Full Text

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BACKGROUND: Contemporary chronic total occlusion (CTO) percutaneous coronary intervention (PCI) practice has received limited study. AIM: To examine the contemporary CTO PCI practice. METHODS: We performed an online, anonymous, international survey of CTO PCI operators. RESULTS: Five hundred forty-five CTO PCI operators and 190 interventional cardiology fellows with an interest in CTO PCI participated in this survey. Almost half were from the United States (41%), most (93%) were men, and the median h/week spent in the hospital was 58. Median annual case numbers were 205 (150-328)

for PCIs and 20 (5-50) for CTO PCIs. Almost one-fifth (17%) entered CTO cases into registries, such as PROGRESS-CTO (55%) and EuroCTO (20%). More than one-third worked at academic institutions (39%), 31% trained dedicated CTO fellows, and 22% proctored CTO PCI. One-third (34%) had dedicated CTO PCI days. Most (51%) never discharged CTO patients the same day, while 17% discharged CTO patients the same day >50% of the time. After successful guidewire crossing, 38% used intravascular imaging >90% of the time. Most used CTO scores including J-CTO (81%), PROGRESS-CTO (35%), and PROGRESS-CTO complications scores (30%). Coronary artery perforation was encountered within the last month by 19%. On a scale of 0-10, the median comfort levels in treating coronary artery perforation were: covered stents 8.8 (7.0-10), coil embolization 5.0 (2.1-8.5), and fat embolization 3.7 (0.6-7.3). Most (51%) participants had a complication cart/kit and 25% conducted regular complication drills with catheterization laboratory staff. CONCLUSION: Contemporary CTO PCI practices vary widely. Further research on barriers to following the guiding principles of CTO PCI may improve patient outcomes.

Cardiology/Cardiovascular Research
Singh H, **Ahmed O**, **Allen E**, and **Othman H**. A Case of Stress Cardiomyopathy With Nab-Paclitaxel Infusion. *J Investig Med High Impact Case Rep* 2023; 11:23247096231209554. PMID: 37919938. Full Text

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Stress cardiomyopathy is a transient left ventricular dysfunction caused by physiologic or pathologic stressors. Anaphylaxis is a hypersensitivity disorder that can lead to a rapid life-threatening respiratory collapse. It happens due to exposure to allergens including medications. During anaphylaxis, there is a compensatory release of catecholamines that can lead to stress cardiomyopathy. In this case, nab-paclitaxel infusion led to anaphylaxis with respiratory failure. Echocardiogram showed features of diffuse hypokinesis with preserved basal segment contractility, and cardiac catheterization did not show any evidence of obstructive coronary artery disease. The overall clinical picture suggested stress cardiomyopathy. The patient was treated with guideline-directed medical therapy which resulted in normalization of the ejection fraction with no symptoms of congestive heart failure at any point. The patient was thereafter resumed on a reduced dose of nab-paclitaxel. This case report adds to the spectrum of infusion-related reactions associated with paclitaxel and demonstrates the course of events in the management of anaphylaxis and stress cardiomyopathy in this scenario.

Cardiology/Cardiovascular Research
Steinberg RS, Nayak A, Okoh A, Wang J, Matiello E, Morris AA, **Cowger JA**, and Nohria A. Associations Between Preimplant Cancer Type and Left Ventricular Assist Device Outcomes: An INTERMACS Registry Analysis. *Asaio j* 2023; Epub ahead of print. PMID: 38039542. Full Text

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We used the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database to examine whether history of a solid versus hematologic malignancy impacts outcomes after left ventricular assist device (LVAD) implantation. We included LVAD recipients (2007-2017) with cancer history reported (N = 14,799, 21% female, 24% Black). Multivariate models examined the association between cancer type and post-LVAD mortality and adverse events. Competing risk analyses compared death and heart transplantation between cancer types and those without cancer in bridge-to-transplant (BTT) patients. A total of 909 (6.1%) patients had a history of cancer (4.9% solid tumor, 1.3% hematologic malignancy). Solid tumors were associated with higher mortality (adjusted hazard ratio [aHR] = 1.31, 95% confidence interval [CI] = 1.09-1.57), major bleeding (aHR = 1.15, 95% CI = 1.00-1.32), and pump thrombosis (aHR = 1.52, 95% CI = 1.09-2.13), whereas hematologic malignancies were associated with increased major infection (aHR = 1.43, 95% CI = 1.14-1.80). Compared to BTT patients without a history of cancer, solid tumor patients were less likely to undergo transplantation (adjusted subdistribution HR

[aSHR] = 0.63, 95% CI = 0.45-0.89) and hematologic malignancy patients were as likely to experience death (aSHR = 1.16, 95% CI = 0.63-2.14) and transplantation (aSHR = 0.69, 95% CI = 0.44-1.08). Cancer history and type impact post-LVAD outcomes. As LVAD utilization in cancer survivors increases, we need strategies to improve post-LVAD outcomes in these patients.

Cardiology/Cardiovascular Research
Sukhon F, **Jabri A**, Al-Abdouh A, Alameh A, Alhuneafat L, **Jebaje ZA**, Khader S, Mhanna M, **Koenig G**, **Alaswad K**, **Villablanca P**, and **AlQarqaz M**. Liberal versus Conservative Transfusion Strategy for Patients with Acute Myocardial Infarction and Anemia: A Systematic Review and Meta-analysis. *Curr Probl Cardiol* 2023; 102247. Epub ahead of print. PMID: 38040217. Full Text

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BACKGROUND: A hemoglobin (Hb) level goal of 7-8 g/dL is a standard care threshold, prompting blood transfusion. The debate over whether acute myocardial infarction (MI) patients benefit from a more liberal transfusion strategy prompted a meta-analysis of relevant trials. METHODS: We performed a meta-analysis of randomized controlled trials (RCTs) comparing liberal and restrictive transfusion strategies in anemic MI patients. Primary outcomes were recurrent MI and death/MI, while secondary outcomes included stroke, revascularization, heart failure, and all-cause mortality. Due to the limited trials, we utilized the Paul-Mendele method with Hartung Knapp adjustment. RESULTS: Involving 2155 patients with liberal transfusion and 2170 with conservative transfusion across four RCTs, liberal transfusion did not significantly reduce MI (relative risk [RR] 0.85; 95% CI 0.72 - 1.02, p = 0.07) or death/MI (RR 0.88; 95% CI 0.45 - 1.71, p = 0.57). No significant differences were observed in all-cause mortality (RR 0.82; 95% CI 0.25 - 2.68, p = 0.63), stroke (RR 0.89; 95% CI 0.48 - 1.64, p = 0.50), revascularization (RR 0.93; 95% CI 0.48 - 1.80, p = 0.68), or heart failure (RR 1.14; 95% CI 0.04 - 28.84, p = 0.88). CONCLUSION: Our meta-analysis supports current medical guidelines, reinforcing the practice of limiting transfusions in acute MI patients to those with an Hb level of 7 or 8 g/dL. Liberal transfusion strategies did not show improved clinical outcomes.

Cardiology/Cardiovascular Research
Ungureanu C, Yamane M, Kayaert P, Knaapen P, Mashayekhi K, **Alaswad K**, Spratt JC, Gasparini GL, Dens J, Lepièce C, Carlier S, Sgueglia GA, and Avran A. The safety and feasibility of live-stream proctoring for CTO procedures. *J Invasive Cardiol* 2023; 35(10). PMID: 37984322. Request Article

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OBJECTIVE: To assess the technical feasibility of a new method of educational training, based on audio-video (AV) communication between an interventional cardiologist and the cath lab staff members in one location and a remote expert proctor. METHODS: Overall, 9 patients underwent a percutaneous coronary intervention (PCI) targeting a chronic total occlusion (CTO) between June 2021 and January 2022 at a single Belgian center using the virtual proctoring approach. For this assessment, the strategic planning of the CTO PCI and all the decisions throughout the intervention were the responsibility of the proctor. The operator was guided via an AV link, by the proctor throughout the procedure. RESULTS: The operator performed each procedural step, guided by the remote proctor, who had continuous access to all relevant interventional details. No major adverse cardiac events (MACE) occurred during the index hospitalization or within 6 months follow-up. CONCLUSIONS: A new method of virtual proctoring based on live AV communication is feasible, even in the case of highly complex CTO PCI procedures. This strategy also appears safe and may provide the patient the benefit of incremental expertise. This approach is facilitated by advances in AV communication and allows physicians to share expertise irrespective of location. It could increase global interaction between colleagues and facilitate sharing of knowledge, which are both key aspects in the development of CTO PCI. This preliminary experience could serve as a basis for future large studies to study the potential role and benefits of virtual proctoring for complex CTO PCI procedures.

Cardiology/Cardiovascular Research

Zahr F, Smith RL, Gillam LD, Chadderdon S, Makkar R, von Bardeleben RS, Ruf TF, Kipperman RM, Rassi AN, Szerlip M, Goldman S, Inglessis-Azuaje I, Yadav P, Lurz P, Davidson CJ, Mumtaz M, Gada H, Kar S, Kodali SK, Laham R, Hiesinger W, Fam NP, Keßler M, **O'Neill WW**, Whisenant B, Kliger C, Kapadia S, Rudolph V, Choo J, Hermiller J, Morse MA, Schofer N, Gafoor S, Latib A, Mahoney P, Kaneko T, Shah PB, Riddick JA, Muhammad KI, Boekstegers P, Price MJ, Praz F, Koulogiannis K, Marcoff L, Hausleiter J, and Lim DS. One-Year Outcomes From the CLASP IID Randomized Trial for Degenerative Mitral Regurgitation. *JACC Cardiovasc Interv* 2023; Epub ahead of print. PMID: 37962288. Full Text

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BACKGROUND: The CLASP IID (Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical) trial is the first randomized controlled trial comparing the PASCAL system and the MitraClip system in prohibitive risk patients with significant symptomatic degenerative mitral regurgitation (DMR). OBJECTIVES: The study sought to report primary and secondary endpoints and 1-year outcomes for the full cohort of the CLASP IID trial. METHODS: Prohibitive-risk patients with 3+/4+ DMR were randomized 2:1 (PASCAL:MitraClip). One-year assessments included secondary effectiveness endpoints (mitral regurgitation [MR] ≤2+ and MR ≤1+), and clinical, echocardiographic, functional, and quality-of-life outcomes. Primary safety (30-day composite major adverse events [MAE]) and effectiveness (6-month MR ≤2+) endpoints were assessed for the full cohort. RESULTS: Three hundred patients were randomized (PASCAL: n = 204; MitraClip: n = 96). At 1 year, differences in survival, freedom from heart failure hospitalization, and MAE were nonsignificant (P > 0.05 for all). Noninferiority of the PASCAL system compared with the MitraClip system persisted for the primary endpoints in the full cohort (For PASCAL vs MitraClip, the 30-day MAE rates were 4.6% vs 5.4% with a rate difference of -0.8% and 95% upper confidence bound of 4.6%. The 6-month MR≤2+ rates were 97.9% vs 95.7% with a rate difference of 2.2% and 95% lower confidence bound (LCB) of -2.5%, for, respectively). Noninferiority was met for the secondary effectiveness endpoints at 1 year (MR≤2+ rates for PASCAL vs MitraClip were 95.8% vs 93.8% with a rate difference of 2.1% and 95% LCB of -4.1%. The MR≤1+ rates were 77.1% vs 71.3% with a rate difference of 5.8% and 95% LCB of -5.3%, respectively). Significant improvements in functional classification and quality of life were sustained in both groups (P <0.05 for all vs baseline). CONCLUSIONS: The CLASP IID trial full cohort met primary and secondary noninferiority endpoints, and at 1 year, the PASCAL system demonstrated high survival, significant MR reduction, and sustained improvements in functional and quality-of-life outcomes. Results affirm the PASCAL system as a beneficial therapy for prohibitive-surgical-risk patients with significant symptomatic DMR.

Center for Health Policy and Health Services Research

Metz VE, Ray GT, Palzes V, Binswanger I, Altschuler A, Karmali RN, **Ahmedani BK**, Andrade SE, Boscarino JA, Clark RE, Haller IV, Hechter RC, Roblin DW, Sanchez K, Bailey SR, McCarty D, Stephens KA, Rosa CL, Rubinstein AL, and Campbell CI. Prescription Opioid Dose Reductions and Potential Adverse Events: a Multi-site Observational Cohort Study in Diverse US Health Systems. *J Gen Intern Med* 2023; Epub ahead of print. PMID: 37930512. Full Text

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BACKGROUND: In response to the opioid crisis in the United States, population-level prescribing of opioids has been decreasing; there are concerns, however, that dose reductions are related to potential adverse events. OBJECTIVE: Examine associations between opioid dose reductions and risk of 1-month potential adverse events (emergency department (ED) visits, opioid overdose, benzodiazepine prescription fill, all-cause mortality). DESIGN: This observational cohort study used electronic health record and claims data from eight United States health systems in a prescription opioid registry (Clinical Trials Network-0084). All opioid fills (excluding buprenorphine) between 1/1/2012 and 12/31/2018 were used to identify baseline periods with mean morphine milligram equivalents daily dose of ≥ 50 during six consecutive months. PATIENTS: We identified 60,040 non-cancer patients with ≥ one 2-month dose reduction period (600,234 unique dose reduction periods). MAIN MEASURES: Analyses examined associations between dose reduction levels (1- < 15%, 15- < 30%, 30- < 100%, 100% over 2 months) and potential adverse events in the month following a dose reduction using logistic regression analysis, adjusting for patient characteristics. KEY RESULTS: Overall, dose reduction periods involved mean reductions of 18.7%. Compared to reductions of 1- < 15%, dose reductions of 30- < 100% were associated with higher odds of ED visits (OR 1.14, 95% CI 1.10, 1.17), opioid overdose (OR 1.41, 95% CI 1.09-1.81), and all-cause mortality (OR 1.39, 95% CI 1.16-1.67), but lower odds of a benzodiazepine fill (OR 0.83, 95% CI 0.81-0.85). Dose reductions of 15- < 30%, compared to 1- < 15%, were associated with higher odds of ED visits (OR 1.08, 95% CI 1.05-1.11) and lower odds of a benzodiazepine fill (OR 0.93, 95% CI 0.92-0.95), but were not associated with opioid overdose and all-cause mortality. CONCLUSIONS: Larger reductions for patients on opioid therapy may raise risk of potential adverse events in the month after reduction and should be carefully monitored.

Center for Health Policy and Health Services Research

Rabinowitz JA, **Kahn GD**, **Felton JW**, Drabick DAG, and Wilcox HC. Correlates of Informant Discrepancies in Self-Harm Among Youth Involved in Child Protective Services. *Child Youth Serv Rev* 2023; 155. PMID: 38053918. Request Article

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Youth involved with child protective services (CPS) are at elevated risk for engaging in self-harm. Participation in interventions or treatments that may reduce youths' self-harm behaviors often depends on the accurate reporting of their self-injurious behaviors. However, informants often disagree on the presence or severity of self-harm engagement, making the identification of youth in need of treatment more challenging. The current study aims to characterize discrepancies between youth and caregiver reports of children's self-harm among a sample of youth with a history of CPS involvement, and to identify factors (e.g., demographics, youth and caregiver psychological impairments, aspects of the caregiving

environment) associated with these discrepancies. Participants (N = 258) were drawn from a large, nationally representative sample of youth under the age of 18 (mean age = 13.8) and their caregivers who were investigated by CPS. Multinomial logistic regressions were used to examine correlates of discrepancies in caregiver and youth reports of youth self-harm. Results indicated that 10% of caregiver-child dyads agreed on children's engagement in self-harm. In 33% of cases, only the child reported self-harm and in 57% of cases, only the caregiver reported youth self-harm. Being a biological caregiver, child female sex, higher levels of internalizing symptoms; higher post-traumatic stress disorder (PTSD) symptoms; and greater caregiver alcohol use was associated with a lower likelihood of caregivers reporting self-harm only. Older child age; lower externalizing symptoms; higher PTSD symptoms, and greater levels of caregiver emotional security and structure were linked to lower odds of children reporting self-harm only. These results underscore important factors to consider when assessing self-harm among youth involved with CPS and have potential implications for practice guidelines in this population.

Center for Health Policy and Health Services Research

Secrest S, **Miller-Matero LR**, Chrusciel T, Salas J, Sullivan MD, **Zabel C**, Lustman P, **Ahmedani B**, Carpenter RW, and Scherrer JF. Baseline Characteristics From a New Longitudinal Cohort of Patients With Noncancer Pain and Chronic Opioid Use in the United States. *J Pain* 2023; Epub ahead of print. PMID: 37907114. Request Article

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Retrospective cohort studies have consistently observed that long-term prescription opioid use is a risk factor for new major depressive episodes. However, prospective studies are needed to confirm these findings and establish evidence for causation. The Prescription Opioids and Depression Pathways cohort study is designed for this purpose. The present report describes the baseline sample and associations between participant characteristics and odds of daily versus nondaily opioid use. Second, we report associations between participant characteristics and odds of depression, dysthymia, anhedonia, and vital exhaustion. Patients with noncancer pain were eligible if they started a new period of prescription opioid use lasting 30 to 90 days. Participants were 54.8 (standard deviation ± 11.3) years of age, 57.3% female and 73% White race. Less than college education was more common among daily versus nondaily opioid users (32.4% vs 27.3%; P = .0008), as was back pain (64.2% vs 51.3%; P < .0001), any nonopioid substance use disorder (12.8% vs 4.8%; P < .0001), and current smoking (30.7% vs 18.4% P < .0001). High pain interference (50.9% vs 28.4%; P < .0001) was significantly associated with depression, as was having more pain sites (6.9 ± 3.6 vs 5.7 ± 3.6; P < .0001), and benzodiazepine comedication (38.2% vs 23.4%; P < .0001). High pain interference was significantly more common among those with anhedonia (46.8% vs 27.4%; P < .0001), and more pain sites (7.0 ± 3.7 vs 5.6 ± 3.6; P < .0001) were associated with anhedonia. Having more pain sites (7.9 ± 3.6 vs 5.5 ± 3.50; P < .0001) was associated with vital exhaustion, as was back pain (71.9% vs 56.8%; P = .0001) and benzodiazepine comedication (42.8% vs

22.8%; P < .0001). Patients using prescription opioids for noncancer pain have complex pain, psychiatric, and substance use disorder comorbidities. Longitudinal data will reveal whether long-term opioid therapy leads to depression or other mood disturbances such as anhedonia and vital exhaustion. PERSPECTIVE: This study reports baseline characteristics of a new prospective, noncancer pain cohort study. Risk factors for adverse opioid outcomes were most common in those with depression and vital exhaustion and less common in dysthymia and anhedonia. Baseline data highlight the complexity of patients receiving long-term opioid therapy for noncancer pain.

Center for Health Policy and Health Services Research
Yarborough BJH, Stumbo SP, Schneider JL, **Ahmedani BK**, Daida YG, Hooker SA, Negriff S, Rossom RC, and Lapham G. Impact of Opioid Dose Reductions on Patient-Reported Mental Health and Suicide-Related Behavior and Relationship to Patient Choice in Tapering Decisions. *J Pain* 2023; Epub ahead of print. PMID: 37952862. Request Article

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Mental health and suicide-related harms resulting from prescription opioid tapering are poorly documented and understood. Six health systems contributed opioid prescribing data from January 2016 to April 2020. Patients 18 to 70 years old with evidence of opioid tapering participated in semi-structured interviews. Individuals who experienced suicide attempts were oversampled. Family members of suicide decedents who had experienced opioid tapering were also interviewed. Interviews were analyzed using thematic analysis. The study participants included 176 patients and 16 family members. Patients were 68% female, 80% White, and 15% Hispanic, mean age 58. All family members were female spouses of White, non-Hispanic male decedents. Among the subgroup (n = 60) who experienced a documented suicide attempt, reported experiencing suicidal ideation during tapering, or were family members of suicide decedents, 40% reported that opioid tapering exacerbated previously recognized mental health issues, and 25% reported that tapering triggered new-onset mental health concerns. Among participants with suicide behavior, 47% directly attributed it to opioid tapering. Common precipitants included increased pain, reduced life engagement, sleep problems, withdrawal, relationship dissolution, and negative consequences of opioid substitution with other substances for pain relief. Most respondents reporting suicide behavior felt that the decision to taper was made by the health care system or a clinician (67%) whereas patients not reporting suicide behavior were more likely to report it was their own decision (42%). This study describes patient-reported mental health deterioration or suicide behavior while tapering prescription opioids. Clinicians should screen for, monitor, and treat suicide behavior while assisting patients in tapering opioids. PERSPECTIVE: This work describes changes in patient-reported mental health and suicide behavior while tapering prescription opioids. Recommendations for improving care include mental health and suicide risk screening during and following opioid tapering.

Center for Health Policy and Health Services Research
Young JL, Powell RN, **Zabel C**, Saal J, Welling LLM, Fortain J, and Ceresnie A. Development and validation of the ADHD Symptom and Side Effect Tracking - Baseline Scale (ASSET-BS): a novel short screening measure for ADHD in clinical populations. *BMC Psychiatry* 2023; 23(1):806. PMID: 37932675. Full Text

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OBJECTIVE: The aim was to develop and test a novel screen of adult ADHD, with a specific focus on clinical use. We designed a series of three studies to accomplish this aim. METHOD: Study One (n = 155) and Study Two (n = 591) collected data via surveys to conduct exploratory and confirmatory factor analyses, respectively. Study Three analyzed the scale's psychometrics in a clinical sample (n = 151). RESULTS: Study One and Study Two identified a 10-item scale with a two-factor structure. Study Three found good discriminant validity, sensitivity = 80.0%, specificity = 80.2%, and convergent validity with both the Brown Executive Function/Attention Scales, r (131) = .76, p < .001, and the Conner's Adult ADHD Rating Scales r (131) = .71, p < .001. CONCLUSION: The scale demonstrated effectiveness in screening for ADHD in a psychiatric outpatient population. Its results may be used to identify patients that may benefit from thorough ADHD diagnostic procedures.

Center for Individualized and Genomic Medicine Research

Luzum JA, Campos-Staffico AM, **Li J**, **She R**, **Gui H**, **Peterson EL**, **Liu B**, **Sabbah HN**, Donahue MP, Kraus WE, **Williams LK**, and **Lanfear DE**. Genome-Wide Association Study of Beta-Blocker Survival Benefit in Black and White Patients with Heart Failure with Reduced Ejection Fraction. *Genes (Basel)* 2023; 14(11). PMID: 38002962. Full Text

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In patients with heart failure with reduced ejection fraction (HFrEF), individual responses to beta-blockers vary. Candidate gene pharmacogenetic studies yielded significant but inconsistent results, and they may have missed important associations. Our objective was to use an unbiased genome-wide association study (GWAS) to identify loci influencing beta-blocker survival benefit in HFrEF patients. Genetic variant × beta-blocker exposure interactions were tested in Cox proportional hazards models for all-cause mortality stratified by self-identified race. The models were adjusted for clinical risk factors and propensity scores. A prospective HFrEF registry (469 black and 459 white patients) was used for discovery, and linkage disequilibrium (LD) clumped variants with a beta-blocker interaction of $p < 5 \times 10(-5)$, were tested for Bonferroni-corrected validation in a multicenter HFrEF clinical trial (288 black and 579 white patients). A total of 229 and 18 variants in black and white HFrEF patients, respectively, had interactions with beta-blocker exposure at $p < 5 \times 10(-5)$ upon discovery. After LD-clumping, 100 variants and 4 variants in the black and white patients, respectively, remained for validation but none reached statistical significance. In conclusion, genetic variants of potential interest were identified in a discovery-based GWAS of beta-blocker survival benefit in HFrEF patients, but none were validated in an independent dataset. Larger cohorts or alternative approaches, such as polygenic scores, are needed.

Dermatology

Almeida LMC, Ianhez M, Dal'Forno T, Picosse FR, Ravelli F, Kamamoto C, Sarlos P, and **Gold LFS**. Long-term maintenance treatment of rosacea: experts' opinion. *Int J Dermatol* 2023; Epub ahead of print. PMID: 38013632. Full Text

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BACKGROUND: Rosacea is a chronic inflammatory dermatosis characterized by remissions and flares. Although the rosacea active treatment phase is well established, the long-term maintenance phase is still challenging. OBJECTIVE: To discuss and make recommendations on how to treat patients during the long-term maintenance phase for the main rosacea phenotypes. METHODS: A panel of six board-certified Brazilian dermatologists and one American dermatologist gathered to compose a consensus based upon an initial statement on how to treat rosacea during the long-term maintenance phase based on the methodology Nominal Group Technique. The experts discussed each factor based upon an initial statement on how to treat rosacea patients in the long-term maintenance phase. A sequence of comprehensive narrative reviews was performed; a questionnaire preparation about the definition of the maintenance phase and its management was presented; an interpersonal discussion and ranking of the ideas were conducted. Recommendations were made if the specialists had 75% agreement. RESULTS: The maintenance treatment phase, which starts by achieving IGA 0 or 1 grades at the active phase, should be considered at least during the 9-month period after remission. The recommendations of all treatments target this period. Daily skincare regimen and sunscreen are crucial. Active treatment phase should be recommended if signs or symptoms reappear or worsen. CONCLUSION: Maintenance phase success depends on patient's adherence to daily skin care, appropriate treatments, continued follow-up with dermatologist, and self-assessment to identify new signs and symptoms indicating disease relapse.

Dermatology
Fakhoury JW, Buechler CR, and **Veenstra J**. Influence of medical comorbidities, smoking, and alcohol on mycosis fungoides progression and mortality. *Int J Dermatol* 2023; Epub ahead of print. PMID: 37997446. Full Text

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Dermatology
Maghfour J, **Li P**, **Piontkowski A**, **Ozog D**, **Mi QS**, and **Veenstra J**. Melanoma incidence and mortality: Exploring the impact of regional ultraviolet (UV) radiation and socioeconomic status in the context of Breslow thickness. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 37949120. Full Text

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Dermatology
Passeron T, **Lim HW**, Goh CL, Kang HY, Ribeyre C, Demessant-Flavigny AL, Le Floc'h C, Kerob D, Krutmann J, Comte C, Dreno B, and Leccia MT. Thirty years of promoting sun safety in France: The messages are heard but not followed! *J Eur Acad Dermatol Venereol* 2023; Epub ahead of print. PMID: 37915260. Full Text

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Dermatology
Rau A, and **Kerr H**. Can ChatGPT be my Dermatologist? *Arch Dermatol Res* 2023; 316(1):2. PMID: 37971538. Full Text

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Dermatology
Shareef SJ, Jackson S, **Lane BN**, Kallabat E, **Boopathy D**, **Fakhoury JW**, and **Lim HW**. Photoprotective measures among adolescents stratified by region: An analysis utilizing the National College Health Assessment. *Photodermatol Photoimmunol Photomed* 2023; Epub ahead of print. PMID: 38017654. Full Text

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BACKGROUND/PURPOSE: Exposure to sunlight has been shown to cause pigmentary alterations, photoaging and photocarcinogenesis. Understanding photoprotective patterns in adolescent populations is beneficial to public health initiatives. We utilized data provided by the American College Health Association's National College Health Assessment to evaluate photoprotective behaviors among adolescent populations. METHODS: Behavioral questions related to photoprotection were analyzed from the American College Health Association (ACHA) National College Health Assessment (NCHA) (Version III). RESULTS: When comparing races, Black/African American respondents had the lowest association of practicing photoprotective behaviors in comparison to white respondents ($p < .05$). When comparing US geographic regions, the south had the lowest association of photoprotective measures ($p < .05$). LIMITATIONS: The response rate of each institution varied, although there was still a large quantity of respondents. Finally, we cannot discern the specific reasoning for adolescent populations not using sunscreen. CONCLUSION: These data identify demographics where efforts to enhance education on photoprotective behaviors, specifically among skin of color and southern population, to support public health initiatives.

Dermatology
Weiss K, Abimbola O, Mueller D, Basak R, Basch E, Parisse T, **Hamad J**, Nielsen M, Tan HJ, Wallen E, Bjurlin M, and Smith AB. Feasibility, Acceptability, and Outcomes of a Mobile Health Tool for Radical Cystectomy Recovery. *J Urol* 2023; Epub ahead of print. PMID: 37972245. Full Text

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PURPOSE: Postoperative education and symptom tracking are essential following cystectomy to reduce readmission rates and information overload. To address these issues, an Internet-based tool was

developed to provide education, alerts, and symptom tracking. We aimed to evaluate the tool's feasibility, acceptability, and impact on complication and readmission rates. MATERIALS AND METHODS: Thirty-three eligible patients over 18 years old scheduled for cystectomy were enrolled. Patients were asked to use the mobile health (mHealth) tool daily for the first 2 weeks, then less frequently up to 90 days after discharge. Descriptive statistics were used to summarize study variables. Feasibility was defined as at least 50% of patients using the tool once a week, and acceptability as patient satisfaction of > 75%. RESULTS: Use of the mHealth tool was feasible, with 90% of patients using it 1 week after discharge, but engagement declined over time to 50%, with technological difficulties being the main reason for nonengagement. Patient and provider acceptability was high, with satisfaction > 90%. Within 90 days, 36% experienced complications after discharge and 30% were readmitted. Engagement with the mHealth application varied but was not statistically associated with readmission (P = .21). CONCLUSIONS: The study showed that the electronic mobile health intervention for patients undergoing cystectomy was feasible, acceptable, and provided valuable educational content and symptom management. Future larger studies are needed to determine the tool's effectiveness in improving patient outcomes and its potential implementation into routine clinical care.

Diagnostic Radiology
Ali A, Morris JM, Decker SJ, Huang YH, Wake N, Rybicki FJ, and Ballard DH. Clinical situations for which 3D printing is considered an appropriate representation or extension of data contained in a medical imaging examination: neurosurgical and otolaryngologic conditions. *3D Print Med* 2023; 9(1):33. PMID: 38008795. Full Text

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BACKGROUND: Medical three dimensional (3D) printing is performed for neurosurgical and otolaryngologic conditions, but without evidence-based guidance on clinical appropriateness. A writing group composed of the Radiological Society of North America (RSNA) Special Interest Group on 3D Printing (SIG) provides appropriateness recommendations for neurologic 3D printing conditions. METHODS: A structured literature search was conducted to identify all relevant articles using 3D printing technology associated with neurologic and otolaryngologic conditions. Each study was vetted by the authors and strength of evidence was assessed according to published guidelines. RESULTS: Evidence-based recommendations for when 3D printing is appropriate are provided for diseases of the calvaria and skull base, brain tumors and cerebrovascular disease. Recommendations are provided in accordance with strength of evidence of publications corresponding to each neurologic condition combined with expert opinion from members of the 3D printing SIG. CONCLUSIONS: This consensus guidance document, created by the members of the 3D printing SIG, provides a reference for clinical standards of 3D printing for neurologic conditions.

Diagnostic Radiology
Knisely B, Noland SS, and Melville DM. Ultrasound versus MRI in the evaluation of the thumb metacarpophalangeal joint. *J Ultrason* 2023; 23(95):e214-e222. PMID: 38020517. Full Text

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An intricate and unique combination of ligamentous, fibrocartilaginous, and osseous structures stabilize the thumb metacarpophalangeal joint. Both ultrasound and high-resolution magnetic resonance imaging are extremely useful in evaluating these critical structures. This article reviews common injuries of the thumb metacarpophalangeal joint, while highlighting the merits, limitations, and pitfalls of the two imaging modalities. A clear appreciation of each method, paired with anatomic knowledge, will lend greater confidence and accuracy to diagnosing impactful injuries and guiding intervention.

Diagnostic Radiology
Lee J, Chadalavada SC, Ghodadra A, **Ali A**, Arribas EM, Chepelev L, Ionita CN, Ravi P, Ryan JR, Santiago L, Wake N, Sheikh AM, Rybicki FJ, and Ballard DH. Clinical situations for which 3D Printing is considered an appropriate representation or extension of data contained in a medical imaging examination: vascular conditions. *3D Print Med* 2023; 9(1):34. PMID: 38032479. Full Text

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BACKGROUND: Medical three-dimensional (3D) printing has demonstrated utility and value in anatomic models for vascular conditions. A writing group composed of the Radiological Society of North America (RSNA) Special Interest Group on 3D Printing (3DPSIG) provides appropriateness recommendations for vascular 3D printing indications. METHODS: A structured literature search was conducted to identify all relevant articles using 3D printing technology associated with vascular indications. Each study was vetted by the authors and strength of evidence was assessed according to published appropriateness ratings. RESULTS: Evidence-based recommendations for when 3D printing is appropriate are provided for the following areas: aneurysm, dissection, extremity vascular disease, other arterial diseases, acute venous thromboembolic disease, venous disorders, lymphedema, congenital vascular malformations, vascular trauma, vascular tumors, visceral vasculature for surgical planning, dialysis access, vascular research/development and modeling, and other vasculopathy. Recommendations are provided in accordance with strength of evidence of publications corresponding to each vascular condition combined with expert opinion from members of the 3DPSIG. CONCLUSION: This consensus appropriateness ratings document, created by the members of the 3DPSIG, provides an updated reference for clinical standards of 3D printing for the care of patients with vascular conditions.

Diagnostic Radiology
Oliveira R, Correia MA, Marto JP, Carvalho Dias M, Mohamed GA, Nguyen TN, Nogueira RG, Aboul-Nour H, **Marin H**, **Bou Chebl A**, Mohammaden MH, Al-Bayati AR, Haussen DC, Abdalkader M, Fifi JT, Ortega-Gutierrez S, Yavagal DR, Mayer SA, Tsivgoulis G, Neto LL, and Aguiar de Sousa D. Reocclusion after successful endovascular treatment in acute ischemic stroke: systematic review and meta-analysis. *J Neurointerv Surg* 2023; 15(10):964-970. PMID: 36328479. Full Text

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BACKGROUND: Endovascular treatment (EVT) is the standard of care for selected patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO). OBJECTIVE: To systematically review the available data on: (1) incidence, predictors, and outcomes of patients with reocclusion after successful EVT for AIS and, (2) the characteristics, complications, and outcomes of patients with reocclusion treated with repeated EVT (rEVT) within 30 days of the first procedure. METHODS: PubMed was searched (between January 2012 and April 2021) to identify studies reporting reocclusion following successful EVT (Thrombolysis in Cerebral Infarction ≥2b) in patients with AIS due to LVO. Pooled incidence of reocclusion per 100 patients with successful recanalization following EVT was calculated using a random-effects model with Freeman-Tukey double arcsine transformation. Extracted incidences of reocclusion according to etiology and use of intravenous thrombolysis were pooled using random-effects meta-analytic models. RESULTS: A total of 840 studies was identified and seven studies qualified for the quantitative analysis, which described 91 same-vessel reocclusions occurring within the first 7 days after treatment among 2067 patients (4.9%; 95% CI 3% to 7%, I(2)=70.2%). Large vessel atherosclerosis was associated with an increased risk of reocclusion (OR=3.44, 95% CI 1.12 to 10.61, I(2)=50%). We identified 90 patients treated with rEVT for recurrent LVO, described in five studies. The rates of procedural complications, mortality, and unfavorable functional outcome at 3 months were 18.0%, 18.9%, and 60.3%, respectively. CONCLUSION: In cohorts of patients with AIS due to LVO, 5% of patients experienced reocclusion within 7 days after successful EVT. Repeated EVT can be a safe and effective treatment for selected patients with reocclusion.

Emergency Medicine

Gunaga S, and Zygowiec J. Primary Palliative Care in the Emergency Department and Acute Care Setting. *Cancer Treat Res* 2023; 187:115-135. PMID: 37851223. Request Article

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Amidst a global COVID pandemic, the palliative care community and healthcare systems around the country continue to explore opportunities to improve early patient and family access to end-of-life care resources. They need not look any further than the Emergency Departments (ED) located on their campuses and around their communities for this chance. As advances in medical therapies continue to extend disease specific life expectancies and as the American population continues to age, we will continue to see older adults with chronic medical illnesses visiting the ED in their final stages of life (Smith et al. in Health Aff (Millwood) 31(6):1277-1285, 2012; Albert et al. in NCHS Data Brief 130:1-8, 2013). If the ED is to continue to be the primary portal of hospital entry for patients requiring emergent care for acute and chronic terminal illnesses, then it stands to reason that it should also be equally prepared to provide the earliest access to palliative care and advance care planning resources for patients and families who may want and benefit from these services. This chapter will explore the unique horizon of opportunities that exist for emergency medicine and the palliative care specialty to fulfill this obligation. Discussion will be centered around core principles in screening, assessment, and management of palliative care needs in the ED, importance of goals of care conversations, and the coordination of early palliative care and hospice consults that can facilitate safe transitions of care.

Emergency Medicine
Smith M, Krishnan SV, **Leamon A**, Galwankar S, Sinha TP, Kumar VA, **Laere JV**, Gallien J, and Bhoi S. Removing Barriers to Emergency Medicine Point-of-Care Ultrasound: Illustrated by a Roadmap for Emergency Medicine Point-of-Care Ultrasound Expansion in India. *J Emerg Trauma Shock* 2023; 16(3):116-126. PMID: 38025509. Full Text

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Point-of-care ultrasound (PoCUS) has a potentially vital role to play in emergency medicine (EM), whether it be in high-, medium-, or low-resourced settings. However, numerous barriers are present which impede EM PoCUS implementation nationally and globally: (i) lack of a national practice guideline or scope of practice for EM PoCUS, (ii) resistance from non-PoCUS users of ultrasound imaging (USI) and lack of awareness from those who undertake parallel or post-EM patient care, and (iii) heterogeneous pattern of resources available in different institutes and settings. When combined with the Indian Preconception and Prenatal Diagnostic Techniques (PCPNDT) Act, this has led to the majority of India's 1.4 billion citizens being unable to access EM PoCUS. In order to address these barriers (globally as well as with specific application to India), this article outlines the three core principles of EM PoCUS: (i) the remit of the EM PoCUS USI must be well defined a priori, (ii) the standard of EM PoCUS USI must be the same as that of non-PoCUS users of USI, and (iii) the imaging performed should align with subsequent clinical decision-making and resource availability. These principles are contextualized using an integrated PoCUS framework approach which is designed to provide a robust foundation for consolidation and expansion across different PoCUS specialisms and health-care settings. Thus, a range of mechanisms (from optimization of clinical practice through to PoCUS educational reform) are presented to address such barriers. For India, these are combined with specific mechanisms to address the PCPNDT Act, to provide the basis for influencing national legislation and instigating an addendum to the Act. By mapping to the recent Lancet Commission publication on transforming access to diagnostics, this provides a global and cross-discipline perspective for the recommendations.

Emergency Medicine
Supples MW, Snavely AC, Ashburn NP, Allen BR, Christenson RH, **Nowak R**, Wilkerson RG, Mumma BE, Madsen T, Stopyra JP, and Mahler SA. Performance of the 0/2-Hour hs-cTnT Accelerated Diagnostic Protocol in a Multisite United States Cohort. *Acad Emerg Med* 2023; Epub ahead of print. PMID: 37925594. Full Text

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BACKGROUND: The diagnostic performance of the high-sensitivity troponin T (hs-cTnT) 0/2-hour algorithm is unclear among U.S. emergency department (ED) patients with acute chest pain. METHODS: A pre-planned subgroup analysis of the STOP-CP cohort study was conducted. Participants with 0- and 2-hour hs-cTnT measures prospectively enrolled at eight U.S. EDs from 1/2017-9/2018, were stratified into rule-out, observation, and rule-in zones using the hs-cTnT 0/2-hour algorithm alone and combined with the History, ECG, Age and Risk Factor (HEAR) score. The primary outcome was adjudicated 30-day cardiac death or MI (CDMI). The sensitivity and negative predictive value (NPV) of the 0/2-hour rule out zone and specificity and positive predictive value (PPV) of the rule in zone for 30-day CDMI were calculated. RESULTS: Of the 1307 patients accrued, 53.6% (700/1307) were male and 58.6% (762/1307) were white, with a mean age of 57.5±12.7 years. At 30 days, CDMI occurred in 12.9% (168/1307) of participants. The 0/2-hour algorithm ruled-out 61.4% (802/1307) of patients. Among rule-out patients, 1.9% (15/802) experienced 30-day CDMI, resulting in a sensitivity of 91.1% (95% CI 85.7-94.9%) and NPV of 98.1% (95% CI 96.9-98.9%). The 0/2-hour algorithm ruled-in 12.4% (162/1307) patients of whom 61.7% (100/162) experienced 30-day CDMI. The rule-in zone specificity was 94.6% (95% CI 93.1-95.8%) and PPV was 61.7% (95% CI 53.8-69.2%) for 30-day CDMI. The 0/2-hour algorithm combined with HEAR score ruled-out 30.7% (401/1307) of patients with a sensitivity and NPV for 30-day CDMI of 98.2% (95% CI 94.9-99.6%) and 99.3% (95% CI 97.8-99.8%), respectively. CONCLUSIONS: The hs-cTnT 0/2-hour algorithm ruled out most patients. With NPV of <99% for 30-day cardiac death or MI, the hs-cTnT 0/2-hour algorithm, many emergency physicians may not consider it safe to use for U.S. ED patients. When combined with a low-risk HEAR score, NPV was >99% for 30-day cardiac death or MI at the cost of reduced efficacy.

Emergency Medicine

Zeamer AL, Salive MC, An X, Beaudoin FL, House SL, Stevens JS, Zeng D, Neylan TC, Clifford GD, Linnstaedt SD, Rauch SL, Storrow AB, **Lewandowski C**, Musey PI, Jr., Hendry PL, Sheikh S, Jones CW, Punches BE, Swor RA, Hudak LA, Pascual JL, Seamon MJ, Harris E, Pearson C, Peak DA, Merchant RC, Domeier RM, Rathlev NK, O'Neil BJ, Sergot P, Sanchez LD, Bruce SE, Kessler RC, Koenen KC, McLean SA, Bucci V, and Haran JP. Association between microbiome and the development of adverse posttraumatic neuropsychiatric sequelae after traumatic stress exposure. *Transl Psychiatry* 2023; 13(1):354. PMID: 37980332. Full Text

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Patients exposed to trauma often experience high rates of adverse post-traumatic neuropsychiatric sequelae (APNS). The biological mechanisms promoting APNS are currently unknown, but the microbiota-gut-brain axis offers an avenue to understanding mechanisms as well as possibilities for intervention. Microbiome composition after trauma exposure has been poorly examined regarding neuropsychiatric outcomes. We aimed to determine whether the gut microbiomes of trauma-exposed

emergency department patients who develop APNS have dysfunctional gut microbiome profiles and discover potential associated mechanisms. We performed metagenomic analysis on stool samples (n = 51) from a subset of adults enrolled in the Advancing Understanding of RecOvery afteR traumA (AURORA) study. Two-, eight- and twelve-week post-trauma outcomes for post-traumatic stress disorder (PTSD) (PTSD checklist for DSM-5), normalized depression scores (PROMIS Depression Short Form 8b) and somatic symptom counts were collected. Generalized linear models were created for each outcome using microbial abundances and relevant demographics. Mixed-effect random forest machine learning models were used to identify associations between APNS outcomes and microbial features and encoded metabolic pathways from stool metagenomics. Microbial species, including Flavonifractor plautii, Ruminococcus gnavus and, Bifidobacterium species, which are prevalent commensal gut microbes, were found to be important in predicting worse APNS outcomes from microbial abundance data. Notably, through APNS outcome modeling using microbial metabolic pathways, worse APNS outcomes were highly predicted by decreased L-arginine related pathway genes and increased citrulline and ornithine pathways. Common commensal microbial species are enriched in individuals who develop APNS. More notably, we identified a biological mechanism through which the gut microbiome reduces global arginine bioavailability, a metabolic change that has also been demonstrated in the plasma of patients with PTSD.

Endocrinology and Metabolism

Rao SD. Unrecognized and Undertreated Vertebral Fractures: What Else We Must Do. *J Endocr Soc* 2023; 7(12):bvad139. PMID: 38024649. Full Text

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Endocrinology and Metabolism

Shah VN, **Qui S**, Stoneback J, Qamar L, Ferguson VL, Kohrt WM, Snell-Bergeon JK, and **Rao SD**. Bone Structure and Turnover in Postmenopausal Women With Long-Standing Type 1 Diabetes. *JBMR Plus* 2023; 7(11):e10831. PMID: 38025041. Full Text

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Compromised bone structural and mechanical properties are implicated in the increased fracture risk in type 1 diabetes (T1D). We investigated bone structure and turnover by histomorphometry in postmenopausal women with T1D and controls without diabetes using tetracycline double-labeled transiliac bone biopsy. After in vivo tetracycline double labeling, postmenopausal women with T1D of at least 10 years and without diabetes underwent transiliac bone biopsy. An expert blinded to the study group performed histomorphometry. Static and dynamic histomorphometry measurements were performed and compared between the two groups. The analysis included 9 postmenopausal women with T1D (mean age 58.4 ± 7.1 years with 37.9 ± 10.9 years of diabetes and HbA1c 7.1% ± 0.4%) and 7 postmenopausal women without diabetes (mean age 60.9 ± 3.3 years and HbA1c 5.4% ± 0.2%). There were no significant differences in serum PTH (38.6 ± 8.1 versus 51.9 ± 23.9 pg/mL), CTX (0.4 ± 0.2 versus 0.51 ± 0.34 ng/mL), or P1NP (64.5 ± 26.2 versus 87.3 ± 45.3 ng/mL). Serum 25-hydroxyvitamin D levels were higher in T1D than in controls (53.1 ± 20.8 versus 30.9 ± 8.2 ng/mL, $p < 0.05$). Bone structure metrics (bone volume, trabecular thickness, trabecular number, and cortical thickness) were similar between the groups. Indices of bone formation (osteoid volume, osteoid surface, and bone formation rate) were 40% lower in T1D and associated with lower activation frequency. However, the differences in bone formation were not statistically significant. Long-standing T1D may affect bone turnover, mainly bone formation, without significantly affecting bone structure. Further research is needed to understand bone turnover and factors affecting bone turnover in people with T1D.

Gastroenterology
Bishu S, **Ginnebaugh B**, Chu J, and Levy BH, 3rd. Microbiome-Based Therapeutics in Digestive Diseases: What They Are and How Are They Regulated. *Clin Transl Gastroenterol* 2023; 14(11):e00636. PMID: 38018836. Full Text

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Gastroenterology
Faisal MS, **Gonzalez HC**, and **Gordon SC**. Primary Biliary Cholangitis: Epidemiology, Diagnosis, and Presentation. *Clin Liver Dis* 2024; 28(1):63-77. PMID: 37945163. Full Text

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Using ursodeoxycholic acid as a standard treatment and for its ability to test for antimitochondrial antibody to accelerate diagnosis, survival of primary biliary cholangitis patients has approached that of the general population, leading to a change in nomenclature from primary biliary cirrhosis to primary biliary cholangitis to more accurately describe the disease.

Gastroenterology
Shimada S, **Yoshida A**, **Abouljoud M**, **Miyake K**, **Ivanics T**, **Shamaa T**, **Venkat D**, **Moonka D**, **Trudeau S**, **Reed E**, and **Nagai S**. Post-transplant outcomes and financial burden of donation after circulatory death donor liver transplant after the implementation of acuity circle policy. *Clin Transplant* 2023; e15190. Epub ahead of print. PMID: 37964683. Full Text

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BACKGROUND: After implementation of the Acuity Circles (AC) allocation policy, use of DCD liver grafts has increased in the United States. METHODS: We evaluated the impact of AC on rates of DCD-liver transplants (LT), their outcomes, and medical costs in a single practice. Adult LT patients were classified into three eras: Era 1 (pre-AC, 1/01/2015-12/31/2017); Era 2 (late pre-AC era, 1/01/2018-02/03/2020); and Era 3 (AC era, 05/10/2020-09/30/2021). RESULTS: A total of 520 eligible LTs were performed; 87 were DCD, and 433 were DBD. With each successive era, the proportion of DCD increased (Era 1: 11%; Era 2: 20%; Era 3: 24%; $p < .001$). DCD recipients had longer ICU stays, higher re-admission/re-operation rates, and higher incidence of ischemic cholangiopathy compared to those with DBD. Direct, surgical, and ICU costs during first admission were higher with DCD than DBD (+8.0%, $p < .001$; +4.2%, $p < .001$; and +33.3%, $p = .001$). DCD-related costs increased after Era 1 (Direct: +4.9% [Era 2 vs. 1] and +12.4% [Era 3 vs. 1], $p = .04$; Surgical: +17.7% and +21.7%, $p < .001$). In the AC era, there was a significantly higher proportion of donors ≥50 years, and more national organ sharing. Compared to DCD from donors <50 years, DCD from donors ≥50 years was associated with significantly higher total direct, surgical, and ICU costs (+12.6%, $p = .01$; +9.5%, $p = .01$; +84.6%, $p = .03$). CONCLUSIONS: The

proportion of DCD-LT, especially from older donors, has increased after the implementation of AC policies. These changes are likely to be associated with higher costs in the AC era.

Global Health Initiative
Shallal A, Jarrah J, **Prentiss T**, **Suleyman G**, **Veve MP**, Banat A, **Zervos J**, Mousa AB, Msadeh L, Zerriouh Thneibat FM, **Zervos M**, Al-Raiby J, Alsawalha L, and Zayed B. Lessons from the field: Supporting infection prevention and control and antimicrobial stewardship in Amman, Jordan. *J Infect Public Health* 2023; 16 Suppl 1:78-81. PMID: 37945495. Full Text

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BACKGROUND: To reduce antimicrobial resistance (AMR), appropriate antimicrobial prescribing is critical. In conjunction with Infection Prevention & Control (IPC) programs, Antimicrobial Stewardship Programs (ASP) have been shown to improve prescribing practices and patient outcomes. Low- and middle-income countries (LMIC) face challenges related to inadequate ASP policies and guidelines at both the national and healthcare facility (HCF) levels. METHODS: To address this challenge, the World Health Organization (WHO) created a policy guidance and practical toolkit for implementation of ASPs in LMIC. We utilized this document to support a situational analysis and two-day ASP-focused workshop. In follow-up, we invited these attendees, additional HCF and hospital directors to attend a workshop focused on the benefits of supporting these programs. RESULTS: Over the course of a total three days, we recruited hospital directors, ASP team members, and IPC officers from fifteen different healthcare facilities in Jordan. We describe the courses and coordination, feedback from participants, and lessons learned for future implementation. CONCLUSIONS: Future efforts will include more time for panel-type discussion. which will assist in further delineating enablers and barriers. Also planned is a total three-day workshop; with the first two days being with ASP/IPC teams, and the final third day being with hospital directors and leadership. The WHO policy guidance and toolkit are useful tools to address overuse of antimicrobial agents. Strong leadership support is needed for successful implementation of ASP and IPC. Discussions on quality/safety, as well as cost analyses, are important to generate interest of stakeholders.

Hematology-Oncology
Barravecchia I, Lee JM, Manassa J, Magnuson B, Ferris SF, Cavanaugh S, **Steele NG**, Espinoza CE, Galbán CJ, Ramnath N, Frankel TL, Pasca di Magliano M, and Galban S. Modeling Molecular Pathogenesis of Idiopathic Pulmonary Fibrosis-Associated Lung Cancer in Mice. *Mol Cancer Res* 2023; Epub ahead of print. PMID: 38015750. Full Text

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Idiopathic Pulmonary Fibrosis (IPF) is characterized by progressive, often fatal loss of lung function due to overactive collagen production and tissue scarring. IPF patients have a sevenfold-increased risk of developing lung cancer. The COVID-19 pandemic has increased the number of patients with lung diseases, and infection can worsen prognoses for those with chronic lung diseases and disease-

associated cancer. Understanding the molecular pathogenesis of IPF associated lung cancer is imperative for identifying diagnostic biomarkers and targeted therapies that will facilitate prevention of IPF and progression to lung cancer. To understand how IPF-associated fibroblast activation, matrix remodeling, epithelial- mesenchymal transition, and immune modulation influences lung cancer predisposition, we developed a mouse model to recapitulate the molecular pathogenesis of pulmonary fibrosis-associated lung cancer using the bleomycin and Lewis Lung Carcinoma models. We demonstrate that development of pulmonary fibrosis-associated lung cancer is likely linked to increased abundance of tumor-associated macrophages and a unique gene signature that supports an immune-suppressive microenvironment through secreted factors. Not surprisingly, pre-existing fibrosis provides a pre-metastatic niche and results in augmented tumor growth, and tumors associated with bleomycin-induced fibrosis are characterized by a dramatic loss of cytokeratin expression, indicative of epithelial-to-mesenchymal transition. Implications: This characterization of tumors associated with lung diseases provides new therapeutic targets that may aid in the development of treatment paradigms for lung cancer patients with pre-existing pulmonary diseases. .

Hematology-Oncology

Gonzalez-Mosquera LF, **Rous FA**, Rogers A, **Smith N**, **Goyert G**, and **Gadgeel S**. ALK Rearrangement Positive Lung Adenocarcinoma in Pregnancy Treated With Alectinib: A Case Report. *Clin Lung Cancer* 2023; Epub ahead of print. PMID: 38057186. Full Text

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There are few reported cases of ALK gene rearranged (ALK+) non-small cell lung cancer (NSCLC) during pregnancy. There is a lack of information on the safety of ALK inhibitors in pregnant patients. We present a 25-year-old African American woman who was diagnosed with metastatic ALK+ lung adenocarcinoma at 15 weeks of gestation. Treatment with alectinib was initiated at 18 weeks' gestation with resultant radiological treatment response. The patient did not experience any adverse effects from alectinib during her pregnancy. An elective induction of labor at 39 weeks resulted in an uncomplicated vaginal delivery. This case adds to available data and provides insight on the safety of using alectinib in a pregnant, ALK+ NSCLC patient, allowing the patient to continue her pregnancy to term while treating advanced lung adenocarcinoma.

Hematology-Oncology

Oh DY, Maqueda MA, Quinn DI, O'Dwyer PJ, Chau I, Kim SY, Duran I, Castellano D, Berlin J, Mellado B, Williamson SK, Lee KW, Marti F, Mathew P, Saif MW, **Wang D**, Chong E, Hilger-Rolfe J, Dean JP, and Arkenau HT. Ibrutinib combination therapy for advanced gastrointestinal and genitourinary tumours: results from a phase 1b/2 study. *BMC Cancer* 2023; 23(1):1056. PMID: 37919668. Full Text

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Tufts Medical Center, Boston, MA, USA.
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Henry Ford Hospital, Detroit, MI, USA.
Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA.
Sarah Cannon Research Institute - United Kingdom (SCRI-UK) and University College London, Cancer Institute, London, UK.

BACKGROUND: Ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase, is approved for the treatment of various B-cell malignancies and chronic graft-versus-host disease. Based on encouraging preclinical data, safety and efficacy of ibrutinib combined with companion drugs for advanced renal cell carcinoma (RCC), gastric/gastroesophageal junctional adenocarcinoma (GC), and colorectal adenocarcinoma (CRC) were evaluated. METHODS: Ibrutinib 560 mg or 840 mg once daily was administered with standard doses of everolimus for RCC, docetaxel for GC, and cetuximab for CRC. Endpoints included determination of the recommended phase 2 dose (RP2D) of ibrutinib in phase 1b and efficacy (overall response rate [ORR] for GC and CRC; progression-free survival [PFS] for CRC) in phase 2. RESULTS: A total of 39 (RCC), 46 (GC), and 50 (RCC) patients were enrolled and received the RP2D. Safety profiles were consistent with the individual agents used in the study. Confirmed ORRs were 3% (RCC), 21% (GC), and 19% (CRC). Median (90% CI) PFS was 5.6 (3.9-7.5) months in RCC, 4.0 (2.7-4.2) months in GC, and 5.4 (4.1-5.8) months in CRC. CONCLUSIONS: Clinically meaningful increases in efficacy were not observed compared to historical controls; however, the data may warrant further evaluation of ibrutinib combinations in other solid tumours. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02599324.

Hematology-Oncology
Ohri N, Jolly S, Cooper BT, Kabarriti R, Bodner WR, Klein J, Guha C, Viswanathan S, Shum E, Sabari JK, Cheng H, Gucalp RA, Castellucci E, Qin A, **Gadgeel SM**, and Halmos B. Selective Personalized Radioimmunotherapy for Locally Advanced Non-Small-Cell Lung Cancer Trial. *J Clin Oncol* 2023; Jco2300627. Epub ahead of print. PMID: 37988638. Full Text

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PURPOSE: Standard therapy for locally advanced non-small-cell lung cancer (LA-NSCLC) is concurrent chemoradiotherapy followed by adjuvant durvalumab. For biomarker-selected patients with LA-NSCLC, we hypothesized that sequential pembrolizumab and risk-adapted radiotherapy, without chemotherapy, would be well-tolerated and effective. METHODS: Patients with stage III NSCLC or unresectable stage II NSCLC and an Eastern Cooperative Oncology Group performance status of 0-1 were eligible for this trial. Patients with a PD-L1 tumor proportion score (TPS) of ≥50% received three cycles of induction pembrolizumab (200 mg, once every 21 days), followed by a 20-fraction course of risk-adapted thoracic radiotherapy (55 Gy delivered to tumors or lymph nodes with metabolic volume exceeding 20 cc, 48 Gy delivered to smaller lesions), followed by consolidation pembrolizumab to complete a 1-year treatment course. The primary study end point was 1-year progression-free survival (PFS). Secondary end points

included response rates after induction pembrolizumab, overall survival (OS), and adverse events. RESULTS: Twenty-five patients with a PD-L1 TPS of ≥50% were enrolled. The median age was 71, most patients (88%) had stage IIIA or IIIB disease, and the median PD-L1 TPS was 75%. Two patients developed disease progression during induction pembrolizumab, and two patients discontinued pembrolizumab after one infusion because of immune-related adverse events. Using RECIST criteria, 12 patients (48%) exhibited a partial or complete response after induction pembrolizumab. Twenty-four patients (96%) received definitive thoracic radiotherapy. The 1-year PFS rate is 76%, satisfying our efficacy objective. One- and 2-year OS rates are 92% and 76%, respectively. The most common grade 3 adverse events were colitis (n = 2, 8%) and esophagitis (n = 2, 8%), and no higher-grade treatment-related adverse events have occurred. CONCLUSION: Pembrolizumab and risk-adapted radiotherapy, without chemotherapy, are a promising treatment approach for patients with LA-NSCLC with a PD-L1 TPS of ≥50%.

Hematology-Oncology
Qin A, Wells L, Malhotra B, **Gadgeel S**, Schneider BJ, Ramnath N, Rice JD, and Kalemkerian GP. A Phase II Trial of Pevonedistat and Docetaxel in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. *Clin Lung Cancer* 2023; Epub ahead of print. PMID: 37977950. Full Text

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BACKGROUND: Postimmunotherapy (IO) treatment options for stage IV non-small-cell lung cancer (NSCLC) remain limited. Docetaxel alone or in combination with ramucirumab remains a standard of care, but response rates and survival benefit are suboptimal. Cullin-RING ligases (CRL) catalyze degradation of tumor suppressor proteins and are overactivated in NSCLC. Neddylation, which is catalyzed by the NEDD8 activating enzyme (NAE), is required for the activation of CRLs. Pevonedistat, a first-in-class small molecule NAE inhibitor, exerted antitumor activity when combined with docetaxel in preclinical studies. METHODS: We conducted a phase II, single-arm, investigator-initiated study evaluating the efficacy of pevonedistat plus docetaxel in patients with relapsed/refractory stage IV NSCLC. Patients received docetaxel 75 mg/m(2) on day 1 and pevonedistat 25 mg/m(2) on days 1, 3 and 5 of a 21-day cycle. The primary endpoint was objective response rate (ORR). RESULTS: From March 5, 2018 to January 26, 2021, we enrolled 31 patients. The ORR was 22% (1 CR, 5 PR), median PFS was 4.1 months, and median OS was 13.2 months. The incidence of Grade ≥3 adverse events (AE) was 53% in patients (n = 30) who received at least 1 dose of both drugs, with the most frequent being neutropenia and AST/ALT elevation. One patient was taken off study for a Grade 4 transaminase elevation. There were no Grade 5 toxicities. CONCLUSION: Our data suggest that the combination of docetaxel and pevonedistat is safe and exerts activity in patients with relapsed NSCLC. These encouraging results suggest that the neddylation pathway is an antitumor pathway that should be further studied.

Hematology-Oncology
Yan W, Menjivar RE, Bonilla ME, **Steele NG**, Kemp SB, Du W, Donahue KL, Brown K, Carpenter ES, Avritt FR, Irizarry-Negron VM, Yang S, Burns WR, Zhang Y, Pasca di Magliano M, and Bednar F. Notch signaling regulates immunosuppressive tumor-associated macrophage function in pancreatic cancer. *Cancer Immunol Res* 2023; Epub ahead of print. PMID: 37931247. Full Text

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Pancreatic ductal adenocarcinoma (PDA) continues to have a dismal prognosis. The poor survival of patients with PDA has been attributed to a high rate of early metastasis and low efficacy of current therapies, which partly result from its complex immunosuppressive tumor microenvironment. Previous studies from our group and others have shown that tumor-associated macrophages (TAMs) are instrumental in maintaining immunosuppression in PDA. Here, we explored the role of Notch signaling, a key regulator of immune response, within the PDA microenvironment. We identified Notch pathway components in multiple immune cell types within human and mouse pancreatic cancer. TAMs, the most abundant immune cell population in the tumor microenvironment, expressed high levels of Notch receptors, with cognate ligands such as JAG1 expressed on tumor epithelial cells, endothelial cells, and fibroblasts. TAMs with activated Notch signaling expressed higher levels of immunosuppressive mediators, suggesting that Notch signaling plays a role in macrophage polarization within the PDA microenvironment. Genetic inhibition of Notch in myeloid cells led to reduced tumor size and decreased macrophage infiltration in an orthotopic PDA model. Combination of pharmacological Notch inhibition with PD-1 blockade resulted in increased cytotoxic T-cell infiltration, tumor cell apoptosis, and smaller tumor size. Our work implicates macrophage Notch signaling in the establishment of immunosuppression and indicates that targeting the Notch pathway may improve the efficacy of immune-based therapies in PDA patients.

Henry Ford Health + Michigan State University Health Sciences
Awdish RL. A Kind of Faith. *Chest* 2023; 164(5):1296-1297. PMID: 37945192. Full Text

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Henry Ford Health + Michigan State University Health Sciences
Bossick AS, **Abood JA**, **Oaks A**, **Vilkins A**, **Shukr G**, **Chamseddine P**, and **Wegienka GR**. Racial disparities between measures of area deprivation and financial toxicity, and uterine volume in myomectomy patients. *BMC Womens Health* 2023; 23(1):603. PMID: 37964227. Full Text

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BACKGROUND: At time of myomectomy, a surgical procedure to remove uterine fibroids, Black women tend to have larger uteri than White women. This makes Black patients less likely to undergo a minimally invasive myomectomy which has been shown to have less postoperative pain, less frequent postoperative fever and shorter length of stay compared to abdominal myomectomies. The associations between individual financial toxicity and community area deprivation and uterine volume at the time of myomectomy have not been investigated. METHODS: We conducted a secondary data analysis of patients with fibroids scheduled for myomectomy using data from a fibroid treatment registry in [location]. We used validated measures of individual-level Financial Toxicity (higher scores = better financial status) and community-level Area Deprivation (ADI, high scores = worse deprivation). To examine associations with log transformed uterine volume, we used linear regression clustered on race (Black vs. White). RESULTS: Black participants had worse financial toxicity, greater deprivation and larger uterine volumes compared with White participants. A greater Financial Toxicity score (better financial status) was associated with lower uterine volume. For every 10 unit increase in Financial Toxicity, the mean total uterine volume decreased by 9.95% (Confidence Interval [CI]: -9.95%, -3.99%). ADI was also associated with uterine volume. A single unit increase in ADI (worse deprivation) was associated with a 5.13% (CI:

2.02%, 7.25%) increase in mean uterine volume. CONCLUSION: Disproportionately worse Financial Toxicity and ADI among Black patients is likely due to structural racism - which now must be considered in gynecologic research and practice. TRIAL REGISTRATION: Not applicable.

Henry Ford Health + Michigan State University Health Sciences
Maghfour J, **Li P**, **Piontkowski A**, **Ozog D**, **Mi QS**, and **Veenstra J**. Melanoma incidence and mortality: Exploring the impact of regional ultraviolet (UV) radiation and socioeconomic status in the context of Breslow thickness. *J Am Acad Dermatol* 2023; Epub ahead of print. PMID: 37949120. Full Text

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Henry Ford Health + Michigan State University Health Sciences
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BACKGROUND: A hemoglobin (Hb) level goal of 7-8 g/dL is a standard care threshold, prompting blood transfusion. The debate over whether acute myocardial infarction (MI) patients benefit from a more liberal transfusion strategy prompted a meta-analysis of relevant trials. METHODS: We performed a meta-analysis of randomized controlled trials (RCTs) comparing liberal and restrictive transfusion strategies in anemic MI patients. Primary outcomes were recurrent MI and death/MI, while secondary outcomes included stroke, revascularization, heart failure, and all-cause mortality. Due to the limited trials, we utilized the Paul-Mendele method with Hartung Knapp adjustment. RESULTS: Involving 2155 patients with liberal transfusion and 2170 with conservative transfusion across four RCTs, liberal transfusion did not significantly reduce MI (relative risk [RR] 0.85; 95% CI 0.72 - 1.02, p = 0.07) or death/MI (RR 0.88; 95% CI 0.45 - 1.71, p = 0.57). No significant differences were observed in all-cause mortality (RR 0.82; 95% CI 0.25 - 2.68, p = 0.63), stroke (RR 0.89; 95% CI 0.48 - 1.64, p = 0.50), revascularization (RR 0.93; 95% CI 0.48 - 1.80, p = 0.68), or heart failure (RR 1.14; 95% CI 0.04 - 28.84, p = 0.88). CONCLUSION: Our meta-analysis supports current medical guidelines, reinforcing the practice of limiting transfusions in acute MI patients to those with an Hb level of 7 or 8 g/dL. Liberal transfusion strategies did not show improved clinical outcomes.

Hospital Medicine
Lóser MK, Horowitz JK, England P, Esteitie R, **Kaatz S**, McLaughlin E, Munroe E, Heath M, Posa P, Flanders SA, and Prescott HC. Institutional Structures and Processes to Support Sepsis Care: A Multihospital Study. *Crit Care Explor* 2023; 5(11):e1004. PMID: 37954901. Full Text

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OBJECTIVES: To identify opportunities for improving hospital-based sepsis care and to inform an ongoing statewide quality improvement initiative in Michigan. DESIGN: Surveys on hospital sepsis processes, including a self-assessment of practices using a 3-point Likert scale, were administered to 51 hospitals participating in the Michigan Hospital Medicine Safety Consortium, a Collaborative Quality Initiative sponsored by Blue Cross Blue Shield of Michigan, at two time points (2020, 2022). Forty-eight hospitals also submitted sepsis protocols for structured review. SETTING: Multicenter quality improvement consortium. SUBJECTS: Fifty-one hospitals in Michigan. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Of the included hospitals, 92.2% (n = 47/51) were nonprofit, 88.2% (n = 45/51) urban, 11.8% (n = 6/51) rural, and 80.4% (n = 41/51) teaching hospitals. One hundred percent (n = 51/51) responded to the survey, and 94.1% (n = 48/51) provided a sepsis policy/protocol. All surveyed hospitals used at least one quality improvement approach, including audit/feedback (98.0%, n = 50/51) and/or clinician education (68.6%, n = 35/51). Protocols included the Sepsis-1 (18.8%, n = 9/48) or Sepsis-2 (31.3%, n = 15/48) definitions; none (n = 0/48) used Sepsis-3. All hospitals (n = 51/51) used at least one process to facilitate rapid sepsis treatment, including order sets (96.1%, n = 49/51) and/or stocking of commonly used antibiotics in at least one clinical setting (92.2%, n = 47/51). Treatment protocols included guidance on antimicrobial therapy (68.8%, n = 33/48), fluid resuscitation (70.8%, n = 34/48), and vasopressor administration (62.5%, n = 30/48). On self-assessment, hospitals reported the lowest scores for peridischarge practices, including screening for cognitive impairment (2.0%, n = 1/51 responded "we are good at this") and providing anticipatory guidance (3.9%, n = 2/51). There were no meaningful associations of the Centers for Medicare and Medicaid Services' Severe Sepsis and Septic Shock: Management Bundle performance with differences in hospital characteristics or sepsis policy document characteristics. CONCLUSIONS: Most hospitals used audit/feedback, order sets, and clinician education to facilitate sepsis care. Hospitals did not consistently incorporate organ dysfunction criteria into sepsis definitions. Existing processes focused on early recognition and treatment rather than recovery-based practices.

Infectious Diseases

Shallal A, Jarrah J, **Prentiss T**, **Suleyman G**, **Veve MP**, Banat A, **Zervos J**, Mousa AB, Msadeh L, Zerriouh Thneibat FM, **Zervos M**, Al-Raiby J, Alsawalha L, and Zayed B. Lessons from the field: Supporting infection prevention and control and antimicrobial stewardship in Amman, Jordan. *J Infect Public Health* 2023; 16 Suppl 1:78-81. PMID: 37945495. Full Text

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BACKGROUND: To reduce antimicrobial resistance (AMR), appropriate antimicrobial prescribing is critical. In conjunction with Infection Prevention & Control (IPC) programs, Antimicrobial Stewardship Programs (ASP) have been shown to improve prescribing practices and patient outcomes. Low- and middle-income countries (LMIC) face challenges related to inadequate ASP policies and guidelines at both the national and healthcare facility (HCF) levels. METHODS: To address this challenge, the World Health Organization (WHO) created a policy guidance and practical toolkit for implementation of ASPs in

LMIC. We utilized this document to support a situational analysis and two-day ASP-focused workshop. In follow-up, we invited these attendees, additional HCF and hospital directors to attend a workshop focused on the benefits of supporting these programs. RESULTS: Over the course of a total three days, we recruited hospital directors, ASP team members, and IPC officers from fifteen different healthcare facilities in Jordan. We describe the courses and coordination, feedback from participants, and lessons learned for future implementation. CONCLUSIONS: Future efforts will include more time for panel-type discussion. which will assist in further delineating enablers and barriers. Also planned is a total three-day workshop; with the first two days being with ASP/IPC teams, and the final third day being with hospital directors and leadership. The WHO policy guidance and toolkit are useful tools to address overuse of antimicrobial agents. Strong leadership support is needed for successful implementation of ASP and IPC. Discussions on quality/safety, as well as cost analyses, are important to generate interest of stakeholders.

Internal Medicine

Barssoum K, Abumoawad A, Chowdhury M, Agrawal A, AbdelMassih R, Renjithlal S, Mohamed AH, Alhuarrat M, Abdou C, Saleh M, **Ellauzi R**, Khalife W, Rai D, Chatila K, and Jneid H. Perioperative outcomes of hypertrophic cardiomyopathy: An insight from the National Readmission Database. *Int J Cardiol* 2023; 131601. Epub ahead of print. PMID: 37979792. Full Text

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BACKGROUND: Data regarding hypertrophic obstructive cardiomyopathy (HOCM) patients undergoing noncardiac surgery is lacking. We sought to examine the perioperative outcomes of HOCM patients undergoing noncardiac surgery using a national database. METHODS: We used the National readmission database from 2016 to 2019. We identified HOCM, heart undergoing noncardiac surgery using ICD 10 codes. We examined hospital outcomes as well as 90 days readmission outcomes. RESULTS: We identified 16,098 HOCM patients and 21,895,699 non-HOCM patients undergoing noncardiac surgery. The HOCM group had more comorbidities at baseline. After adjustment for major clinical predictors, the HOCM group experienced more in-hospital death, odds ratio (OR) 1.33 (1.216-1.47), P < 0.001, acute myocardial infarction (AMI), OR 1.18 (1.077-1.292), P < 0.001, acute heart failure odds ratio OR 1.3 to (1.220-1.431), P < 0.001, 90 days readmission OR 1.237 (1.069-1.432), P < 0.01, cardiogenic shock OR 2.094 (1.855-2.363), P < 0.001. Cardiac arrhythmia was the most common cause of readmission, out of the arrhythmias atrial fibrillation was the most prevalent. Acute heart failure was the most common complication of readmission. There was no difference in major adverse cardiovascular events (MACE), and AMI between both groups and readmission. CONCLUSION: HOCM patients undergoing noncardiac surgery may be at increased risk of in-hospital and readmission events. Acute heart failure was the most common complication during index admission, while cardiac arrhythmias were the most common complication during readmission. More research is needed to address this patient population further.

Internal Medicine

Chaudhary AJ, Qureshi MH, El Sharu H, and **Prostak J**. An Interesting Case of Recurrent Postprandial Cardiogenic Syncope Caused by Type III Hiatal Hernia. *Cureus* 2023; 15(10):e47791. PMID: 38021578. Full Text

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Patients with syncope often present a diagnostic challenge due to the diverse causes of this condition. While a careful assessment can identify the underlying cause in many cases, syncope can arise from a variety of sources, including structural anomalies. Among these, hiatal hernia (HH) is a relatively common yet unusual condition associated with syncope. HH involves the protrusion of abdominal organs into the mediastinum through the diaphragmatic esophageal hiatus, with types III and IV being capable of causing cardiac problems. We report a case of a 92-year-old patient with a known HH history who experienced recurrent syncope episodes triggered by heavy meals. Extensive evaluation ruled out cardiac and neurological causes. Imaging revealed a large HH compressing the left atrium. Despite being an infrequent occurrence, such cases highlight the potential for atrial compression-induced syncope, which can be effectively managed with proton pump inhibitors and lifestyle modifications, as demonstrated by our patient's positive outcome.

Internal Medicine
Enwereji N, and Mallett J. Concomitant confluent and reticulated papillomatosis and acanthosis nigricans in patients with skin of color and need for early interventions for insulin resistance. *Int J Womens Dermatol* 2023; 9(4):e119. PMID: 37927368. Full Text

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Internal Medicine
Gupta K, Hinkamp C, **Andrews T**, Meloche C, Minhas AMK, Slipczuk L, Vaughan E, Habib FZ, Sheikh S, Kalra D, and Virani SS. Highlights of Cardiovascular Disease Prevention Studies Presented at the 2023 European Society of Cardiology Congress. *Curr Atheroscler Rep* 2023; Epub ahead of print. PMID: 37975955. Full Text

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PURPOSE OF REVIEW: To summarize selected late-breaking science on cardiovascular (CV) disease prevention presented at the 2023 European Society of Cardiology (ESC) congress. RECENT FINDINGS: The NATURE-PARADOX was a naturally randomized trial that used genetic data from the UK Biobank registry to create "cumulative exposure to low-density lipoprotein-cholesterol (LDL-C)" biomarker and evaluate its association with major CV events regardless of plasma LDL-C levels or age. Safety and efficacy data of inclisiran, a PCSK9-interfering mRNA (PCSK9i) administered subcutaneously twice annually, were presented. Data on two new PCSK9is were presented, recaticimab, an oral drug, and lerodalcibep, a subcutaneous drug with a slightly different architecture than currently available PSCK9is. A phase 1 trial on muvalaplin, an oral lipoprotein (a) inhibitor, was presented. An atherosclerotic CV disease (ASCVD) risk prediction algorithm for the Asian population using SCORE2 data was presented. Long-term follow-up of patients enrolled in the CLEAR outcomes trial showed sustained and more significant ASCVD risk reduction with bempedoic acid in high-risk patients. The late-breaking clinical

science at the 2023 congress of the ESC extends the known safety and efficacy data of a PCSK9i with the introduction of new drugs in this class. Using cumulative exposure to LDL-C rather than a single value will help clinicians tailor the LDL-C reduction strategy to individual risk and is an important step towards personalized medicine.

Internal Medicine
Javaid S, Frasier K, and **Chaudhary AJ**. Impact of obesity on in-hospital mortality and morbidity among patients admitted for antineoplastic chemotherapy: a nationwide analysis. *Clin Transl Oncol* 2023; Epub ahead of print. PMID: 37947942. Full Text

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BACKGROUND: Obesity is a complex and multifactorial medical condition that can have far reaching consequences on cancer patients, particularly those undergoing treatment such as chemotherapy. Our study focuses to comprehensively explore the various adverse outcomes in obese patients receiving chemotherapy during hospitalization. METHODS: The National Inpatient Sample 2020 was used using the ICD-10 codes to identify patients hospitalized with a primary discharge diagnosis of neoplastic chemotherapy with or without a secondary diagnosis of obesity. Statistical analysis using Stata software was done, and primary and secondary outcomes were obtained after adjusting for confounders using multivariate regression analysis. RESULTS: Mortality was similar in both obese and non-obese patients. Length of stay and total hospitalization charges were increased in obese patients. Obese patients had higher odds of developing acute respiratory failure and were more likely to require non-invasive and invasive mechanical ventilation. CONCLUSION: Our study concluded that obesity could be considered an independent predictor of worse outcomes in patients admitted for neoplastic chemotherapy. Notably, addressing obesity could help to improve the efficacy of treatment for cancer patients while simultaneously reducing any negative consequences associated with being obese.

Internal Medicine
Javaid S, Frasier K, **Chaudhary AJ**, and Del Castillo O. The Burden of Heart Failure and Its Impact on Mortality and Outcomes in Hospitalized Multiple Myeloma Patients: A Nationwide Study. *Cureus* 2023; 15(10):e47570. PMID: 38022174. Full Text

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Background Multiple myeloma is a hematologic malignancy characterized by its association with a range of cardiovascular comorbidities, most notably heart failure. Our study aims to investigate the impact of heart failure on individuals who are hospitalized for multiple myeloma. Methods In this retrospective cohort study, we assembled a cohort of patients diagnosed with multiple myeloma from the National Inpatient Sample (NIS) data from 2019 to 2020. Within this study population, patients were classified according to the presence or absence of heart failure as a secondary diagnosis, with further stratification into distinct groups such as heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). The primary outcome studied was inpatient mortality. Secondary outcomes were length of stay, total hospitalization charges, acute respiratory failure, acute kidney injury, intensive care unit (ICU) admission, and mechanical ventilation. Confounders were adjusted using multivariate regression analysis. Results Among the 38,735 patients admitted with multiple myeloma, 5.6% (2,195 patients) were diagnosed with HFpEF, while 3% (1,170 patients) had HFrEF. The mortality rate was significantly higher in HFpEF patients compared to HFrEF and non-heart failure individuals (aOR: 1.68, [CI: 1.17-2.43]; P = 0.005). Length of hospital stay did not differ between these two groups; however, total hospitalization charges were more significant in the presence of heart failure versus

without heart failure (coefficient: 33597; CI: 1730-65463; P = 0.04; and coefficient: 26107; CI: 5414-46800; P = 0.01 for HFrEF and HFpEF, respectively). Similarly, a significant increase in the odds of acute respiratory failure, care at the ICU, and requirement for mechanical ventilation was observed in patients with both types of heart failure compared to those without heart failure. Conclusion HFpEF was associated with high mortality rates and greater incidence of acute kidney injury in multiple myeloma patients compared to those with HFrEF and non-heart failure counterparts. However, both heart failure subtypes were associated with heightened total hospitalization charges and the increased likelihood of encountering acute respiratory failure, admission to the ICU, and the utilization of mechanical ventilation compared to patients without heart failure.

Internal Medicine
Singh H, **Ahmed O**, **Allen E**, and **Othman H**. A Case of Stress Cardiomyopathy With Nab-Paclitaxel Infusion. *J Investig Med High Impact Case Rep* 2023; 11:23247096231209554. PMID: 37919938. Full Text

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Stress cardiomyopathy is a transient left ventricular dysfunction caused by physiologic or pathologic stressors. Anaphylaxis is a hypersensitivity disorder that can lead to a rapid life-threatening respiratory collapse. It happens due to exposure to allergens including medications. During anaphylaxis, there is a compensatory release of catecholamines that can lead to stress cardiomyopathy. In this case, nab-paclitaxel infusion led to anaphylaxis with respiratory failure. Echocardiogram showed features of diffuse hypokinesis with preserved basal segment contractility, and cardiac catheterization did not show any evidence of obstructive coronary artery disease. The overall clinical picture suggested stress cardiomyopathy. The patient was treated with guideline-directed medical therapy which resulted in normalization of the ejection fraction with no symptoms of congestive heart failure at any point. The patient was thereafter resumed on a reduced dose of nab-paclitaxel. This case report adds to the spectrum of infusion-related reactions associated with paclitaxel and demonstrates the course of events in the management of anaphylaxis and stress cardiomyopathy in this scenario.

Internal Medicine
Zimbrean PC, Rubman S, Andacoglu O, Bakhai D, Clifton E, Deng Y, Doshi M, Emamaullee J, Gan G, Holmes R, Jaber L, Jackson WE, Joyce M, Kalil R, Kumar V, Laflen J, Lentine KL, **Prashar R**, Winder GS, Yadav A, and Liapakis A. Psychosocial evaluation of living liver donors-State of current practices in the United States. *Liver Transpl* 2023; Epub ahead of print. PMID: 37861339. Full Text

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We surveyed living donor liver transplant programs in the United States to describe practices in the psychosocial evaluation of living donors focused on (1) composition of psychosocial team; (2) domains, workflow, and tools of the psychosocial assessment; (3) absolute and relative mental health-related contraindications to donation; and (4) postdonation psychosocial follow-up. We received 52 unique responses, representing 33 of 50 (66%) of active living donor liver transplant programs. Thirty-one (93.9%) provider teams included social workers, 22 (66.7%) psychiatrists, and 14 (42.4%) psychologists. Validated tools were rarely used, but domains assessed were consistent. Respondents rated active alcohol (93.8%), cocaine (96.8%), and opioid (96.8%) use disorder, as absolute contraindications to donation. Active suicidality (97%), self-injurious behavior (90.9%), eating disorders (87.9%), psychosis (84.8%), nonadherence (71.9%), and inability to cooperate with the evaluation team (78.1%) were absolute contraindications to donation. There were no statistically significant differences in absolute psychosocial contraindications to liver donation between geographical areas or between large and small programs. Programs conduct postdonation psychosocial follow-up (57.6%) or screening (39.4%), but routine follow-up of declined donors is rarely conducted (15.8%). Psychosocial evaluation of donor candidates is a multidisciplinary process. The structure of the psychosocial evaluation of donors is not uniform among programs though the domains assessed are consistent. Psychosocial contraindications to living liver donation vary among the transplant programs. Mental health follow-up of donor candidates is not standardized.

Nephrology

Nwaedozie S, Zhang H, **Najjar Mojarrab J**, Sharma P, Yeung P, Umukoro P, Soodi D, Gabor R, Anderson K, and Garcia-Montilla R. Novel predictors of permanent pacemaker implantation following transcatheter aortic valve replacement. *World J Cardiol* 2023; 15(11):582-598. PMID: 38058399. Full Text

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BACKGROUND: Conduction and rhythm abnormalities requiring permanent pacemakers (PPM) are short-term complications following transcatheter aortic valve replacement (TAVR), and their clinical outcomes remain conflicting. Potential novel predictors of post-TAVR PPM, like QRS duration, QTc prolongation, and supraventricular arrhythmias, have been poorly studied. AIM: To evaluate the effects of baseline nonspecific interventricular conduction delay and supraventricular arrhythmia on post-TAVR PPM requirement and determine the impact of PPM implantation on clinical outcomes. METHODS: A retrospective cohort study that identified patients with TAVR between January 1, 2012 to December 31, 2019. The group was dichotomized into those with post-TAVR PPM and those without PPM. Both groups were followed for one year. RESULTS: Out of the 357 patients that met inclusion criteria, the mean age was 80 years, 188 (52.7%) were male, and 57 (16%) had a PPM implantation. Baseline demographics, valve type, and cardiovascular risk factors were similar except for type II diabetes mellitus (DM), which was more prevalent in the PPM cohort (59.6% vs 40.7%; P = 0.009). The PPM cohort had a significantly higher rate of pre-procedure right bundle branch block, prolonged QRS > 120 ms, prolonged QTc > 470 ms, and supraventricular arrhythmias. There was a consistently significant increase in the odds ratio (OR) of PPM implantation for every 20 ms increase in the QRS duration above 100 ms: QRS 101-120 [OR: 2.44; confidence intervals (CI): 1.14-5.25; P = 0.022], QRS 121-140 (OR: 3.25; CI: 1.32-7.98; P = 0.010), QRS 141-160 (OR: 6.98; CI: 3.10-15.61; P < 0.001). After model adjustment for baseline risk factors, the OR remained significant for type II DM (aOR: 2.16; CI: 1.18-3.94; P = 0.012), QRS > 120 (aOR: 2.18; CI: 1.02-4.66; P = 0.045) and marginally significant for supraventricular arrhythmias (aOR: 1.82; CI: 0.97-

3.42; P = 0.062). The PPM cohort had a higher adjusted OR of heart failure (HF) hospitalization (aOR: 2.2; CI: 1.1-4.3; P = 0.022) and nonfatal myocardial infarction (MI) (aOR: 3.9; CI: 1.1-14; P = 0.031) without any difference in mortality (aOR: 1.1; CI: 0.5-2.7; P = 0.796) at one year. CONCLUSION: Pre-TAVR type II DM and QRS duration > 120, regardless of the presence of bundle branch blocks, are predictors of post-TAVR PPM. At 1-year post-TAVR, patients with PPM have higher odds of HF hospitalization and MI.

Neurology
Friedman HS, Prados MD, Wen PY, **Mikkelsen T**, Schiff D, Abrey LE, Yung WKA, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, and Cloughesy T. Bevacizumab Alone and in Combination With Irinotecan in Recurrent Glioblastoma. *J Clin Oncol* 2023; 41(32):4945-4952. PMID: 37935104. Full Text

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PURPOSE: We evaluated the efficacy of bevacizumab, alone and in combination with irinotecan, in patients with recurrent glioblastoma in a phase II, multicenter, open-label, noncomparative trial. PATIENTS AND METHODS: One hundred sixty-seven patients were randomly assigned to receive bevacizumab 10 mg/kg alone or in combination with irinotecan 340 mg/m(2) or 125 mg/m(2) (with or without concomitant enzyme-inducing antiepileptic drugs, respectively) once every 2 weeks. Primary end points were 6-month progression-free survival and objective response rate, as determined by independent radiology review. Secondary end points included safety and overall survival. RESULTS: In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, estimated 6-month progression-free survival rates were 42.6% and 50.3%, respectively; objective response rates were 28.2% and 37.8%, respectively; and median overall survival times were 9.2 months and 8.7 months, respectively. There was a trend for patients who were taking corticosteroids at baseline to take stable or decreasing doses over time. Of the patients treated with bevacizumab alone or bevacizumab plus irinotecan, 46.4% and 65.8%, respectively, experienced grade ≥ 3 adverse events, the most common of which were hypertension (8.3%) and convulsion (6.0%) in the bevacizumab-alone group and convulsion (13.9%), neutropenia (8.9%), and fatigue (8.9%) in the bevacizumab-plus-irinotecan group. Intracranial hemorrhage was noted in two patients (2.4%) in the bevacizumab-alone group (grade 1) and in three patients (3.8%) patients in the bevacizumab-plus-irinotecan group (grades 1, 2, and 4, respectively). CONCLUSION: Bevacizumab, alone or in combination with irinotecan, was well tolerated and active in recurrent glioblastoma.

Neurology
Oliveira R, Correia MA, Marto JP, Carvalho Dias M, Mohamed GA, Nguyen TN, Nogueira RG, Aboul-Nour H, **Marin H**, **Bou Chebl A**, Mohammaden MH, Al-Bayati AR, Haussen DC, Abdalkader M, Fifi JT, Ortega-Gutierrez S, Yavagal DR, Mayer SA, Tsivgoulis G, Neto LL, and Aguiar de Sousa D. Reocclusion after successful endovascular treatment in acute ischemic stroke: systematic review and meta-analysis. *J Neurointerv Surg* 2023; 15(10):964-970. PMID: 36328479. Full Text

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BACKGROUND: Endovascular treatment (EVT) is the standard of care for selected patients with acute ischemic stroke (AIS) due to large vessel occlusion (LVO). OBJECTIVE: To systematically review the available data on: (1) incidence, predictors, and outcomes of patients with reocclusion after successful EVT for AIS and, (2) the characteristics, complications, and outcomes of patients with reocclusion treated with repeated EVT (rEVT) within 30 days of the first procedure. METHODS: PubMed was searched (between January 2012 and April 2021) to identify studies reporting reocclusion following successful EVT (Thrombolysis in Cerebral Infarction ≥2b) in patients with AIS due to LVO. Pooled incidence of reocclusion per 100 patients with successful recanalization following EVT was calculated using a random-effects model with Freeman-Tukey double arcsine transformation. Extracted incidences of reocclusion according to etiology and use of intravenous thrombolysis were pooled using random-effects meta-analytic models. RESULTS: A total of 840 studies was identified and seven studies qualified for the quantitative analysis, which described 91 same-vessel reocclusions occurring within the first 7 days after treatment among 2067 patients (4.9%; 95% CI 3% to 7%, I(2)=70.2%). Large vessel atherosclerosis was associated with an increased risk of reocclusion (OR=3.44, 95% CI 1.12 to 10.61, I(2)=50%). We identified 90 patients treated with rEVT for recurrent LVO, described in five studies. The rates of procedural complications, mortality, and unfavorable functional outcome at 3 months were 18.0%, 18.9%, and 60.3%, respectively. CONCLUSION: In cohorts of patients with AIS due to LVO, 5% of patients experienced reocclusion within 7 days after successful EVT. Repeated EVT can be a safe and effective treatment for selected patients with reocclusion.

Neurology

Varelas PN, Kananeh M, Brady P, Holden D, **Mehta C**, Ata A, Abdelhak T, Greer D, and **Rehman M**. The Relationship Between Manifestation of Diabetes Insipidus and Estimated Glomerular Filtration Rate in Brain Death. *Crit Care Med* 2023; Epub ahead of print. PMID: 37966309. Full Text

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OBJECTIVES: Systematic reviews have revealed that up to 50% of patients with brain death have residual hypothalamic/pituitary activity based on the absence of central diabetes insipidus (DI). We hypothesized that different degrees of renal dysfunction may impact the presence of DI in patients with brain death. DESIGN: Single-center prospective data collection. SETTING: ICUs in a tertiary academic hospital. PATIENTS: All adult patients declared brain dead over 12 years. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: DI was diagnosed by polyuria, low urine specific gravity, and increasing serum sodium, measured in close proximity. Renal function was assessed by the estimated glomerular filtration rate (eGFR), calculated using the simplified modification of diet in renal disease equation. Analysis was completed in 192 of 234 patients with brain death after excluding those with missing data, those younger than 18 years and those on vasopressin infusions. One hundred twenty-two patients (63.5%) developed DI and 70 patients (36.5%) did not. The proportion of DI decreased significantly with decreasing eGFR: for eGFR greater than 60 mL/min, DI was present in 77.2%; for eGFR 15-60 mL/min, DI was present in 54.5%; for eGFR 14.9-9.8 mL/min, DI was present in 32%; none of the 14 patients with eGFR less than or equal to 9.7 mL/min ever experienced DI ($p < 0.001$). Using logistic regression, for every 10 mL/min decrease in eGFR, the odds of DI decreased 0.83 times (95% CI, 0.76-0.90, $p < 0.001$). CONCLUSIONS: Renal dysfunction significantly impacts DI's clinical manifestation in brain death. We report that patients who experience brain death with severe renal dysfunction may not develop clinical signs of DI.

Neurology

Zhang Y, Tedja R, **Millman M**, Wong T, Fox A, Chehade H, Gershater M, Adzibolosu N, Gogoi R, Anderson M, Rutherford T, **Zhang Z**, **Chopp M**, Mor G, and Alvero AB. Adipose-derived exosomal miR-421 targets CBX7 and promotes metastatic potential in ovarian cancer cells. *J Ovarian Res* 2023; 16(1):233. PMID: 38037081. Full Text

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BACKGROUND: Chromobox protein homolog 7 (CBX7), a member of the Polycomb repressor complex, is a potent epigenetic regulator and gene silencer. Our group has previously reported that CBX7 functions as a tumor suppressor in ovarian cancer cells and its loss accelerated formation of carcinomatosis and drove tumor progression in an ovarian cancer mouse model. The goal of this study is to identify specific signaling pathways in the ovarian tumor microenvironment that down-regulate CBX7. Given that adipocytes are an integral component of the peritoneal cavity and the ovarian tumor microenvironment, we hypothesize that the adipose microenvironment is an important regulator of CBX7 expression. RESULTS: Using conditioned media from human omental explants, we found that adipose-derived exosomes mediate CBX7 downregulation and enhance migratory potential of human ovarian cancer cells. Further, we identified adipose-derived exosomal miR-421 as a novel regulator of CBX7 expression and the main effector that downregulates CBX7. CONCLUSION: In this study, we identified miR-421 as a specific signaling pathway in the ovarian tumor microenvironment that can downregulate CBX7 to induce epigenetic change in OC cells, which can drive disease progression. These findings suggest that targeting exosomal miR-421 may curtail ovarian cancer progression.

Neurosurgery

Bove I, Cheok SK, Feng JJ, Briggs RG, Ruzevick J, Cote DJ, Shah I, Little A, Laws E, **Castro AV**, Carmichael J, Shiroishi M, Hurth K, and Zada G. Clinical implications of pituitary adenomas exhibiting dual transcription factor staining: A case series of 27 patients. *World Neurosurg* 2023; Epub ahead of print. PMID: 37967742. Full Text

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OBJECTIVE: According to the 2017 WHO classification of neuro-endocrine tumors, pituitary adenomas (PAs) are classified according to immunoexpression of the pituitary-specific transcription factors (TFs). A small subset of PAs exhibit multiple TF staining on immunohistochemistry and we present a series of 27 pathologically-confirmed cases of dual TF staining PAs (dsTF-PAs), and report clinically relevant implications. METHODS: A retrospective chart review of a multi-institutional database of patients with PAs surgically resected between 2008-2021 was performed. PAs expressing immunopositivity 2+ TFs. Patient demographics, neuro-imaging characteristics, histopathologic findings, and clinical data were collected. RESULTS: Twenty-seven patients had pathologically verified dual staining for transcription factors, of whom 17 were female (63%), with ages ranging from 20-84 years. . Twenty-three (85.2%) patients harbored functional PAs, with acromegaly being the most common functional subtype (86.4%). The most common dsTF-PA combination was PIT-1/SF-1 (85.2%). Six PAs exhibited Knosp cavernous sinus invasion grades of 3 or 4 and the Ki-67 labeling index was ≥3% in 6 patients (24.0%) and all stained for PIT-1/SF-1. Hormonal remission was achieved in 78% of functional dsTF-PAs. No PAs showed evidence of recurrence or progression over the mean follow-up period of 28.5 months. CONCLUSIONS: PAs exhibiting dual TF staining (dsTF-PAs) represent a small but clinically relevant diagnostic subset of PAs according to the 2021 WHO criteria, as a majority are GH-producing. Precise classification using TF staining plays a key role in understanding the biology of these tumors. Favorable outcomes can be achieved in this subset of PAs with evolving TF classification.

Neurosurgery
Kantak PA, **Bartlett S**, **Chaker A**, **Harmon S**, **Mansour T**, **Pawloski J**, **Telemi E**, **Yeo H**, **Winslow S**, Cohen J, **Scarpace L**, **Robin A**, and **Rock JP**. Augmented Reality Registration System for Visualization of Skull landmarks. *World Neurosurg* 2023; Epub ahead of print. PMID: 38013107. Full Text

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BACKGROUND: Augmented reality (AR) is an emerging technology in neurosurgery with the potential to become a strategic tool in the delivery of care and education for trainees. Advances in the technology have demonstrated promising use for improving visualization and spatial awareness of critical neuroanatomical structures. In this report, we employ a novel AR registration system for the visualization and targeting of skull landmarks. METHODS: A markerless AR system was used to register 3D reconstructions of suture lines onto the head via a head mounted display. Participants were required to identify craniometric points with and without AR assistance. Targeting error was measured as the Euclidian distance between the user-defined location and the true craniometric point on the subjects' head. RESULTS: All participants successfully registered 3D reconstructions onto the subjects' head. Targeting accuracy was significantly improved with AR (3.59 ± 1.29 mm) . Across all target points, AR increased accuracy by an average of 19.96 ± 3.80 mm. Post-test surveys revealed that participants felt

the technology increased their confidence in identifying landmarks (4.6/5) and that the technology will be useful for clinical care (4.2/5). CONCLUSIONS: While several areas of improvement and innovation can further enhance the use of AR in neurosurgery, this report demonstrates the feasibility of a markerless headset-based AR system for visualizing craniometric points on the skull. As the technology continues to advance, AR is expected to play an increasingly significant role in neurosurgery, transforming how surgeries are performed and improving patient care.

Neurosurgery
Kasir R, Zakko P, Hasan S, Aleem I, Park D, **Nerenz D**, **Abdulhak M**, Perez-Cruz M, **Schwalb J**, Saleh ES, Easton R, and Khalil JG. The Duration of Symptoms Influences Outcomes After Lumbar Microdiscectomies: A Michigan Spine Surgery Improvement Collaborative. *Global Spine J* 2023; Epub ahead of print. PMID: 37918421. Full Text

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STUDY DESIGN: Retrospective Cohort. OBJECTIVE: We investigate whether duration of symptoms a patient experiences prior to lumbar microdiscectomy affects pain, lifestyle, and return to work metrics after surgery. METHODS: A retrospective review of patients with a diagnosis of lumbar radiculopathy undergoing microdiscectomy was conducted using a statewide registry. Patients were grouped based on self-reported duration of symptoms prior to surgical intervention (Group 1: symptoms less than 3 months; Group 2: symptoms between 3 months and 1 year; and Group 3: symptoms greater than 1 year). Radicular pain scores, PROMIS PF Physical Function measure (PROMIS PF), EQ-5D scores, and return to work rates at 90 days, 1 year, and 2 years after surgery were compared using univariate and multivariate analysis. RESULTS: There were 2408 patients who underwent microdiscectomy for lumbar disc herniation for radiculopathy with 532, 910, and 955 in Groups 1, 2, and 3, respectively. Postoperative leg pain was lower for Group 1 at 90 days, 1 year, and 2 years compared to Groups 2 and 3 ($P < .05$). Postoperative PROMIS PF and EQ-5D scores were higher for Group 1 at 90 days, 1 year, and 2 years compared to Groups 2 and 3 ($P < .05$). CONCLUSION: Patients with prolonged symptoms prior to surgical intervention experience smaller improvements in postoperative leg pain, PROMIS PF, and EQ-5D than those who undergo surgery earlier. Patients undergoing surgery within 3 months of symptom onset have the highest rates of return to work at 1 year after surgery.

Neurosurgery
Sarma AK, Popli G, **Anzalone A**, Contillo N, Cornell C, Nunn AM, Rowland JA, Godwin DW, Flashman LA, Couture D, and Stapleton-Kotloski JR. Use of magnetic source imaging to assess recovery after severe traumatic brain injury-an MEG pilot study. *Front Neurol* 2023; 14:1257886. PMID: 38020602. Full Text

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RATIONALE: Severe TBI (sTBI) is a devastating neurological injury that comprises a significant global trauma burden. Early comprehensive neurocritical care and rehabilitation improve outcomes for such patients, although better diagnostic and prognostic tools are necessary to guide personalized treatment plans. METHODS: In this study, we explored the feasibility of conducting resting state magnetoencephalography (MEG) in a case series of sTBI patients acutely after injury (~7 days), and then about 1.5 and 8 months after injury. Synthetic aperture magnetometry (SAM) was utilized to localize source power in the canonical frequency bands of delta, theta, alpha, beta, and gamma, as well as DC-80 Hz. RESULTS: At the first scan, SAM source maps revealed zones of hypofunction, islands of preserved activity, and hemispheric asymmetry across bandwidths, with markedly reduced power on the side of injury for each patient. GCS scores improved at scan 2 and by scan 3 the patients were ambulatory. The SAM maps for scans 2 and 3 varied, with most patients showing increasing power over time, especially in gamma, but a continued reduction in power in damaged areas and hemispheric asymmetry and/or relative diminishment in power at the site of injury. At the group level for scan 1, there was a large excess of neural generators operating within the delta band relative to control participants, while the number of neural generators for beta and gamma were significantly reduced. At scan 2 there was increased beta power relative to controls. At scan 3 there was increased group-wise delta power in comparison to controls. CONCLUSION: In summary, this pilot study shows that MEG can be safely used to monitor and track the recovery of brain function in patients with severe TBI as well as to identify patient-specific regions of decreased or altered brain function. Such MEG maps of brain function may be used in the future to tailor patient-specific rehabilitation plans to target regions of altered spectral power with neurostimulation and other treatments.

Obstetrics, Gynecology and Women's Health Services

Bossick AS, **Abood JA**, **Oaks A**, **Vilkins A**, **Shukr G**, **Chamseddine P**, and **Wegienka GR**. Racial disparities between measures of area deprivation and financial toxicity, and uterine volume in myomectomy patients. *BMC Womens Health* 2023; 23(1):603. PMID: 37964227. Full Text

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BACKGROUND: At time of myomectomy, a surgical procedure to remove uterine fibroids, Black women tend to have larger uteri than White women. This makes Black patients less likely to undergo a minimally invasive myomectomy which has been shown to have less postoperative pain, less frequent postoperative fever and shorter length of stay compared to abdominal myomectomies. The associations between individual financial toxicity and community area deprivation and uterine volume at the time of myomectomy have not been investigated. METHODS: We conducted a secondary data analysis of patients with fibroids scheduled for myomectomy using data from a fibroid treatment registry in [location]. We used validated measures of individual-level Financial Toxicity (higher scores = better financial status) and community-level Area Deprivation (ADI, high scores = worse deprivation). To examine associations with log transformed uterine volume, we used linear regression clustered on race (Black vs. White). RESULTS: Black participants had worse financial toxicity, greater deprivation and larger uterine volumes compared with White participants. A greater Financial Toxicity score (better financial status) was associated with lower uterine volume. For every 10 unit increase in Financial Toxicity, the mean total uterine volume decreased by 9.95% (Confidence Interval [CI]: -9.95%, -3.99%). ADI was also associated with uterine volume. A single unit increase in ADI (worse deprivation) was associated with a 5.13% (CI: 2.02%, 7.25%) increase in mean uterine volume. CONCLUSION: Disproportionately worse Financial Toxicity and ADI among Black patients is likely due to structural racism - which now must be considered in gynecologic research and practice. TRIAL REGISTRATION: Not applicable.

Obstetrics, Gynecology and Women's Health Services

Gonzalez-Mosquera LF, **Rous FA**, Rogers A, **Smith N**, **Goyert G**, and **Gadgeel S**. ALK Rearrangement Positive Lung Adenocarcinoma in Pregnancy Treated With Alectinib: A Case Report. *Clin Lung Cancer* 2023; Epub ahead of print. PMID: 38057186. Full Text

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There are few reported cases of ALK gene rearranged (ALK+) non-small cell lung cancer (NSCLC) during pregnancy. There is a lack of information on the safety of ALK inhibitors in pregnant patients. We present a 25-year-old African American woman who was diagnosed with metastatic ALK+ lung adenocarcinoma at 15 weeks of gestation. Treatment with alectinib was initiated at 18 weeks' gestation with resultant radiological treatment response. The patient did not experience any adverse effects from alectinib during her pregnancy. An elective induction of labor at 39 weeks resulted in an uncomplicated vaginal delivery. This case adds to available data and provides insight on the safety of using alectinib in a pregnant, ALK+ NSCLC patient, allowing the patient to continue her pregnancy to term while treating advanced lung adenocarcinoma.

Obstetrics, Gynecology and Women's Health Services
Mendez D, **Annira S**, **Ayyash M**, and **Stanton T**. Haemoperitoneum due to ovarian rupture after oocyte retrieval procedure. *BMJ Case Rep* 2023; 16(11). PMID: 37977832. Full Text

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Transvaginal ultrasound-guided oocyte retrieval is the gold-standard technique for oocyte retrieval that has few associated procedural and post-procedural complications. Rarely, severe complications can occur including haemoperitoneum, for which the incidence reported in the literature is approximately 0.08-0.22%. In this report, we present the case of a nulliparous woman in her late 30s who presented to the hospital with severe abdominal pain following transvaginal ultrasound-guided oocyte retrieval and was found to have extensive haemoperitoneum attributed to ovarian rupture.

Orthopedics/Bone and Joint Center
Dancy ME, Alexander AS, **Abbas MJ**, Rolnick N, Alder KD, Lu Y, and Okoroha KR. No Differences in Exercise Performance, Perceptual Response, or Safety Were Observed Among 3 Blood Flow Restriction Devices. *Arthrosc Sports Med Rehabil* 2023; 5(6):100822. PMID: 38058769. Full Text

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PURPOSE: To compare 3 separate blood flow restriction (BFR) systems in their capacity to reduce repetitions to failure, impact perceptual responses, and cause adverse events during a low-load free-flow exercise. METHODS: The study included healthy subjects aged 18 years or older who presented to an ambulatory-care sports medicine clinic. On day 1, participants' demographic characteristics and anthropomorphic measurements were recorded. Each participant performed dumbbell biceps curl repetitions to failure using 20% of his or her 1-repetition maximum weight with each arm. Participants were exposed to 3 different tourniquet systems for familiarization. On day 2, each participant's arm was randomized to a cuff system, and the participant performed 2 sets of biceps curl repetitions to failure with the cuff inflated. Repetitions to failure, rating of perceived effort (RPE), rating of perceived discomfort, and pulse oxygenation levels were recorded after each set. On day 3, participants completed a survey of their

perceived delayed-onset muscle soreness. RESULTS: The final analysis was performed on 42 arms, with 14 limbs per system. The study population had a mean age of 28.7 ± 2.4 years and a mean body mass index of 24.9 ± 4.3. All 3 systems successfully reduced repetitions to failure compared with unrestricted low-load exercise from baseline to BFR set 1 and from baseline to BFR set 2. There were no significant between-group differences among BFR systems regarding the number of repetitions to failure performed at baseline versus BFR set 1 or BFR set 2. The Delfi Personalized Tourniquet System (PTS) cohort had the greatest reductions in repetitions to failure from BFR set 1 to BFR set 2 (P = .002) and reported the highest RPE after set 2 (P = .025). CONCLUSIONS: The Delfi PTS, SmartCuffs Pro, and BStrong BFR systems were each safe and were able to significantly reduce repetitions to failure compared with a low-load free-flow condition when used in a BFR exercise protocol. The Delfi PTS system may produce a higher RPE with prolonged use in comparison to the other systems. LEVEL OF EVIDENCE: Level II, prospective cohort study.

Orthopedics/Bone and Joint Center

Hahn AK, Holmberg K, Hammarstedt JE, Philp F, DeMeo P, Lai VJ, Kindya MC, Paci JM, Farrow LD, Vardiabasis N, Nye D, Frey S, **Moutzouros V**, Purnell GJ, Wang P, Vaccariello M, Schweizer SK, Phillips DJ, Frank DA, and Akhavan S. Intraobserver and Interobserver Reliability of the Snyder and Expanded SLAP Classification System: A Video Study. *Orthop J Sports Med* 2023; 11(11):23259671231204851. PMID: 37954863. Full Text

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BACKGROUND: Superior labral anterior and posterior (SLAP) tears are a common finding in overhead athletes. The original classification system produced by Snyder in 1990 contained 4 types of SLAP tears and was later expanded to 10 types. The classification has been challenging because of inconsistencies between surgeons making diagnoses and treatments based on the diagnosis. Furthermore, patient factors-such as age and sports played-affect the treatment algorithms, even across similarly classified SLAP tears. PURPOSE: To (1) assess the interobserver and intraobserver reliability of the Snyder and expanded SLAP (ESLAP) classification systems and (2) determine the consistency of treatment for a given SLAP tear depending on different clinical scenarios. STUDY DESIGN: Cohort study (diagnosis); Level of evidence, 3. METHODS: A total of 20 arthroscopic surgical videos and magnetic resonance imaging scans of patients with SLAP tears were sent to 20 orthopaedic sports medicine surgeons at various stages of training. Surgeons were asked to identify the type of SLAP tear using the Snyder and ESLAP classifications. Surgeons were then asked to determine the treatment for a SLAP tear using 4 clinical scenarios: (1) in the throwing arm of an 18-year-old pitcher; (2) in the dominant arm of an 18-year-old overhead athlete; (3) a 35-year-old overhead athlete; (4) or a 50-year-old overhead athlete. Responses were recorded, and the cases were shuffled and sent back 6 weeks after the initial responses. Results were then analyzed using the Fleiss kappa coefficient (κ) to determine interobserver and intraobserver degrees of agreement. RESULTS: There was moderate intraobserver reliability in both the Snyder and ESLAP classifications (κ = 0.52) and fair interobserver reliability for both classification systems (Snyder, κ = 0.31; ESLAP, κ = 0.30; P < .0001) among all surgeons. Additionally, there was only fair agreement (κ = 0.30; P < .0001) for the treatment modalities chosen by the reviewers for each case. CONCLUSION: This study demonstrated that SLAP tears remain a challenging problem for orthopaedic surgeons in diagnostics and treatment plans. Therefore, care should be taken in the preoperative

discussion with the patient to consider all the possible treatment options because this may affect the postoperative recovery period and patient expectations.

Orthopedics/Bone and Joint Center
Keith KM, **Castle JP**, **Abed V**, **Wager SG**, **Patel M**, **Gaudiani MA**, **Yedulla NR**, and **Makhni EC**. Many patients fail to achieve MCID for PROMIS upper extremity and pain interference following nonoperative management of rotator cuff tears. *JSES Int* 2023; 7(6):2337-2343. PMID: 37969490. Full Text

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BACKGROUND: Efficacy of nonoperative treatment for rotator cuff tears has been debated, especially for full-thickness tears. The purpose of this study was to a) define the minimal clinically important difference (MCID) of nonoperative treatment with regard to Patient-Reported Outcomes Measurement Information System (PROMIS) pain interference (PI) and upper extremity (UE), and b) determine the proportion of patients with both partial and full-thickness tears (PTRCT, FTRCT) who achieve this improvement following initial nonoperative treatment. We hypothesized that >75% of PTRCT and FTRTC patients would achieve MCID for PROMIS PI and UE. METHODS: We performed a retrospective cohort study evaluating nonoperatively managed patients with image-confirmed PTRCT and FTRCT. Treatment modalities and follow-up PROMIS scores at least 6 months after their initial visit were recorded. Using a distribution technique, MCID was calculated. RESULTS: A total of 111 FTRCT and 68 PTRCT patients were included with at least 6 months of follow-up. At 6 months from initial presentation, the MCID for PROMIS UE was 3.75 and 3.95 for FTRCT and PTRCT patients, respectively. For PROMIS PI, the MCID was 3.35 and 3.90 for FTRCT and PTRCT, respectively. In total, 41% of FTRCT and 41% of PTRCT achieved MCID for PROMIS UE. Thirty-four percent of FTRCT and 35% of PTRCT achieved MCID for PROMIS PI. CONCLUSION: The majority of patients undergoing nonoperative treatment for supraspinatus/infraspinatus rotator cuff tears did not achieve MCID at 6 months for PROMIS PI (34% for FTRCT and 35% for PTRCT) or UE (41% for FTRCT and 41% for PTRCT).

Orthopedics/Bone and Joint Center
Nulty S, **Fore J**, **Madison J**, and **Day CS**. Revenue Generation and Follow-up for a Hand Trauma Program for Emergency Department Patients in an Inner-City Metropolitan Area. *J Am Acad Orthop Surg Glob Res Rev* 2023; 7(11). PMID: 37976438. Full Text

From Henry Ford Health, Detroit, MI.

BACKGROUND: Although hand trauma care has proved to be profitable, loss of trauma patients from a system may lead to revenue loss. Our study aimed to (1) elucidate the economic effect of hand trauma programs, (2) quantify the potential fiscal effect of loss of follow-up, and (3) determine factors contributing to leakage of patients from the healthcare system. METHODS: Revenue data were retrospectively extracted for all adult hand trauma patients within a multicenter healthcare system from 2014 to 2018. Demographic and encounter factors were analyzed using Wilcoxon rank-sum test for differences in continuous variables, Pearson chi square test for categorical variables, and odds ratios. A follow-up model was created using logistic regression. RESULTS: A total of 56,995 (31% new, 69% established) hand trauma encounters were recorded. Follow-up was markedly affected by many factors, including new vs. established patients. Of the 17,748 new patients, 8638 (48.6%) returned for subsequent care, generating $34M. The patients who did not return may have lost $176M for the system. CONCLUSIONS: Many factors lead to loss of follow-up. Understanding these factors can help target efforts to minimize leakage of hand trauma patients. Hand trauma introduces new patients to hospitals, generating notable revenue. Leakage of hand trauma patients has substantial revenue losses.

Orthopedics/Bone and Joint Center
Okoroha KR, Tramer JS, Khalil LS, Jildeh TR, **Abbas MJ**, **Buckley PJ**, **Lindell C**, and **Moutzouros V**. Effects of a Perioperative Blood Flow Restriction Therapy Program on Early Quadriceps Strength and Patient-Reported Outcomes After Anterior Cruciate Ligament Reconstruction. *Orthop J Sports Med* 2023; 11(11):23259671231209694. PMID: 38035216. Full Text

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BACKGROUND: Quadriceps muscle atrophy remains a limiting factor in returning to activity after anterior cruciate ligament reconstruction (ACLR). Blood flow restriction (BFR) therapy may accelerate quadriceps strengthening in the perioperative period. PURPOSE: To evaluate postoperative isometric quadriceps strength in patients who underwent ACLR with a perioperative BFR program. STUDY DESIGN: Randomized controlled trial; Level of evidence, 1. METHODS: Patients indicated for ACLR were randomized into 2 groups, BFR and control, at their initial clinic visit. All patients underwent 2 weeks of prehabilitation preoperatively, with the BFR group performing exercises with a pneumatic cuff set to 80% limb occlusion pressure placed over the proximal thigh. All patients also underwent a standardized postoperative 12-week physical therapy protocol, with the BFR group using pneumatic cuffs during exercise. Quadriceps strength was measured as peak and mean torque during seated leg extension and presented as quadriceps index (percentage vs healthy limb). Patient-reported outcomes (PROs), knee range of motion, and quadriceps circumference were also gathered at 6 weeks, 3 months, and 6 months postoperatively, and adverse effects were recorded. RESULTS: Included were 46 patients, 22 in the BFR group (mean age, 25.4 ± 10.6 years) and 24 in the control group (mean age, 27.5 ± 12.0 years). At 6 weeks postoperatively, the BFR group demonstrated significantly greater strength compared with the controls (quadriceps index: 57% ± 24% vs 40% ± 18%; P = .029), and the BFR group had significantly better Patient-Reported Outcomes Measurement Information System-Physical Function (42.69 ± 5.64 vs 39.20 ± 5.51; P = .001) and International Knee Documentation Committee (58.22 ± 7.64 vs 47.05 ± 13.50; P = .011) scores. At 6 weeks postoperatively, controls demonstrated a significant drop in the peak torque generation of the operative versus nonoperative leg. There were no significant differences in strength or PROs at 3 or 6 months postoperatively. Three patients elected to drop out of the BFR group secondary to cuff intolerance during exercise; otherwise, no other severe adverse events were reported. CONCLUSION: Integrating BFR into perioperative physical therapy protocols led to improved strength and increased PROs at 6 weeks after ACLR. No differences in strength or PROs were found at 3 and 6 months between the 2 groups. REGISTRATION: NCT04374968 (ClinicalTrials.gov identifier).

Orthopedics/Bone and Joint Center

Rahman TM, **Shaw JH**, **Mehaidli A**, **Hennekes M**, **Hansen L**, **Castle JP**, **Kulkarni M**, and **Silverton CD**. The Impact of Social Determinants of Health on Outcomes and Complications After Total Knee Arthroplasty: An Analysis of Neighborhood Deprivation Indices. *J Bone Joint Surg Am* 2023; Epub ahead of print. PMID: 37995211. Full Text

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BACKGROUND: Social determinants of health (SDOH) are important factors in the delivery of orthopaedic care. The purpose of this study was to investigate the relationship between outcomes following total knee arthroplasty (TKA) and both the Social Vulnerability Index (SVI) and the Area Deprivation Index (ADI). METHODS: The Michigan Arthroplasty Registry Collaborative Quality Initiative (MARCQI) database was utilized to identify TKA cases for inclusion. Demographic characteristics and medical history were documented. The SVI, its subthemes, and the ADI were analyzed. Outcome data included length of stay, discharge disposition, postoperative change in the Knee Injury and Osteoarthritis Outcome Score, Joint Replacement (KOOS, JR), 90-day incidences of emergency department (ED) visits, readmission, death, deep venous thrombosis (DVT) and/or pulmonary embolism (PE), periprosthetic fracture, implant failure, periprosthetic joint infection (PJI), and all-cause reoperation. Database cross-referencing was completed to document aseptic and septic revisions beyond 90 days postoperatively. Bivariate quartile-stratified and multivariable analyses were used to associate deprivation metrics with outcomes. RESULTS: A total of 19,321 TKA cases met inclusion criteria. Baseline patient characteristics

varied among the SVI and/or ADI quartiles, with patients of non-White race and with a greater number of comorbidities noted in higher deprivation quartiles. Higher SVI and/or ADI quartiles were correlated with an increased rate of discharge to a skilled nursing facility ($p < 0.05$). A higher SVI and/or ADI quartile was associated with increased incidences of ED visits and readmissions postoperatively ($p < 0.05$). DVT and/or PE and long-term aseptic revision were the complications most strongly associated with higher deprivation metrics. Upon multivariable analysis, greater length of stay and greater incidences of ED visits, readmissions, DVT and/or PE, and aseptic revision remained significantly associated with greater deprivation based on multiple metrics. CONCLUSIONS: Greater deprivation based on multiple SVI subthemes, the composite SVI, and the ADI was significantly associated with increased length of stay, non-home discharge ED visits, and readmissions. The SVI and the ADI may be important considerations in the perioperative assessment of patients who undergo TKA. LEVEL OF EVIDENCE: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Orthopedics/Bone and Joint Center
Zhong J, Lee NJ, Padaki A, Crutchfield C, Ahmad CS, Trofa D, and **Sean Lynch T**. Increased age and modified fragility index increases risk of short-term complications after anterior cruciate ligament reconstruction surgery. *Knee* 2023; 46:8-18. PMID: 37972422. Full Text

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BACKGROUND: Large data analysis of anterior cruciate ligament reconstruction (ACLR) short-term complications on age will help surgeons stratify and counsel at-risk patients. The purpose of this study is to assess if older patients are at greater risk for short-term complications after ACLR. METHODS: This retrospective cohort study included patients who underwent elective ACLR with or without concomitant meniscal procedures in the National Surgical Quality Improvement Program from 2005 to 2017. Patients were divided into age groups 16-30, 31-45, and > 45. Modified fragility index-5 (mFI-5), demographics and short-term outcomes were examined with bivariate and multivariate analysis to determine if age was a risk factor for complications. RESULTS: A total of 23,581 patients (35.4% female) were included in this analysis. Mean age was 32.1 ± 10.8 years. Older patients had higher mFI-5 scores ($p < 0.001$), shorter operative times ($p < 0.001$), lower use of only general anesthesia ($p < 0.001$). The oldest patients had similar rates of complications as the two younger groups. Older age was an independent risk factor for VTE, but decreased risk of prolonged operations. A mFI-5 > 0 increased risk factors for readmission (Odds ratio 2.2, P = 0.006). Infection was the most common cause 30-day readmissions (40/135, 29.6%). CONCLUSION: In the early postoperative period, older age is an independent risk factor for VTE and younger age is a significant factor for prolonged surgeries. Having an mFI-5 > 0 increased risk factors for readmission.

Orthopedics/Bone and Joint Center
Zingas NH, and **King BW**. The Association of Cavovarus Foot Deformity With an Os Peroneum. *Foot Ankle Spec* 2023; Epub ahead of print. PMID: 37982456. Full Text

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OBJECTIVE: We sought to assess whether the presence of an os peroneum is correlated with cavovarus foot alignment in patients without a neurologic explanation for their foot shape. We hypothesized that a large os peroneum would increase the power of the peroneus longus and lead to a forefoot-driven, hindfoot varus deformity. MATERIALS AND METHODS: This was a retrospective cohort study conducted at a single institution and reviewed patients with 3 weightbearing views of the foot on plain radiography.

Patients were characterized into having either no os peroneum (235), a small os peroneum (18), or a large os peroneum (23). The control group included the first 101 of the 235 patients without an os peroneum based on a power analysis of the primary outcome, which was the difference in the mean Meary's angle (lateral talo-first metatarsal angle) between groups. The kite angle (anterior-posterior [AP] talocalcaneal angle), as well as 4 other angles were measured as secondary outcomes. RESULTS: Those with a large os peroneum had on a mean 7.7° ($P < .01$) more apex dorsal angulation of Meary's angle than controls, and a kite angle 4.2° varus to that of the control group. There were no differences between the small os peroneum and control groups. CONCLUSION: These findings add to the existing literature surrounding the etiology of cavovarus foot shape and link the presence of an ossified os peroneum, an oftentimes incidental radiographic finding, to cavovarus foot deformity in those without an underlying neurologic diagnosis. LEVELS OF EVIDENCE: Therapeutic, Level III: Retrospective Case-Control.

Otolaryngology – Head and Neck Surgery

Domack A, Sandelski MM, Ali S, Blackwell KE, Buchakjian M, Bur AM, Cannady SB, Castellanos CX, Ducic Y, **Ghanem TA**, Huang AT, Jackson RS, Kokot N, Li S, Pipkorn P, Puram SV, Rezaee R, Rajasekaran K, Shnayder Y, Sinha UK, Sukato D, Suresh N, Tamaki A, Thomas CM, Thorpe EJ, Wax MK, Yang S, Ziegler A, and Pittman AL. Free Flap Outcomes for Head and Neck Surgery in Patients with COVID-19. *Laryngoscope* 2023; Epub ahead of print. PMID: 37937733. Full Text

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INTRODUCTION: Coronavirus disease 2019 (COVID-19) affects the vascular system, subjecting patients to a hypercoagulable state. This is of particular concern for the success of microvascular free flap reconstruction. This study aims to report head and neck free flap complications in patients with COVID-19 during the perioperative period. We believe these patients are more likely to experience flap complications given the hypercoagulable state. METHODS: This is a multi-institutional retrospective case series of patients infected with COVID-19 during the perioperative period for head and neck free flap reconstruction from March 2020 to January 2022. RESULTS: Data was collected on 40 patients from 14 institutions. Twenty-one patients (52.5%) had a positive COVID-19 test within 10 days before surgery and 7 days after surgery. The remaining patients had a positive test earlier than 10 days before surgery. A positive test caused a delay in surgery for 16 patients (40.0%) with an average delay of 44.7 days (9-198 days). Two free flap complications (5.0%) occurred with no free flap deaths. Four patients (10.0%) had surgical complications and 10 patients had medical complications (25.0%). Five patients (12.5%) suffered from postoperative COVID-19 pneumonia. Three deaths were COVID-19-related and one from cancer recurrence during the study period. CONCLUSION: Despite the heightened risk of coagulopathy in COVID-19 patients, head and neck free flap reconstructions in patients with COVID-19 are not at higher risk for free flap complications. However, these patients are at increased risk of medical complications. LEVEL OF EVIDENCE: 4 Laryngoscope, 2023.

Otolaryngology – Head and Neck Surgery

Donaldson LB, **Deeb RH**, **Momin S**, **Eide JG**, and **Craig JR**. Cadaveric and Computed Tomography Analysis of the Anterior Ethmoidal Artery Flap. *Laryngoscope* 2023; Epub ahead of print. PMID: 37950636. Full Text

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BACKGROUND: The anterior ethmoidal artery (AEA) flap has been successful in repairing anterior nasal septal perforations and has been presumed to be axially based on AEA branches coursing through or around the cribriform plate (CP). However, limited evidence supports the flap's axial supply. The purposes of this cadaveric and computed tomography (CT) study were to assess the arterial anatomy from the CP to the septum, and to determine AEA flap length to predict ideal flap base width. METHODS: Ten fresh latex-injected cadavers were utilized for endoscopic dissection to identify arteries traversing the CPs on each side. First, arterial trajectories along the dorsal septum were recorded. Measurements were then made bilaterally along the septum from the middle turbinate (MT) axilla to the nasal branch of the AEA (NBAEA) traversing the CP. Additionally, 100 sinus CTs were reviewed to measure AEA flap lengths bilaterally. RESULTS: From 10 cadavers, 20 sides were utilized for measurements. In all cadavers, the AEA septal branches coursed diagonally or horizontally along the dorsal septum, and never directly vertically. The mean distance from the MT axilla to the NBAEA was 1.24 ± 1.93 cm (range = 1-1.5 cm). Based on CTs, the mean AEA flap length was 6.40 ± 0.60 cm. CONCLUSIONS: Based on the non-vertical courses of AEA septal branches, the AEA flap is more likely a random transposition flap than an axial flap. Average AEA flap length ranged from 6.0 to 7.0 cm. Assuming 3:1 length:width ratios, AEA flap base widths should be about 2.0-2.3 cm. LEVEL OF EVIDENCE: N/A Laryngoscope, 2023.

Pathology and Laboratory Medicine

Alhamar M, **Uzuni A**, **Mehrotra H**, **Elbashir J**, **Galusca D**, **Nagai S**, **Yoshida A**, **Abouljoud MS**, and Otrock ZK. Predictors of intraoperative massive transfusion in orthotopic liver transplantation. *Transfusion* 2023; Epub ahead of print. PMID: 37961982. Full Text

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BACKGROUND: Although transfusion management has improved during the last decade, orthotopic liver transplantation (OLT) has been associated with considerable blood transfusion requirements which poses some challenges in securing blood bank inventories. Defining the predictors of massive blood transfusion before surgery will allow the blood bank to better manage patients' needs without delays. We evaluated the predictors of intraoperative massive transfusion in OLT. STUDY DESIGN AND METHODS: Data were collected on patients who underwent OLT between 2007 and 2017. Repeat OLTs were excluded. Analyzed variables included recipients' demographic and pretransplant laboratory variables, donors' data, and intraoperative variables. Massive transfusion was defined as intraoperative transfusion of ≥10 units of packed red blood cells (RBCs). Statistical analysis was performed using SPSS version 17.0. RESULTS: The study included 970 OLT patients. The median age of patients was 57 (range: 16-74) years; 609 (62.7%) were male. RBCs, thawed plasma, and platelets were transfused intraoperatively to 782 (80.6%) patients, 831 (85.7%) patients, and 422 (43.5%) patients, respectively. Massive transfusion was documented in 119 (12.3%) patients. In multivariate analysis, previous right abdominal surgery, the recipient's hemoglobin, Model for End Stage Liver Disease (MELD) score, cold ischemia time, warm ischemia time, and operation time were predictive of massive transfusion. There was a direct significant correlation between the number of RBC units transfused and plasma (Pearson correlation coefficient r = .794) and platelets (r = .65). DISCUSSION: Previous abdominal surgery, the recipient's hemoglobin, MELD score, cold ischemia time, warm ischemia time, and operation time were predictive of intraoperative massive transfusion in OLT.

Pathology and Laboratory Medicine

Arshad M, Trepanier A, **Hashmi SS**, Naeem R, Mehmood S, and Ashfaq M. Medical students' self-perceived knowledge and clinical comfort with genetics in Pakistan. *J Genet Couns* 2023; Epub ahead of print. PMID: 37960989. Full Text

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Pakistan has a high rate of genetic disorders and neonatal mortality concurrent with noted lack of genetic and geneticists. To meet the needs of the patient population, the responsibility of providing clinical genetic services falls on general and specialty physicians. However, their education regarding these essential services is not standardized in medical school curricula nor has it ever been evaluated. The purpose of this work is to describe the self-perceived knowledge, clinical comfort, and perspectives of Pakistani medical students toward their medical genetics' education. A web-based survey was distributed electronically to medical schools around the country. The survey comprised of four sections: (1) participant demographics, (2) self-perceived medical genetics knowledge, (3) level of comfort in applying genetic knowledge and skills, and (4) attitudes toward medical genetics education. Descriptive statistics and a one-way analysis of variance were used for data analysis. Medical students in years 3, 4, and 5 (n = 473) from 25 medical schools participated in this research representing medical education in four Pakistani provinces. Most medical students reported "minimal" to "basic" knowledge of genetic testing methodology (64.7%), cancer genetics (64.9%), prenatal genetic testing (63.02%), and treatment strategies for genetic disease (72.9%). A plurality of students (37%) reported they were uncomfortable with interpreting and communicating genetic test results to patients. Medical students also expressed dissatisfaction with their medical genetics (40%) and genetic training (42%). The self-perceived knowledge and clinical comfort with genetics among Pakistani medical students was limited, especially regarding genetic testing. A significant portion (74.5%) expressed desire for additional genetics education during medical school to aid in their role as future physicians. It is important for physicians-in-training to have a solid understanding of genetic concepts, technologies, and genetic to best support their patients. As endorsed by the participating medical students, this study supports inclusion of more robust genetics' education into Pakistan's medical school curricula.

Pathology and Laboratory Medicine

Lockwood CM, Borsu L, **Cankovic M**, Earle JSL, Gocke CD, Hameed M, Jordan D, Lopategui JR, Pullambhatla M, Reuther J, Rumilla KM, Tafe LJ, Temple-Smolkin RL, Terraf P, and Tsimberidou AM. Recommendations for Cell-Free DNA Assay Validations: A Joint Consensus Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn* 2023; 25(12):876-897. PMID: 37806433. Full Text

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Diagnosing, selecting therapy for, and monitoring cancer in patients using a minimally invasive blood test represents a significant advance in precision medicine. Wide variability exists in how circulating tumor DNA (ctDNA) assays are developed, validated, and reported in the literature, which hinders clinical adoption and may negatively impact patient care. Standardization is needed for factors affecting ctDNA assay performance and reporting, including pre-analytical variables, analytical considerations, and elements of laboratory assay reporting. The Association for Molecular Pathology Clinical Practice Committee's Liquid Biopsy Working Group (LBxWG), including organizational representation from the American Society of Clinical Oncology and the College of American Pathologists, has undertaken a full-text data extraction of 1228 ctDNA publications that describe assays performed in patients with lymphoma and solid tumor malignancies. With an emphasis on clinical assay validation, the LBxWG has developed a set of 13 best practice consensus recommendations for validating, reporting, and publishing clinical ctDNA assays. Recommendations include reporting key pre-analytical considerations and assay performance metrics; this analysis demonstrates these elements are inconsistently included in publications. The LBxWG recommendations are intended to assist clinical laboratories with validating and reporting ctDNA assays and to ensure high-quality data are included in publications. It is expected that these recommendations will need to be updated as the body of literature continues to mature.

Pathology and Laboratory Medicine

Molina J, **Dabaja A**, **Gupta N**, **Alruwaii FI**, **Hassan O**, and **Al-Obaidy KI**. Adipocytic Differentiation in a Sertoli Cell Tumor. *Int J Surg Pathol* 2023; Epub ahead of print. PMID: 38018140. Full Text

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Testicular sex cord-stromal tumors are clonal neoplasms, with the majority being of Leydig cell followed by Sertoli cell origins. In Leydig cell tumors, adipocytic differentiation has been previously reported as a possible distinguishing feature, which has not been reported in other sex cord-stromal tumors. Herein, we report a case of a 48-year-old man who presented with an incidentally discovered 1.1 cm testicular mass, for which he underwent partial orchiectomy. Microscopically, the tumor showed features consistent with sex cord-stromal tumor with strong and diffuse nuclear and cytoplasmic reaction for B-catenin immunohistochemistry, supporting the diagnosis of Sertoli cell tumor. A novel adipocytic differentiation, reported previously in Leydig cell tumors, was present in this tumor.

Pathology and Laboratory Medicine

Weiss J, **Gibbons K**, Ehyaee V, Perez-Silos V, Zevallos A, Maienschein-Cline M, Brister E, Sverdlov M, Shah E, Balakrishna J, Symes E, Frederiksen JK, Gann PH, Post R, Lopez-Hisijos N, Reneau J, Venkataraman G, Bailey N, Brown NA, Xu ML, Wilcox RA, **Inamdar K**, and Murga-Zamalloa C. Specific Polo-Like Kinase 1 Expression in Nodular Lymphocyte-Predominant Hodgkin Lymphoma Suggests an Intact Immune Surveillance Program. *Am J Pathol* 2023; Epub ahead of print. PMID: 37923249. Full Text

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Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) is a rare and relatively indolent B-cell lymphoma. Characteristically, the [lymphocyte-predominant (LP)] tumor cells are embedded in a microenvironment enriched in lymphocytes. More aggressive variants of mature B-cell and peripheral T-cell lymphomas exhibit nuclear expression of the polo-like kinase 1 (PLK1) protein, stabilizing c-MYC and associated with worse clinical outcomes. We demonstrate frequent expression of PLK1 in the LP cells in NLPHL cases (100%; n = 76). In contrast, <5% of classic Hodgkin lymphoma cases (n = 70) show PLK1 expression within the tumor cells. Loss-of-function approaches demonstrated that the expression of PLK1 promotes cell proliferation and increased c-MYC stability in NLPHL cell lines. Correlation with clinical parameters revealed that the increased expression of PLK1 was associated with advanced-stage disease in patients with NLPHL. A multiplex immunofluorescence panel coupled with artificial intelligence algorithms was used to correlate the composition of the tumor microenvironment with the proliferative stage of LP cells. The results showed that LP cells with PLK1 (high) expression were associated with increased numbers of cytotoxic and T-regulatory T cells. Overall, the findings demonstrate that PLK1 signaling increases NLPHL proliferation and constitutes a potential vulnerability that can be targeted with PLK1 inhibitors. In addition, the findings suggest that an active immune surveillance program in NLPHL may be a critical mechanism limiting PLK1-dependent tumor growth.

Pharmacy

Clifford Rashotte M, Yoong D, **Naccarato M**, Pico Espinosa OJ, Fisher K, Bogoch, II, and Tan DH. Appropriate usage of post-exposure prophylaxis-in-pocket for HIV prevention by individuals with low-frequency exposures. *Int J STD AIDS* 2023; Epub ahead of print. PMID: 37963270. Full Text

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PEP-In-Pocket (Post-Exposure Prophylaxis-In-Pocket, or "PIP") is a biobehavioural HIV prevention strategy wherein patients are proactively identified and given a prescription for HIV post-exposure prophylaxis (PEP) medications to self-initiate in case of high-risk exposures. We evaluated this strategy in a prospective observational study at two hospital-based clinics in Toronto, Canada. HIV-negative adults using PIP underwent chart review and completed quarterly electronic questionnaires over 12 months. The primary objective was to quantify appropriate PIP initiation, defined as starting PIP within 72 h of a high-risk exposure. Secondary objectives were to quantify HIV seroconversions, changes in sexual risk behaviour, sexual satisfaction, and satisfaction with the PIP strategy. From 11/2017 to 02/2020, 43 participants enrolled and completed ≥1 questionnaire. PIP was self-initiated on 27 occasions by 15 participants, of which 24 uses (89%) were appropriate, 2 were unnecessary, and 1 was for an unknown exposure. Chart review identified no inappropriate non-use. Over 32 person-years of testing follow-up, we observed zero HIV seroconversions. Sexual risk declined modestly over follow-up, with a HIRI-MSM (HIV Incidence Risk Index for MSM) change of -0.39 (95% CI = -0.58, -0.21 per 3 months, $p < .001$). Sexual satisfaction was stable over time. At 12 months, 31 (72%) remained on PIP, 8 (19%) had transitioned to pre-exposure prophylaxis and 4 (9%) were lost-to-follow-up. Among participants who remained on PIP and completed questionnaires at 12 months, 24/25 (96%) strongly/somewhat agreed that PIP decreased their anxiety about contracting HIV and 25/25 (100%) strongly/somewhat agreed that they would recommend PIP to a friend. PIP is a feasible HIV prevention strategy in carefully selected individuals at modest HIV risk.

Pharmacy

Dobry P, **Poparad-Stezar A**, Bacon O, **Boji S**, and Giuliano C. Does Melatonin Decrease the Use of As-Needed Antipsychotics or Benzodiazepines in Noncritically Ill Hospitalized Patients? A Multicenter Retrospective Cohort Study. *J Integr Complement Med* 2023; Epub ahead of print. PMID: 37976107. Full Text

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Background: Delirium is a common neuropsychiatric syndrome without an FDA-approved treatment. Commonly used modalities show little improvement in outcomes; therefore, prevention efforts are imperative. Abnormalities in the sleep/wake cycle have been linked to delirium, and melatonin has been proposed to replace the hypothesized low levels of endogenous melatonin and restore sleep/wake cycle synchronization. Objectives: The primary objective of this study was to evaluate the association between melatonin, benzodiazepines (BZDs) or zolpidem (ZLP), and the use of as-needed antipsychotics and BZDs for delirium in noncritically ill adult patients. Methods: This was a multicenter retrospective cohort study of noncritically ill adult patients admitted to two separate health systems from August 2012 to December 2018 receiving either melatonin or nonmelatonin medications (ZLP or BZDs) for sleep. The coprimary endpoint was the proportion of patients receiving a pro re nata (PRN) antipsychotic or BZD 5 days from the patient's first dose of melatonin, BZD, or ZLP. Secondary outcomes included evaluation of the coprimary outcome in patients 65 years of age or older, total number of PRN antipsychotic and BZD doses, and length of stay. Results: Two hundred and twenty-five patients were included in the final analysis. Administration of BZD or ZLP was associated with a higher risk of subsequent BZD administration as compared with melatonin (OR 2.78, 95% CI 1.2-1.87) and ZLP (OR 2.78, 95% CI 1.25-6.17). BZD or ZLP had no impact on PRN antipsychotic use compared with melatonin (OR 1.09, 95% CI 0.51-2.35) and ZLP (OR 1.16, 95% CI 0.56-2.4). Conclusion: Melatonin use was found to be associated with a significant decrease in PRN BZD use in noncritically ill patients hospitalized on general floors; however, there was no observed association with overall PRN antipsychotic use. These results suggest that using melatonin may help decrease utilization of medications commonly used to manage delirium.

Pharmacy

Kunz Coyne AJ, Alosaimy S, Lucas K, Lagnf AM, Morrisette T, Molina KC, DeKerlegand A, Schrack MR, Kang-Birken SL, Hobbs AL, Agee J, Perkins NB, 3rd, Biagi M, Pierce M, Truong J, Andrade J, Bouchard J, Gore T, King MA, Pullinger BM, Claeys KC, **Herbin S**, Cosimi R, Tart S, Veve MP, Jones BM, Rojas LM, Feehan AK, Scipione MR, Zhao JJ, Witucki P, and Rybak MJ. Eravacycline, the first four years: health outcomes and tolerability data for 19 hospitals in 5 U.S. regions from 2018 to 2022. *Microbiol Spectr* 2023; e0235123. Epub ahead of print. PMID: 38018984. Full Text

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The rise of multidrug-resistant (MDR) pathogens, especially MDR Gram-negatives, poses a significant challenge to clinicians and public health. These resilient bacteria have rendered many traditional antibiotics ineffective, underscoring the urgency for innovative therapeutic solutions. Eravacycline, a broad-spectrum fluorocycline tetracycline antibiotic approved by the FDA in 2018, emerges as a promising candidate, exhibiting potential against a diverse array of MDR bacteria, including Gram-negative, Gram-positive, anaerobic strains, and Mycobacterium. However, comprehensive data on its real-world application remain scarce. This retrospective cohort study, one of the largest of its kind, delves into the utilization of eravacycline across various infectious conditions in the USA during its initial 4 years post-FDA approval. Through assessing clinical, microbiological, and tolerability outcomes, the research offers pivotal insights into eravacycline's efficacy in addressing the pressing global challenge of MDR bacterial infections.

Pharmacy

Shallal A, Jarrah J, **Prentiss T**, **Suleyman G**, **Veve MP**, Banat A, **Zervos J**, Mousa AB, Msadeh L, Zerriouh Thneibat FM, **Zervos M**, Al-Raiby J, Alsawalha L, and Zayed B. Lessons from the field: Supporting infection prevention and control and antimicrobial stewardship in Amman, Jordan. *J Infect Public Health* 2023; 16 Suppl 1:78-81. PMID: 37945495. Full Text

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WHO Jordan Country Office, Ministry of Interior Circle, Mohammad Jamjoum Street, PO Box 811547, Amman 11181, Jordan.

BACKGROUND: To reduce antimicrobial resistance (AMR), appropriate antimicrobial prescribing is critical. In conjunction with Infection Prevention & Control (IPC) programs, Antimicrobial Stewardship Programs (ASP) have been shown to improve prescribing practices and patient outcomes. Low- and middle-income countries (LMIC) face challenges related to inadequate ASP policies and guidelines at both the national and healthcare facility (HCF) levels. METHODS: To address this challenge, the World Health Organization (WHO) created a policy guidance and practical toolkit for implementation of ASPs in LMIC. We utilized this document to support a situational analysis and two-day ASP-focused workshop. In follow-up, we invited these attendees, additional HCF and hospital directors to attend a workshop focused on the benefits of supporting these programs. RESULTS: Over the course of a total three days, we recruited hospital directors, ASP team members, and IPC officers from fifteen different healthcare facilities in Jordan. We describe the courses and coordination, feedback from participants, and lessons learned for future implementation. CONCLUSIONS: Future efforts will include more time for panel-type discussion. which will assist in further delineating enablers and barriers. Also planned is a total three-day workshop; with the first two days being with ASP/IPC teams, and the final third day being with hospital directors and leadership. The WHO policy guidance and toolkit are useful tools to address overuse of antimicrobial agents. Strong leadership support is needed for successful implementation of ASP and IPC. Discussions on quality/safety, as well as cost analyses, are important to generate interest of stakeholders.

Public Health Sciences

Blackwell CK, Sherlock P, Jackson KL, Hofheimer JA, Cella D, Algermissen MA, Alshawabkeh AN, Avalos LA, Bastain T, Blair C, Bosquet Enlow M, Brennan PA, Breton C, Bush NR, Chandran A, Collazo S, Conradt E, Crowell SE, Deoni S, Elliott AJ, Frazier JA, Ganiban JM, Gold DR, Herbstman JB, **Joseph C**, Karagas MR, Lester B, Lasky-Su JA, Leve LD, LeWinn KZ, Mason WA, McGowan EC, McKee KS, Miller RL, Neiderhiser JM, O'Connor TG, Oken E, O'Shea TM, Pagliaccio D, Schmidt RJ, Singh AM, Stanford JB, Trasande L, Wright RJ, Duarte CS, and Margolis AE. Development and psychometric validation of the Pandemic-Related Traumatic Stress Scale for children and adults. *Psychol Assess* 2023; 35(11):1054-1067. PMID: 37902671. Request Article

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Department of Family Medicine, University of Michigan Medical School.
Department of Psychology, Penn State University.
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Department of Public Health Services, University of California-Davis School of Medicine.
Department of Pediatrics, University of Wisconsin School of Medicine and Public Health.
Department of Family and Preventative Medicine, University of Utah School of Medicine.

To assess the public health impact of the COVID-19 pandemic on mental health, investigators from the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) research program developed the Pandemic-Related Traumatic Stress Scale (PTSS). Based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) acute stress disorder symptom criteria, the PTSS is designed for adolescent (13-21 years) and adult self-report and caregiver-report on 3-12-year-olds. To evaluate psychometric properties, we used PTSS data collected between April 2020 and August 2021 from non-pregnant adult caregivers (n = 11,483), pregnant/postpartum individuals (n = 1,656), adolescents (n = 1,795), and caregivers reporting on 3-12-year-olds (n = 2,896). We used Mokken scale analysis to examine unidimensionality and reliability, Pearson correlations to evaluate relationships with other relevant variables, and analyses of variance to identify regional, age, and sex differences. Mokken analysis resulted in a moderately strong, unidimensional scale that retained nine of the original 10 items. We detected small to moderate positive associations with depression, anxiety, and general stress, and negative associations with life satisfaction. Adult caregivers had the highest PTSS scores, followed by adolescents, pregnant/postpartum individuals, and children. Caregivers of younger children, females, and older youth had higher PTSS scores compared to caregivers of older children, males, and younger youth, respectively. (PsycInfo Database Record (c) 2023 APA, all rights reserved).

Public Health Sciences

Bossick AS, **Abood JA**, **Oaks A**, **Vilkins A**, **Shukr G**, **Chamseddine P**, and **Wegienka GR**. Racial disparities between measures of area deprivation and financial toxicity, and uterine volume in myomectomy patients. *BMC Womens Health* 2023; 23(1):603. PMID: 37964227. Full Text

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BACKGROUND: At time of myomectomy, a surgical procedure to remove uterine fibroids, Black women tend to have larger uteri than White women. This makes Black patients less likely to undergo a minimally invasive myomectomy which has been shown to have less postoperative pain, less frequent postoperative fever and shorter length of stay compared to abdominal myomectomies. The associations between individual financial toxicity and community area deprivation and uterine volume at the time of myomectomy have not been investigated. METHODS: We conducted a secondary data analysis of patients with fibroids scheduled for myomectomy using data from a fibroid treatment registry in [location]. We used validated measures of individual-level Financial Toxicity (higher scores = better financial status) and community-level Area Deprivation (ADI, high scores = worse deprivation). To examine associations

with log transformed uterine volume, we used linear regression clustered on race (Black vs. White). RESULTS: Black participants had worse financial toxicity, greater deprivation and larger uterine volumes compared with White participants. A greater Financial Toxicity score (better financial status) was associated with lower uterine volume. For every 10 unit increase in Financial Toxicity, the mean total uterine volume decreased by 9.95% (Confidence Interval [CI]: -9.95%, -3.99%). ADI was also associated with uterine volume. A single unit increase in ADI (worse deprivation) was associated with a 5.13% (CI: 2.02%, 7.25%) increase in mean uterine volume. CONCLUSION: Disproportionately worse Financial Toxicity and ADI among Black patients is likely due to structural racism - which now must be considered in gynecologic research and practice. TRIAL REGISTRATION: Not applicable.

Public Health Sciences

de Bakker M, Petersen TB, Rueten-Budde AJ, Akkerhuis KM, Umans VA, Brugts JJ, Germans T, Reinders MJT, Katsikis PD, van der Spek PJ, Ostroff R, **She R**, **Lanfear D**, Asselbergs FW, Boersma E, Rizopoulos D, and Kardys I. Machine learning-based biomarker profile derived from 4210 serially measured proteins predicts clinical outcome of patients with heart failure. *Eur Heart J Digit Health* 2023; 4(6):444-454. PMID: 38045440. Full Text

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Amsterdam University Medical Centers, Department of Cardiology, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
Health Data Research UK and Institute of Health Informatics, University College London, Gower St, London, WC1E 6BT, UK.
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AIMS: Risk assessment tools are needed for timely identification of patients with heart failure (HF) with reduced ejection fraction (HFrEF) who are at high risk of adverse events. In this study, we aim to derive a small set out of 4210 repeatedly measured proteins, which, along with clinical characteristics and established biomarkers, carry optimal prognostic capacity for adverse events, in patients with HFrEF. METHODS AND RESULTS: In 382 patients, we performed repeated blood sampling (median follow-up: 2.1 years) and applied an aptamer-based multiplex proteomic approach. We used machine learning to select the optimal set of predictors for the primary endpoint (PEP: composite of cardiovascular death, heart transplantation, left ventricular assist device implantation, and HF hospitalization). The association between repeated measures of selected proteins and PEP was investigated by multivariable joint models. Internal validation (cross-validated c-index) and external validation (Henry Ford HF PharmacoGenomic Registry cohort) were performed. Nine proteins were selected in addition to the MAGGIC risk score, N-terminal pro-hormone B-type natriuretic peptide, and troponin T: suppression of tumourigenicity 2, tryptophanyl-tRNA synthetase cytoplasmic, histone H2A Type 3, angiotensinogen, deltex-1, thrombospondin-4, ADAMTS-like protein 2, anthrax toxin receptor 1, and cathepsin D. N-terminal pro-hormone B-type natriuretic peptide and angiotensinogen showed the strongest associations [hazard ratio (95% confidence interval): 1.96 (1.17-3.40) and 0.66 (0.49-0.88), respectively]. The multivariable model

yielded a c-index of 0.85 upon internal validation and c-indices up to 0.80 upon external validation. The c-index was higher than that of a model containing established risk factors (P = 0.021). CONCLUSION: Nine serially measured proteins captured the most essential prognostic information for the occurrence of adverse events in patients with HFrEF, and provided incremental value for HF prognostication beyond established risk factors. These proteins could be used for dynamic, individual risk assessment in a prospective setting. These findings also illustrate the potential value of relatively 'novel' biomarkers for prognostication. CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/ct2/show/NCT01851538?term=nCT01851538&draw=2&rank=1 24.

Public Health Sciences

Luzum JA, Campos-Staffico AM, **Li J**, **She R**, **Gui H**, **Peterson EL**, **Liu B**, **Sabbah HN**, Donahue MP, Kraus WE, **Williams LK**, and **Lanfear DE**. Genome-Wide Association Study of Beta-Blocker Survival Benefit in Black and White Patients with Heart Failure with Reduced Ejection Fraction. *Genes (Basel)* 2023; 14(11). PMID: 38002962. Full Text

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In patients with heart failure with reduced ejection fraction (HFrEF), individual responses to beta-blockers vary. Candidate gene pharmacogenetic studies yielded significant but inconsistent results, and they may have missed important associations. Our objective was to use an unbiased genome-wide association study (GWAS) to identify loci influencing beta-blocker survival benefit in HFrEF patients. Genetic variant × beta-blocker exposure interactions were tested in Cox proportional hazards models for all-cause mortality stratified by self-identified race. The models were adjusted for clinical risk factors and propensity scores. A prospective HFrEF registry (469 black and 459 white patients) was used for discovery, and linkage disequilibrium (LD) clumped variants with a beta-blocker interaction of $p < 5 \times 10(-5)$, were tested for Bonferroni-corrected validation in a multicenter HFrEF clinical trial (288 black and 579 white patients). A total of 229 and 18 variants in black and white HFrEF patients, respectively, had interactions with beta-blocker exposure at $p < 5 \times 10(-5)$ upon discovery. After LD-clumping, 100 variants and 4 variants in the black and white patients, respectively, remained for validation but none reached statistical significance. In conclusion, genetic variants of potential interest were identified in a discovery-based GWAS of beta-blocker survival benefit in HFrEF patients, but none were validated in an independent dataset. Larger cohorts or alternative approaches, such as polygenic scores, are needed.

Public Health Sciences

Santarossa S, **Sitarik AR**, **Cassidy-Bushrow AE**, and Comstock SS. Prenatal physical activity and the gut microbiota of pregnant women: results from a preliminary investigation. *Phys Act Nutr* 2023; 27(2):1-7. PMID: 37583065. Full Text

Department of Public Health Sciences, Henry Ford Health System, Michigan, USA.
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PURPOSE: To determine whether physical activity (PA), specifically meeting the recommended 150 minutes of moderate-intensity PA per week, is associated with gut microbiota composition in pregnant women. METHODS: In an ongoing birth cohort study, questions from the Behavioral Risk Factor Surveillance System, which provides data on PA variables, were used to determine whether pregnant women met or exceeded the PA recommendations. To profile the composition of gut bacterial microbiota, 16S rRNA sequencing was performed on stool samples obtained from pregnant women. Differences in alpha diversity metrics (richness, Pielou's evenness, and Shannon's diversity) according to PA were determined using linear regression, whereas beta diversity relationships (Canberra and Bray-Curtis) were assessed using Permutational multivariate analysis of variance (PERMANOVA). Differences in relative

taxon abundance were determined using DESeq2. RESULTS: The complete analytical sample included 23 women that were evaluated for both PA and 16S rRNA sequencing data (median age [Q1; Q3] = 30.5 [26.6; 34.0] years; 17.4% Black), and 11 (47.8%) met or exceeded the PA recommendations. Meeting or exceeding the PA recommendations during pregnancy was not associated with gut microbiota richness, evenness, or diversity, but it was related to distinct bacterial composition using both Canberra (p = 0.005) and Bray-Curtis (p = 0.022) distances. Significantly lower abundances of Bacteroidales, Bifidobacteriaceae, Lactobacillaceae, and Streptococcaceae were observed in women who met or exceeded the PA recommendations (all false discovery rates adjusted, p < 0.02). CONCLUSION: Pregnant women who met or exceeded the PA recommendations showed altered gut microbiota composition. This study forms the basis for future studies on the impact of PA on gut microbiota during pregnancy.

Public Health Sciences

Shareef SJ, Jackson S, **Lane BN**, Kallabat E, **Boopathy D**, **Fakhoury JW**, and **Lim HW**. Photoprotective measures among adolescents stratified by region: An analysis utilizing the National College Health Assessment. *Photodermatol Photoimmunol Photomed* 2023; Epub ahead of print. PMID: 38017654. Full Text

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BACKGROUND/PURPOSE: Exposure to sunlight has been shown to cause pigmentary alterations, photoaging and photocarcinogenesis. Understanding photoprotective patterns in adolescent populations is beneficial to public health initiatives. We utilized data provided by the American College Health Association's National College Health Assessment to evaluate photoprotective behaviors among adolescent populations. METHODS: Behavioral questions related to photoprotection were analyzed from the American College Health Association (ACHA) National College Health Assessment (NCHA) (Version III). RESULTS: When comparing races, Black/African American respondents had the lowest association of practicing photoprotective behaviors in comparison to white respondents (p < .05). When comparing US geographic regions, the south had the lowest association of photoprotective measures (p < .05). LIMITATIONS: The response rate of each institution varied, although there was still a large quantity of respondents. Finally, we cannot discern the specific reasoning for adolescent populations not using sunscreen. CONCLUSION: These data identify demographics where efforts to enhance education on photoprotective behaviors, specifically among skin of color and southern population, to support public health initiatives.

Public Health Sciences

Shin SS, Shah A, North-Kabore J, Rowthorn V, Fiori KP, Dudding R, Plum RA, **Parke DM**, George C, Thomas S, Pinkett R, Porter KMP, Sirois A, Cordeiro V, and Ogbolu Y. Global Learning for Health Equity: A Survey of Five Global Learning Sites in the United States. *Community Health Equity Res Policy* 2023; Epub ahead of print. PMID: 37947506. Full Text

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Global learning is the practice of adopting and adapting global ideas to local challenges. To advance the field of global learning, we performed a case study of five communities that had implemented global health models to advance health equity in a U.S. setting. Surveys were developed using a Consolidated Framework for Implementation Research (CFIR) framework, and each site completed surveys to characterize their global learning experience with respect to community context, the learning and implementation process, implementation science considerations, and health equity. The immense diversity of sites and their experiences underscored the heterogenous nature of global learning. Nonetheless, all cases highlighted core themes of addressing social determinants of health through strong community engagement. Cross-sector participation and implementation science evaluation were strategies applied by many but not all sites. We advocate for continued global learning that advances health equity and fosters equitable partnerships with mutual benefits to origination and destination sites.

Public Health Sciences

Trentham-Dietz A, Corley DA, Del Vecchio NJ, Greenlee RT, Haas JS, Hubbard RA, Hughes AE, Kim JJ, Kobrin S, Li CI, Meza R, **Neslund-Dudas CM**, and Tiro JA. Data gaps and opportunities for modeling cancer health equity. *J Natl Cancer Inst Monogr* 2023; 2023(62):246-254. PMID: 37947335. Full Text

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Population models of cancer reflect the overall US population by drawing on numerous existing data resources for parameter inputs and calibration targets. Models require data inputs that are appropriately representative, collected in a harmonized manner, have minimal missing or inaccurate values, and reflect adequate sample sizes. Data resource priorities for population modeling to support cancer health equity include increasing the availability of data that 1) arise from uninsured and underinsured individuals and those traditionally not included in health-care delivery studies, 2) reflect relevant exposures for groups historically and intentionally excluded across the full cancer control continuum, 3) disaggregate categories (race, ethnicity, socioeconomic status, gender, sexual orientation, etc.) and their intersections that conceal important variation in health outcomes, 4) identify specific populations of interest in clinical

databases whose health outcomes have been understudied, 5) enhance health records through expanded data elements and linkage with other data types (eg, patient surveys, provider and/or facility level information, neighborhood data), 6) decrease missing and misclassified data from historically underrecognized populations, and 7) capture potential measures or effects of systemic racism and corresponding intervenable targets for change.

Public Health Sciences
Wang A, Shen J, Rodriguez AA, **Neslund-Dudas CM**, **Rybicki BA**, et al. Characterizing prostate cancer risk through multi-ancestry genome-wide discovery of 187 novel risk variants. *Nat Genet* 2023; 55(12):2065-2074. PMID: 37945903. Full Text

The transferability and clinical value of genetic risk scores (GRSs) across populations remain limited due to an imbalance in genetic studies across ancestrally diverse populations. Here we conducted a multi-ancestry genome-wide association study of 156,319 prostate cancer cases and 788,443 controls of European, African, Asian and Hispanic men, reflecting a 57% increase in the number of non-European cases over previous prostate cancer genome-wide association studies. We identified 187 novel risk variants for prostate cancer, increasing the total number of risk variants to 451. An externally replicated multi-ancestry GRS was associated with risk that ranged from 1.8 (per standard deviation) in African ancestry men to 2.2 in European ancestry men. The GRS was associated with a greater risk of aggressive versus non-aggressive disease in men of African ancestry (P = 0.03). Our study presents novel prostate cancer susceptibility loci and a GRS with effective risk stratification across ancestry groups.

Public Health Sciences
Younis M, **Al-Antary N**, Dalbah R, Qarajeh A, Khanfar AN, Kar AA, Reddy R, and Alzghoul BN. Echocardiography and pulmonary hypertension in patients with chronic obstructive pulmonary disease undergoing lung transplantation evaluation. *Am J Med Sci* 2023; Epub ahead of print. PMID: 37967751. Full Text

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BACKGROUND: The use of echocardiography in pulmonary hypertension (PH) in advanced chronic obstructive pulmonary disease (COPD) is understudied. We aimed to compare the performance of echocardiography with right heart catheterization (RHC) in the diagnosis of PH in COPD patients undergoing lung transplant evaluation. METHODS: We included 111 patients with severe COPD who underwent RHC in a single center as part of lung transplantation evaluation. COPD-PH and severe COPD-PH were defined based on RHC per the 6(th) world symposium on pulmonary hypertension. Echocardiographic probability of PH was described according to the European Society of Cardiology guidelines. Summary and univariate analyses were performed. RESULTS: The mean age (±SD) was 62 (8) and 47% (n=52) were men. A total of 82 patients (74 %) had COPD-PH. The sensitivity, specificity, positive predictive, and negative predictive values of echocardiography in diagnosing COPD-PH were 43 %, 83 %, 88 %, and 34 % respectively and for severe COPD-PH were 67 %, 75 %, 50 %, and 86 % respectively. Echocardiography was consistent with RHC in ruling in/out PH in 53% (n=59) of patients. After controlling for age, sex. BMI, pack year, echocardiography-RHC time difference, GOLD class, FVC, and CT finding of emphysema, higher TLC decreased consistency (parameter estimate=-0.031; odds ratio: 0.97, 95%CI 0.94-0.99; p=0.037) and higher DLCO increased consistency (parameter

estimate=0.070; odds ratio: 1.07, 95%CI 0.94-0.99; p=0.026). CONCLUSIONS: Echocardiography has high specificity but low sensitivity for the diagnosis of PH in advanced COPD. Its performance improves when ruling out severe COPD-PH. This performance correlates inversely with lung hyperinflation.

Pulmonary and Critical Care Medicine
Awdish RL. A Kind of Faith. *Chest* 2023; 164(5):1296-1297. PMID: 37945192. Full Text

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Radiation Oncology
Kumarasiri A, **Chetty IJ**, **Devpura S**, **Pradhan D**, **Aref I**, **Elshaikh MA**, and **Movsas B**. Radiation therapy margin reduction for patients with localized prostate cancer: A prospective study of the dosimetric impact and quality of life. *J Appl Clin Med Phys* 2023; e14198. Epub ahead of print. PMID: 37952248. Full Text

Department of Radiation Oncology, Henry Ford Health, Detroit, Michigan, USA.

OBJECTIVES: To investigate the impact of reducing Clinical Target Volume (CTV) to Planning Target Volume (PTV) margins on delivered radiation therapy (RT) dose and patient reported quality-of-life (QOL) for patients with localized prostate cancer. METHODS: Twenty patients were included in a single institution IRB-approved prospective study. Nine were planned with reduced margins (4 mm at prostate/rectum interface, 5 mm elsewhere), and 11 with standard margins (6/10 mm). Cumulative delivered dose was calculated using deformable dose accumulation. Each daily CBCT dataset was deformed to the planning CT (pCT), dose was computed, and accumulated on the resampled pCT using a parameter-optimized, B-spline algorithm (Elastix, ITK/VTK). EPIC-26 patient reported QOL was prospectively collected pre-treatment, post-treatment, and at 2-, 6-, 12-, 18-, 24-, 36-, 48-, and 60-month follow-ups. Post -RT QOL scores were baseline corrected and standardized to a [0-100] scale using EPIC-26 methodology. Correlations between QOL scores and dosimetric parameters were investigated, and the overall QOL differences between the two groups (QOL(Margin-reduced) -QOL(control)) were calculated. RESULTS: The median QOL follow-up length for the 20 patients was 48 months. Difference between delivered dose and planned dose did not reach statistical significance ($p > 0.1$) for both targets and organs at risk between the two groups. At 4 years post-RT, standardized mean QOL(Margin-reduced) -QOL(control) were improved for Urinary Incontinence, Urinary Irritative/Obstructive, Bowel, and Sexual EPIC domains by 3.5, 14.8, 10.2, and 16.1, respectively (higher values better). The control group showed larger PTV/rectum and PTV/bladder intersection volumes (7.2 ± 5.8, 18.2 ± 8.1 cc) than the margin-reduced group (2.6 ± 1.8, 12.5 ± 8.3 cc), though the dose to these intersection volumes did not reach statistical significance ($p > 0.1$) between the groups. PTV/rectum intersection volume showed a moderate correlation ($r = -0.56$, $p < 0.05$) to Bowel EPIC domain. CONCLUSIONS: Results of this prospective study showed that margin-reduced group exhibited clinically meaningful improvement of QOL without compromising the target dose coverage.

Radiation Oncology
Mao W, **Kim J**, and **Chetty IJ**. Association of Internal and External Motion Based on Cine MR Images Acquired During Real-Time Treatment on MRI-Guided Linear Accelerator for Patients With Lung Cancer. *Adv Radiat Oncol* 2024; 9(1):101271. PMID: 38033355. Full Text

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PURPOSE: With the recent clinical implementation of magnetic resonance imaging (MRI)-guided linear accelerators, a large number of real-time planar MR images has been acquired during lung cancer treatment as a standard of care. In this study, associations among lung tumor, diaphragm, and external skin movement were studied based on MR cine imaging during the entire duration of each treatment fraction. METHODS AND MATERIALS: This retrospective study used 181,798 planar MRI frames acquired over 55 treatment/imaging sessions of 13 patients with lung cancer treated on 2 MRI-guided linear accelerators. From each planar MR image frame, in-house software automatically extracted 9

features: the superior-interior (SI) and posterior-anterior (PA) positions of a lung tumor; the area of the lung (Lung_Area); the posterior (Dia_Post), dome/apex (Dia_Dome), and anterior (Dia_Ant) points of a diaphragmatic curve; the diaphragm curve point (Dia_Max); and the chest (Chest) and belly (Belly) skin points experienced the maximum range of motions. Correlation analyses were performed among the 9 features for every session. Lung tumor motion range and standard deviations were calculated based on positions obtained in cine images and compared with motion ranges obtained from 4-dimensional computed tomography images. RESULTS: In the study, 177,009 frames of images were successfully analyzed. For all patients, correlation coefficients were as follows: 0.91 ± 0.10 between any 2 features among Lung_Area, Dia_Post, Dia_Dome, and Dia_Max; 0.82 ± 0.21 between SI and any feature among Lung_Area, Dia_Post, Dia_Dome, and Dia_Max; 0.75 ± 0.24 between SI and Belly. Six of 13 patients were considered large amplitude motion (patients with lung tumor SI motion standard deviation >5 mm). Furthermore, 92,956 frames of images were analyzed for the 6 large-amplitude motion patients. For this set, correlation coefficients were 0.93 ± 0.07 between any 2 features among Lung_Area, Dia_Post, Dia_Dome, and Dia_Max; 0.94 ± 0.06 between SI and any feature among Lung_Area, Dia_Post, Dia_Dome, and Dia_Max; and 0.90 ± 0.09 between SI and Belly. CONCLUSIONS: Both belly and diaphragmatic motions as assessed by cine MRI are highly correlated with large amplitude lung tumor motion in the longitudinal axis.

Radiation Oncology

Mishra AK, Gupta A, Dagar G, Das D, Chakraborty A, Haque S, Prasad CP, Singh A, Bhat AA, Macha MA, Benali M, Saini KS, Previs RA, Saini D, Saha D, Dutta P, **Bhatnagar AR**, Darswal M, Shankar A, and Singh M. CAR-T-Cell Therapy in Multiple Myeloma: B-Cell Maturation Antigen (BCMA) and Beyond. *Vaccines (Basel)* 2023; 11(11). PMID: 38006053. Full Text

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Significant progress has been achieved in the realm of therapeutic interventions for multiple myeloma (MM), leading to transformative shifts in its clinical management. While conventional modalities such as surgery, radiotherapy, and chemotherapy have improved the clinical outcomes, the overarching challenge of effecting a comprehensive cure for patients afflicted with relapsed and refractory MM (RRMM) endures. Notably, adoptive cellular therapy, especially chimeric antigen receptor T-cell (CAR-T) therapy, has

exhibited efficacy in patients with refractory or resistant B-cell malignancies and is now also being tested in patients with MM. Within this context, the B-cell maturation antigen (BCMA) has emerged as a promising candidate for CAR-T-cell antigen targeting in MM. Alternative targets include SLAMF7, CD38, CD19, the signaling lymphocyte activation molecule CS1, NKG2D, and CD138. Numerous clinical studies have demonstrated the clinical efficacy of these CAR-T-cell therapies, although longitudinal follow-up reveals some degree of antigenic escape. The widespread implementation of CAR-T-cell therapy is encumbered by several barriers, including antigenic evasion, uneven intratumoral infiltration in solid cancers, cytokine release syndrome, neurotoxicity, logistical implementation, and financial burden. This article provides an overview of CAR-T-cell therapy in MM and the utilization of BCMA as the target antigen, as well as an overview of other potential target moieties.

Research Administration

Chamogeorgakis T, Toumpoulis I, Bonios MJ, **Lanfear D**, **Williams C**, Koliopoulou A, and **Cowger J**. Treatment Strategies and Outcomes of Right Ventricular Failure Post Left Ventricular Assist Device Implantation: An INTERMACS Analysis. *Asaio j* 2023; Epub ahead of print. PMID: 38029763. Full Text

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Right heart failure (RHF) management after left ventricular assist device (LVAD) implantation includes inotropes, right ventricular mechanical support, and heart transplantation. The purpose of this study is to compare different RHF treatment strategies in patients with a magnetically levitated centrifugal LVAD. A total of 6,632 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patients from 2013 to 2020 were included. Of which, 769 (69.6%) patients (group 1) were supported with inotropes (≥14 days post-LVAD implantation), 233 (21.1%) patients (group 2) were supported with temporary right ventricular assist device (RVAD) that was implanted during LVAD implant, 77 (7.0%) patients (group 3) with durable centrifugal RVAD implanted during the LVAD implant, and 26 (2.4%) patients (group 4) were supported with RVAD (temporary or permanent), which was implanted at a later stage. Groups 1 and 4 had higher survival rates in comparison with group 2 (hazard ratio [HR] = 0.513, 95% confidence intervals [CIs] = 0.402-0.655, $p < 0.001$, versus group 1) and group 3 (HR = 0.461, 95% CIs = 0.320-0.666, $p < 0.001$, versus group 1). Patients in group 3 showed higher heart transplantation rates at 12 and 36 months as compared with group 1 (40.4% and 46.6% vs. 21.9% and 37.4%, respectively), group 2 (40.4% and 46.6% vs. 25.8% and 39.3%, respectively), and group 4 (40.4% and 46.6% vs. 3.8% and 12.0%, respectively). Severe RHF post-LVAD is associated with poor survival. Patients with LVAD who during the perioperative period are in need of right ventricular temporary or durable mechanical circulatory support constitute a group at particular risk. Improvement of devices tailored for right ventricular support is mandatory for further evolution of the field.

Research Administration

de Bakker M, Petersen TB, Rueten-Budde AJ, Akkerhuis KM, Umans VA, Brugts JJ, Germans T, Reinders MJT, Katsikis PD, van der Spek PJ, Ostroff R, **She R**, **Lanfear D**, Asselbergs FW, Boersma E, Rizopoulos D, and Kardys I. Machine learning-based biomarker profile derived from 4210 serially measured proteins predicts clinical outcome of patients with heart failure. *Eur Heart J Digit Health* 2023; 4(6):444-454. PMID: 38045440. Full Text

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Amsterdam University Medical Centers, Department of Cardiology, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands.
Health Data Research UK and Institute of Health Informatics, University College London, Gower St, London, WC1E 6BT, UK.
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AIMS: Risk assessment tools are needed for timely identification of patients with heart failure (HF) with reduced ejection fraction (HFrEF) who are at high risk of adverse events. In this study, we aim to derive a small set out of 4210 repeatedly measured proteins, which, along with clinical characteristics and established biomarkers, carry optimal prognostic capacity for adverse events, in patients with HFrEF. METHODS AND RESULTS: In 382 patients, we performed repeated blood sampling (median follow-up: 2.1 years) and applied an aptamer-based multiplex proteomic approach. We used machine learning to select the optimal set of predictors for the primary endpoint (PEP: composite of cardiovascular death, heart transplantation, left ventricular assist device implantation, and HF hospitalization). The association between repeated measures of selected proteins and PEP was investigated by multivariable joint models. Internal validation (cross-validated c-index) and external validation (Henry Ford HF PharmacoGenomic Registry cohort) were performed. Nine proteins were selected in addition to the MAGGIC risk score, N-terminal pro-hormone B-type natriuretic peptide, and troponin T: suppression of tumourigenicity 2, tryptophanyl-tRNA synthetase cytoplasmic, histone H2A Type 3, angiotensinogen, deltex-1, thrombospondin-4, ADAMTS-like protein 2, anthrax toxin receptor 1, and cathepsin D. N-terminal pro-hormone B-type natriuretic peptide and angiotensinogen showed the strongest associations [hazard ratio (95% confidence interval): 1.96 (1.17-3.40) and 0.66 (0.49-0.88), respectively]. The multivariable model yielded a c-index of 0.85 upon internal validation and c-indices up to 0.80 upon external validation. The c-index was higher than that of a model containing established risk factors (P = 0.021). CONCLUSION: Nine serially measured proteins captured the most essential prognostic information for the occurrence of adverse events in patients with HFrEF, and provided incremental value for HF prognostication beyond established risk factors. These proteins could be used for dynamic, individual risk assessment in a prospective setting. These findings also illustrate the potential value of relatively 'novel' biomarkers for prognostication. CLINICAL TRIAL REGISTRATION: https://clinicaltrials.gov/ct2/show/NCT01851538?term=nCT01851538&draw=2&rank=1 24.

Research Administration

Luzum JA, Campos-Staffico AM, **Li J**, **She R**, **Gui H**, **Peterson EL**, **Liu B**, **Sabbah HN**, Donahue MP, Kraus WE, **Williams LK**, and **Lanfear DE**. Genome-Wide Association Study of Beta-Blocker Survival Benefit in Black and White Patients with Heart Failure with Reduced Ejection Fraction. *Genes (Basel)* 2023; 14(11). PMID: 38002962. Full Text

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In patients with heart failure with reduced ejection fraction (HFrEF), individual responses to beta-blockers vary. Candidate gene pharmacogenetic studies yielded significant but inconsistent results, and they may have missed important associations. Our objective was to use an unbiased genome-wide association

study (GWAS) to identify loci influencing beta-blocker survival benefit in HFrEF patients. Genetic variant × beta-blocker exposure interactions were tested in Cox proportional hazards models for all-cause mortality stratified by self-identified race. The models were adjusted for clinical risk factors and propensity scores. A prospective HFrEF registry (469 black and 459 white patients) was used for discovery, and linkage disequilibrium (LD) clumped variants with a beta-blocker interaction of $p < 5 \times 10(-5)$, were tested for Bonferroni-corrected validation in a multicenter HFrEF clinical trial (288 black and 579 white patients). A total of 229 and 18 variants in black and white HFrEF patients, respectively, had interactions with beta-blocker exposure at $p < 5 \times 10(-5)$ upon discovery. After LD-clumping, 100 variants and 4 variants in the black and white patients, respectively, remained for validation but none reached statistical significance. In conclusion, genetic variants of potential interest were identified in a discovery-based GWAS of beta-blocker survival benefit in HFrEF patients, but none were validated in an independent dataset. Larger cohorts or alternative approaches, such as polygenic scores, are needed.

Sleep Medicine

Roth T, Thorpy MJ, Kushida CA, Horsnell M, and Gudeman J. Once-nightly sodium oxybate (FT218) improved symptoms of disrupted nighttime sleep in people with narcolepsy: a plain language summary. *J Comp Eff Res* 2023; 12(12):e230133. PMID: 37971303. Full Text

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WHAT IS THIS SUMMARY ABOUT? This is a plain language summary of a published article in the journal CNS Drugs. Narcolepsy is a rare sleep condition. Most people with narcolepsy experience disrupted nighttime sleep and have poor quality of sleep. Sometimes these symptoms are not easily diagnosed as a symptom of narcolepsy. Sodium oxybate is an approved treatment for narcolepsy. The only version of sodium oxybate that was available until 2023 required people to take their sodium oxybate at bedtime and then again in the middle of the night. The US Food and Drug Administration (FDA for short) has approved a once-nightly bedtime dose of sodium oxybate (ON-SXB for short, also known as FT218 or LUMRYZ(™)) to treat symptoms of narcolepsy in adults. These symptoms are daytime sleepiness and cataplexy, which is an episode of sudden muscle weakness. The once-nightly bedtime dose of ON-SXB removes the need for a middle-of-the-night dose of sodium oxybate. The REST-ON clinical study compared ON-SXB to a placebo (a substance that contains no medicine) to determine if it was better at treating symptoms of disrupted nighttime sleep associated with narcolepsy. This summary looks at whether; ON-SXB was better than placebo at treating symptoms of disrupted nighttime sleep. WHAT WERE THE RESULTS? Compared to people who took placebo, people who took ON-SXB had fewer number of changes from deeper to lighter sleep stages and woke up less during the night. They also reported that they slept better at night and felt more refreshed when waking up in the morning. People with narcolepsy sometimes take alerting agents to help with sleepiness during the day, but alerting agents can cause difficulty sleeping at night. This study showed that people who took ON-SXB had better nighttime sleep even if they were taking alerting agents during the day. The most common side effects of ON-SXB included dizziness, nausea (feeling sick to your stomach), vomiting, headache, and bedwetting. WHAT DO THE RESULTS MEAN? A once-nightly bedtime dose of ON-SXB is a narcolepsy treatment option for people without the need for a middle-of-the-night dose of sodium oxybate.

Sleep Medicine

Wickwire EM, Collen J, Capaldi VF, Williams SG, Assefa SZ, Adornetti JP, Huang K, Venezia JM, Jones RL, Johnston CW, Thomas C, Thomas MA, Mounts C, **Drake CL**, Businelle MS, Grandner MA, Manber R, and Albrecht JS. Patient Engagement and Provider Effectiveness of a Novel Sleep Telehealth Platform and Remote Monitoring Assessment in the US Military: Pilot Study Providing Evidence-Based Sleep Treatment Recommendations. *JMIR Form Res* 2023; 7:e47356. PMID: 37971788. Full Text

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BACKGROUND: Sleep problems are common and costly in the US military. Yet, within the military health system, there is a gross shortage of trained specialist providers to address sleep problems. As a result, demand for sleep medicine care far exceeds the available supply. Telehealth including telemedicine, mobile health, and wearables represents promising approaches to increase access to high-quality and cost-effective care. OBJECTIVE: The purpose of this study was to evaluate patient engagement and provider perceived effectiveness of a novel sleep telehealth platform and remote monitoring assessment in the US military. The platform includes a desktop web portal, native mobile app, and integrated wearable sensors (ie, a commercial off-the-shelf sleep tracker [Fitbit]). The goal of the remote monitoring assessment was to provide evidence-based sleep treatment recommendations to patients and providers. METHODS: Patients with sleep problems were recruited from the Internal Medicine clinic at Walter Reed National Military Medical Center. Patients completed intensive remote monitoring assessments over 10 days (including a baseline intake questionnaire, daily sleep diaries, and 2 daily symptom surveys), and wore a Fitbit sleep tracker. Following the remote monitoring period, patients received assessment results and personalized sleep education in the mobile app. In parallel, providers received a provisional patient assessment report in an editable electronic document format. Patient engagement was assessed via behavioral adherence metrics that were determined a priori. Patients also completed a brief survey regarding ease of completion. Provider effectiveness was assessed via an anonymous survey. RESULTS: In total, 35 patients with sleep problems participated in the study. There were no dropouts. Results indicated a high level of engagement with the sleep telehealth platform, with all participants having completed the baseline remote assessment, reviewed their personalized sleep assessment report, and completed the satisfaction survey. Patients completed 95.1% of sleep diaries and 95.3% of symptom surveys over 10 days. Patients reported high levels of satisfaction with most aspects of the remote monitoring assessment. In total, 24 primary care providers also participated and completed the anonymous survey. The results indicate high levels of perceived effectiveness and identified important potential benefits from adopting a sleep telehealth approach throughout the US military health care system. CONCLUSIONS: Military patients with sleep problems and military primary care providers demonstrated high levels of engagement and satisfaction with a novel sleep telehealth platform and remote monitoring assessment. Sleep telehealth approaches represent a potential pathway to increase access to evidence-based sleep medicine care in the US military. Further evaluation is warranted.

Surgery

Abu-Rumaileh M, Haddad RA, Yosef M, Esfandiari NH, Kraftson A, Khairi S, Lager C, Bushman J, Khalatbari S, Tincopa M, **Varban O**, Bozadjieva-Kramer N, and Oral EA. Impact of Nonalcoholic Fatty Liver Disease (NAFLD) on Weight Loss After Bariatric Surgery. *Obes Surg* 2023; 33(12):3814-3828. PMID: 37940737. Full Text

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OBJECTIVE: Obesity and associated comorbidities, such as NAFLD, impose a major healthcare burden worldwide. Bariatric surgery remains the most successful approach for sustained weight loss and the resolution of obesity-related complications. However, the impact of preexisting NAFLD on weight loss after bariatric surgery has not been previously studied. The goal of this study is to assess the impact of preexisting NAFLD on weight loss outcomes up to 5 years after weight loss surgery. RESEARCH DESIGN AND METHODS: Data from the Michigan Bariatric Surgery Cohort (MI-BASiC) was extracted to examine the effect of baseline NAFLD on weight loss outcomes. The cohort included a total of 714 patients older than 18 years of age undergoing gastric bypass (GB; 380 patients) or sleeve gastrectomy (SG; 334 patients) at the University of Michigan between January 2008 and November 2013. Repeated measure analysis was used to determine if preexisting NAFLD was a predictor of weight loss outcomes up to 5 years post-surgery. RESULTS: We identified 221 patients with an established clinical diagnosis of NAFLD at baseline. Multivariable repeated measure analysis with adjustment for covariates shows that patients with preexisting NAFLD had a significantly lower percentage of total and excess weight loss compared to patients without preexisting NAFLD. Furthermore, our data show that baseline dyslipidemia is an indicator of the persistence of NAFLD after bariatric surgery. CONCLUSIONS: Our data show that patients' body weight loss in response to bariatric surgery is impacted by factors such as preexisting NAFLD. Additionally, we show that NAFLD may persist or recur in a subset of patients after surgery, and thus careful continued follow-up is recommended.

Surgery

Alhamar M, **Uzuni A**, **Mehrotra H**, **Elbashir J**, **Galusca D**, **Nagai S**, **Yoshida A**, **Abouljoud MS**, and Otrock ZK. Predictors of intraoperative massive transfusion in orthotopic liver transplantation. *Transfusion* 2023; Epub ahead of print. PMID: 37961982. Full Text

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BACKGROUND: Although transfusion management has improved during the last decade, orthotopic liver transplantation (OLT) has been associated with considerable blood transfusion requirements which poses some challenges in securing blood bank inventories. Defining the predictors of massive blood transfusion before surgery will allow the blood bank to better manage patients' needs without delays. We evaluated the predictors of intraoperative massive transfusion in OLT. STUDY DESIGN AND METHODS: Data were collected on patients who underwent OLT between 2007 and 2017. Repeat OLTs were excluded. Analyzed variables included recipients' demographic and pretransplant laboratory variables, donors' data, and intraoperative variables. Massive transfusion was defined as intraoperative transfusion of ≥10 units of

packed red blood cells (RBCs). Statistical analysis was performed using SPSS version 17.0. RESULTS: The study included 970 OLT patients. The median age of patients was 57 (range: 16-74) years; 609 (62.7%) were male. RBCs, thawed plasma, and platelets were transfused intraoperatively to 782 (80.6%) patients, 831 (85.7%) patients, and 422 (43.5%) patients, respectively. Massive transfusion was documented in 119 (12.3%) patients. In multivariate analysis, previous right abdominal surgery, the recipient's hemoglobin, Model for End Stage Liver Disease (MELD) score, cold ischemia time, warm ischemia time, and operation time were predictive of massive transfusion. There was a direct significant correlation between the number of RBC units transfused and plasma (Pearson correlation coefficient r = .794) and platelets (r = .65). DISCUSSION: Previous abdominal surgery, the recipient's hemoglobin, MELD score, cold ischemia time, warm ischemia time, and operation time were predictive of intraoperative massive transfusion in OLT.

Surgery
Chamogeorgakis T, Toumpoulis I, Bonios MJ, **Lanfear D**, **Williams C**, Koliopoulou A, and **Cowger J**. Treatment Strategies and Outcomes of Right Ventricular Failure Post Left Ventricular Assist Device Implantation: An INTERMACS Analysis. *Asaio j* 2023; Epub ahead of print. PMID: 38029763. Full Text

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Right heart failure (RHF) management after left ventricular assist device (LVAD) implantation includes inotropes, right ventricular mechanical support, and heart transplantation. The purpose of this study is to compare different RHF treatment strategies in patients with a magnetically levitated centrifugal LVAD. A total of 6,632 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) patients from 2013 to 2020 were included. Of which, 769 (69.6%) patients (group 1) were supported with inotropes (≥14 days post-LVAD implantation), 233 (21.1%) patients (group 2) were supported with temporary right ventricular assist device (RVAD) that was implanted during LVAD implant, 77 (7.0%) patients (group 3) with durable centrifugal RVAD implanted during the LVAD implant, and 26 (2.4%) patients (group 4) were supported with RVAD (temporary or permanent), which was implanted at a later stage. Groups 1 and 4 had higher survival rates in comparison with group 2 (hazard ratio [HR] = 0.513, 95% confidence intervals [CIs] = 0.402-0.655, p < 0.001, versus group 1) and group 3 (HR = 0.461, 95% CIs = 0.320-0.666, p < 0.001, versus group 1). Patients in group 3 showed higher heart transplantation rates at 12 and 36 months as compared with group 1 (40.4% and 46.6% vs. 21.9% and 37.4%, respectively), group 2 (40.4% and 46.6% vs. 25.8% and 39.3%, respectively), and group 4 (40.4% and 46.6% vs. 3.8% and 12.0%, respectively). Severe RHF post-LVAD is associated with poor survival. Patients with LVAD who during the perioperative period are in need of right ventricular temporary or durable mechanical circulatory support constitute a group at particular risk. Improvement of devices tailored for right ventricular support is mandatory for further evolution of the field.

Surgery
Kwon H, and **Popoff AM**. Stenosis in Esophageal Cancer: A Poor Prognostic Indicator. *Ann Surg Oncol* 2023; Epub ahead of print. PMID: 38019320. Full Text

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Surgery
Shimada S, **Yoshida A**, **Abouljoud M**, **Miyake K**, **Ivanics T**, **Shamaa T**, **Venkat D**, **Moonka D**, **Trudeau S**, **Reed E**, and **Nagai S**. Post-transplant outcomes and financial burden of donation after circulatory death donor liver transplant after the implementation of acuity circle policy. *Clin Transplant* 2023; e15190. Epub ahead of print. PMID: 37964683. Full Text

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BACKGROUND: After implementation of the Acuity Circles (AC) allocation policy, use of DCD liver grafts has increased in the United States. METHODS: We evaluated the impact of AC on rates of DCD-liver transplants (LT), their outcomes, and medical costs in a single practice. Adult LT patients were classified into three eras: Era 1 (pre-AC, 1/01/2015-12/31/2017); Era 2 (late pre-AC era, 1/01/2018-02/03/2020); and Era 3 (AC era, 05/10/2020-09/30/2021). RESULTS: A total of 520 eligible LTs were performed; 87 were DCD, and 433 were DBD. With each successive era, the proportion of DCD increased (Era 1: 11%; Era 2: 20%; Era 3: 24%; $p < .001$). DCD recipients had longer ICU stays, higher re-admission/re-operation rates, and higher incidence of ischemic cholangiopathy compared to those with DBD. Direct, surgical, and ICU costs during first admission were higher with DCD than DBD (+8.0%, $p < .001$; +4.2%, $p < .001$; and +33.3%, $p = .001$). DCD-related costs increased after Era 1 (Direct: +4.9% [Era 2 vs. 1] and +12.4% [Era 3 vs. 1], $p = .04$; Surgical: +17.7% and +21.7%, $p < .001$). In the AC era, there was a significantly higher proportion of donors ≥50 years, and more national organ sharing. Compared to DCD from donors <50 years, DCD from donors ≥50 years was associated with significantly higher total direct, surgical, and ICU costs (+12.6%, $p = .01$; +9.5%, $p = .01$; +84.6%, $p = .03$). CONCLUSIONS: The proportion of DCD-LT, especially from older donors, has increased after the implementation of AC policies. These changes are likely to be associated with higher costs in the AC era.

Urology
Butaney M, **Wilder S**, **Wang Y**, **Bhayani S**, Qi J, Van Till M, Mirza M, Johnson A, **Perkins S**, Noyes S, Weizer A, Johnson L, **Patel A**, Semerjian A, Lane BR, and **Rogers C**. Positive surgical margins in partial nephrectomy: a collaborative effort to maintain surgical quality. *BJU Int* 2023; Epub ahead of print. PMID: 37953479. Full Text

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Michigan State University College of Human Medicine, Grand Rapids, MI, USA.

Urology
Molina J, **Dabaja A**, **Gupta N**, **Alruwaii FI**, **Hassan O**, and **Al-Obaidy KI**. Adipocytic Differentiation in a Sertoli Cell Tumor. *Int J Surg Pathol* 2023; Epub ahead of print. PMID: 38018140. Full Text

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Testicular sex cord-stromal tumors are clonal neoplasms, with the majority being of Leydig cell followed by Sertoli cell origins. In Leydig cell tumors, adipocytic differentiation has been previously reported as a possible distinguishing feature, which has not been reported in other sex cord-stromal tumors. Herein, we report a case of a 48-year-old man who presented with an incidentally discovered 1.1 cm testicular mass, for which he underwent partial orchiectomy. Microscopically, the tumor showed features consistent with sex cord-stromal tumor with strong and diffuse nuclear and cytoplasmic reaction for B-catenin immunohistochemistry, supporting the diagnosis of Sertoli cell tumor. A novel adipocytic differentiation, reported previously in Leydig cell tumors, was present in this tumor.

Urology
Sessine MS, Radoiu CS, Qi J, Labardee C, Burks F, George AK, Lane BR, Lim K, **Dabaja A**, Morgan TM, Cher ML, Semerjian AM, and Ginsburg KB. Can MRI Help Inform Which Men With a History of Multifocal High-Grade Prostatic Intraepithelial Neoplasia or Atypical Small Acinar Proliferation Remain at an Elevated Risk for Clinically Significant Prostate Cancer? *J Urol* 2023; Epub ahead of print. PMID: 37930976. Full Text

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PURPOSE: We investigated the association of MRI findings in men with a previous diagnosis of atypical small acinar proliferation (ASAP) or multifocal high-grade intraepithelial neoplasia (HGPIN) with pathologic findings on repeat biopsy. MATERIALS AND METHODS: We retrospectively reviewed patients with ASAP/multifocal HGPIN undergoing a repeat biopsy in the Michigan Urological Surgery Improvement Collaborative registry. We included men with and without an MRI after the index biopsy demonstrating ASAP/multifocal HGPIN but before the repeat biopsy. Men with an MRI prior to the index biopsy were excluded. We compared the proportion of men with ≥GG2 CaP (Grade Group 2 prostate cancer) on repeat biopsy among the following groups with the $\chi(2)$ test: no MRI, PIRADS (Prostate Imaging-Reporting and Data System) ≥ 4, and PIRADS ≤3. Multivariable models were used to estimate the adjusted association between MRI findings and ≥GG2 CaP on repeat biopsy. RESULTS: Among the 207 men with a previous diagnosis of ASAP/multifocal HGPIN that underwent a repeat biopsy, men with a PIRADS ≥4 lesion had a higher proportion of ≥GG2 CaP (56%) compared with men without an MRI (12%, $P < .001$). A lower proportion of men with PIRADS ≤3 lesions had ≥ GG2 CaP (3.0%) compared with men without an MRI (12%, $P = .13$). In the adjusted model, men with a PIRADS 4 to 5 lesion had higher odds (OR: 11.4, $P < .001$) of ≥ GG2 CaP on repeat biopsy. CONCLUSIONS: MRI is a valuable diagnostic tool to triage which men with a history of ASAP or multifocal HGPIN on initial biopsy should undergo or avoid repeat biopsy without missing clinically significant CaP.

Urology

Soputro NA, Chavali JS, Ferguson EL, Ramos-Carpinteyro R, Calvo RS, Nguyen J, Moschovas MC, **Wilder S**, Okhawere K, De La Rosa RS, Saini I, **Peabody J**, **Badani KK**, **Rogers C**, Joseph J, Nix J, Patel V, Stifelman M, Ahmed M, Crivellaro S, Kim M, and Kaouk JH. Complications of single-port robot-assisted radical prostatectomy: multi-institutional analysis from the Single-Port Advanced Research Consortium (SPARC). *BJU Int* 2023; Epub ahead of print. PMID: 37971182. Full Text

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OBJECTIVE: To evaluate the perioperative complications of single-port robot-assisted radical prostatectomy (SP-RARP). PATIENTS AND METHODS: A retrospective review was performed on the prospectively maintained, Institutional Review Board-approved, multi-institutional Single-Port Advanced Research Consortium (SPARC) database. A total of 1103 patients were identified who underwent three different approaches of SP-RARP between 2019 and 2022 using the purpose-built SP robotic platform. In addition to baseline clinical, perioperative outcomes, this study comprehensively analysed for any evidence of intraoperative complication, as well as postoperative complication and readmission within 90 days of the respective surgery. RESULTS: Of the 244, 712, and 147 patients who underwent transperitoneal, extraperitoneal, and transvesical SP-RARP, respectively, intraoperative complications

were noted in five patients (0.4%), all of which occurred during the transperitoneal approach. Two patients had bowel serosal tears, two had posterior button-holing of the bladder necessitating repair, and one patient had an obturator nerve injury. Postoperative complications were noted in 143 patients (13%) with major complications (Clavien-Dindo Grade ≥III) only identified in 3.7% of the total cohort. The most common complications were lymphocele (3.9%), acute urinary retention (2%), and urinary tract infection (1.9%). The 90-day re-admission rate was 3.9%. CONCLUSION: The SP-RARP is a safe and effective procedure with low complication and readmission rates regardless of the approach. These results are comparable to current multi-port RARP literature.

Urology
Wilder S, **Wang Y**, Van Til M, Qi J, Mirza M, Gadzinski A, Maatman T, Lane BR, and **Rogers CG**. Practice-Level Variation in Opioid-Free Discharge Following Surgery for T1 Renal Masses: A MUSIC-KIDNEY Analysis. *Urol Pract* 2023; Epub ahead of print. PMID: 37987620. Full Text

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INTRODUCTION: Opioid prescription following surgery has played a role in the current opioid epidemic. We evaluated practice-level variation in opioid prescribing following surgery for cT1 renal masses and examined the relationships between opioid-free discharge and postoperative emergency department visits (ED) and readmissions. METHODS: We retrospectively examined all T1 renal mass (RM) patients with data regarding postoperative opioid prescriptions within the MUSIC-KIDNEY registry from April 2021 to March 2023. Patients were stratified into those who received opioids at discharge and those with opioid-free discharge. Associations with patient, tumor, and surgical factors were evaluated. Rates of postoperative ED visits and readmissions within 30 days were compared between cohorts. Practice-level variation was assessed. RESULTS: Of 414 patients who underwent surgery for T1RM across 15 practices in MUSIC-KIDNEY, 23.7% had opioid-free discharge. Practice level variation in rates of opioid-free discharge ranged from 6.7% to 55.0%. For patients prescribed opioids, the median number of pills was 10 (IQR 6-12). Patients with cT1b masses were more likely to have opioid-free discharge (44.9% vs 32%, OR 0.44; 95% CI 0.22-0.89). Rates of 30-day ED visits (7.0% vs 3.1%) and readmissions (4.1% vs 2.0%) were lower in the opioid-free discharge group but did not reach statistical significance. CONCLUSION: MUSIC-KIDNEY data suggests opioid-free discharge is not associated with increased rates of postoperative ED visits or readmissions. There exists wide practice-level variation in opioid prescriptions following surgery for T1RM in the state of Michigan. Similar variation likely exists throughout the United States, and best surgical practice suggests reduction in opioid prescribing after nephrectomy.

Urology
Wright HC, **Kachroo N**, Jain R, Kamal M, Fedrigon Iii D, Corrigan D, Zampini A, De S, Noble M, Isac W, Monga M, and Sivalingam S. Can perioperative antibiotic choice impact rates of infectious complications after PCNL? A single-blind prospective randomized trial. *J Endourol* 2023; Epub ahead of print. PMID: 37917100. Full Text

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OBJECTIVE: National guidelines recommend peri-procedural antibiotics prior to percutaneous nephrolithotomy (PCNL), yet it is not clear which is superior. We conducted a randomized trial to compare two guideline recommended antibiotics: ciprofloxacin (cipro) versus cefazolin, on PCNL outcomes, focusing on the development of systemic inflammatory response syndrome (SIRS) criteria. METHODS: Adult patients who were not considered high risk for surgical or infectious complications undergoing PCNL were randomized to receive either cipro or cefazolin perioperatively. All had negative pre-operative urine cultures. Demographic and peri-operative data were collected, including SIRS criteria, intra-operative urine culture, duration of hospitalization, and need for intensive care. SIRS is defined by ≥2 of the following: body temperature < 96.8 °F or >100.4 °F, heart rate > 90 bpm, respiratory rate >20 per minute, WBC count <4000 or > 12,000 cells/mm³. RESULTS: One hundred and forty seven patients were enrolled and randomized (79 cefazolin, 68 cipro). All pre-operative characteristics were similar (p>0.05), except for mean age, which was higher in the cipro group (64 vs. 57, p=0.03). Intra and post-operative findings were similar, with no difference between groups (p>0.05), except a longer mean hospital stay in the cefazolin group (2 hours longer, p=0.02). There was no difference between SIRS episodes on both univariate and multivariate analysis. CONCLUSIONS: Despite the relatively broader coverage for urinary tract pathogens with ciprofloxacin, this prospective randomized trial did not show superiority over cefazolin. Our findings therefore support two appropriate options for perioperative antibiotic prophylaxis in patients undergoing PCNL who are non-high risk for infectious complications.

Conference Abstracts

Administration

Herrgott GA, **Asmaro KP**, **Wells M**, **Nelson K**, **Thomas B**, **Hasselbach LA**, **Transou A**, **Cazacu S**, **Tundo KM**, **Nadimidla S**, **Scarpace L**, Barnholtz-Sloan J, Sloan AE, Selman WR, **DeCarvalho AC**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Craig J**, **Kalkanis S**, **Snyder J**, **Walbert T**, **Rock J**, **Noushmehr H**, and **Castro AVB**. Methylation-based Machine Learning Classifiers Discriminate Sellar Tumors By Lobe Origin Using Liquid Biopsy Or Surgical Specimens. *J Endocr Soc* 2023; 7:A705. Full Text

G.A. Herrgott, Henry Ford Health, Detroit, MI, United States

Background: The differential diagnosis of challenging sellar tumor cases can be inconclusive through imaging features and could benefit from noninvasive diagnostic approaches, such as liquid biopsy (LB). Similar to tissue, LB specimens carry tumor-specific DNA methylation signatures amenable to the construction of accurate machine learning models able to discriminate CNS tumors. We aimed to develop methylation-based classifiers which classify sellar tumors by lobe of origin, using either LB or tumor tissue specimens. Methodology: We analyzed the DNA methylome (EPIC array) of tumor tissue (T) and LB specimens from adult patients with tumors representing each of the three pituitary lobes (Anterior: T=177; LB=37; Intermediate: T= 7; LB: 10 and Posterior: T=44, LB=2 cases). Using the most variably methylated CpG probes derived from the unsupervised variance-based analyses across tumors from different lobes, we applied multi-class linear discriminant analysis to constructmachine learningmodels to classify sellar tumor tissue and/or LB specimens. Results: We generated classifiers based on lobe-specific methylation

signatures that were able to discriminate across sellar tumors either using tissue and/or LB specimens (500 and 600 CpGs, respectively) with observed accuracies of ~99% across independent validation. DISCUSSION/CONCLUSION: Our findings suggest that methylation-based classifiers constitute an accurate diagnostic approach to discriminate sellar tumors according to the lobe origin, either pre-surgically through a blood draw or through surgical tumor specimens. These classifiers are objective approaches that could complement imaging and pathology reports for an accurate diagnosis of inconclusive cases, ultimately leading to optimal management of the patients with these diseases.

Anesthesiology

Demirel D, Kakdas YC, Barker J, Keane J, **Mitchell J**, Jones S, Jones D, De S, and Jackson C. Donning and Doffing Simulator for Healthcare Workers Caring for COVID-19 Patients. *Surg Endosc* 2023; 37:S455. Full Text

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Personal Protective Equipment (PPE) is used by healthcare workers to minimize exposures to environmental hazards and to prevent the spread of pathogens. With the untimely introduction of COVID-19 into our lives, PPE standards and procedures assumed an even more crucial role in protecting healthcare workers and patients. Established training methods for donning and doffing PPE exist, such as instructor-led training and video lessons. While instructor-led training is practical, it also requires instructor time and PPE resources for implementation, both of which were limited during the pandemic. Conversely, videobased lessons are affordable, safe, and require fewer resources, but they lack the practical hands-on experience essential for learning. In this study, we developed a VR-based training environment to simulate donning and doffing PPE for rapid sequence induction (RSI) with a COVID-19-positive patient. The simulation places the learner in a virtual environment that includes an anteroom and a contaminated operating room; both were designed with guidance from medical experts to ensure we replicated the physical training environment. Learners are instructed on donning and doffing procedures, interact with the virtual PPE to test their knowledge and skills, and receive feedback. Our VR-based simulation provides an alternative learning environment that utilizes the advantages of more traditional training methods (e.g., hands-on, low-cost, preserved situational context of a simulated OR) while limiting their disadvantages (e.g., in-person instruction, use of limited resources) and introducing advantages (e.g., quantitative feedback, 24/7 availability). At the end of this virtual training experience, learners will be able to protect themselves and their patients by taking the proper safety precautions while also remaining safe and utilizing fewer precious healthcare resources.

Behavioral Health Services/Psychiatry/Neuropsychology

Finotti M, **Jesse M**, Pillai A, Liapakis A, **Venkat D**, **Salgia R**, Kumar V, **Manivannan A**, **Lu M**, **Zhang T**, Verna E, and Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation. *Am J Transplant* 2023; 23(6):S864-S865. Full Text

Purpose: Living donor liver transplantation (LDLT) is a viable option to increase access to liver transplantation (LT). However, there are well-documented racial and gender-based inequities in access to deceased donor LT. Very little is empirically known about living liver donor (LLD) characteristics in relation to their recipients. Therefore, we aimed to explore the odds of receiving LDLT across LLD and recipient characteristics. Methods: We explored gender, interactions between LLD-recipient race/ethnicity, and other relevant factors on LDLT utilizing national data from the United Network for Organ Sharing (UNOS) for all adult LLD and their recipients who underwent LDLT from 1/1/2012 through 10/1/2022. Results: 3469 LDLTs occurred (5.46% of all LTs). A majority of LLDs were female (n 1864, 54%), mean 37.16 years of age (SD 10.41), and White race (n 2791, 81%), followed by Hispanic (n 423, 12%), Black (n 116, 3%), Asian (n 85, 2%), and Other (n 47, 1%). LDLT recipients were predominantly male (n 1843, 53%), mean 53.35 years of age (SD 13.22), and White race (n 2787, 80%), followed by Hispanic (n 437, 13%), Black (n 118, 3%), Asian (n 92, 3%), and Other (n 35, 1%). Of note, 42.9% (n 1487) of LLDs were not biologically related to their recipient. As reported in Table 1, men are both less likely to receive or be a LLD than women. Examining the donor by recipient race interactions, LDLT is more likely to occur between LLD and recipients with the same racial/ethnic category than differing race/ethnicity (regardless of comparator). When race/ethnicity is different between LLD-recipient, four significant interactions

occurred indicating that White LLDs are less likely to donate to Black recipients than Hispanic or Others/Unknown and Asian donors are more likely to donate to Others/Unknown than either Hispanic or White recipients. Conclusions: While biological relatives are assumed to be the same race/ethnicity, nearly half of LLDs are not biologically related to their recipient and yet all racial groups were more likely to donate within their own racial category, adjusting for liver disease category and functional status. Also, despite representing the majority of waitlisted and transplanted patients, men were less likely to receive LDLT, but men are also less likely to be a LLD. These results provide a starting point to foster efforts towards diversifying the LLD population. CITATION INFORMATION: Jesse M., Pillai A., Liapakis A., Venkat D., Salgia R., Kumar V., Manivannan A., Lu M., Zhang T., Verna E., Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.Jesse: None. E.Verna: None. N.Parikh: Consultant;; Eisai, Eli Lilly, Research Grant Site Overall Principal Investigator;; Genentech. A.Pillai: n/a. A.Liapakis: None. D.Venkat: n/a. R.Salgia: n/a. V.Kumar: None. A.Manivannan: n/a. M.Lu: n/a. T.Zhang: n/a. [Figure presented]

Cardiology/Cardiovascular Research

Bonnet G, Rommel KP, Falah B, Lansky A, Zhang Y, Schonning M, Redfors B, Burkhoff D, Cohen D, Patel R, **Basir B**, **O'Neill W**, and Granada J. TCT-145 Relationship Between Preprocedural Blood Pressure and Outcomes in Patients Undergoing Impella-Supported High-Risk PCI: Insights From the cVAD PROTECT III Study. *J Am Coll Cardiol* 2023; 82(17):B56-B57. Full Text

Background: Temporary left ventricular assist devices (LVADs) are often used to prevent hypotension during high-risk percutaneous coronary intervention (HRPCI). The impact of preprocedural blood pressure (BP) on outcomes during HRPCI is unknown. Methods: Patients from the cVAD PROTECT III study undergoing Impella-supported HRPCI were divided based on preprocedural BP. Procedural outcomes included hypotensive episodes and in-hospital death. Clinical endpoints were 90-day major adverse cardiovascular and cerebrovascular events (MACCE: all-cause death, myocardial infarction, stroke/transient ischemic attack, and repeated revascularization) and 1 year mortality. Results: Patients (n = 1,159) who underwent Impella-supported HRPCI with baseline BP were evaluated: mean arterial pressure (MAP) >100 mm Hg (n = 242), >90-100 mm Hg (n = 264), >80-90 mm Hg (n = 306), and ≤80 mm Hg (n = 347). Lower preprocedural MAP was associated with baseline anemia, history of heart failure, left main disease, and transfer from another hospital. In-hospital and procedural outcomes did not differ between groups. However, 90-day MACCE rates and 1-year mortality increased with decreasing baseline BP levels (Figure 1). The association between BP category and 1-year mortality remained significant after adjustment (P < 0.001). [Formula presented] Conclusion: In a cohort of protected HRPCI with Impella, procedural hemodynamic stability was high. Although there was no association between baseline BP levels and in-hospital outcomes, lower preprocedural BP was associated with higher rates of 1-year mortality, which was related to differences in baseline clinical characteristics. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Falah B, Redfors B, Zhang Y, Thompson J, Abu-Much A, Bharadwaj A, **Basir B**, Patel R, Batchelor W, and **O'Neill W**. TCT-143 Prognostic Implications of Anemia in Impella-Supported HRPCI: Insights From the cVAD PROTECT III Study. *J Am Coll Cardiol* 2023; 82(17):B55-B56. Full Text

Background: Anemia is prevalent among patients with cardiovascular disease and is associated with adverse outcomes. However, data regarding the impact of anemia in high-risk percutaneous coronary intervention (HRPCI) are limited. Methods: Patients undergoing Impella-supported HRPCI in the prospective multicenter cVAD PROTECT III study were assessed for anemia based on baseline hemoglobin levels according to the World Health Organization criteria. Patients were stratified into one of 3 groups (no anemia, mild anemia, and moderate or severe anemia). Major adverse cardiovascular and cerebrovascular events (MACCE: defined as all-cause death, myocardial infarction, stroke/transient ischemic attack, and repeated revascularization) at 30 and 90 days, and major bleeding events were analyzed based on baseline anemia status. Results: Of 1,072 patients, 62.0% (n = 665) had baseline anemia, with 18.7% (n = 200) having moderate or severe anemia. Anemic patients were older and more likely to have comorbidities. Anemia was associated with higher MACCE rates at 30 days (moderate to

severe: 12.3%; mild: 9.8%; no anemia: 5.4%; P = 0.02) and 90 days (moderate to severe: 18.7%; mild: 14.6%; none: 8.3%; P = 0.004). Major bleeding at 30 days was higher in anemic patients (3.5% vs 1.2%; P = 0.03). [Formula presented] Conclusion: Baseline anemia in Impella-supported HRPCI predicts high risk of MACCE and major bleeding, emphasizing its significance as a prognostic factor. Whether specific management strategies can mitigate anemia-associated MACCE risk after HRPCI should be further studied. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Mutlu D, Kostantinis S, Bagur R, Rempakos A, Simsek B, Karacsonyi J, Allana S, Alexandrou M, Gorgulu S, **Alaswad K**, **Basir B**, Davies R, Krestyaninov O, Khelimskii D, Frizzell J, Love M, Elbarouni B, Patel M, Mahmud E, Jaber W, Rinfret S, Nicholson W, ElGuindy A, Goktekin O, Mastrodemos O, Rangan B, Sandoval Y, Burke MN, Brilakis E, and Ybarra L. TCT-98 Calcium Modification Strategies in Dissection and Re-Entry Versus Wiring Techniques in Chronic Total Occlusion Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2023; 82(17):B38-B39. Full Text

Background: The use of calcium modification strategies in dissection and re-entry compared with wiring techniques in chronic total occlusion (CTO) percutaneous coronary intervention (PCI) has received limited study. Methods: We analyzed the procedural outcomes of 1,241 CTO PCIs that required the use of 1 or more calcium modification strategies at 42 centers from 2012 to 2023. Results: A calcium modification strategy was used as part of a dissection and re-entry strategy in 23% and as part of wiring technique in 77%. The most common calcium modification strategy in the dissection and re-entry group was scoring balloon (29.5%) and rotational atherectomy (29.5%), followed by laser atherectomy (20.7%) and intravascular lithotripsy (IVL) (18.3%). In the wiring group, rotational atherectomy (38.3%) was the most frequently used calcium modification therapy, followed by laser atherectomy (25.8%), IVL (17.8%), and scoring balloon (15.3%). Technical success was overall similar (95.1% vs 96.9%; P = 0.155) in the 2 groups, but was higher when IVL (100.0% vs 96.2%; P = 0.011) or scoring balloon (98.6% vs 94.0%; P = 0.049) was used in wiring cases. The incidence of major adverse cardiovascular events (MACE) was higher in the dissection and re-entry group (5.3% vs 2.4%; P = 0.014), especially among cases where scoring balloon (8.4% vs 2.1%; P = 0.023) or rotational atherectomy (9.5% vs 3.6%; P = 0.019) was used. [Formula presented] Conclusion: The use of calcium modification strategies in dissection and re-entry was associated with similar technical success but higher incidence of MACE and perforation compared with wiring techniques. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research
Shah T, Lemor A, Thompson J, Protty M, Mamas M, Kinnaird T, Bharadwaj A, Truesdell A, Zhang Y, Hussain Y, Falah B, Cohen D, Redfors B, Baron S, Witzke C, Dixon S, Lansky A, **Basir B**, and **O'Neill W**. TCT-219 Performance of Existing Risk Models in Impella-Supported High-Risk Percutaneous Coronary Intervention. *J Am Coll Cardiol* 2023; 82(17):B85. Full Text

Background: High-risk percutaneous coronary intervention (HRPCI) procedures supported by percutaneous left ventricular assist devices are becoming increasingly common. To make the most informed decisions, it is important to be able to accurately assess risk before these interventions. Methods: PROTECT III is a prospective, multicenter, observational study enrolling consecutive patients undergoing Impella-supported HRPCI at 46 U.S. centers. Major adverse cardiac and cerebrovascular events—the composite of death, myocardial infarction, stroke/transient ischemic attack, or repeat revascularization—were adjudicated by an independent clinical events committee. Two existing risk scores were applied for each patient: the National Cardiovascular Data Registry bedside risk score (for in-hospital mortality) and the British Cardiovascular Intervention Society Complex High-Risk Indicated PCI (BCIS-CHIP) risk score (for major adverse cardiac and cerebrovascular events). Results: Performance of the 2 risk scores (observed vs expected event rates by risk decile) are displayed in Figure 1, with both models showing poor calibration. The National Cardiovascular Data Registry risk score had moderate discrimination (c-index 0.71; 95% CI: 0.69-0.73) while the BCIS-CHIP risk score had poor discrimination (c-index 0.61; 95% CI: 0.59-0.64). [Formula presented] Conclusion: Existing risk scores perform relatively poorly in contemporary patients undergoing percutaneous left ventricular assist device–supported HRPCI.

Risk scores designed specifically for this population are needed to support optimal clinical decision-making. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Cardiology/Cardiovascular Research

Wanamaker B, Seth M, Menees D, Frizzell J, Dawson K, **Alaswad K**, Sutter D, Dixon S, **Basir B**, Schreiber T, Gurm H, and Sukul D. TCT-274 Chronic Total Occlusion Specialist Outcomes in Non-CTO Percutaneous Coronary Intervention: Insights From BMC2. *J Am Coll Cardiol* 2023; 82(17):B108. Full Text

Background: Chronic total occlusion (CTO) percutaneous coronary intervention (PCI) carries elevated procedural risk given the technical challenges of such procedures. It is unclear whether CTO PCI experience translates to procedural or outcome differences in non-CTO PCI. Methods: We analyzed non-CTO PCI cases from 48 nonfederal hospitals in Michigan from 4/1/2020 to 12/31/2022 to compare cases performed by operators with and without CTO experience. CTO specialists were defined as those who performed at least 30 CTO cases in the 3 years preceding the analysis. Cases were matched 1:1 without replacement based on a propensity score model including patient demographics and baseline risk factors, lesion location, and markers of increased procedural complexity. Results: Of the 367 operators in the analysis, there were 20 (5.5%) who met the criteria for CTO specialization. These operators performed 4,147 (10.4%) of the 39,963 non-CTO PCIs during the study period. CTO specialists were more likely to treat left main lesions (11.1% vs 4.2%; P < 0.001) and patients with a history of heart failure (46.1% vs 37.1%; P < 0.001). After matching, no statistically or clinically significant baselines differences remained. CTO specialists in the matched cohort were more likely to use intravascular imaging for PCI optimization (39.5% vs 31.4%; P < 0.001) and had lower contrast use. No significant differences were observed in clinical outcomes, including death, acute kidney injury, and major bleeding. [Formula presented] Conclusion: In a real-world PCI registry, CTO specialists were more likely to treat left main lesions and patients with heart failure. After matching, CTO experience was associated with decreased contrast use and increased use of intravascular imaging for PCI optimization in non-CTO cases. CTO experience was not associated with a difference in adverse events or in-hospital outcomes. Categories: CORONARY: Complex and Higher Risk Procedures for Indicated Patients (CHIP)

Center for Health Policy and Health Services Research

Rossom R, Penfold R, Owen-Smith A, Simon G, and **Ahmedani B**. Suicide Deaths Before and During the COVID 19 Pandemic. *Eur Psychiatry* 2023; 66:S88. Full Text

R. Rossom, HealthPartners Institute, Minneapolis, United States

Introduction: With stressors that are often associated with suicide increasing during the coronavirus disease 2019 (COVID-19) pandemic, there has been concern that suicide mortality rates may also be increasing. Our objective was to determine whether suicide mortality rates increased during the COVID-19 pandemic. With stressors that are often associated with suicide increasing during the corona virus disease 2019 (COVID-19) pandemic, there has been concern that suicide mortality rates may alsobe increasing. Objectives: Our objective was to determine whether suicide mortality rates increased during the COVID-19 pandemic. Methods: We conducted an interrupted time-series study using data from January 2019 through December 2020 from 2 large integrated health care systems. The population at risk included all patients or individuals enrolled in a health plan at HealthPartners in Minnesota or Henry Ford Health in Michigan. The primary outcome was change in suicide mortality rates, expressed as annualized crude rates of suicide death per 100,000 people in 10 months following the start of the pandemic in March 2020 compared with the 14 months prior. We conducted an interrupted time-series study using data fromJanuary 2019 through December 2020 from 2 large integrated health care systems. The population at risk included all patients or individuals enrolledin a health plan at HealthPartners in Minnesota or Henry Ford HealthSystem in Michigan. The primary outcome was change in suicide mortality rates, expressed as annualized crude rates of suicide death per 100,000 people in 10 months following the start of the pandemic in March2020 compared with the 14 months prior. Results: There were 6,434,675 people at risk in the sample, with 55% women and a diverse sample across ages, race/ethnicity, and insurance type. From January 2019 through February 2020, there was a slow increase in the suicide mortality rate, with rates then decreasing by 0.45 per 100,000 people per month from March 2020 through December

2020 (SE= 0.19, P=0.03). There were 6,434,675 people at risk in the sample, with 55% women and a diverse sample across ages, race/ethnicity, and insurance type. From January 2019 through February 2020, there was a slow increase in the suicide mortality rate, with rates then decreasing by 0.45 per 100,000 people per month from March 2020 through December 2020 (SE= 0.19, P=0.03). Conclusions: Overall suicide mortality rates did not increase with the pandemic, and in fact slightly declined from March to December 2020. Our findings should be confirmed across other settings and, when available, using final adjudicated state mortality data. Overall suicide mortality rates did not increase with the pandemic, and in fact slightly declined from March to December 2020. Our findings should be confirmed across other settings and, when available, using final adjudicated state mortality data.

Dermatology

Cunningham A, Mueller A, Getzinger J, **Obri M**, **Kerr H**, and **Jafri S**. Dermatologic Manifestations and Outcomes of Patients with Graft vs Host Disease Following Liver Transplant in a Real World Setting. *Am J Transplant* 2023; 23(6):S1180. Full Text

Purpose: The objective is to evaluate cutaneous manifestations and outcomes of patients with Graft Vs Host Disease (GVHD) following liver transplant. Methods: A retrospective review was conducted at an urban academic center to track cutaneous and multi-organ manifestations of GVHD s/p liver transplant. We analyzed the indication for liver transplant, cutaneous symptoms at initial presentation, 6 months, and 1 year, treatments, and survival rates. We compared outcomes in patients with cutaneous GVHD (cGVHD), cutaneous GVHD with additional organ involvement (AOI), and non-cutaneous GVHD. Results: 13 patients were diagnosed with GVHD s/p liver transplant. 30.8% developed cGVHD, 46.2% developed cGVHD with AOI, and 23.1% developed non-cutaneous GVHD. Mean age was 66.1 years. 76.9% were male. Indications for liver transplant were HCV cirrhosis (15.4%), familial amyloidosis (7.7%), NASH cirrhosis (53.8%), and alcoholic cirrhosis (23.1%). 100% of patients were treated with triamcinolone 0.1% and corticosteroids. Following liver transplant, the mean onset of cGVHD was 31.6 days (range 2-64). At initial presentation, 90% of patients had a diffuse, erythematous maculopapular rash on the chest, abdomen, and back. 60% of patients reported pruritus. Regarding multi-organ involvement, 69.2% developed GVHD with AOI. 11.1% of patients developed bilateral non-granulomatous uveitis (mean onset 7 months). 44.4% of patients developed colitis (mean onset 39.7 days). 88.9% of patients developed pancytopenia (mean onset 42.6 days). At both 6 and 12 months, 66.6% of patients had complete resolution of cGVHD. The mean duration until complete cutaneous resolution in patients with cGVHD vs cGVHD with AOI was 7.6 and 1.9 months, respectively. At both 6 and 12 months, 100% of patients had improvement of pruritus and degree of regional spread. A non-pruritic maculopapular rash remained in 33.3% of patients at 1 year. Common complications s/p liver transplant were bacteremia (69.2%), pneumonia (46.2%), UTIs (46.2%). The incidence of bacteremia in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 83.3, and 100%. The incidence of pneumonia in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 50, and 66.7%. The incidence of UTIs in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 66.6, and 33.3%. Regarding survival, 53.8% of our GVHD patients are deceased. The mean survival duration s/p liver transplant was 86.4 days (range 39-167). 41.7% of all patients survived at the 6 months, 1 year, and 3 years. 100% of cGVHD patients survived to 6 months, 1 year, and 3 years. Notably, only 12.5% of cGVHD with AOI patients survived to 6 months, 1 year, and 3 years. Conclusions: The incidence of GVHD s/p liver transplant is approximately 0.5-2%. Based on our results, mortality is significantly increased at 6 months, 1 year, and 3 years in patients with cGVHD with AOI. Early recognition and treatment is crucial for patient prognosis. CITATION INFORMATION: Mueller A., Getzinger J., Obri M., Kerr H., Jafri S. Dermatologic Manifestations and Outcomes of Patients with Graft vs Host Disease Following Liver Transplant in a Real World Setting AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: A.Mueller: None. J.Getzinger: n/a. M.Obri: None. H.Kerr: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Dermatology

Eichenfield LF, Hebert AA, **Gold LS**, Cartwright M, Moro L, Han J, Squittieri N, and Mazzetti A. 42299 Long-term safety and efficacy of 1% clascoterone cream in patients <12 years old with acne vulgaris. *J Am Acad Dermatol* 2023; 89(3):AB190. Full Text

Background: Clascoterone cream 1% is approved for the treatment of acne vulgaris in patients aged 2:12 years based on results in two 12-week, vehicle-controlled, phase 3 studies in patients with moderate-to-severe acne. Long-term safety and efficacy of clascoterone in patients aged 2:12 years from the extension study [1] are presented. Methods: All patients who continued into the open-label, long-term extension study (NCT02682264) applied clascoterone twice daily to the entire face and, if desired, any truncal acne, for up to 9 months. Patients achieving Investigator's Global Assessment score of 0 or 1 (IGA 0/1) could stop treatment and resume if/when acne worsened. Safety was assessed from treatment-emergent adverse events (TEAEs) and local skin reactions (LSRs [telangiectasia, skin atrophy, striae rubrae, erythema, edema, scaling/dryness, stinging/burning, and pruritus]) in all treated patients. Efficacy was assessed from percentage of patients with IGA 0/1 among those who completed the extension study without significant protocol deviations (per-protocol [PP] population). Results: Of 598 patients treated in the extension study, 108 (18.1%) experienced 187 TEAEs, with similar frequency between patients previously treated with vehicle (52/287 [18.1%]) vs clascoterone (56/311 [18.0%]). Frequency of LSRs was low throughout the study. Percentage of PP patients with facial and truncal IGA 0/1 increased over time to 48.9% (156/319) and 52.4% (65/124), respectively, at end of study and was greatest in patients applying clascoterone for 12 months (face, 67/119 [56.3%]). Conclusions: Clascoterone cream 1% maintained a favorable safety and efficacy profile for up to 12 months in patients aged 2:12 years.

Dermatology
Gold LS, Dashputre AA, Kamleh M, Borroto D, Lin T, Harding G, and Joseph G. 40660 Clinically Meaningful Improvement on the Acne Quality of Life Following Treatment with IDP- 126 Gel for Moderate-to-Severe Acne: A Post Hoc Exploratory Pooled Analysis of Phase III Trial Data. *J Am Acad Dermatol* 2023; 89(3):AB26. Full Text

Acne is the most common skin condition affecting up to 25 million Americans annually and has been shown to negatively impact patient's quality of life (QoL).[1] The Acne Quality of Life Questionnaire (Acne-QoL) was included as an exploratory endpoint in two multicenter, randomized, double-blind, vehicle-controlled Phase III studies of patients (≥9 years) with moderate-to-severe acne receiving IDP- 126 Gel or vehicle. A post hoc exploratory analysis was conducted using pooled data (N=309) from both Phase III studies to assess whether changes from baseline to week 12 in Acne-QoL domain scores (self-perception; role-emotional; role-social; acne symptoms) significantly differ between IDP-126 Gel and vehicle and whether these differences were clinically meaningful to patients, based on responder thresholds defined by McLeod et al.[2]. Acne-QoL domain scores significantly (all $p < 0.001$) improved for patients treated with IDP-126 Gel vs. vehicle in all four domains: role-emotional (mean difference: 4.1), self-perception (mean difference: 3.8), acne symptoms (mean difference: 2.6) and role-social (mean difference: 2.0). The proportion of responders was significantly higher (all $p < 0.05$) in the IDP-126 Gel group vs. vehicle for all Acne-QoL domains—self-perception (Odds Ratio [OR]:4.32, 95% Confidence Interval [CI]: 2.16-8.65), acne symptoms (OR:3.90, 95% CI: 2.11-7.23), role-social (OR:3.59, 95% CI: 1.73- 7.47) and role-emotional (OR:2.50, 95% CI: 1.36-4.58). Overall, in this post hoc exploratory analysis of pooled data from two Phase III studies, participants with moderate-to-severe acne reported statistically significant and clinically meaningful improvements in all four Acne-QoL domains after 12 weeks of treatment with IDP-126 Gel.

Dermatology
Passeron T, Dreno B, Puig S, Goh CL, **Lim HW**, Ly F, Kang HY, Morita A, Candiani JO, Schalka S, Wei L, Le Floc'h C, Kerob D, and Krutmann J. Sun exposure and associated risks in 17 countries: UK results. *Br J Dermatol* 2023; 188:iv160. Full Text

T. Passeron, Department of Dermatology, Côte d'Azur University, Nice University Hospital Center, Nice, France

Primary and secondary prevention of skin cancer varies considerably from one country to another. This survey investigates knowledge and behaviours regarding sun exposure in the UK. This UK survey (n=1000) was conducted online from 28 September to 18 October 2021 and was part of a worldwide survey (n=17 001) conducted in 17 countries (five continents). Automated selection from the Ipsos online panel ensured samples of 1000 individuals in each country fit the quotas method based on sex, age,

employment status and country regions. Data covered demographics, phototype, exposure habits and practices, and knowledge and understanding of risks. The population comprised 49% men [mean (SD) age 46.6 (15.7) years]; 61% were of skin phototypes I-II. Seventy-six per cent of Britons stated that a tanned skin looks attractive vs. 72% worldwide. Seventy per cent of Britons indicated that a tan gives a healthy look, a different perception compared with worldwide (64%). Most Britons were aware of sun-related skin health issues, a better awareness compared with worldwide (94% vs. 88%). Sixty-one per cent did know that sun protection is useful when the weather is overcast, a similar knowledge as worldwide (61%). Furthermore, 15% indicated it was safe to expose themselves without protection when already tanned, a better knowledge than worldwide (23%). In terms of photoprotection, 15% said they protected themselves from the sun all year round, a lower score compared with worldwide (23%). In detail, Britons were more likely to put sunscreen on their face (71% vs. 60%), on their hands, neck and ears (64% vs. 52%), and on the arms, legs and chest (69% vs. 55%) compared with the global population. However, Britons were less likely to try to stay in the shade (73% vs. 77% worldwide) or avoid midday sun exposure (53% vs. 66%). Of those who applied sunscreen, 69% applied it only once or twice a day - a slightly better practice compared with the worldwide average (74%). In terms of knowledge, 71% did not understand the difference between ultraviolet (UV)A and UVB vs. 70% worldwide. Although the risks of sun exposure are widely recognized, sun protection practice is inadequate. This survey provides insight into the need for additional photoprotection education in the UK.

Dermatology

Warren RB, Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine A, **Stein Gold L**, Blauvelt A, Simpson EL, Chu CY, Liu ZT, Gontijo Lima R, Pillai S, Gil EG, and Seneschal J. Efficacy and safety of lebrikizumab at 16 weeks: Pooled analyses from ADvocate1 and ADvocate2 phase III trials in patients with moderate-to-severe atopic dermatitis. *Br J Dermatol* 2023; 188:iv54. Full Text

R.B. Warren, Dermatology Centre, Manchester NIHR Biomedical Research Centre, University of Manchester, Manchester, United Kingdom

Lebrikizumab (LEB) is a high-affinity monoclonal antibody targeting interleukin (IL)-13, preventing IL-13 signalling via the IL-4Rα/IL-13Rα1 receptor complex. Here, we report 16-week efficacy and safety outcomes of LEB monotherapy in patients with moderate-to-severe atopic dermatitis from two 52-week, randomized, double-blinded, placebo-controlled phase III trials, ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967). Eligible adults and adolescents (aged 12-17 years, weighing≥40 kg) from ADvocate1 and ADvocate2 were randomized (2 : 1) to subcutaneous LEB 250 mg (500 mg loading dose at baseline and week 2) or placebo every 2 weeks (Q2W). Efficacy analyses included proportions of patients achieving Investigator's Global Assessment (IGA) 0/1 and Eczema Area and Severity Index (EASI)-75 (coprimary endpoints), EASI-90, and pruritus numeric rating scale (NRS) ≥ 4-point improvement from baseline to week 16. This was a pooled analysis of ADvocate1 and ADvocate2, where IGA 0/1 and EASI-75 and EASI-90 were analysed in 564 and 287 patients (LEB 250 mg and placebo), respectively, and pruritus NRS in 516 and 264 patients, respectively. Cochran-Mantel-Haenszel with Markov chain Monte Carlo multiple imputation was performed. Patients treated with LEB 250 mg and placebo for 16 weeks achieved, respectively, IGA 0/1 response rates of 38.1% (n=215) and 11.7% (n=34; P<0.001) EASI-75 responses of 55.4% (n=313) and 17.2% (n=49 P<0.001); EASI-90 responses of 34.5% (n=195) and 9.2% (n=26) (P<0.001); and pruritus NRS≥4-point improvement responses of 42.9% (n=221) and 12.2% (n=32; P<0.001) The percentage of patients reporting one or more treatment emergent adverse event(s) was lower in the LEB group (49.6%) than in the placebo group (59.0%; P=0.009). These data suggest that LEB 250 mg Q2W for 16 weeks is an efficacious and safe treatment option for adult and adolescent patients with moderate-to-severe atopic dermatitis.

Dermatology

Wollenberg A, Warren RB, Silverberg JI, Guttman-Yassky E, Thaçi D, Irvine AD, **Gold LS**, Blauvelt A, Simpson EL, Chu CY, Liu ZT, Lima RG, Pillai S, Gil EG, and Seneschal J. EVOLUTION OF EASI RESPONSE WITH LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS: POOLED RESULTS FROM TWO PHASE 3 TRIALS (ADVOCATE1 AND ADVOCATE2) AT WEEK 16. *Acta Derm Venereol* 2023; 103:53. Full Text

A. Wollenberg, LMU-Department of Dermatology and Allergology, Munich, Germany

Lebrikizumab (LEB) i s a h igh-affinity m onoclonal a ntibody targeting interleukin-13 for the treatment of moderate-to-severe atopic dermatitis (AD). Phase III ADvocate1 (NCT04146363) and ADvocate2 (NCT04178967) trials evaluated the efficacy and safety of LEB monotherapy in moderate-to-severe AD. To evaluate the evolution of Eczema Area and Severity Index (EASI) responses up to week 16 using pooled data from ADvocate1 and ADvocate2. Eligible moderate-to-severe AD patients (adults and adolescents [12-17 years, weighing ≥ 40 kg]) were randomized 2:1 to LEB 250 mg or placebo every 2 weeks for 16 weeks (induction period). EASI percentage improvement categories from baseline to week 16 are: EASI<50, EASI ≥50 to <75, EASI ≥75 to <90 and EASI ≥90. Analyses were performed in the modified Intention- To-Treat population (mITT). Patients who received rescue medication or discontinued treatment due to lack of efficacy were considered as non-responders. Missing data were handled through Markov chain Monte Carlo multiple imputation (MCMC-MI). Over 16 weeks (the induction phase), patients treated with LEB showed a positive EASI response evolution (29.2% EASI<50, 15.3% EASI ≥50 to <75, 20.9% EASI ≥75 to <90 and 34.5% EASI ≥90) compared to those in the PBO arm (67.0% EASI<50, 15.8% EASI ≥50 to <75, 8.0% EASI ≥75 to <90 and 9.2% EASI ≥90). Data from the pooled analysis of two Phase 3 trials showed that 70.7% of patients treated with LEB 250 mg every 2 weeks in monotherapy for the first 16 weeks achieved EASI≥50 and more than one third of patients achieved EASI≥90.

Diagnostic Radiology

Obri MS, **Kamran W**, **Almajed M**, and **Obri M**. Interventional Radiology-Guided Splenic Artery Embolism in Liver Transplant Patients: A 10-Year Experience. *Am J Transplant* 2023; 23(6):S1187. Full Text

Purpose: This study aims to evaluate the efficacy and safety of splenic artery embolism (SAE) for the management of portal hypertension in patients who have had liver transplants Methods: A retrospective analysis was conducted on liver transplant patients who had underwent interventional radiology (IR) guided SAE post-transplant at a single tertiary transplant center from 2012 to 2022. The primary outcome of intervention efficacy was quantified by peak hepatic artery resistive indices and main portal vein velocities. Ultrasound with doppler obtained before and after the intervention were reviewed for these parameters. The average changes were calculated at a 95% confidence interval. Adverse events were also recorded at the time of the procedure and within one year of the procedure. Secondary outcomes that were measured included platelet count before and 1 month after procedure, spleen size, and need for subsequent splenectomy. Results: All 28 of the patients were white and 18 were males. The mean age of patient was 52.5 years (21-71 years) and time after transplant was 149.5 Days (2-1588 days). 96.4% of SAE were technically successful (n=27). 21 patients had main portal vein (MPV) velocities available and 24 had peak hepatic artery resistive indices (RI) available. In these patients, hepatic artery RI decreased by an average of 0.063 (95% CI 0.014-0.112) after SAE. MPV velocity decreased by an average of 47.2 cm/s (95% CI 27.3-67.1) after SAE. Absolute platelet count increased by an average of 60.0 K/uL (95% CI 36.7-83.3) with a 115.6% increase (95% CI 64.9- 166.3). 10.4% of patients (n=3) developed a procedure-related complication, all of which were femoral access site aneurysms. 0% of patients (n=0) patients suffered from bleeding, infections, or abscesses after the procedure. 10.7% of patients (n=3) required splenectomy after SAE. 1 splenectomy was due to technical failure and 2 were due to refractory symptoms. The change in spleen size was available in 26 patients and the average decrease is size was 1.07 cm (0.78-1.36) or 7% (5-9%) at a 95% confidence interval. Conclusions: IR-guided splenic artery embolism in liver transplant patients is a safe and effective procedure that carries an acceptable complication risk. Patients saw an improvement in both the hepatic artery resistive indices and main portal vein velocity post-embolization. CITATION INFORMATION: Obri M., Kamran W., Almajed M., Obri M. Interventional Radiology-Guided Splenic Artery Embolism in Liver Transplant Patients: A 10-Year Experience AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.S.Obri: None. W.Kamran: n/a. M.Almajed: n/a. M.Obri: n/a.

Emergency Medicine

Gunaga S, **Al-Hage A**, **Buchheister A**, **Welchans M**, **Awada M**, **Smiles B**, **Savage A**, **Latack K**, **Schultz L**, and **Miller J**. 365 Trends in Hospice and Palliative Medicine Consults Initiated in the Emergency Department: A Seven-Year Utilization Analysis. *Ann Emerg Med* 2023; 82(4):S161-S162. Full Text

Objectives: Emergency departments (EDs) play a central role in end-of-life care, yet early integration of high-quality palliative care and hospice services is often under-utilized. Studies have shown that early access to these services improves patient outcomes, goal-concordant care and reduces health care costs. Translation of this evidence into clinical practice remains inconsistent, and the extent to which these services are utilized remains unclear. This retrospective cross-sectional cohort study aimed to describe the clinical prevalence and trends of ED ordered hospice and palliative medicine consults over a seven-year period in a large metropolitan health system. Methods: We conducted a retrospective cohort study of electronic health records (EHR) from five EDs within a large, integrated urban and suburban health system. The study period spanned from January 1st, 2016, to December 31st, 2022, and included data from all ED visits by patients > 18 years old who had a hospice and/or palliative medicine consult ordered in the ED. A variety of patient specific demographic, clinical, and outcome variables were collected. The yearly number of hospice and palliative medicine consults ordered in each ED were also obtained and compared by year and by site. Across years, we compared incident rates of hospice and palliative consults per 1,000 ED patients who were over 50 years old, had an ESI ≤ 3, and were admitted. Data analysis included descriptive statistics, chi-square testing, and regression analysis to examine trends over time. Results: A total of 6,097 hospice and palliative medicine consults were ordered in the ED for 5,687 ED encounters, and 5,345 unique patients meeting the inclusion criteria. The mean age of participants was 77.9 years ±13.7, with 57.2% being female and 74.7% identifying as White. Of the total cohort, 90.6% (5,152) were admitted to the hospital, 7.2% (410) were discharged home, 2.0% (112) died in the ED, and 55.2% (2,843) died during their hospital stay. Hospice and palliative medicine consults initiated in the ED showed a significant annual increase from 324 in 2016 to 1,328 in 2022, representing a 410% overall increase ($p < 0.001$). This seven-year trend is detailed in Figure 1. ED-ordered hospice consults outnumbered palliative consults 1.68 to 1 in 2016; however, in 2022 that ratio flipped to where ED palliative consults were 1.66 times more common. After the onset of the COVID-19 pandemic, there was a significant 188% increase in daily ED hospice and palliative consults when compared to pre-pandemic levels ($p < 0.001$). The calculated prevalence of hospice and palliative medicine consults in the ED for patients who were over 50 years old, had an ESI ≤ 3, and were admitted was 5.9 consults for every 1,000 visits (0.59%) in 2016. This prevalence significantly increased to 19.7 consults (1.97%) for every 1,000 visits in 2022 ($p < 0.001$). Conclusions: This study reveals an increasing trend of ED initiated hospice and palliative consults in our health system. Though promising, this effort likely only touches the surface of the unmet palliative needs of our ED patients and families. Further research is required to examine if these trends are observed across other healthcare facilities nationwide and to identify potential obstacles to implementation. [Formula presented] No, authors do not have interests to disclose

Endocrinology and Metabolism

Alfares K, **Han HJ**, and **Athimulam S**. Neurosarcoidosis Induced Panhypopituitarism. *J Endocr Soc* 2023; 7:A677-A678. Full Text

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Introduction: We hereby present a rare case of neurosarcoidosis causing panhypopituitarism. According to Martin-Grace et al who conducted a literature search for the timeframe of 2002 to 2014, there were only 8 cases of neurosarcoidosis associated pan hypopituitarism. Case Report: A 35-year-old male with a known diagnosis of sarcoidosis on skin biopsies presented to the hospital for altered mental status, hypernatremia, hypotension and hypothermia. He reported symptoms of polyuria and polydipsia for several weeks prior to admission. MRI of the brain revealed a 3cm mass in the suprasellar region involving the hypothalamus and bilateral optic tracts with mass effect on the anterior third ventricle. No discrete pituitary or stalk lesion was identified. A ventriculostomy tube was placed for developing hydrocephalus. Biopsy of the suprasellar mass revealed non-caseating granuloma, confirming neurosarcoidosis. Laboratory work up revealed elevated serum sodium at 167 mmol/L, high serum osmolality at 381 mOsm/kg and low urine osmolality at 381 mOsm/kg, consistent with diabetes insipidus. Anterior pituitary hormone profile work up revealed low 8am serum cortisol (1.9 mcg/ dL) and inappropriately normal ACTH (34 pg/ml), low serum free testosterone (<2.5 ng/dL) and low Luteinizing hormone (0.7 mIU/ml) and low follicular stimulating hormone (< 2.6 mIU/ml), low free T4 at 0.4 ng/dL and inappropriately normal TSH at 2.77 uIU/mL. Serum prolactin was mildly elevated at 86.8ng/mL.

Angiotensin converting enzyme level was within normal range at 33 U/L. A diagnosis of panhypopituitarism was made. Treatment was initiated with high dose IV corticosteroids for management of secondary adrenal insufficiency and neurosarcoidosis. He was also started on IV desmopressin and IV levothyroxine for management of his panhypopituitarism. He was transitioned to oral therapy on discharge. Discussion: Panhypopituitarism secondary to neurosarcoidosis is a rare presentation. Panhypopituitarism from sarcoidosis can occur due to infiltration of the pituitary gland or infiltration of the hypothalamus affecting the hypothalamicpituitary axis. Sarcoidosis should be considered a differential when evaluating patients with symptoms consistent with panhypopituitarism. Prompt diagnosis and initiation of corticosteroids and deficient hormones can be lifesaving.

Endocrinology and Metabolism

Bhadada S, Chakraborty AM, Kumari P, Pal R, Sood A, Dahiya D, and **Rao SD**. Comparison Between Sporadic Primary Hyperparathyroidism And Multiple Endocrine Neoplasia Type 1 (MEN1)-Associated Primary Hyperparathyroidism: A Retrospective Analysis Of The Indian PHPT Registry. *J Endocr Soc* 2023; 7:A258-A259. Full Text

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Introduction: Multiple endocrine neoplasia type 1 (MEN1)-associated tumours are located in parathyroid, pituitary and pancreatoduodenal locations. Though heterogenous, the most consistent presentation of MEN1 is primary hyperparathyroidism (PHPT) seen in almost 100% of cases. Comparisons between sporadic and MEN1 PHPT patients are sparse in the literature. Objective: To retrospectively compare the demography, clinical manifestations, management, and outcome of sporadic PHPT and MEN1-associated PHPT patients. Design and setting: A registry-based (www.indianphptregistry.com) retrospective cohort study from a tertiary care hospital in North India. Methods and patients: The medical records and clinical data of sporadic PHPT patients and MEN1-associated PHPT patients registered in the Indian PHPT registry were analysed. Result: A total of 616 PHPT patients have been registered in the electronic registry, 72 of whom (11.68%) were MEN1-associated PHPT. The mean age of sporadic PHPT patients was 43.4 ± 14.3, whereas MEN1-associated PHPT was 35.8 ± 13.5 years ($p<0.05$). Among MEN1-associated PHPT cases, 66 (90%) were index cases at the time of presentation, and the rest were detected on family screening. For both sporadic PHPT and MEN1-associated PHPT, the most common presenting symptom was bone pain, followed by renal stone disease. Sporadic PHPT and MEN1 PHPT both had comparable mean calcium (11.9 ± 1.5 vs 11.9 ± 1.6 mg/dl), mean phosphate (2.7 ± 1 vs 2.58 ± 0.7 mg/dl), median PTH (314; IQR 161-984 pg/ml vs 292; IQR 180-818 pg/ml) level at presentation. Median 25-hydroxyvitamin D level was 19.3; IQR 10.4-30.4 ng/dl, and 15; IQR 8.1-25.1 ng/dl ($p<0.05$) for sporadic PHPT and MEN1-associated PHPT respectively. Multiglandular disease was common in MEN1-associated PHPT (40.2%) compared to sporadic cases (3%). Median tumour weight was higher in sporadic cases (2.5; IQR 0.8-7.3 gm) compared to MEN1 cases (1.9; IQR 1.08-4.05 gm). Ultrasound neck and Sesta-MIBI concordance rate among sporadic cases was 57%, whereas MEN1 cases were 70.8%. Median post-surgery decline in PTH and calcium was more in the case of sporadic PHPT in comparison to MEN1-associated PHPT 84.81% vs 46.7% and 23.4% vs 16.59 % respectively ($p<0.05$). Discussion: MEN1-associated PHPT patients presented at an earlier age than sporadic cases. There was no statistical difference in PTH, calcium or phosphate levels between the two cohorts, but 25-hydroxyvitamin D levels were lower in MEN1-associated PHPT. Localisation was better in the case of the MEN-1 cohort as per as the Sesta-MIBI and USG concordance was concerned. Postoperative fall of PTH and calcium was more in sporadic cases than in MEN1 cases.

Endocrinology and Metabolism

Bhan A, **Simon R**, **Jacobsen G**, **Yaseen A**, **Navaratnarajah P**, **Sweidan A**, and **Rao SD**. Clinical Relevance Of 24-hour Urine Calcium Measurement In Patients With Primary Hyperparathyroidism (PHPT). *J Endocr Soc* 2023; 7:A246-A247. Full Text

A. Bhan, Henry Ford Hospital, Bloomfield Hills, MI, United States

Introduction: PHPT is the third most common endocrine disease and the most common cause of hypercalcemia in outpatient setting, presents with mild to moderate hypercalcemia with unsuppressed or

elevated serum PTH levels, and most patients are asymptomatic. A 24-hour urine Ca measurement to exclude both hypo-and hypercalciuria is used to recommend parathyroidectomy. The purpose of our study is to evaluate the clinical relevance of urine Ca measurement in evaluating patients with PHPT. Methods: A retrospective electronic medical record review was performed on all adult patients with PHPT in whom a 24-hour urine Ca was measured between 2015-2019. Patients with secondary HPT, those without a 24-hour urine Ca measurement, and patients with serum Cr >1.5 mg/dl were excluded. Results: 393 patients met inclusion criteria for subsequent analyses. For the entire cohort, mean serum Ca was 10.9 ± 0.6 mg/dl, Cr 0.9 ± 0.2 mg/dl and PTH 111± 65 pg/ml with no significant difference between groups by gender, race, or stone history. Mean urine Ca for the entire cohort was 254 ± 170 mg/day. 46% and 35% had urine Ca >250 or >300 mg/d respectively. Multiple linear regression results indicated that higher serum Ca ($p=0.004$), lower serum Cr ($p<0.001$), white race ($p<0.001$), and higher urine sodium ($p<0.001$) were all significantly predictive of higher UCa. However, the mean urine Ca did not differ between patients with and without nephrolithiasis (276 ± 182 Vs. 280 ± 247 mg/d; $p=0.174$). Discussion: The most recent guidelines for the management of asymptomatic PHPT recommend measurement of 24-hour urine Ca in all PHPT patients. However, the validity, sensitivity and specificity of such an approach has never been formally evaluated, considering wide variability of urine Ca excretion in the population and lack of difference in urine Ca between patients with and without nephrolithiasis. Previous guidelines discussed this issue and determined that measurement of a 24-hour urine collection is cumbersome and adds very little to patient management. Our study questions the clinical relevance of re-including 24-hour urine Ca in the latest guidelines. Conclusions: Our study suggests that measurement of 24-hour urine Ca in the routine evaluation of patients with PHPT is unhelpful.

Endocrinology and Metabolism

Faber A, **Lam H**, and **Simon R**. Metastatic Insulinoma Diagnosed Postpartum. *J Endocr Soc* 2023; 7:A1165-A1166. Full Text

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Introduction: Insulinomas are rare neuroendocrine tumors derived from the beta cells of the pancreas. These tumors generally occur at a rate of four cases per million per year, and they are seen across all demographics. Affected patients present with symptoms of hypoglycemia, including confusion, diaphoresis, and palpitations. Insulinomas occur as single or multiple tumors, and can be benign or malignant. Insulinomas with metastases are defined as malignant. The primary treatment is surgical resection. However, in the case of metastatic insulinomas prognosis can be quite poor with limited treatment options. Case Presentation: A 24-year-old female employed as a nurse with otherwise negative medical history originally presented around 3 months postpartum with epigastric pain which was attributed to gas. Symptoms progressed to include lightheadedness, palpitations, and sweating. She checked her blood glucose during these events and noted it to be consistently in the 30s-40s. She would treat these episodes with food and had short-term improvement in symptoms. She presented to an outside hospital where imaging revealed: hepatomegaly with innumerable hypodense liver lesions, hypo-enhancing pancreatic head lesion, sclerotic focus in T4 vertebral body, as well as multiple enlarged upper abdominal lymph nodes including peripancreatic, porta hepatis, and gastrohepatic. Liver biopsy revealed well-differentiated neuroendocrine tumor, WHO grade 3 likely from a pancreatic primary and chemotherapy was initiated with carboplatin and paclitaxel with some response. However, hypoglycemia became refractory to management with 5% dextrose drip, so she was transferred to our facility for escalation of care. TPN was initiated and dextrose drip was escalated eventually to 40% dextrose. She was also given octreotide, hydrocortisone, and eventually diazoxide. Given degree of tumor burden as well as abdominal ascites and clinical condition, surgery was deemed high risk and not recommended. Tumor board meeting was held and her chemotherapy regimen was changed to Carboplatin/Etoposide/Atezolizumab. She subsequently underwent hepatic artery embolization twice with improvement of hypoglycemia. Despite decreasing dextrose drip requirements by over 50%, patient was unable to be liberated from dextrose infusion and had multiple discussions about management options and prognosis. The patient eventually elected to go home with home hospice. Discussion: Insulinoma diagnosed in pregnancy or shortly after pregnancy is extremely rare. There are only three case reports of malignant insulinoma diagnosed in or after pregnancy. Given the degree of extensive metastases at time of presentation, we expect our patient's insulinoma was present prior to delivery. Hypoglycemia may have

only manifested in the postpartum period when there was decreased levels of placenta-derived counterregulatory hormones.

Endocrinology and Metabolism
Faber A, and **Levy S**. Hyperosmolar Hyperglycemic State Presenting As Seizures. *J Endocr Soc* 2023; 7:A497. Full Text

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Introduction: Hyperosmolar hyperglycemic state (HHS), also known as hyperosmotic hyperglycemic nonketotic state (HHNK), is one of the most severe complications of diabetes mellitus. HHS is a medical emergency defined by high serum osmolality and hyperglycemia as well as the absence of ketoacidosis in most cases. Wepresent an unusual case of a young man presenting with seizures who on further investigation was found to have HHS. Case Description: A 44-year-old man presented to the hospital for a possible seizure at home. His medical history is significant for EBV+ B-cell lymphoma receiving chemotherapy, HIV on HAART therapy, and prior history of cryptococcus meningitis in 2019. He did not have history of seizures or diabetes mellitus. He reported that five days prior to admission, he began experiencing polydipsia and polyuria, which later progressed to lethargy. The day of admission his mother found him on the floor with generalized body shaking with significant shaking of the right arm, urinary incontinence, and blood in his mouth from tongue biting. He was taken to the hospital due to concern for seizure. Workup revealed elevated blood glucose of 972 and elevated serum osmolality of 322. He did not present with overwhelming ketosis; his beta-hydroxybutyrate was 0.57, he did not have an anion gap, and ketones were not present in his urine. His A1c was elevated at 9.9%. The differential diagnosis for this patient's seizure included chemotherapy side effect, intracranial pathology, infectious etiology in the setting of known HIV, or HHS. Hematology evaluated the chemotherapy regimen and stated it was not likely the cause of his seizures. Neurology assessed the patient with a CT head, MRI brain, EEG, and lumbar puncture, all of which were negative. The CSF from the lumbar puncture underwent intensive testing, which was negative for HSV, VDRL, CMV, EBV, VZV, Lyme disease, and JC virus. Neurology initially started the patient on anti-seizure medication, however later stated his seizure was likely provoked from hyperglycemia and discontinued the medication. Infectious workup included chest X-ray, blood cultures, and urinalysis, all of which were negative. Endocrinology was consulted and recommended initiating basal and bolus insulin as well as testing for GAD antibodies. Unfortunately, the patient left the hospital against medical advice and GAD antibody testing was not completed. Discussion: The most common symptoms of HSS include hyperglycemia, polyuria, and polydipsia. Though neurological symptoms can occur, they are not common. The neurologic symptoms are typically not seen until the serum osmolality reaches 320 - 330 mOs/kg, and this patient's serum osmolality was elevated at 322 mOs/kg. Though seizure is not well understood in hyperglycemia, treatment for HHS-induced seizures focuses on aggressive management of the underlying hyperglycemic state.

Endocrinology and Metabolism
Han HJ, **Lam H**, **Rao SD**, and **Athimulam S**. Prevalence of Vertebral Fractures In Patients With Adrenal Adenomas. *J Endocr Soc* 2023; 7:A96. Full Text

H.J. Han, Henry Ford Health, Clinton Township, MI, United States

Background: Approximately 5% of adults undergoing cross-sectional imaging are reported to have an adrenal adenoma. Although most adenomas are considered non-functioning (NFAT), up to 48% can present with mild autonomous cortisol secretion (MACS). Published studies have reported an increased prevalence of vertebral fractures (VFx) in MACS. However, findings are limited by sample size, selection bias and lack of diversity in patient population. Objective: To determine the prevalence of vertebral fractures and associated risk factors in patients with adrenal adenomas Design: Retrospective cross-sectional study of patients with adrenal adenomas over a 10-year period (Jan 2012 - Dec 2021). Setting: Academic primary and tertiary care setting Main outcomes measured: 1) MACS was diagnosed based on cortisol level ≥ 1.8cmg/dL after overnight 1mg dexamethasone suppression testing (DST) and NFAT if cortisol < 1.8mcg/dL. Patients who did not undergo 1mg DST were categorized as unknown cortisol status (UCS).2) Bone mineral density (BMD), T- and Zscores of the lumbar spine (LS). 3)Vertebral

morphometry, as assessed by Genant scale, to identify asymptomatic vertebral fractures. Results: Preliminary results included 198 patients with adrenal adenomas [(135 women (67%) with a median age of 67y, 106 Black (54%), 83 White (42%) and 9 other races (4%)]. 74 patients (37%) were diagnosed with NFAT, 42 (21%) with MACS, and 82 (41%) with UCS. Prevalence of vertebral fractures by vertebral morphometry assessment was 6%. (n=12, 5 Black, 7 White). In those with VFx (8 UCS, 2 MACS, 2 NFAT), Black patients had lower BMD (Mean BMD ± SD in Black vs Caucasians: 0.85 ± 018 vs 1.02 ± 0.24 g/cm2, p=0.26). Overall, there was no significant difference in mean LS BMD ± SD (0.97 ± 0.23 vs 1.03 ± 0.20 g/cm2, p=0.41) and mean T-score LS ± SD (-1.11 ± 2.28 vs -0.60 ± 1.71, p=0.49), in patients with and without vertebral fractures, respectively. Conclusions: Patients with adrenal adenoma are at risk of vertebral fractures despite normal or osteopenic BMD. Black patients with adrenal adenomas and vertebral fractures have lower BMD compared to White patients. 41% (n=82, 61% AA, 30% Caucasians, 2% Other) of patients were classified as unknown cortisol status indicating further need to educate health care professionals on evaluation of adrenal adenomas to improve health care outcomes and disparities in management.

Endocrinology and Metabolism
Kumari P, Arya AK, Dahiya D, Sachdeva N, Kaur J, Saikia UN, Bhadada S, and **Rao SD**. EZH2 Upregulation And Lysine 27 Trimethylation at Histone 3 Is Associated With Severe Sporadic Primary Hyperparathyroidism. *J Endocr Soc* 2023; 7:A257-A258. Full Text

P. Kumari, Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Introduction: The enhancer of zeste homolog 2 (EZH2) is a histone methyltransferase that regulates gene activity through histone modifications of lysine (K) at H3 histone and has a crucial role in tumor development. However, the level of methylation at H3 histone and its association with EZH2 expression in sporadic primary hyperparathyroidism (PHPT) are not known. This study was designed to investigate how global levels of histone methylation were associated with altered expression of EZH2 in promoting parathyroid tumorigenesis. Methodology: A total of 30 parathyroid tumors (15 non-severe, 15 severe, and 5 normal parathyroid tissues) were collected during 2020-2021. The global histone methylation of major methylation sites at lysine (K) K4, K9, K27, K36, and K79 was evaluated from blood and tissue samples using a calorimetric ELISA (H3 global modification kit, Epegentek, USA). Gene and protein expression of EZH2 were performed by quantitative realtime PCR and immunohistochemistry respectively. Histone methylation and expression data were correlated with indices of disease severity. Results: We found that the global levels of H3K27me1 and me3 were significantly upregulated, whereas, H3K4me3 and H3K36me2 were significantly downregulated in tumors from patients with severe PHPT compared to tumors from non-severe PHPT and controls. Moreover, H3K27me3 showed the highest upregulation (8-fold) in severe PHPT. Additionally, EZH2 gene expression was significantly upregulated in severe PHPT [Mean ± S.E; (9.1 ± 1.6 vs. 1.2 ± 0.3, p = 0.005), but not in non-severe (4.2 ± 2.7 vs. 1.2 ± 0.3, p = 0.4) PHPT, compared to normal parathyroid tissues. Furthermore, the protein expression was also consistent with the gene expression, with 86% (n= 13/15) nuclear positivity for EZH2 in tumors from severe PHPT and 40% (6 of 15) in tumors from non-severe PHPT compared to normal parathyroid tissue (negative staining). Correlation analysis revealed that EZH2 gene expression is positively related with S.Ca (r = 0.44, p = 0.003), PTH (r = 0.59, p = 0.000), tumor weight (r = 0.455, p = 0.002), EZH2 protein expression (r = 0.7, p = 0.000), and Ki67 proliferative marker (r = 0.66, p = 0.002). Conclusions: Increased global trimethylation of K27 at histone 3 (H3K27me3) was associated with increased EZH2 expression in sporadic PHPT and was predictive of a more severe clinical phenotype. Sources of research support: (ICMR), New Delhi Extramural Research Grant 2020.

Endocrinology and Metabolism
Lam H, **Han HJ**, and **Athimulam S**. Cardiometabolic Risk and Outcomes In Patient With Adrenal Adenomas. *J Endocr Soc* 2023; 7:A97. Full Text

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Background: Approximately 5% of adults undergoing cross-sectional imaging are reported to have an adrenal adenoma. Although most adenomas are considered non-functioning (NFAT), up to 48% can present with mild autonomous cortisol secretion (MACS). Published studies have reported an increased prevalence of cardiometabolic risk factors, cardiac and cerebrovascular events in MACS patients. Objective: To determine the prevalence of cardiometabolic disease and outcomes in a population-based cohort of patients with adrenal adenomas. Design: Retrospective cross-sectional study of patients with adrenal adenomas over a 10-year period (Jan 2012 - Dec 2021). Setting: Academic primary and tertiary care setting. Main outcomes measured: Prevalence of cardiometabolic disease, cardiovascular events requiring procedure (percutaneous coronary intervention, PCI or coronary artery bypass graft, CABG) and cerebrovascular events. MACS was diagnosed based on cortisol level ≥ 1.8cmg/dL after overnight 1mg dexamethasone suppression testing (DST) and NFAT if cortisol < 1.8mcg/dL. Patients who did not undergo 1mg DST were categorized as unknown cortisol status (UCS). Results: Preliminary results include 198 patients with adrenal adenomas [(135 women (67%) with a median age of 67y, 106 Black (54%), 83 White (42%) and 9 other races (4%)]. 74 (37%) were diagnosed with NFAT, 42 (21%) with MACS, and 82 (41%) with UCS. Hypertension (n=163,83%; MACS vs NFAT vs UCS: 23% vs 34% vs 43%) is the most prevalent cardiometabolic risk factor, followed by hyperlipidemia (n=146, 75%; MACS vs NFAT vs UCS: 21% vs 38% vs 41%), prediabetes (n=94, 50%; MACS vs NFAT vs UCS: 18% vs 43% vs 39%) and type 2 diabetes mellitus (n=82,43%; MACS vs NFAT vs UCS: 22% vs 35% vs 43%), respectively. 14% of patients with adrenal adenomas underwent procedures (PCI or CABG) for cardiovascular events (MACS vs NFAT vs UCS: 33% vs 26% vs 41%) and 11% were diagnosed with cerebrovascular events (MACS vs NFAT vs UCS: 29% vs 19% vs 52%). Conclusions: Patients with adrenal adenomas and mild autonomous cortisol secretion (MACS) are at increased risk of cardiovascular events requiring intervention and cerebrovascular events, compared to nonfunctioning adrenal tumors. 41% (n=82, 61% Blacks, 30% White, 2% Others) of patient population was classified as unknown cortisol status indicating further need to educate health care professionals on evaluation of adrenal adenomas to improve health care outcomes and disparities in management.

Endocrinology and Metabolism

Yaseen A, and **Lam H**. Hypoglycemia After Bariatric Surgery Caused By Insulinoma. *J Endocr Soc* 2023; 7:A546-A547. Full Text

A. Yaseen, Henry Ford Health System, Detroit, MI, United States

Introduction: Post bariatric surgery hypoglycemia occurs at least 6 to 12 months after bariatric surgery, presents as postprandial neuroglycopenia with documented blood glucose <54 mg/dl occurring 1 to 3 hours after meals, resolving with carbohydrate intake, and normal fasting glucose. Fasting hypoglycemia or hypoglycemia>4 hours after caloric intake is not typical of post-bariatric hypoglycemia and should raise concern for other etiologies, specifically insulinoma. Clinical Case: A 62 year old female who had Roux-en-Y gastric bypass (RYGB) surgery 18 years ago presented with confusion and a blood glucose level of 35 mg/dl.She had been having episodic hypoglycemia fasting and nonfasting for 4 years prior to presentation. Initial workup revealed serum insulin 10 uIU/ml, C-peptide 2.3 ng/ml, and serum glucose of 19 mg/dl. A dextrose 20% in water intravenous infusion was started in addition to octreotide injections, acarbose, and diazoxide. Prednisone was added later and acarbose discontinued. Magnetic resonance imaging of the abdomen and magnetic resonance cholangiopancreatography showed a 1.8 x 1.3 cm enhancing lesion within the pancreatic tail. Selective arteriography and intra-arterial calcium stimulation with hepatic venous sampling revealed significant elevation of insulin after calcium gluconate injection into the accessory pancreatic tail artery arising from the superior mesenteric artery which supplies the hypervascular pancreatic tail mass. Patient had an exploratory laparotomy and splenic preserving distal pancreatectomy. Surgical pathology revealed a 2.1 cm grade 1, well-differentiated neuroendocrine tumor that was limited to the pancreas. Hypoglycemia resolved after surgery and she was discharged on glargine insulin and metformin. 1 month after surgery, C-peptide was 0.3 ng/ml, serum glucose was 101 mg/dl and HbA1c was 6.5%. Discussion and Conclusion: The incidence of hypoglycemia after RYGB is uncertain but has been reported to be 0.1 to 0.4% of cases. Only 9 cases of insulinoma in patients with a history of gastric surgery have been reported, 7 of 9 (78%) being female with an average age of 56 years old. Symptoms included fasting and postprandial hypoglycemia occurring 6 months to 20 years after bariatric surgery. CT, MRI, and endoscopic ultrasound have been found to have excellent sensitivity for

preoperative localization of insulinoma. Selective arteriography and intra-arterial calcium stimulation with hepatic venous sampling is recommended when non-invasive imaging modalities fail to localize the tumor. Surgical resection remains the mainstay for cure. Dietary modification and pharmacological therapy with diazoxide or somatostatin analogues are used in poor surgical candidates. Insulinoma after RYGB is rare, but needs to be considered in patients with hypoglycemia occurring in the fasting state, as this is atypical for post-bariatric hypoglycemia.

Family Medicine

Schon S, Jiang C, Ferrell EL, **Valbuena F**, Neff L, Carnethon M, and Marsh EE. Obesity And Adiposity Are Associated With Decreased Anti-Mullerian Hormone (AMH) Levels In A Reproductive Aged Latina/LatinX Population. *J Endocr Soc* 2023; 7:A864. Full Text

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Objective: Research suggests that obesity has an adverse effect on ovarian reserve, as assessed by AMH. Prior studies have explored this association predominantly in non-Hispanic Caucasian and African American cohorts. In addition, few studies have utilized metrics beyond BMI to characterize adiposity. The objective of this study was to examine the association of obesity/adiposity with AMH in a Latina/LatinX population using multiple measures of obesity/adiposity. Materials & Methods: This cross-sectional study utilized data from the Environment, Leiomyomas, Latinas, and Adiposity Study (ELLAS). ELLAS is a prospective longitudinal cohort study following Latina/LatinX females for 5 years. ELLAS used community based participatory research principles for engagement. Participants were between the ages of 21-50 at time of enrollment. Data from the first study visit were utilized for analysis. Assessment included anthropometrics, measurement of body composition using bioelectrical impedance analysis (BIA) (Tanita MC-280U) and serum AMH (pico-AMH assay, Ansh Labs). The association between BMI on AMH was assessed as a continuous and categorical outcome. Adiposity based on body fat %, and visceral adiposity index (VAI) was studied in relation to AMH using linear regression models. Statistical associations were determined using Chi-square, Wilcoxon rank-sum and linear or logistic regression as appropriate. Results: 621 women completed the first study visit and had BMI and AMH data available. BIA data was available on 591 participants. The mean age of participants was 37.5 ± 7.0 years. The mean BMI was 30.1 ± 6.8 kg/m2 with 261 (42%) of participants classified as having obesity by BMI (≥30 kg/m2). 214 women (34.5%) reported irregular menses and 89 reported currently taking hormonal contraception (HC) (14.3%). BMI was negatively associated with AMH (β=-0.055 p=0.014), however, this association was no longer significant after adjusting for age. Similarly, body fat % and VAI were also negatively associated with AMH (β=-0.058 p= 0.013, and β=-0.256 p<0.001), however this association was attenuated after adjusting for age. When the analysis was restricted to women not taking HC and with regular menses (n=290), higher BMI remained negatively associated with AMH after adjusting for age (β=-0.04, p=0.003). Similarly, higher body fat % and VAI were also negatively associated with AMH after adjusting for age (β=-0.04, p=0.005, and β=-0.090 p=0.009). Highest lifetime BMI was also associated with AMH after adjusting for age (β=-0.03, p=0.03). Conclusions: Among a cohort of Latina/LatinX females with normal menses, obesity and adiposity as assessed by BMI, body fat % and visceral adiposity index were negatively associated with AMH. This suggests that excess adiposity may compromise ovarian reserve and demonstrates the importance of assessing baseline gynecologic characteristics.

Gastroenterology

Abu Jawdeh BG, **Sreedhar S**, **Lu M**, **Moonka D**, and **Jafri S**. The Efficacy of Everolimus in Liver Transplant Patients. *Am J Transplant* 2023; 23(6):S855. Full Text

Purpose: The objective of our study is to illuminate the long term impact of everolimus on renal function in liver transplant patients in a real world setting. Methods: We completed a single institution, retrospective chart review of patients who had a liver transplant from 2013-2020. 774 patients were included and everolimus status was noted. Everolimus use was classified as: “never used”, “ongoing use”, and “short-term use”. Additionally, glomerular filtration rates (GFR) and creatinine values were noted for 2 months, 1 year, and 3 years post-transplant. Patient outcomes including survival were evaluated. A logistic regression was performed for discrete time to event (death) model with varying covariates (GFR <60 and

everolimus status). We also calculated means, hazard ratios (HR), and odds ratios (OR) for comparisons. Results: Of 774 patients, 496 were never on everolimus, 162 were briefly on the medication, and 116 were actively taking it. 277 patients were female. The average time patients were on the medication was 3.32 months with a standard deviation (SD) of 0.40, ranging from 0-69.08 months. Race was categorized into African American (85 patients), White (570 patients), Asian (13 patients), and other (106 patients). The average age was 55.51 years for patients who were never on everolimus, 58.99 years for short-term use, and 57.66 years for ongoing everolimus use. The use of everolimus had a marginal effect on GFR <60 (P=0.07). The status of ongoing use was trending towards renal protection against a GFR <60 when compared with never on everolimus (HR=0.372, 95%CI=0.139- 0.999, P=0.08). Everolimus status had no impact on survival. One year survival for the ongoing treatment group compared to the never on group was not significantly different (HR=1.951, 95%CI=1.103-3.452, P=0.06). The three-year hazard ratio was 1.474 (95%CI=0.838-2.594, P=0.34) and the five-year hazard ratio was 1.37 (95%CI=0.752-2.496, P=0.44). Individuals that were not African American had an increased likelihood of survival (HR=0.544, 95%CI=0.355- 0.834, P <0.05). Finally, female sex increased the risk of a posttransplant GFR <60 (OR=2.87, 95%CI=1.78-4.68, P<0.05). Conclusions: Everolimus treatment status had no impact on survival. Ongoing everolimus treatment trended towards renal protection against GFR <60 compared to never using the medication. However, African American race decreased the likelihood of survival. Finally, female sex increased the risk of a GFR <60. Future studies evaluating everolimus over a longer period of time would be valuable. CITATION INFORMATION: Sreedhar S., Lu M., Moonka D., Jafri S. The Efficacy of Everolimus in Liver Transplant Patients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: S.Sreedhar: None. M.Lu: n/a. D.Moonka: None. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Gastroenterology

Cunningham A, Mueller A, Getzinger J, **Obri M**, **Kerr H**, and **Jafri S**. Dermatologic Manifestations and Outcomes of Patients with Graft vs Host Disease Following Liver Transplant in a Real World Setting. *Am J Transplant* 2023; 23(6):S1180. Full Text

Purpose: The objective is to evaluate cutaneous manifestations and outcomes of patients with Graft Vs Host Disease (GVHD) following liver transplant. Methods: A retrospective review was conducted at an urban academic center to track cutaneous and multi-organ manifestations of GVHD s/p liver transplant. We analyzed the indication for liver transplant, cutaneous symptoms at initial presentation, 6 months, and 1 year, treatments, and survival rates. We compared outcomes in patients with cutaneous GVHD (cGVHD), cutaneous GVHD with additional organ involvement (AOI), and non-cutaneous GVHD. Results: 13 patients were diagnosed with GVHD s/p liver transplant. 30.8% developed cGVHD, 46.2% developed cGVHD with AOI, and 23.1% developed non-cutaneous GVHD. Mean age was 66.1 years. 76.9% were male. Indications for liver transplant were HCV cirrhosis (15.4%), familial amyloidosis (7.7%), NASH cirrhosis (53.8%), and alcoholic cirrhosis (23.1%). 100% of patients were treated with triamcinolone 0.1% and corticosteroids. Following liver transplant, the mean onset of cGVHD was 31.6 days (range 2-64). At initial presentation, 90% of patients had a diffuse, erythematous maculopapular rash on the chest, abdomen, and back. 60% of patients reported pruritus. Regarding multi-organ involvement, 69.2% developed GVHD with AOI. 11.1% of patients developed bilateral non-granulomatous uveitis (mean onset 7 months). 44.4% of patients developed colitis (mean onset 39.7 days). 88.9% of patients developed pancytopenia (mean onset 42.6 days). At both 6 and 12 months, 66.6% of patients had complete resolution of cGVHD. The mean duration until complete cutaneous resolution in patients with cGVHD vs cGVHD with AOI was 7.6 and 1.9 months, respectively. At both 6 and 12 months, 100% of patients had improvement of pruritus and degree of regional spread. A non-pruritic maculopapular rash remained in 33.3% of patients at 1 year. Common complications s/p liver transplant were bacteremia (69.2%), pneumonia (46.2%), UTIs (46.2%). The incidence of bacteremia in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 83.3, and 100%. The incidence of pneumonia in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 50, and 66.7%. The incidence of UTIs in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 66.6, and 33.3%. Regarding survival, 53.8% of our GVHD patients are deceased. The mean survival duration s/p liver transplant was 86.4 days (range 39-167). 41.7% of all patients survived at the 6 months, 1 year, and 3 years. 100% of cGVHD patients survived to 6 months, 1 year, and 3 years. Notably, only 12.5% of cGVHD with AOI patients survived to 6 months, 1 year, and 3 years. Conclusions: The incidence of GVHD s/p liver transplant is approximately 0.5-2%. Based on our results, mortality is significantly increased at 6 months, 1 year, and 3 years in patients with cGVHD with

AOI. Early recognition and treatment is crucial for patient prognosis. CITATION INFORMATION: Mueller A., Getzinger J., Obri M., Kerr H., Jafri S. Dermatologic Manifestations and Outcomes of Patients with Graft vs Host Disease Following Liver Transplant in a Real World Setting AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: A.Mueller: None. J.Getzinger: n/a. M.Obri: None. H.Kerr: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Gastroenterology
Dean R, Yazdanfar M, Zepeda J, Levy C, **Gordon SC**, Forman L, Lammert C, Assis DN, Pratt D, Gungabissoon U, McGirr A, Mukherjee S, McLaughlin M, and Bowlus C. Investigating the cholestatic pruritus of primary sclerosing cholangitis (ItCh-PSC): a study of patients participating in the consortium for autoimmune liver disease (CALiD). *J Hepatol* 2023; 78:388. Full Text

Background and aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that causes significant impairments to quality of life. Compared with other cholestatic liver diseases, pruritus has not been well studied in patients with PSC. The aim of this study was to determine the prevalence, severity and treatment patterns for pruritus among patients with PSC. Method: Patients with PSC were identified from a multicentre, retrospective cohort study of the Consortium for Autoimmune Liver Disease (CALiD). Electronic medical records were searched for keyword terms “itch” and “pruritus” to identify “pruritus” encounters. The severity of pruritus was graded for each pruritus encounter as absent, mild, moderate or severe based on descriptors in the medical record. Medications and endoscopic retrograde cholangiopancreatography (ERCP) planned to treat pruritus was recorded. Patients with more than one pruritus encounter were categorised according to the encounter with the maximum severity of pruritus. Results: A total of 724 patients were included in the study. Pruritus terms were recorded in 1178 encounters from the medical records of 372 (51.4%) patients. Patients with a pruritus encounter (N = 372, 51.4%) compared with those without (N = 352, 48.6%) had a lower frequency of small duct PSC (4% vs 8%, p = 0.02) but were comparable in terms of inflammatory bowel disease (IBD), cirrhosis, hepatic decompensation, and baseline laboratories, except for international normalised ratio (INR) 1.2 + 0.4 vs 1.2 + 0.4, p = 0.02). Among those with a pruritus encounter, the maximum pruritus severity was graded as mild in 142 (38.2%), moderate in 140 (37.6%), severe in 77 (20.7%), and pruritus was recorded as absent in 13 (3.5%) patients. IBD diagnosis, PSC type, cirrhosis and hepatic decompensation did not differ by the maximum severity of pruritus (Table). However, baseline alkaline phosphatase (ALP), aspartate transaminase (AST) and total bilirubin were greater in those with more severe itch. Anti-pruritic medication usage among patients with any degree of itch included bile acid-binding resins (36.5%), hydroxyzine (22.6%), rifampin (11.4%) and sertraline (9.7%). Two or more medications were used by 46.7% of patients with severe itch. ERCP was planned in 13 (2.5%), 34 (8.4%), 27 (17.3%) encounters with mild, moderate and severe pruritus, respectively. Conclusion: Pruritus in patients with PSC is notwell documented but is frequent and often severe. Patients who experience severe pruritus have more severe liver disease and frequently require multiple antipruritic medications and ERCP. These results establish the clinical significance of pruritus in PSC and support the need for prospective studies to accurately ascertain itch prevalence and the unmet need for therapies to treat pruritus among patients with PSC. [Figure presented]

Gastroenterology
Finotti M, **Jesse M**, Pillai A, Liapakis A, **Venkat D**, **Salgia R**, Kumar V, **Manivannan A**, **Lu M**, **Zhang T**, Verna E, and Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation. *Am J Transplant* 2023; 23(6):S864-S865. Full Text

Purpose: Living donor liver transplantation (LDLT) is a viable option to increase access to liver transplantation (LT). However, there are well-documented racial and gender-based inequities in access to deceased donor LT. Very little is empirically known about living liver donor (LLD) characteristics in relation to their recipients. Therefore, we aimed to explore the odds of receiving LDLT across LLD and recipient characteristics. Methods: We explored gender, interactions between LLD-recipient race/ethnicity, and other relevant factors on LDLT utilizing national data from the United Network for Organ Sharing (UNOS) for all adult LLD and their recipients who underwent LDLT from 1/1/2012 through 10/1/2022. Results: 3469 LDLTs occurred (5.46% of all LTs). A majority of LLDs were female (n 1864, 54%), mean 37.16 years of age (SD 10.41), and White race (n 2791, 81%), followed by Hispanic (n 423, 12%), Black (n 116,

3%), Asian (n 85, 2%), and Other (n 47, 1%). LDLT recipients were predominantly male (n 1843, 53%), mean 53.35 years of age (SD 13.22), and White race (n 2787, 80%), followed by Hispanic (n 437, 13%), Black (n 118, 3%), Asian (n 92, 3%), and Other (n 35, 1%). Of note, 42.9% (n 1487) of LLDs were not biologically related to their recipient. As reported in Table 1, men are both less likely to receive or be a LLD than women. Examining the donor by recipient race interactions, LDLT is more likely to occur between LLD and recipients with the same racial/ethnic category than differing race/ethnicity (regardless of comparator). When race/ethnicity is different between LLD-recipient, four significant interactions occurred indicating that White LLDs are less likely to donate to Black recipients than Hispanic or Others/Unknown and Asian donors are more likely to donate to Others/Unknown than either Hispanic or White recipients. Conclusions: While biological relatives are assumed to be the same race/ethnicity, nearly half of LLDs are not biologically related to their recipient and yet all racial groups were more likely to donate within their own racial category, adjusting for liver disease category and functional status. Also, despite representing the majority of waitlisted and transplanted patients, men were less likely to receive LDLT, but men are also less likely to be a LLD. These results provide a starting point to foster efforts towards diversifying the LLD population. CITATION INFORMATION: Jesse M., Pillai A., Liapakis A., Venkat D., Salgia R., Kumar V., Manivannan A., Lu M., Zhang T., Verna E., Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.Jesse: None. E.Verna: None. N.Parikh: Consultant;; Eisai, Eli Lilly, Research Grant Site Overall Principal Investigator;; Genentech. A.Pillai: n/a. A.Liapakis: None. D.Venkat: n/a. R.Salgia: n/a. V.Kumar: None. A.Manivannan: n/a. M.Lu: n/a. T.Zhang: n/a. [Figure presented]

Gastroenterology

Gordon SC, Steffens A, Weber L, McNiff K, and Yehoshua A. Evaluating utilization and management of comedications with potential for drug-drug interactions among patients with chronic hepatitis C initiating treatment with sofosbuvir/velpatasvir or glecaprevir/pibrentasvir. *J Hepatol* 2023; 78:1208. Full Text

Background and aims: Direct-acting antiviral (DAA) agents for treatment of chronic hepatitis C (HCV) include glecaprevir/pibrentasvir (GLE/PIB), a protease inhibitor with known drug-drug interaction (DDI) effects, and sofosbuvir/velpatasvir (SOF/VEL), a protease inhibitor-free regimen with a more favorable DDI profile. This analysis compared rates and management of comedications with DDI risk (DDI comedications) among patients initiating DAA treatment with SOF/VEL or GLE/PIB. Method: Adults initiating SOF/VEL or GLE/PIB from July 2016–April 2020 were identified from US administrative claims data in the Optum Research Database. The index date was the first claim for SOF/VEL or GLE/PIB. Continuous enrollment 12 months before (baseline) and 6 months after the index date was required. Patients with baseline liver disease, HCV treatment, or HIV were excluded. Demographics and DDI comedication use were measured. All DDI comedications associated with GLE/PIB and SOF/VEL and DDI comedication severity, defined from more to less severe as red, amber, or yellow, were from the Liverpool HEP Drug Interactions Database. DDI comedication discontinuation, dose decrease, and change to medication with no DDI risk during DAA treatment were measured in the subset of patients with prevalent DDI comedications 90 days prior to index. Results: Among 4,528 patients meeting study criteria, 66.6% of GLE/PIB initiators and 43.7% of SOF/VEL initiators had any baseline DDI comedication use ($p < 0.01$). Compared with SOF/VEL initiators, GLE/PIB initiators had higher baseline rates of red (21.4% vs 2.3%), amber (51.9% vs 41.6%), and yellow (31.4% vs 2.8%, all $p < 0.01$) DDI comedications. DDI comedication use decreased during DAA treatment but remained higher in GLE/PIB initiators vs SOF/VEL initiators (41.5% vs 28.9%, $p <0.01$). Overall, 979 GLE/PIB and 658 SOF/VEL initiators used prevalent DDI comedications in the 90 days pre-index. Of these, GLE/PIB vs SOF/VEL initiators had similar mean age (61.6 vs 61.8 years), proportions of female (42.2% vs 38.8%) and commercially insured (32.0% vs 29.5%) patients; baseline compensated cirrhosis was lower among GLE/PIB vs SOF/VEL initiators (5.8% vs 9.6%, $p < 0.01$). A higher proportion of GLE/PIB vs SOF/VEL initiators discontinued at least 1 DDI comedication before initiating DAA treatment (52.2% vs 38.0%, $p < 0.01$). During DAA treatment, GLE/PIB vs SOF/VEL initiators had higher rates of dose decrease (10.8% vs 6.8%, $p = 0.026$) and change to medication with no DDI risk (3.5% vs 1.1%, $p = 0.014$). Conclusion: Use of DDI comedications was identified among a substantial proportion of patients, with higher rates of DDI comedication use and actions taken to manage DDI comedication use in GLE/PIB vs SOF/VEL initiators. Additional research is needed to assess real-world consequences of potential DDIs. [Figure presented]

Gastroenterology

Maheshwari R, **Gupta D**, **Nagai S**, **Muszkat Y**, **Beltran N**, and **Jafri S**. Management of Graft vs Host Disease Following Intestinal Transplantation. *Am J Transplant* 2023; 23(6):S733. Full Text

Purpose: We present four patients with multi-visceral transplant (MVT) complicated by graft-versus-host disease (GvHD). Methods: We reviewed 26 cases following MVT for incidence of GvHD. Four patients that received MVT between 2011-2022 were evaluated for outcomes following surgery, including patient characteristics, diagnosis, organs involved, treatment, complications, and outcomes. Results: Four patients receiving MVT developed GvHD. 75% were male, median age at transplant was 45.75 (range 39-54), three were white, and one was black. Three patients presented for MVT due to pancreatic neuroendocrine tumor with liver metastasis and had GvHD which affected the skin. The other patient presented for MVT due to alcoholic cirrhosis complicated by portal and splenic thrombosis and chronic pancreatitis and had GvHD which affected the skin and bone marrow. All four patients had liver, pancreas, and small bowel transplants and received steroids. One patient with skin involvement also received photopheresis and etanercept. The patient with bone marrow involvement also received etanercept. Graft and patient survival at one and three years for those with skin involvement was 100% (3/3) and 50% (1/2) and for bone marrow involvement was 0% (0/1) and 0% (0/1) respectively. Infection within one month of GvHD diagnosis occurred in 33% (1/3) of patients with skin involvement (acute bacterial pneumonia) and 100% (1/1) with bone marrow involvement (septic shock). There were no signs of CMV or transplant rejection within one month of GvHD diagnosis. In patients where induction agents were noted, three received thymoglobulin and one also received rituximab. At GvHD diagnosis, all four patients were on prednisone. Of those with skin involvement, two were on tacrolimus with one also on solumedrol, and a third was on everolimus. The patient with bone marrow involvement initially had a blood STR of <1% donor and 99% recipient and a skin STR of 17% donor and 83% recipient. Retesting showed only recipient DNA two weeks after. Two patients with skin involvement had STR available. One had a blood STR of <1% donor and 99% recipient and a skin STR of 6% donor and 94% recipient while the second had a skin STR of 18% donor and 82% recipient. In patient one, retesting showed only recipient DNA two weeks after. Patient two was not retested. The patient with bone marrow involvement expired due to septic shock from E.coli, Klebsiella pneumoniae and Candida. Conclusions: GvHD occurs when the primary T cells of the allogenic grafted tissue recognize the host's proteins as foreign resulting in an immune response against the host. Biopsy and pathologic evaluation are required for diagnosis. High clinical suspicion for GvHD in MVT is necessary as early recognition and treatment improve outcomes. CITATION INFORMATION: Gupta D., Nagai S., Muszkat Y., Beltran N., Jafri S. Management of Graft vs Host Disease Following Intestinal Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: D.Gupta: None. S.Nagai: None. Y.Muszkat: n/a. N.Beltran: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Gastroenterology

Obri MS, **Samad M**, **Alluri S**, **Alhaj Ali S**, **Almajed MR**, **Ichkhanian Y**, and **Jafri S**. Pulmonary Complications of Everolimus in Liver Transplant Patients: A 10-year Experience. *Am J Transplant* 2023; 23(6):S1007-S1008. Full Text

Purpose: The study aims to evaluate the safety of everolimus as part of the immunosuppression regimen in liver transplant patients. Methods: A retrospective study was conducted at a single, tertiary liver transplant center and was comprised of patients who had undergone liver transplant from 2009 to 2019. Patients were divided into two group depending on whether or not they had received everolimus during their post-transplant course. The primary outcome measured was the development of new pulmonary complications that have been associated with everolimus use. These complications include chronic obstructive pulmonary disease, pulmonary interstitial fibrosis, and pulmonary hypertension. The complications were measured by comparing pre- and post-transplant pulmonary function tests (PFTs) or by evaluating lung anatomy on computerized tomography (CT) scans. Secondary outcomes measured included everolimus discontinuation rates, re-transplant rates, and the rate of rejection between the two groups. Results: 450 patients were included in the study. 64% of the patients were male (n=288) and 83.6% of the patients were white. 65% (n=294) of the patients were never prescribed everolimus and 35% (n=156) of patients were prescribed everolimus throughout their transplant course. On average,

patients were prescribed everolimus 208 days (range 35-2261 days) after transplant and the mean last known followup of the patients after everolimus initiation was 1529 days (2-2631). In regards to the primary outcome, 4% (n=6) of patients had a new pulmonary complication after everolimus initiation (n=6) and 6.3% of the control group patients had a new pulmonary complication (n=19). A chi-square statistic was used to calculate and the value was 1.33 with a p-value of 0.249. The result is not significant at p <.05. Of note, 51.3% (n=80) of the everolimus patients had to discontinue the medication throughout their use, with non-pulmonary adverse effects being the primary cause of discontinuation. The most common stand-alone causes of discontinuation were proteinuria, oral ulcers, and cost. 76.3% of the patients had multiple reasons for discontinuation. Secondary outcomes such as re-transplant rates and rejection rates had no significant difference between the everolimus and control group Conclusions: Everolimus appears to be safe from a pulmonary toxicity stand point, with no significant difference between patients who are taking everolimus and patients who are not. Furthermore, there was no significant difference in rejection and re-transplant rates. Of note, there was a significant amount of patients discontinuing the medication, primarily due to side effects. Larger multi-center studies would be needed to evaluate the side effects of everolimus and the tolerability of patients who had undergone liver transplant. CITATION INFORMATION: Obri M., Samad M., Alluri S., Alhaj Ali S., Almajed M., Ichkhanian Y., Jafri S. Pulmonary Complications of Everolimus in Liver Transplant Patients: A 10-year Experience AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.S.Obri: None. M.Samad: n/a. S.Alluri: n/a. S.Alhaj ali: n/a. M.R.Almajed: n/a. Y.Ichkhanian: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Gastroenterology

Vo E, **Shimada S**, **Miyake K**, **Venkat D**, **Gonzalez H**, **Moonka D**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Adverse Effects of New-Onset Diabetes After Liver Transplantation. *Am J Transplant* 2023; 23(6):S1006-S1007. Full Text

Purpose: While diabetes is considered as a risk factor for poor outcomes after liver transplantation (LT), the impact of new-onset diabetes after LT (NODAT) on post-transplant outcomes remains to be elucidated. The aims of this study are to identify the clinical characteristics of NODAT and to investigate its impacts on post-transplant outcomes. Methods: Adult patients underwent LT at our center between 2014 and 2020 were evaluated. Inclusion criteria include use of tacrolimus as initial immunosuppression regimen and those who survived 3 months at least post-LT. To evaluate possible impact of NODAT on post-LT outcomes, those who developed NODAT within 3 months after LT were classified as NODAT group. In addition, patients were further classified into the following 2 groups; prior history of diabetes before LT (PHDBT) and non-diabetes (ND) groups. Patient characteristics of NODAT and post-LT conditional outcomes after 3 months, and cardiovascular and/or pulmonary complications, were compared. Results: A total of 83 and 225 and 263 patients were classified into NODAT, PHDBT, and ND groups. The proportion of cholestatic liver disease (21.7, 5.3, and 12.9%, P<0.001) and rejection within 30 days (42.2, 7.1, and 4.6%, P<0.001) in NODAT, PHDBT, and ND, respectively. Mean serum tacrolimus concentration trough level in the first week after LT was 7.12, 6.12, and 6.12 ng/ml in these 3 groups, respectively (P<0.001). Duration of corticosteroids were significantly longer in NODAT (416 days) compared to PHDBD (289 days) or ND (228 days) (P<0.001). (Table 1). Three-year graft and patient survival after 3 months were significantly worse in NODAT than in ND (Graft: 80.5% vs. 95.0%, P<0.001, Patient: 82.0% vs. 95.4%, P<0.001) but similar to PHDBT (Figures 1 and 2). Adjusted risk of 3-year graft loss and patient death were significantly higher in NODAT compared to ND (Graft; adjusted hazard ratio [aHR] 3.41, p=0.004, Patient; aHR 3.61, p=0.004). Incidence rates of cardiovascular or pulmonary complications after LT in NODAT were significantly higher than in ND (Cardiovascular; 16.9% vs. 3.8%, P<0.001; Pulmonary; 20.5% vs. 11.0%, P=0.04,) but similar to PHDBT (Cardiovascular vs. 16.9%, P=0.99; Pulmonary vs. 20.0%, P=0.99). Conclusions: Cholestatic liver disease, high tacrolimus concentration, and early rejection might be risk factors for NODAT. NODAT was associated with the worse long-term outcomes and increases risk of cardiovascular and/or pulmonary complications. CITATION INFORMATION: Shimada S., Miyake K., Venkat D., Gonzalez H., Moonka D., Rizzari M., Yoshida A., Abouljoud M., Nagai S. Adverse Effects of New-Onset Diabetes After Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: S.Shimada: None. K.Miyake: None. D.Venkat: n/a. H.Gonzalez: n/a. D.Moonka: None. M.Rizzari: None. A.Yoshida: n/a. M.Abouljoud: None. S.Nagai: None. [Figure presented]

Gastroenterology

Wheeler M, **Baik I**, **Gonzalez H**, **Jantz A**, **Poparad-Stezar A**, **Summers B**, **Venkat D**, **Samaniego-Picota M**, and **Fitzmaurice M**. Evaluating the Use of Glucagon-Like Peptide 1 Receptor Agonists (GLP1 RA) in a Matched Cohort of Kidney and Liver Transplant Recipients. *Am J Transplant* 2023; 23(6):S947. Full Text

Purpose: To assess the safety and efficacy of GLP1 RA in a matched cohort of kidney transplant (KT) and liver transplant (LT) recipients who received these agents compared to patients who did not Methods: This single-center, retrospective analysis evaluated KT and LT recipients who were initiated on a GLP1 RA for at least 3 months (mo) matched to a nonintervention comparator group (non-GLP1 RA) based on organ type and diagnosis of diabetes mellitus present at time of transplant. The primary endpoint was change in hemoglobin A1C (HbA1c) at 6 mo. Secondary endpoints included weight (kg), BMI (kg/m2), insulin requirements, and number of oral diabetic agents (ODAs). Safety outcomes included incidence of adverse events (AEs), biopsy-proven acute rejection (BPAR), graft loss, and mortality. Results: Of the 74 patients included, 37 received GLP1 RA matched to 37 patients who did not. Baseline characteristics shown in Table 1. More patients in the GLP1 RA group were on ODAs and 10 patients (27%) initiated on an agent <1 year from transplant. Change in median HbA1c in GLP1 RA group from baseline to 6 mo was -0.5% [(7.0% (6.4-8.9); 6.5% (5.6-7.3)] compared to +0.6% in the non-GLP1 RA group [(5.8% (5.5-6.8); 6.6% (5.8-7.6)], p=0.53. Median change in total daily insulin units was -13 units vs +15 units in the GLP1 RA vs non-GLP1 RA group (p=0.16). GLP1 RA group median change in weight was -7.4 kg vs -0.3 kg in non-GLP1 RA group (p=0.02). BMI change was -3.1 kg/m2 in GLP1 RA vs +0.7 kg/m2 in non-GLP1 RA, p=0.02. In GLP1 RA group, 7 patients (38.9%) experienced an AEs related to drug with 4 (10.8%) leading to discontinuation. Common AE being abdominal pain. One patient (2.7%) discontinued drug due to cost, 3 patients (8.1%) found it ineffective, and 1 (2.7%) had a drug-unrelated discontinuation. Eight patients (21.6%) in each group experienced BPAR. In the GLP1 RA group, 1 patient had graft loss compared to 2 patients in the non-GLP1 RA. No patient deaths occurred with GLP1 RA while 2 patient deaths in the comparator group. Conclusions: GLP1 RA lowered median HbA1c after 6 mo with subsequent clinically and statistically significant reductions in weight, BMI, and insulin requirements in both KT and LT recipients. AE rates are similar to reported literature. GLP1 RAs are safe and effective at all time points of initiation, including <1 year posttransplant, making them useful agents for management of metabolic complications in this patient population. CITATION INFORMATION: Baik I., Gonzalez H., Jantz A., Poparad-Stezar A., Summers B., Venkat D., Samaniego-Picota M., Fitzmaurice M. Evaluating the Use of Glucagon-Like Peptide 1 Receptor Agonists (GLP1 RA) in a Matched Cohort of Kidney and Liver Transplant Recipients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: I.Baik: None. H.Gonzalez: n/a. A.Jantz: n/a. A.Poparadstezar: n/a. B.Summers: n/a. D.Venkat: n/a. M.Samaniego-picota: None. M.Fitzmaurice: n/a. [Figure presented]

Gastroenterology

Yoon Y, **Obri MS**, Sarowar A, **Almajed MR**, and **Jafri S**. Is Alkaline Phosphatase a Predictor of Mortality in Liver Transplant Patients? *Am J Transplant* 2023; 23(6):S1182-S1183. Full Text

Purpose: We aim to evaluate the association between alkaline phosphatase (ALP) and rejection and mortality rates in patients who underwent liver transplantation at 1 and 3 years. Methods: A retrospective study was performed. Patients who received a liver transplant from 2015-2019 were included in the study. Patients' indication of transplant and date of transplant and death were recorded. ALP was measured at the time of transplant, 3 months, 6 months, and 1 year after transplant when available. Mortality rates at 1 and 3 years were measured for patients with an ALP greater than 130 and with an ALP greater than 200 at the respective time periods. ALP values were stratified based on the available literature that suggests that a value great that 130 IU/L is abnormal. Patients who had evidence of rejection were excluded to not have a confounding variable affecting mortality and were analyzed separately. A chi-square was calculated to compare the relationships. Results: 220 patients met the study criteria and were included. A significant positive correlation was demonstrated between ALP level at the time of transplant and death at 1 and 3 years; the chi-square statistic at 1 year was 9.65 (p=0.008) and at 3 years was 6.55 (p=0.04). ALP level at 3 months after transplant had no statistical significance with mortality. ALP level at 6 months after transplant had a statistically significant positive correlation with mortality at 1 year with a chi-square of 7.67 (p=0.022) but did not have a statistically significant correlation at 3 years (p=0.089). ALP level at

12 months after transplant had a statistically significant positive correlation with mortality at 3 years with chi-square 15.17 (p=0.005). Rates of death per group are listed in Table 1. Of the 383 total transplant patients, 41% (n=157), developed transplant rejection. Of these patients, 28.7% (n=45), had an ALP of greater than 130 at the time of transplant; however, there was no statistically significant correlation between ALP level and rejection as the chi-square was 1.25 (p=0.264). Conclusions: ALP level measured at the time of liver transplant has a statistically significant positive correlation with mortality at 1 and 3 years. ALP level measured at 3, 6, and 12 months had varying levels of statistical significance, although they demonstrated a similar positive correlation. ALP appears to be a promising prognostic marker for post-transplant complications. Further data is necessary to understand the identified correlation. CITATION INFORMATION: Obri M., Sarowar A., Almajed M., Jafri S. Is Alkaline Phosphatase a Predictor of Mortality in Liver Transplant Patients? AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.S.Obri: None. A.Sarowar: n/a. M.R.Almajed: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie. [Figure presented]

Gastroenterology
Yoon Y, **Taye K**, **Suresh S**, and **Jafri S**. Management and Outcomes of Patients Requiring Tracheostomy Post Liver Transplant. *Am J Transplant* 2023; 23(6):S1182. Full Text

Purpose: We evaluated the outcomes of post-liver transplant patients with extended respiratory failure requiring tracheostomy and compared these outcomes to that of patients not requiring tracheostomy. Methods: We compared outcomes of post liver transplant patients at a single institution including those that required tracheostomy following transplantation and those who did not. We reviewed the transplant database of 2158 liver transplant recipients and identified 10 cases that underwent liver transplantation and subsequently required tracheostomy between 2013 and 2020. We compared those cases to 20 controls with no tracheostomy with Kaplan Meier survival curve to compare survival rates. Logistic regression was used to assess associations where the dependent variables are dichotomous. Results: The cases and controls were comparable in terms of age and MELD at transplant with mean age of 56.3 and 56.5 years respectively (p 0.115) and MELD scores of 24 and 25 (p 0.209). All of the cases were Caucasians with 5 males and 5 females. Alcoholic cirrhosis was the most common cause of liver disease in both the cases and controls, underlying 40% and 35% of the liver injuries. Among those who required tracheostomy, 80% were successfully extubated on post-tranplantation day 1; however, eventually developed respiratory failure requiring long-term intubation and ultimately tracheostomy within a median of 118 days post transplantation. In 40% of those requiring tracheostomy pneumonia was the underlying cause of lung injury. Survival at one year in those requiring tracheostomy was only 40% versus 95% of controls (chi-square 11.815, p <0.001). There was no statistically significant difference in rejection rates between the two groups, at 40% and 45% for the cases and controls respectively (p 0.55). Liver transplant recipients with subsequent tracheostomy had significantly longer initial hospital stay following transplantation, with an a mean 32.9 days of hospitalization post-transplant, compared to mean of 11.9 days in the controls with a mean difference of 21 days (95% C.I. 6.2 - 35.7, p <0.001). Conclusions: Liver transplant patients who required tracheostomy had longer initial hospitalization following transplantation and significantly lower survival rates in the first 12 months following transplantation. Rejection rates were not found to different among the two groups. Figure 1. Kaplan-Meier survival cure for liver transplant patient patients who underwent tracheostomy (blue) and those who did not undergo tracheostomy following transplant in the first 12 months following transplant. CITATION INFORMATION: Taye K., Suresh S., Jafri S. Management and Outcomes of Patients Requiring Tracheostomy Post Liver Transplant AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: K.Taye: None. S.Suresh: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie. [Figure presented]

Gastroenterology
Younossi Z, Yılmaz Y, Fan JG, Wong VWS, Kassas ME, Zelber-Sagi S, Allen A, Rinella M, Singal A, **Gordon SC**, Fuchs M, Eskridge W, Alkhouri N, Alswat K, Takahashi H, Kawaguchi T, Ranagan J, Zheng MH, Duseja AK, Burra P, Patrizia C, Arrese M, Kautz A, Ong J, Castera L, Francque S, Kugelmas M, Eguchi Y, Treeprasertsuk S, Fernández MIC, Gomez MR, Newsome PN, Cusi K, Loomba R, Schattenberg J, Yu ML, Diago M, Gerber L, Lam B, Fornaresio L, Nader F, Henry L, Racila A, Golabi P, Stepanova M, Alqahtani S, and Lazarus J. Stigma in NAFLD and NASH: a global survey of patients and providers. *J Hepatol* 2023; 78:627-628. Full Text

Background and aims: Patients with fatty liver disease may experience stigmatization due to the disease or associated comorbidities. Aim: To understand stigma among NAFLD patients and providers. Method: Members of the Global NASH Council created two surveys about experiences and attitudes toward NAFLD and related terms: a 68-item patient and a 41-item provider survey. Results: The surveys were completed by 475 NAFLD patients [12 countries; 58% USA, 20% Middle East/North Africa (MENA), 20% East Asia (EA)] and 555 providers [63% GI/hepatologists,14 countries; 28% USA, 44% MENA, 25% EA]. Of all patients, 71% ever disclosed having NAFLD/NASH to family/friends; the most used words were "fatty liver" and "NAFLD or NASH" (35–54%), while "metabolic disease" or "MAFLD" were rarely used (never by 83–88%). There were 46% who reported experiencing stigma or discrimination (at least sometimes) due to obesity/overweight vs.17% due to NAFLD (Figure). The greatest social-emotional burden among NAFLD patients was feeling partially to blame for their liver disease (69% agree) and others believing that they do not eat properly (58% agree). Providers believed that lack of patient motivation (70%) and training in effective communication (62%) were the biggest obstacles to weight loss discussions. Furthermore, provider discomfort was related to perceived patients' lack of willpower for lifestyle changes and taking care of their diabetes (45–49% providers; 13–17% USA vs. 64–70% MENA, 31–67% EA). Regarding how various diagnostic terms are perceived by patients, there were no substantial differences between "NAFLD," "fatty liver disease (FLD)," "NASH," or "MAFLD": the most popular response was being neither comfortable nor uncomfortable with either term (47%-57%), with some greater discomfort with FLD among U.S. patients (45% uncomfortable). Among providers, 42% (49% USA, 43% MENA, 32% EA) believed that the term "fatty" in the name is stigmatizing, while 38% believed that the term "nonalcoholic" is stigmatizing, more commonly in MENA (47%). Also, 38% of the providers reported the term "FLD" as being stigmatizing (47% USA, 40% MENA, 24% EA). Finally, 54% of the providers (GI/hep 58% vs. 42% other specialties; 46% USA, 59% MENA, 51% EA) believe that a name change may reduce stigma. Conclusion: Perception of NAFLD stigma varies according to patients, providers, geographic location and sub-specialty. NAFLD patients reported the term obesity to be more stigmatizing than NAFLD. [Figure presented]

Gastroenterology
Younossi Z, Yılmaz Y, Yu ML, Isakov V, Fernández MIC, Wong VWS, Eguchi Y, Méndez-Sánchez N, Duseja AK, George J, Bugianesi E, Singal A, Hamid SS, Fan JG, Alswat K, Papatheodoridis G, Kassas ME, Chan WK, **Gordon SC**, Gomez MR, Roberts S, Lam B, Younossi I, Racila A, Henry L, Alqahtani S, and Stepanova M. Prevalence and predictors of clinically significant pruritus in patients with non-alcoholic fatty liver disease (NAFLD): data from the global NASH registry™ (GNR™). *J Hepatol* 2023; 78:863. Full Text

Background and aims: Pruritus is an important but underappreciated symptom of chronic liver diseases. We assessed factors associated with pruritus among patients with NAFLD. Method: Patients with NAFLD seen in real-world clinical practices were prospectively enrolled in the Global NAFLD/NASH Registry (GNR)™. Clinical parameters and patient reported outcomes (PROs; FACIT-F, CLDQ-NASH, WPAI) were collected. Clinically significant pruritus was defined as score ≤4 in the respective itemof CLDQ-NASH (range 1–7; lower score indicates more severe pruritus). Results:We included 4203 NAFLD subjects from 17 countries: age 52 ± 13 years, 48% male, 48% employed, 23% advanced fibrosis and 14% cirrhosis (by biopsy or non-invasive FIB-4), 44% type 2 diabetes (T2D), 21% history of depression and 45% clinically overt fatigue. Furthermore, 78% of those with a biopsy had NASH. The prevalence of clinically significant pruritus among NAFLD was 28%. The highest prevalence of significant pruritus was in patients enrolled in Middle East/North Africa and Latin America (36–39%), the lowest in South Asia (7%). NAFLD patients with pruritus were less commonly employed (42% vs. 51%), more commonly female (61% vs. 49%) and obese (69% vs 63%). Also, they more commonly had T2D (51% vs 41%), advanced fibrosis (27% vs. 22%), anxiety (47% vs. 31%), depression (30% vs 18%), fatigue (58% vs. 40%), abdominal pain (37% vs. 20%), and sleep apnea (27% vs 21%) (all $p < 0.01$) than those without pruritus, despite similar age ($p > 0.05$). NAFLD patients with pruritus experienced significantly lower PRO scores (FACIT-F, CLDQ-NASH, and WPAI) ranging from −4% to −19% of a PRO score range (all $p < 0.0001$) All CLDQ-NASH domain scores were lower in NAFLD patients with pruritus as compared to those without (Figure). In multivariate analysis adjusted for the regions of enrollment, independent predictors of an increased risk of pruritus included female sex, T2D, depression, clinically overt fatigue, abdominal pain,

and the lack of regular (≥3/times week; ≥30 min/time) exercise (odds ratios range 1.30 to 1.96, all p < 0.01). Among patients with 1-year follow-up, lower pruritus scores and higher prevalence of clinically significant pruritus were still observed in patients who had experienced pruritus at baseline: mean pruritus score increased from 3.1 to 4.6 in those with baseline pruritus vs. decreased from 6.4 to 6.0 in those without baseline pruritus while the prevalence of clinically significant pruritus at 1-year follow-up was 52% vs 19%, respectively (all p < 0.0001). [Figure presented] Conclusion: Pruritus is a common and persistent symptom among patients with NAFLD, especially those with T2D and female subjects. Presence of pruritus negatively affects all PRO scores and is impacted by non-hepatic comorbidities.

Gastroenterology
Yuen MF, Heo J, Nahass RG, Wong GLH, Burda T, Bhamidimarri KR, Hu TH, Nguyen T, Lim YS, Chen CY, **Gordon SC**, Holmes J, Chuang WL, Kohli A, Alkhouri N, Gray K, Thi EP, Medvedeva E, Eley T, and Sims K. Preliminary safety and antiviral activity of AB-729 combination treatment with pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection. *J Hepatol* 2023; 78:125. Full Text

Background and aims: AB-729is anN-Acetylgalactosamine(GalNAc)- conjugated single trigger RNA interference therapeutic that targets all HBVRNAtranscripts, resulting in suppression of viral replicationand all viral antigens. AB-729-201 is an ongoing Phase 2a study assessing 24 weeks of AB-729 followed by 12 or 24 weeks of pegylated interferon alfa-2a (IFN) with or without additional AB-729 doses in virally suppressed, HBeAg-negative CHB subjects. We report interim data through 12 weeks of IFN treatment for the first 12 subjects. Method: Forty-three CHB subjects, virally suppressed on stable nucleos (t)ide analog (NA) therapy, were all enrolled to receive AB- 729 60 mg every 8 weeks for 24 weeks (4 doses) during the lead-in phase. After Week 24, the subjects were randomized to 1 of 4 subgroups: A1 (24 weeks IFN + AB-729+NA), A2 (24 weeks IFN + NA), B1 (12 weeks IFN + AB-729 + NA) or B2 (12 weeks IFN + NA). After completing IFN ± AB-729 treatment, subjects continued NA therapy only for an additional 24 weeks and were then evaluated for NA discontinuation based on protocol criteria (ALT <2 x upper limit of normal, undetectable HBV DNA, confirmed HBsAg <100 IU/ml). Safety and antiviral assessments were obtained every 2-4 weeks. HBsAg quantification was assessed via Roche Cobas Elecsys HBsAg II quant II assay (lower limit of quantitation [LLOQ] = 0.05 IU/ml). Results: The median subject age was 46 years, 72% were male, and 79% were Asian. To date, 32 of 43 subjects have been randomized to the 4 IFN sub-groups after completing the 24-week AB-729 lead-in period. The mean (standard error [SE]) baseline HBsAg level for all 43 subjects was 2.98 (0.07) log10 IU/ml and the median (range) was 2.92 (2.7-3.4) log10 IU/ml. The mean (SE) HBsAg decline observed atWeek 24 was -1.65 log10 (0.10, n = 34). All subjects had HBsAg declines of approximately 1 log10 or more from baseline, and 28 of the 32 (88%) randomized subjects reached HBsAg <100 IU/ml. After 6weeks of IFN treatment, mean HBsAg declines from baseline ranged from -1.53 to -2.49 log10 across the 4 sub-groups (3-5 subjects/group), and after 12 weeks of IFN, mean HBsAg declines ranged from -0.74 to -2.20 log10 (2-4 subjects/group). Three subjects had intermittent HBsAg <LLOQ, 2 during the IFN treatment period and 1 at the end of the AB-729 leadin period. Three subjects have completed the NA follow-up period, and 1 subject met the criteria to stop NA therapy. AB-729 treatment has been well-tolerated with no serious adverse events (AEs) or AEs leading to AB-729 discontinuation. AEs during IFN treatment have been typical, with 4 subjects requiring IFN dose reduction or interruption due to neutropenia and 1 due to Grade 3 ALT elevation. Conclusion: AB-729 treatment in virally suppressed CHB subjects was well tolerated and led to mean HBsAg declines of >1.6 log10 after 24 weeks of treatment, comparable to other AB-729 studies. HBsAg levels <100 IU/ml were noted in 88% of the subjects. This interim data analysis suggests addition of IFNwaswell tolerated, and AB-729 + IFN appears to result in continued HBsAg declines in most subjects with 2 subjects reaching HBsAg <LLOQ during IFN treatment, but more data is needed to assess the overall impact on HBsAg responses.

Graduate Medical Education
Gunaga S, **Al-Hage A**, **Buchheister A**, **Welchans M**, **Awada M**, **Smiles B**, **Savage A**, **Latack K**, **Schultz L**, and **Miller J**. 365 Trends in Hospice and Palliative Medicine Consults Initiated in the Emergency Department: A Seven-Year Utilization Analysis. *Ann Emerg Med* 2023; 82(4):S161-S162. Full Text

Objectives: Emergency departments (EDs) play a central role in end-of-life care, yet early integration of high-quality palliative care and hospice services is often under-utilized. Studies have shown that early access to these services improves patient outcomes, goal-concordant care and reduces health care costs. Translation of this evidence into clinical practice remains inconsistent, and the extent to which these services are utilized remains unclear. This retrospective cross-sectional cohort study aimed to describe the clinical prevalence and trends of ED ordered hospice and palliative medicine consults over a seven-year period in a large metropolitan health system. Methods: We conducted a retrospective cohort study of electronic health records (EHR) from five EDs within a large, integrated urban and suburban health system. The study period spanned from January 1st, 2016, to December 31st, 2022, and included data from all ED visits by patients > 18 years old who had a hospice and/or palliative medicine consult ordered in the ED. A variety of patient specific demographic, clinical, and outcome variables were collected. The yearly number of hospice and palliative medicine consults ordered in each ED were also obtained and compared by year and by site. Across years, we compared incident rates of hospice and palliative consults per 1,000 ED patients who were over 50 years old, had an ESI ≤ 3, and were admitted. Data analysis included descriptive statistics, chi-square testing, and regression analysis to examine trends over time. Results: A total of 6,097 hospice and palliative medicine consults were ordered in the ED for 5,687 ED encounters, and 5,345 unique patients meeting the inclusion criteria. The mean age of participants was 77.9 years ±13.7, with 57.2% being female and 74.7% identifying as White. Of the total cohort, 90.6% (5,152) were admitted to the hospital, 7.2% (410) were discharged home, 2.0% (112) died in the ED, and 55.2% (2,843) died during their hospital stay. Hospice and palliative medicine consults initiated in the ED showed a significant annual increase from 324 in 2016 to 1,328 in 2022, representing a 410% overall increase ($p < 0.001$). This seven-year trend is detailed in Figure 1. ED-ordered hospice consults outnumbered palliative consults 1.68 to 1 in 2016; however, in 2022 that ratio flipped to where ED palliative consults were 1.66 times more common. After the onset of the COVID-19 pandemic, there was a significant 188% increase in daily ED hospice and palliative consults when compared to pre-pandemic levels ($p < 0.001$). The calculated prevalence of hospice and palliative medicine consults in the ED for patients who were over 50 years old, had an ESI ≤ 3, and were admitted was 5.9 consults for every 1,000 visits (0.59%) in 2016. This prevalence significantly increased to 19.7 consults (1.97%) for every 1,000 visits in 2022 ($p < 0.001$). Conclusions: This study reveals an increasing trend of ED initiated hospice and palliative consults in our health system. Though promising, this effort likely only touches the surface of the unmet palliative needs of our ED patients and families. Further research is required to examine if these trends are observed across other healthcare facilities nationwide and to identify potential obstacles to implementation. [Formula presented] No, authors do not have interests to disclose

Hematology-Oncology

Alhushki SK, Al-Muhtaseb A, Abushukair H, and **Abu Rous F**. EP03.03-02 Multi-omics Analysis of Immune Determinants of STK11 in Non-Small Cell Lung Cancer. *J Thorac Oncol* 2023; 18(11):S442-S443. Full Text

Introduction: Serine/Threonine-Protein Kinase (STK11) is one of the most common mutated genes in NSCLC. STK11 mutations have been reported to be associated with poor response to immunotherapy in NSCLC through innate resistance to anti-PD-1/PD-L1 therapy. Herein, we analyze the impact of STK11 mutations on NSCLC tumor immune microenvironment (TME) through multi-omic analyses. Methods: The Cancer Genomic Atlas (TCGA) pan cancer lung adenocarcinoma (LUAD, n=566) and squamous cell carcinoma (LUSC, n=487) cohorts were utilized in our analyses. Clinical and genomic data were retrieved through cBioportal. Immune cell infiltration through bulk tissue RNAseq was assessed through the TIMER2.0 web-based tool. The Tumor Immune Dysfunction and Exclusion (TIDE) platform was used to assess STK11 mutations correlation with cytotoxic T-lymphocytes (CTL) dysfunction. Results: In the combined LUAD and LUSC cohort, STK11 mutations were more common in LUAD patients (14%) compared to LUSC (2%). KRAS (53.8% vs 16.5%) and KEAP1 (40.5% vs 12.8%) were the two most common mutations in STK11-mutated tumors compared to STK11 wild-type. STK11 mutations were significantly associated with poor overall survival (median: 31.2 vs 53.7 months; Log-rank p=0.037) and progression-free survival (median: 21.6 vs 55.7 months; $p < 0.001$) compared to STK11 wild-type. In LUAD cohort, STK11 mutations were found to be significantly associated with lower CD8+ T-cells, CD4+ T-cells, M1 macrophages infiltration, and higher T-regulatory cells infiltration ($p<0.05$) compared to STK11 wild-type tumors. STK11 wild-type tumors with top CTL score (high CTL infiltration) had better outcomes

compared to those with bottom CTL score (low CTL infiltration); whereas STK11-mutated tumors with top CTL score had worse survival compared to those with bottom CTL score (p=0.01), which indicates that STK11 mutations are associated with CTL dysfunction (Figure 1). PD-L1, PD-1, CTLA-4, and LAG3 gene expressions were higher among STK11 wild-type tumors (p<0.05). Conclusions: STK11 mutations are associated with high levels of immune-inhibitory cells, and low levels of immune-stimulatory cells and immune checkpoints expression which indicate an immune-cold TME. Moreover, STK11 mutations are associated with CTL dysfunction. These findings can explain its association with poorer outcomes and confirm its role in identifying patients who are less likely to respond to immunotherapy. [Formula presented] Keywords: STK11, Immunotherapy, Non-small Cell Lung Cancer

Hematology-Oncology
Azmi A, Mahdi Z, Bannoura S, Al-Hallak M, Uddin M, Khan H, Muqbil I, Mohammad R, Chen H, **Philip P**, and El-Rayes B. P-76 Genomic and transcriptomic characterization of pancreatic neuroendocrine tumors reveals novel therapeutic candidates. *Ann Oncol* 2023; 34:S40-S41. Full Text

Background: Pancreatic neuroendocrine tumor (pNET) incidence is on the rise and remains an unmet clinical problem in urgent need of new actionable targets. Methods: We performed whole exome sequencing (WES), and transcriptomic (RNA-seq) analysis on 81 primary pNET and 6 normal pancreas tissues. Maftools analysis was performed to identify mutated pathways. Prioritized targets were validated in a validation cohort (39 pNETs and 22 normal) using immunohistochemistry (IHC) and real-time reverse transcription polymerase chain reaction (RT-qPCR). RNAi and small molecule inhibitors were used to evaluate the impact of blocking candidate genes and resultant impact on pNET cell subsistence using different assays such as colony formation, MTT, spheroid disintegration, cell cycle and apoptosis. Results: In the primary pNETs, the most common genomic alterations include frameshift insertions, nonsense mutations, missense mutations and in frame insertions. The Maftools analysis of mutated pathways showed enrichment of RTK/Ras activation, WNT/β-catenin pathway, Notch pathway, Hippo pathway, cell cycle control, TGF-β signaling, PI3K/mTOR signaling, Myc and p53 pathways. Transcriptomic analysis showed activation of VGF nerve growth factor (VGF), Neural Proliferation Differentiation and Control 1 (NPDC1) and Neurotensin (NTS) in pNETs compared to normal tissues. GSEA analysis also showed that the genes which regulate insulin secretion, neurotransmitter secretion, nervous system process and cell cycle were significantly up-regulated in pNETs. There was statistically significant up-regulation of the neuroendocrine markers and the cell cycle and proliferation markers including FEV transcription factor, Syntaxin 1A, Transthyretin, CD47, nuclear signal transport genes XPO1, RCC1, Nup50 and RAN. There was statistically significant up-regulation of the CXCR related signaling molecules including CXCR4, JAK1 and UCHL1. RT-PCR on RNA from validation cohort confirmed the up-regulation of above identified transcripts in FFPE pNET tissues, fresh primary pNETs and established pNET cell lines. RNAi silencing of RCC1, small molecule inhibitor targeting CXCR4 and XPO1 and antibody targeting CD47 suppressed proliferation of BON-1 and QGP-1 pNET cells in multiple 2D and 3D cultures. Conclusions: Our genomic, transcriptomic and validation studies reveal previously not described novel actionable therapeutic targets that warrant further evaluation in pNETs. Legal entity responsible for the study: The authors. Funding: NIH 5R01CA240607. Disclosure: All authors have declared no conflicts of interest.

Hematology-Oncology
Benitz S, **Nasser M**, Steep A, **Loveless I**, **Wen HJ**, **Long D**, **Davis E**, **Rempinski D**, **Louw M**, **Moore J**, **Steele N**, Mahajan U, Regel I, Bednar F, and **Crawford H**. Single-cell epigenomic analysis reveals an important role of the receptor kinase Ror2 in the erosion of cellular identity during pancreatic carcinogenesis. *Pancreatology* 2023; 23:e126. Full Text

Abstract Background: The major driver for pancreatic ductal adenocarcinoma (PDAC) is oncogenic KRAS. However, adult acinar cells, a probable origin of PDAC, are largely refractory to KrasG12D-mediated oncogenic transformation. With the concomitant loss of transcription factors that regulate acinar cell differentiation, such as Pdx1 (Pancreatic and Duodenal Homeobox 1), acinar cells undergo a rapid cell identity switch, known as acinar-to-ductal metaplasia (ADM). How loss of cell identity cooperates with oncogenic Kras to induce pancreatic transformation is largely unclear. Methods: To elucidate mechanisms responsible for the accelerated cellular reprogramming in KrasG12D;Pdx1f/f animals, single-

cell ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) from frozen pancreatic bulk tissue was performed. Chromatin accessibility states were captured at early stages of carcinogenesis and correlated to RNA-seq data. Differentially regulated genes were validated by multiplex RNAscope and immunohistochemistry staining and functionally studied in pancreatic cancer cell lines. Results: Single-cell ATAC-seq proved a powerful tool for defining cell-type identity, cellular reprogramming and target genes in early metaplastic transformation of pancreatic tissue. Notably, acinar cells of KrasG12D;Pdx1f/f animals as well as a proportion of metaplastic lesions in both, KrasG12D and KrasG12D;Pdx1f/f mice, showed elevated accessibility and expression of the Ror2 gene. As a receptor tyrosine kinase, Ror2 controls essential signalling pathways, such as Ras-MAPK signalling. By analysing Ror2 knockout mice, we found that the receptor kinase regulates the identity of metaplastic epithelia. Moreover, Ror2 expression highly correlates with the more aggressive basal-like subtype in mouse and human PDAC. Overexpression of ROR2 in pancreatic cancer cell lines with a classical differentiation induced epithelial-to-mesenchymal transition, characterised by the downregulation of multiple epithelial markers and upregulation of mesenchymal genes. In addition, ROR2-overexpressing cells proliferated much more rapidly, while knockout of ROR2 in pancreatic cancer cells significantly decreased cell proliferation. Conclusion: Our in-depth sequencing data revealed that expression of KrasG12D with the concomitant loss of Pdx1 leads to vast alterations of acinar cell identity. We identified the receptor kinase Ror2 as a regulator of pancreatic cancer initiation and driver of pancreatic cancer cell aggressiveness.

Hematology-Oncology

Bhan A, **Simon R**, **Jacobsen G**, **Yaseen A**, **Navaratnarajah P**, **Sweidan A**, and **Rao SD**. Clinical Relevance Of 24-hour Urine Calcium Measurement In Patients With Primary Hyperparathyroidism (PHPT). *J Endocr Soc* 2023; 7:A246-A247. Full Text

A. Bhan, Henry Ford Hospital, Bloomfield Hills, MI, United States

Introduction: PHPT is the third most common endocrine disease and the most common cause of hypercalcemia in outpatient setting, presents with mild to moderate hypercalcemia with unsuppressed or elevated serum PTH levels, and most patients are asymptomatic. A 24-hour urine Ca measurement to exclude both hypo-and hypercalciuria is used to recommend parathyroidectomy. The purpose of our study is to evaluate the clinical relevance of urine Ca measurement in evaluating patients with PHPT. Methods: A retrospective electronic medical record review was performed on all adult patients with PHPT in whom a 24-hour urine Ca was measured between 2015-2019. Patients with secondary HPT, those without a 24-hour urine Ca measurement, and patients with serum Cr >1.5 mg/dl were excluded. Results: 393 patients met inclusion criteria for subsequent analyses. For the entire cohort, mean serum Ca was 10.9 ± 0.6 mg/dl, Cr 0.9 ± 0.2 mg/dl and PTH 111± 65 pg/ml with no significant difference between groups by gender, race, or stone history. Mean urine Ca for the entire cohort was 254 ± 170 mg/day. 46% and 35% had urine Ca >250 or >300 mg/d respectively. Multiple linear regression results indicated that higher serum Ca ($p=0.004$), lower serum Cr ($p<0.001$), white race ($p<0.001$), and higher urine sodium ($p<0.001$) were all significantly predictive of higher UCa. However, the mean urine Ca did not differ between patients with and without nephrolithiasis (276 ± 182 Vs. 280 ± 247 mg/d; $p=0.174$). Discussion: The most recent guidelines for the management of asymptomatic PHPT recommend measurement of 24-hour urine Ca in all PHPT patients. However, the validity, sensitivity and specificity of such an approach has never been formally evaluated, considering wide variability of urine Ca excretion in the population and lack of difference in urine Ca between patients with and without nephrolithiasis. Previous guidelines discussed this issue and determined that measurement of a 24-hour urine collection is cumbersome and adds very little to patient management. Our study questions the clinical relevance of re-including 24-hour urine Ca in the latest guidelines. Conclusions: Our study suggests that measurement of 24-hour urine Ca in the routine evaluation of patients with PHPT is unhelpful.

Hematology-Oncology

Drilon A, Awad MM, Camidge DR, Forde PM, Alexander M, **Gadgeel SM**, Villaruz LC, Perez J, Navas T, Daly C, Patel S, Li S, Laughlin M, Lowy I, Magnan H, and Rietschel P. EP10.01-03 A Phase 1/2 Study of REGN5093-M114, a METxMET Antibody-Drug Conjugate, in Patients with MET-Overexpressing NSCLC. *J Thorac Oncol* 2023; 18(11):S602-S603. Full Text

Introduction: Mesenchymal epithelial transition factor (MET), also called hepatocyte growth factor receptor (HGFR), is a high-affinity transmembrane protein receptor for HGF. MET is overexpressed in various malignancies, including non-small cell lung cancer (NSCLC). MET overexpression can accompany MET exon 14 alteration or de novo/acquired MET amplification. REGN5093-M114 is an antibody drug conjugate composed of a novel linker-payload (M114, carrying the maytansine derivative M24, a potent inhibitor of microtubule assembly) covalently bound to lysine residues on a MET-targeting human IgG4p bispecific antibody, REGN5093. In preclinical models of MET overexpressing cancers, REGN5093-M114 demonstrated significant dose-dependent antitumor activity. This trial in progress was previously presented at the 2022 annual meeting of the American Society of Clinical Oncology. Methods: This is an open label, phase 1/2, first-in-human, multicenter dose-escalation study with cohort expansion evaluating REGN5093-M114 in patients with MET-overexpressing NSCLC (NCT04982224). Patients must have advanced stage NSCLC for which there are no approved therapies available expected to confer clinical benefit, with tumor overexpressing MET (≥75% tumor cell staining at 2+) as centrally confirmed by immunohistochemistry. For the expansion phase, patients must have at least one lesion that is measurable by RECIST 1.1. REGN5093-M114 will be administered intravenously once every 3 weeks over 30 minutes until disease progression, intolerable adverse events, withdrawal of consent, or study withdrawal. The primary objectives in dose escalation are to evaluate safety, tolerability, PK, and maximum tolerated dose and/or recommended phase 2 dosing regimen of REGN5093-M114. PKs will include the assessment of REGN5093-M114, total antibody, and payload M24 concentrations. The primary objective in dose expansion is to assess preliminary anti-tumor activity of REGN5093-M114 in MET-overexpressing NSCLC as measured by the objective response rate. The secondary objectives of both phases of the study include an evaluation of treatment durability, and the immunogenicity of REGN5093-M114. Currently, this study is enrolling patients. As of 30 March 2023 17 patients across the five dose levels (table 1). [Formula presented] Results: XXXX. Conclusions: XXXX. Keywords: Non small cell lung cancer, Bispecific, Mesenchymal epithelial transition factor

Hematology-Oncology

Fahr L, **Benitz S**, Straub T, Mutter J, Lisiecki H, Mahajan UM, Beyer G, Steiger K, Terrasi A, Schotta G, Imhof A, Lauber K, Kleeff J, Michalski CW, Mayerle J, and Regel I. Expression of Irf3 and Irf7 in tumour cells drives pancreatic cancer development and progression. *Pancreatology* 2023; 23:e134-e135. Full Text

Abstract Background: The interferon regulatory factors 3 and 7 (Irf3 and Irf7) are transcription factors downstream of the Toll-like receptor 3 (Tlr3) signalling pathway. Tlr3 signalling is stimulated by double-stranded RNAs, which are generated during viral infections but also during tissue stress and cell injury. In previous studies, we found Tlr3, Irf3, and Irf7 to be overexpressed in metaplastic acinar cells and pancreatic tumour cells. The purpose of this project is to investigate the functional role of Irf3 and Irf7 in pancreatic carcinogenesis, particularly in non-immune cells. Methods: Pancreatic tumourigenesis was examined at various time points in caerulein-treated Irf3/Irf7 knockout mice with inducible Kras mutation. Furthermore, we generated Tlr3-hyperactivated and Irf3/Irf7 double knockout murine pancreatic tumour cells. These tumour cells were phenotypically characterised in vitro and further used in orthotopic and metastatic mouse models. Additionally, we identified transcriptional alterations in Irf3/Irf7 knockout tumour cells by RNA-Seq. Results: Global loss of Irf3/Irf7 prevents the formation of precursor lesions and pancreatic cancer in caerulein-treated Kras mutant mice. Consequently, depletion of Irf3 and Irf7 in tumour cells leads to reduced invasive capacity and decreased colony formation in vitro. In the orthotopic and metastatic mouse models, injection of Irf3/Irf7 knockout cells markedly impaired tumour and metastasis formation, whereas Tlr3-hyperactivated cells led to increased tumour and metastasis volumes. Our in vivo and in vitro experiments confirmed an immune-independent function of the Tlr3/Irf3/Irf7 signalling pathway in pancreatic tumour cells that is crucial for tumour progression. Conclusion: Our findings suggest that Irf3 and Irf7 expression in tumour cells is required for the development of pancreatic cancer. Moreover, activated Tlr3/Irf3/Irf7 signalling enhances tumour cell aggressiveness in pancreatic cancer cells.

Hematology-Oncology

Gadgeel S, Jänne PA, Spira AI, Ou SHI, Heist RS, Pacheco JM, Johnson ML, Sabari JK, Leventakos K, Mason JA, Velastegui K, Yan X, Chao R, and Riely GJ. MA06.04 KRYSTAL-1: Two-Year Follow-Up of

Adagrasib (MRTX849) Monotherapy in Patients with Advanced/Metastatic KRASG12C-Mutated NSCLC. *J Thorac Oncol* 2023; 18(11):S118. Full Text

Introduction: KRASG12C mutations occur in approximately 14% of patients with NSCLC. Adagrasib, an oral, selective KRASG12C inhibitor, was selected for favorable properties, including long half-life (23 hours), dose-dependent pharmacokinetics, and CNS penetration. Recently, based on data from KRYSTAL-1 (NCT03785249), a multicohort Phase 1/2 study evaluating adagrasib as monotherapy or in combination for patients with KRASG12C-mutated solid tumors, the FDA granted accelerated approval of adagrasib for patients with previously treated KRASG12C-mutated advanced/metastatic NSCLC. Adagrasib is also under review by the EMA and MHRA. Herein, we present data from a two-year follow-up pooled analysis of the Phase 1/1b Cohort and Phase 2 Cohort A of KRYSTAL-1. Methods: In the Phase 1/1b and Phase 2 Cohorts, patients with KRASG12C-mutated advanced/metastatic NSCLC were treated with adagrasib 600 mg orally BID. Study endpoints for both Cohorts included safety and efficacy (ORR, DOR, PFS, and OS). Objective tumor response was assessed per RECIST v1.1 by blinded independent central review (BICR), as were ORR, DOR, and PFS. Results: As of January 1, 2023, 132 patients with KRASG12C-mutated NSCLC had received adagrasib (Phase 1/1b: 16 patients; Phase 2: 116 patients; median follow-up: 26.9 months [95% CI 25.9-29.7]). Overall, the median age of patients was 64 years (range: 25-89), 56.8% were female, and 19.7% had CNS metastases at baseline; patients had received a median of 2 prior therapies, with 97.0% of patients receiving both platinum-based and checkpoint inhibitor therapies. ORR was 43.0% (55/128 evaluable patients); median DOR was 12.4 months (95% CI 7.0-15.1). Median PFS was 6.9 months (95% CI 5.4-8.7), with a 1-year PFS rate of 35.0% (95% CI 25.9-44.2). Median OS was 14.1 months (95% CI 9.2-18.7); 1-year and 2-year OS rates were 52.8% and 31.3%, respectively. Patients with common co-mutations, including KEAP1 (n=25), STK11 (n=44), or TP53 (n=42), had a median OS of 5.7 months (95% CI 3.6-9.2), 9.2 months (95% CI 5.0-12.7), and 18.7 months (95% CI 11.3-27.0), respectively. Patients with CNS metastases at baseline had a median OS of 14.7 months (95% CI 7.5-19.3). Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 61 patients (40.9% grade 3, 3.0% grade 4, and 2.3% grade 5 [pneumonitis, cardiac failure, and pulmonary hemorrhage, 1 patient each]). TRAEs led to dose reduction in 68 patients (51.5%) and treatment discontinuation in 12 patients (9.1%). Overall, 32.6% of patients (43/132) had received adagrasib for >1 year. Additional safety data for patients on adagrasib >1 year and exploratory analyses will also be presented. Conclusions: In this pooled analysis with longer follow-up, adagrasib demonstrated durable clinical activity, with a median OS of 14.1 months and approximately one in three patients alive at two years. Exploratory analyses suggested heterogeneity of clinical benefit based on the presence of co-mutations, which should be further evaluated. The reported safety profile was manageable and consistent with previous reports. A Phase 3 trial evaluating adagrasib monotherapy compared with docetaxel in patients with previously treated advanced KRASG12C-mutated NSCLC is ongoing (NCT04685135). Keywords: KRAS, NSCLC, adagrasib

Hematology-Oncology

Gadgeel S, Rodríguez-Abreu D, Halmos B, Garassino MC, Kurata T, Cheng Y, Jensen E, Shamoun M, Rajagopalan K, and Paz-Ares L. OA14.05 5-Year Survival of Pembrolizumab Plus Chemotherapy for Metastatic NSCLC With PD-L1 Tumor Proportion Score <1%. *J Thorac Oncol* 2023; 18(11):S77-S78. Full Text

Introduction: Pembrolizumab plus chemotherapy significantly improves OS and PFS in patients with previously untreated metastatic NSCLC without EGFR or ALK alterations irrespective of PD-L1 tumor proportion score (TPS). We present 5-year outcomes from a pooled analysis of phase 3 trials of pembrolizumab plus chemotherapy in patients with previously untreated metastatic NSCLC with PD-L1 TPS <1%. Methods: This pooled analysis included individual patient data from the KEYNOTE-189 global (NCT02578680; data cutoff March 8, 2022) and Japan extension (NCT03950674; data cutoff February 7, 2023) studies of metastatic nonsquamous NSCLC without EGFR or ALK alterations and the KEYNOTE-407 global (NCT02775435; data cutoff February 23, 2022) and China extension (NCT03875092; data cutoff February 10, 2023) studies of metastatic squamous NSCLC. In KEYNOTE-189, patients received pembrolizumab or placebo plus pemetrexed and cisplatin or carboplatin; in KEYNOTE-407, patients received pembrolizumab or placebo plus carboplatin and paclitaxel or nab-paclitaxel. PD-L1 expression was centrally assessed using PD-L1 IHC 22C3 pharmDX (Agilent Technologies, Carpinteria, CA). Tumor

response was assessed per RECIST version 1.1 by blinded independent central review (BICR). Efficacy was evaluated in the intention-to-treat population and safety in the as-treated population. Analyses were performed post hoc and are descriptive only. Results: Among 442 patients with PD-L1 TPS <1% included in this analysis, 255 (57.7%) received pembrolizumab plus chemotherapy and 187 (42.3%) received chemotherapy alone. Baseline characteristics were similar across treatment groups except for tumor histology; 111 patients (43.5%) in the pembrolizumab plus chemotherapy group and 119 (63.6%) in the chemotherapy alone group had squamous tumors. Median time from randomization to data cutoff was 60.7 (range, 49.9–72.0) months. OS, PFS, ORR, and PFS2 were improved with pembrolizumab plus chemotherapy versus chemotherapy alone (Table). Treatment-related AEs occurred in 245/254 patients (96.5%) in the pembrolizumab plus chemotherapy group and 175/186 (94.1%) in the chemotherapy alone group, including 150 (59.1%) and 114 (61.3%), respectively, with grade ≥3 AEs. Conclusions: After 5 years of follow-up, pembrolizumab plus chemotherapy provided clinically meaningful improvements in survival outcomes and durable long-term clinical benefit versus chemotherapy alone with manageable safety in metastatic NSCLC with PD-L1 TPS <1%. These results continue to support the use of pembrolizumab plus chemotherapy as a standard of care first-line therapy for metastatic NSCLC, including in tumors with PD-L1 TPS <1%. Keywords: pembrolizumab, NSCLC, PD-L1-negative [Formula presented]

Hematology-Oncology
Gadgeel S, Wang E, Phani S, Wu C, Salas M, Meng J, Diamand F, Esker S, and Lim DWT. EP12.01-64 Metastatic Non-Small Cell Lung Cancer With EGFR Mutations: Treatment Pattern and Outcomes From a Systematic Literature Review. *J Thorac Oncol* 2023; 18(11):S667. Full Text

Introduction: The development of targeted therapies for advanced or metastatic NSCLC (mNSCLC) harboring EGFR-activating mutations has benefited patients. However, disease progression is inevitable and subsequent treatment options offer limited clinical benefit. The objective of this systematic literature review was to identify current treatment patterns and outcomes in EGFR-mutated (EGFRm) NSCLC to inform opportunities for future therapeutic development. Methods: This review searched Embase and MEDLINE for publications from 2017-2022 that included adult patients with mNSCLC treated with pharmacotherapy. Supplemental searches included congress abstracts, clinical trial registries, and bibliographies of reviews published between 2020 and 2022. Phase 3 or 4 clinical trials with ≥50 participants and observational studies with ≥200 participants were included without geographic restriction. Evaluation focused on treatment pathways, clinical management, and outcomes. Results: 13,312 records were identified; 130 included data on patients with EGFRm NSCLC. Third-generation (3G) EGFR tyrosine kinase inhibitors (TKIs) demonstrated median progression-free survival (mPFS) of 18.9-20.8 months in randomized controlled trials (RCTs) and 16.8 months in an observational study of osimertinib, both in the 1L setting. Overall survival (OS) was reported at 38.6 months for trials that had mature data. In the post-EGFR TKI setting, platinum-based chemotherapy (PBC) regimens demonstrated mPFS of 4.3-5.4 months in RCTs, with an OS benefit of 15.6 months when adjusted for crossover. Recent studies of immune checkpoint inhibitors (ICIs) in combination with PBC did not demonstrate an improvement over PBC alone (mPFS, 5.6-6.9 months). In later-line studies in the post-EGFR TKI, post-PBC setting, mPFS ranged from 2.7-2.95 months with salvage regimens including pemetrexed, gemcitabine, docetaxel (monotherapy or in combination with bevacizumab), and paclitaxel. The most commonly reported any-grade AEs with 3G EGFR TKIs in the were diarrhea, rash, and paronychia. Commonly reported AEs included nausea, decreased appetite, and anemia with PBC regimens and nausea, fatigue, and peripheral neuropathy with ICI regimens. Conclusions: Treatment options after a 3G EGFR TKI remain limited, with minimal PFS and OS benefits. PBC- and ICI-based regimens have only demonstrated a PFS benefit of ≈5 months. The benefit of salvage regimens is even less, with PFS below 3 months. The poor outcomes seen in published trials and the paucity of current trials in this setting highlight an unmet need for new therapeutic options. [Formula presented] Keywords: Treatment Patterns, Epidermal Growth Factor Receptor Mutations, Metastatic Non-Small Cell Lung Cancer

Hematology-Oncology
Ghanem AI, **Gilbert M**, **Lin CH**, **Khalil-Moawad R**, **Momin S**, **Chang S**, **Ali H**, and **Siddiqui F**. Treatment Tolerance and Toxicity in Elderly Oropharyngeal Cancer Patients and Implication on Outcomes. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584.

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Purpose/Objective(s): To investigate the tolerance level and toxicity for standard of care treatment for oropharyngeal cancer (OP) in elderly patients and their impact on outcomes. Materials/Methods: Using our in-house head and neck cancer database, we looked for non-metastatic OP cases that received definitive treatment between 1/2009-6/2020. All patients received either definitive radiation therapy (RT) +/- concomitant systemic therapy (ST), or surgery followed by adjuvant RT or RT-ST. For the elderly (age at diagnosis ≥65 years) and young (<65 years) patients, we compared treatment package time (TPT) (time from surgery to RT conclusion) for adjuvant RT, total RT duration and unplanned RT interruptions. ST details and dose/protocol modifications were also compared. We evaluated worst grade of pain and mucositis, hospitalization for non-hydration causes and febrile neutropenia (FN) during RT. Feeding tube (FT) use and weight loss were compared. The independent effect of these indicators on locoregional (LRFS), distant (DRFS) recurrence free and overall (OS) survival was assessed using multivariate analyses (MVA). Results: A cohort of 326 patients was included: 36% elderly (n = 118) and 64% young (n = 208), with no differences in AJCC stage distribution (8th), treatment received and HPV status (HPV+ve: 73% vs 74.6%; p = 0.86). In 23.6 % who received adjuvant RT, median TPT was 86 (range 72-128) and 81 (65-137) days for elderly vs young (p = 0.27); whereas in the definitive RT cases 76.4%, total RT duration was 49 days for both age groups. Overall, prescribed RT course was not completed in 4% and unplanned RT interruptions occurred in 22.8% and both were non-significant between age groups. Among the 261 patients that received ST, elderly utilized more cetuximab (26 vs 12%; p = 0.007). For those who received cisplatin, 20% of elderly had cumulative dose <200 mg/m2 compared to 6% among the younger age group (p = 0.006); and cisplatin was changed to carboplatin or cetuximab in 18% vs 8% (p = 0.019). Delayed/cancelled cycles and dose reductions were similar. There were more hospitalizations (47% vs 27%; p<0.001) and a trend for more FN (9% vs 3%; p = 0.09) with older age, while worst pain and mucositis was similar. FTs were used more in elderly patients (64% vs 50%; p = 0.02), for a median of 97 vs 64 days (p = 0.31); of which 19.5% vs 11% (p = 0.28) were inserted before RT start. However, % weight loss was non-significant. On MVA, longer RT duration, FT use and hospitalizations predicted worse LRFS and DRFS; and they were prognostic for OS in addition to TPT >90 days (p<0.05 for all). Nevertheless, elderly vs young had non-significant 3-year LRFS (91% vs 90% and 67% vs 69%), DRFS (86% vs 90% and 79% vs 81%) & OS (85% vs 81% and 39% vs 52%) for HPV+ve and HPV-ve respectively (p>0.05). Conclusion: Elderly patients with OP need more multi-disciplinary supportive care when receiving RT and concurrent ST. However, survival outcomes are equivalent to younger patients. Ongoing studies should enroll more elderly candidates and stratify endpoints with age.

Hematology-Oncology

Gutta R, **Abu Rous F**, Teslow E, Jaeger E, **Gadgeel S**, and **Potugari B**. P2.09-39 Racial Diversity and Co-Mutational Analysis of Biologically Relevant Alterations in EGFR Mutant Lung Cancers. *J Thorac Oncol* 2023; 18(11):S349. Full Text

Introduction: EGFR alterations have important therapeutic implications in lung cancer (LCa). The incidence of these alterations, their subtypes, and co-mutational status is well described in Caucasian and East Asian but not in African American populations. Using the Tempus database, we analyzed real-world data from EGFR mutant LCas across races, assessing alteration subtypes and co-mutational profiles. Methods: De-identified records with primary LCa diagnosis tested via Tempus xT assay and had ≥1 pathogenic EGFR mutation (SNVs, CNAs, or fusions) were identified. Race was determined based on recorded clinical records, and stratified as Caucasian (CA), African American (AA), Asian Pacific Islander (API), unknown or other. Somatic pathogenic co-mutations were restricted to genes >5% frequency ≥1 race. Data is described using N(%) or median and IQR. Comparisons were made by Chi-squared/Fisher's Exact or Kruskal-Wallis tests. Bonferroni or FDR corrections were applied to pairwise comparisons. Results: Of 17,482 LCa samples with prior Tempus xT assay performed on the most recently received tumor specimen, 55.1% were CA, 7.7% AA, 2.5% API, 3.0% other, and 31.7% unknown. Pathogenic EGFR alterations occurred in 8.9% of CA, 7.8% of AA, 39.5% of API, 15.1% of other, and 11.9% unknown. In the EGFR altered population, average age at diagnosis was 68 (60, 75; p=0.065), 63% female, and 96% had no history of tyrosine kinase inhibitor (TKI) therapy prior to sequencing. Majority

had advanced stage disease and were diagnosed with adenocarcinoma. Frequency of exon 19 deletions differed across races (p=0.017), with the highest frequency in “other” races. L858R mutations also differed (p < 0.001) and was significantly higher in CA versus AA (p=0.034) and API versus CA (p=0.006). EGFR CNVs differed across races (p<0.001), with frequencies highest in AA. No statistically significant differences were observed for T790M or, exon 20 insertions. Lastly, KMT2C co-mutations significantly differed (q=0.003), with 13% AA, 3% CA and 4%, API. Similarly, GLI1 differed across races, with highest frequency in AA (5.8%). There was no difference in TP53, RB1, or NTRK2/3 mutations observed. Conclusions: Significant differences in the prevalence of EGFR alterations were observed across races, with specific co-mutations like KMT2C and GLI1 occurring more frequently in AA compared to CA and API patients. KMT2C may be linked to higher TMB and immunotherapy response, while GLI1 has been shown to be involved in erlotinib resistance. Variabilities in alterations across races may inform more effective treatment strategies for LCa patients. [Formula presented] Keywords: EGFR, Non-Small Cell Lung Cancer, Race

Hematology-Oncology
Hamilton E, Spira A, Adams S, Abuhadra N, Giordano A, Parajuli R, Han H, **Weise A**, Marchesani A, Josephs K, Chaudhry A, and Kalinsky K. XMT-1660: A Phase 1b trial of a B7-H4 targeting antibody drug conjugate (ADC) in endometrial, ovarian, and breast cancers (1250). *Gynecol Oncol* 2023; 176:S158. Full Text

Objectives: Endometrial (EC) and ovarian cancers (OC) are some of the leading causes of cancer death among women. Despite therapeutic advances, many patients eventually develop resistance to available standard-of-care (SOC) therapies. B7-H4 is a poor prognostic factor and is overexpressed in several cancers, including endometrial, ovarian, and breast. As a member of the CD28/B7 family of cell surface proteins, it promotes tumorigenesis by suppressing antitumor immunity. XMT-1660 is a B7-H4-targeted Dolasynthen antibody drug conjugate (ADC) designed with a precise, optimized drug-to-antibody ratio and a DolaLock microtubule inhibitor payload with a controlled bystander effect. In the preclinical setting, XMT-1660 has demonstrated antitumor activity in EC and OC PDX models. Methods: The phase I trial includes a first-in-human dose escalation (DES) portion followed by a dose expansion (EXP) evaluating XMT-1660 in patients with endometrial, ovarian, and breast cancers following progression on SOC. In the DES, BOIN (Bayesian Optimal Interval) design will be used to determine the MTD. The DES will assess the safety and preliminary efficacy and establish recommended phase II dose (RP2D). In the EXP portion, cohorts enrolling EC/OC, TNBC, ER+/HER2- BC are planned, and additional patients may be enrolled based on emerging data. The primary endpoints are safety and tolerability, overall response rate, disease control rate, and duration of response. Patients are not selected by B7-H4 status, but baseline tumor samples are collected for retrospective analysis. The trial is currently enrolling patients.

Hematology-Oncology
Miller M, **Bensenhaver J**, **Cannella C**, **Petersen L**, and **Swain M**. Lessons Learned from the Integration of Reproductive Health Specialists in the Multidisciplinary Care of Women with Locally Advanced Breast Cancers. *Obstet Gynecol* 2023; 141(5):92S. Full Text

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INTRODUCTION: The objective of this study was to investigate whether a multidisciplinary approach to breast cancer care with the inclusion of a reproductive health specialist improves referral rates for fertility counseling and/or preservation. METHODS: An IRB-approved retrospective study including women of reproductive age diagnosed with locally advanced breast cancer and treated at a health system before and after the advent of a comprehensive, multidisciplinary tumor board (cMTB) with a reproductive health specialist was conducted. Rates of referral for fertility counseling and utilization of fertility preservation methods were compared between the cMTB and non-cMTB groups using t tests. Secondary analyses comparing baseline group characteristics and rates of referral/fertility preservation by age, insurance type, and race were performed using x2 tests. RESULTS: Of 306 study participants, 117 were cared for by a non-cMTB and 189 by a cMTB. The groups did not differ in average age, parity, breast cancer subtype, insurance type (public versus private), or treatment site (urban versus suburban); however, the distribution of race was significantly different (P 5.003). Overall, a greater percentage of women in the

cMTB group received referrals for fertility counseling compared to those in the non-cMTB group (23.3% versus 0.9%, P,.001). Of the patients in the cMTB group who were referred for counseling, 20.5% underwent fertility preservation. Within the cMTB group, women younger than 30 were significantly more likely to be referred for fertility counseling (41.7% versus 20.6%, P 5.043) and undergo a fertility preservation procedure (16.7% versus 3.0%, P 5.016) than those aged 31-40. No significant differences in rates of referral or fertility preservation by race or insurance type were noted within each group. CONCLUSION: The inclusion of a reproductive health specialist in a multidisciplinary breast cancer tumor board increased rates of referral for fertility counseling for women of reproductive age. A similar, comprehensive approach to the care of reproductive-aged women with gynecologic malignancies should be considered.

Hematology-Oncology

Nyati S, **Stricker H**, **Barton KN**, **Li P**, **Elshaikh M**, **Ali H**, **Brown SL**, **Hwang C**, **Peabody J**, **Freytag SO**, **Movsas B**, and **Siddiqui F**. Replication Competent Adenovirus-Mediated Cytotoxic and Interleukin-12 Gene Therapy in Prostate Cancer: 36-month Follow-Up Data from a Phase I Clinical Trial. *Mol Ther* 2023; 31(4):297. Full Text

Introduction: Men with locally recurrent prostate cancer, after definitive radiotherapy, have few therapeutic options. Oncolytic adenovirus-mediated cytotoxic gene therapy is an investigational cancer therapy. Delivery of the suicide gene to the tumor is by direct intratumoral or systemic injection of a viral vector containing the suicide gene. Our approach incorporates yeast cytosine deaminase (yCD) and herpes simplex virus thymidine kinase (HSV-1 TK), to confer sensitivity to 5-fluorocytosine (5-FC) and Valganciclovir (vGCV), respectively. The pro-drugs are converted into active drugs that inhibit DNA damage repair. Here we report the safety of oncolytic adenovirus-mediated suicide gene therapy that incorporates an interleukin-12 (IL12) gene for treatment of recurrent prostate cancer. Methods: In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 15 subjects with recurrent prostate cancer (T1c-T2) at escalating doses (1 × 1010, 3 × 1010, 1 × 1011, 3 × 1011, or 1 × 1012 viral particles). Subjects received 5-FC and vGCV for 7 days. The study endpoint was toxicity through day 30. Experimental endpoints included measurements of serum IL12, interferon gamma (IFNγ), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells (PBMC) and proliferation markers were analyzed by flow cytometry. Results and conclusions: Fifteen patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC and vGCV. Approximately 92% of the 115 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of only two patients. Elevated serum IL12, IFNγ, and CXCL10 levels were detected in 57%, 93%, and 79% of subjects, respectively. Serum cytokines demonstrated viral dose dependency, especially apparent in the highest-dose cohorts. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration in cohort 5. The study did not detect a significant difference in the PSA doubling time (PSADT) between pre and post treatment by paired Wilcoxon rank test (p=0.17). There was no correlation between adenoviral dose and PSADT in each cohort separately or pooled (cohorts1-3 and cohorts 4-5). The study maximum tolerated dose (MTD) was not reached indicating 1012 viral particles was safe. This trial confirmed that replication-competent Ad5-IL-12 adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) was well tolerated when administered locally to prostate tumors.

Hematology-Oncology

Qin A, Morgensztern D, Waqar S, Owen D, **Gadgeel S**, Schneider B, Kalemkerian G, Rice J, and Ramnath N. P2.06-08 Phase I/II Study of Rucaparib and Pembrolizumab Maintenance in Stage IV NSCLC after Carboplatin, Pemetrexed, Pembrolizumab. *J Thorac Oncol* 2023; 18(11):S320. Full Text

Introduction: Carboplatin, pemetrexed, and pembrolizumab (CPP) followed by pemetrexed and pembrolizumab (PP) maintenance is a standard of care (SOC) for non-squamous metastatic non-small cell lung cancer (NSCLC) with a progression-free survival (PFS) of 8.8 months. Up to 38% of sporadic NSCLCs harbor somatic mutations in genes of the homologous recombinant repair (HRR) pathway resulting in a “BRCAness” phenotype that predicts sensitivity to PARP inhibitors (PARPi). Treatment with PARPi upregulates PD-L1 expression, which is associated with pembrolizumab response. We therefore

hypothesized that maintenance therapy with a PARPi plus pembrolizumab will improve PFS compared to SOC PP. Methods: This was a single arm, multi-site, investigator-initiated phase I/II study that enrolled treatment-naïve patients with stage IV non-squamous metastatic NSCLC eligible for CPP. Patients without progression after 4 cycles of CPP received maintenance with rucaparib 600 mg PO BID and pembrolizumab 200 mg IV every 21 days. The primary objective was efficacy assessed by PFS. Secondary objectives included overall survival (OS), safety, and objective response rate (ORR). This study was funded by both Merck and Clovis; NCT03559049. Results: From 12/24/2018 to 10/6/2022, we enrolled 25 patients, 11 of whom did not proceed with maintenance. Reasons for not receiving maintenance include progression on CPP (3/11), physician discretion (2/11), AE from CPP (2/11), study termination (2/11), patient passed (1/11, not due to study), and incorrect enrollment (1/11). Here we report the early results of the 14 patients who received at least one cycle of maintenance rucaparib and pembrolizumab. The median age was 59 and 64% were female; all patients had adenocarcinoma histology, and one patient had stable treated brain metastases. The study was closed to accrual and terminated early due to financial insolvency of Clovis. The median PFS from enrollment was 11.4 months and median OS was 37.6 months. The ORR from enrollment was 64% (9/14; 8 PR, 1 CR), 95% CI (0.35-0.87). There were no SAEs reported and the highest grade of AE was Grade 3, which occurred in 50% of patients. The most common treatment related Grade 3 AE was liver enzyme elevations (28.6%) followed by anemia/leukopenia (14.6%). Conclusions: This is the first study to examine an alternative maintenance strategy to PP in stage IV non-squamous NSCLC after CPP. While the overall number of evaluable patients is small, the results suggest that maintenance therapy with the combination of PARPi plus pembrolizumab has a manageable safety profile and shows promising efficacy that warrants investigation in a larger study (Phase 3 studies are ongoing). Sequencing data are being evaluated to understand molecular alterations associated with benefit to PARPi and pembrolizumab. Keywords: maintenance therapy, PARP inhibitor, checkpoint inhibitor

Hematology-Oncology

Schreiner N, Fahr L, **Benitz S**, Zhou Q, Alnatsha A, Imhof A, Mahajan U, Mayerle J, and Regel I. Expression of lysine demethylase 5a (Kdm5a) influences tumour aggressiveness in murine pancreatic cancer cells. *Pancreatology* 2023; 23:e132. Full Text

Abstract Background: Lysine demethylase 5a (KDM5A) is a histone demethylase that specifically eliminates transcriptionally activating tri-methylation of lysine 4 of histone 3 (H3K4me3). KDM5A coordinates many crucial cell events, such as cellular senescence, cell cycle, cell motility and epithelial-to-mesenchymal transition (EMT), which are often deregulated in cancer. In own previous studies, we detected a loss of H3K4me3 modifications at pancreas differentiation genes with a concomitant increased expression of Kdm5a in murine pancreatic tumour lesions, indicating an oncogenic role for Kdm5a. Hence, we suppose that Kdm5a-driven removal of H3K4me3 at pancreas differentiation genes during tumour progression results in an undifferentiated, more aggressive phenotype. Methods: The role of KDM5A in human pancreatic cancer was determined using in silico analysis. A knockout of Kdm5a (Kdm5a-KO) was generated in murine pancreatic tumour cells using the CRISPR/Cas9 system. The Kdm5a-KO was confirmed by sanger sequencing and immunoblot analysis. The Kdm5a-KO tumour cells were characterised phenotypically by cell assays determining colony formation, proliferation, migration, cell cycle and cancer stem cell potential. Transcriptional changes in Kdm5a-KO tumour cells were analysed by RNA sequencing. Results: High expression of KDM5A in pancreatic cancer patient tissue was associated with shorter progression free intervals and worse overall survival. The top 100 positively correlated genes of KDM5A were linked with ‘signalling pathways regulating pluripotency of stem cells’, whereas negatively correlated genes were related to mitochondrial and respiratory regulations. Upon Kdm5a-KO, overall H3K4me3 levels were increased and Kdm5a-KO tumour cells showed significant reduction in proliferation, migration, colony formation and the expression of cancer stem cell markers CD24 and CD44 in comparison to control cells. Furthermore, Kdm5a-KO cells demonstrated a delayed escape from the G0 cell cycle phase after medium starvation. Conclusion: Our data suppose that KDM5A induces cancer stem cell signalling pathways, while a loss of Kdm5a caused reduced abundance of cancer stem cell markers and a less aggressive phenotype of the murine pancreatic tumour cells. An overall enrichment of the activating histone modification H3K4me3 upon Kdm5a deletion suggests an epigenetic reprogramming towards a more differentiated phenotype.

Hematology-Oncology

Siddiqui F, **Nyati S**, **Elshaikh M**, Barton K, **Ali H**, **Brown S**, **Hwang C**, **Peabody J**, **Freytag S**, **Movsas B**, and **Stricker H**. Replication Competent Adenovirus-mediated Cytotoxic and Interleukin-12 Gene Therapy in Prostate Cancer: 36 Month Follow-Up Data from a Phase I Clinical Trial. *Cancer Clin Trials* 2023; 46(6):S13-S14. Full Text

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Background: Men with locally recurrent prostate cancer, after definitive radiotherapy, have few therapeutic options that have a high likelihood of eradicating the tumor with a reasonable degree of safety. Oncolytic adenovirus-mediated cytotoxic gene therapy is an investigational cancer therapy that is currently being evaluated in clinical trials. Delivery of the suicide gene to the tumor is usually accomplished by direct intratumoral or systemic injection of a viral vector containing the suicide gene. Two suicide genes that have been evaluated in preclinical models and in the clinic are the E. Coli coli cytosine deaminase (CD) and herpes simplex virus thymidine kinase (HSV-1 TK), which confer sensitivity to 5-fluorocytosine (5-FC) and ganciclovir (GCV), respectively. The pro-drugs are converted into active drugs that block DNA synthesis. In the past we have evaluated the toxicity and efficacy of oncolytic adenovirus-mediated cytotoxic gene therapy in five different clinical trials in prostate cancer, including a prospective randomized phase 2 study. In this Phase I trial we evaluated the safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL12) gene therapy in recurrent prostate cancer patients. Objectives: Phase I dose-escalation trial to evaluate the maximum tolerated dose (MTD) of replication competent adenovirus type 5 gene therapy with interleukin-12 delivered using ultrasound guided intraprostatic injection. Methods: Replication-competent adenovirus (Ad5-yCD/mutTKSR39- rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/ mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 15 subjects with recurrent prostate cancer (T1c-T2) at escalating doses (1 × 1010, 3 × 1010, 1 × 1011, 3 × 1011, or 1×1012 viral particles). Subjects received oral prodrugs, 5-fluorocytosine (5-FC) and Valganciclovir (vGCV) therapy for 7 days. The study endpoint was toxicity through day 30. Experimental endpoints included measurements of serum IL12, interferon gamma (IFN-gamma), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells (PBMC) and proliferation markers were analyzed by flow cytometry. Results: Fifteen patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC and vGCV. Approximately 92% of the 115 adverse events observed were grade 1/2 requiring no medical intervention. Ad5- yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of only two patients. Elevated serum IL12, IFN-gamma, and CXCL10 levels were detected in 57%, 93%, and 79% of subjects, respectively. Serum cytokines demonstrated viral dose dependency, especially apparent in cohorts 4 and 5. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration in cohort 5. There was no correlation between adenoviral dose and PSA doubling time (PSADT). Conclusions: Ultrasound guided intraprostatic injection of replication competent adenovirus type 5 containing wo suicides genes and interleukin- 12 is well tolerated up to a dose of 1 × 1012 viral particles. The study maximum tolerated dose (MTD) was not reached. Further studies will be done to evaluate efficacy of this therapeutic approach in patients with locally recurrent prostate cancer.

Hematology-Oncology

Singhi EK, Desai A, **Abu Rous F**, and Feldman J. OA10.03 Assessing Availability and Demand for Patient-Friendly Resources in Lung Cancer Care: The Patient Perspective. *J Thorac Oncol* 2023; 18(11):S65-S66. Full Text

Introduction: Open-access publications and online platforms have led to a growing demand for specialized cancer-related information accessible to all, particularly patients (1-2). Plain language summaries of fundamental cancer clinical trials may be a valuable resource for patients to learn more about their disease and treatment options (3). Methods: To understand the patient perspective, we surveyed patients with non-small cell lung cancer (NSCLC) to assess the availability and need for easy-to-understand resources. Patients were also provided an example plain language summary and asked for feedback. Results: Of the 58 patients who responded, the majority were female (90%) with a median age of 62 years. All patients were diagnosed with NSCLC, most at stage 4 (76%). Most respondents lived in the United States (88%) and were white (88%). The highest level of education reported was a Master's

degree (31%). At time of diagnosis, 95% of patients and 67% of caregivers/family members sought additional information about their disease and treatments online. 41% of patients reported that the information they encountered online was very difficult/difficult to understand, and 40% were neutral. Most patients (76%) reported that their oncology provider did not provide them with patient-friendly resources with information about their disease, and 93% of these patients would have preferred to receive such resources from their provider. 55% of patients reported that their oncology provider did not explain the data behind their treatment plan, and 85% of these patients would have preferred to have such information presented in a way they could understand. Feedback on an example plain language summary of the pivotal ADAURA trial evaluating adjuvant osimertinib (Figure 1) demonstrated that 97% of patients found the format of the summary helpful and felt it utilized plain language. The summary helped patients understand the goal of treatment better (91%), recall side effects of treatment better (86%), and understand the data supporting the treatment plan being recommended for a particular patient (95%). Conclusions: Most patients with lung cancer reported a lack of patient-friendly resources. Most patients, caregivers, and family members utilize online resources to learn more about their disease and treatments at time of diagnosis, and would like their oncology provider to explain the data supporting their recommended treatment plan in a patient-friendly manner. Plain language summaries of fundamental cancer clinical trials could effectively address this need, as demonstrated by the positive patient feedback in this study. Larger prospective study is needed to validate our findings. Keywords: patient education, plain language summary, medical communication [Formula presented]

Hypertension and Vascular Research

Pavlov TS, **Arkhipov SN**, **Wu A**, **Meng Z**, **Adrianto I**, and **Ortiz PA**. Transcriptomics Analysis of ADPKD Cysts Shows Remodeling of Purinergic Receptors in Pkd1RC/RC Mice. *J Am Soc Nephrol* 2023; 34:556. Full Text

T.S. Pavlov, Henry Ford Hospital, Detroit, MI, United States

Background: Polycystic kidney diseases (PKD) are characterized by development of multiple cysts, dilations of nephron segments, which replace normal tissues and lead to kidney insufficiency. Methods: To identify new gene pathways affected by cyst development in collecting ducts, we used a bulk RNAseq approach comparing gene expression of normal microdissected cortical collecting ducts (n=3) vs cysts (n=4) microdissected from the same Pkd1RC/RC mice. Results: Bulk-RNA analysis identified 18,000 genes and allowed statistical comparison of over 15,000 genes. Our data reveals that although cysts originate from normal collecting ducts, cystic epithelium show 2692 down-regulated and 2278 upregulated genes ($p<0.05$ pAdj. FDR). Ingenuity Pathways Analysis identifies the following intracellular mechanisms mostly affected by transition: Rac and Rho signaling, fibrosis signaling, epithelial-to-mesenchymal transition, cytoskeleton rearrangement and ERK/MAPK signaling. Our previous publication reported that development of cysts in an autosomal recessive model of PKD is associated with a shift of P2Y to P2X receptor abundance. In the current study we found that in the autosomal dominant Pkd1RC/RC mice model purinergic signaling undergoes similar remodeling. The most abundant ionotropic receptors with reduced expression were P2ry2 and P2ry4, whereas ionotropic receptors P2rx5 and P2rx7 increased expression (2.88 and 1.53, log2). Additionally, analysis detected elevated abundance of P2ry6, P2ry12 and P2ry13 RNA level. We hypothesize that the physiological significance of the predominant P2X signaling in the cysts include their role in regulation of ATP release via pannexin-1 channels. Abnormal ATP accumulation in the cyst space was shown earlier to contribute in cystogenesis and we previously showed that pannexin-1 mediates ATP release to the cyst lumen. In the presented study, RNAscope confirms hyperexpression of P2rx7 mRNA in cysts. In a heterologous CHO cells system, interaction of P2X7 with pannexin-1 upregulates channel activity and both proteins co-immuno precipitate. Conclusions: Development and establishment of ADPKD cysts involves massive transcriptome remodeling of collecting ducts which include a shift in purinergic signaling that facilitates pathogenic pannexin-1 hyperactivity.

Infectious Diseases

Cunningham D, Willey V, Pizzicato LN, Pollack M, Wenziger C, Glasser L, Teng C, Hirpara S, Dube C, and Verduzco-Gutierrez M. Real-World Healthcare Resource Utilization (HCRU) and Costs Among Patients with Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT) with Covid-19

in a Commercially Insured or Medicare Advantage (MA) Population. *Am J Transplant* 2023; 23(6):S674. Full Text

Purpose: Estimate the incidence of COVID-19 and long COVID-19 syndrome and evaluate HCRU and costs associated with COVID-19 among HSCT and SOT patients. Methods: HSCT and SOT patients were retrospectively identified from the Health-Core Integrated Research Database between 4/1/2018 and 3/31/2022 (study end date). The first transplant date or 4/1/2020 was set as the index date, whichever came last. Patients were enrolled in a commercial or MA insurance plan for 1 year prior to index and followed until disenrollment, study end date or death. COVID-19 was identified through diagnosis codes on medical claims and outpatient laboratory results. Incidence rates (IRs) for COVID-19 and long COVID-19 were calculated. Hospitalized patients were classified as severe (intensive care unit stay with noninvasive high flow oxygen or invasive respiratory/cardiovascular support or discharge status of expired) or moderate (all other hospitalizations); length of stay (LOS) and inpatient costs were calculated. All-cause HCRU and costs were calculated for the 30 days pre/post-COVID-19. Results: In total, 28,698 HSCT or SOT patients were identified (mean age: 53 years; 58% male) and followed for 17 months on average. During follow up, 16% of HSCT/SOT patients developed COVID-19; the IRs of COVID-19 and long COVID-19 are shown (Figure). Total mean costs among these patients increased from $9,144 pre-COVID-19 to $30,181 post-COVID-19. Of the 33% of HSCT or SOT patients hospitalized for COVID-19, 46% were severe with a mean LOS of 20 days and total cost of $121,609, while 54% were moderate with a mean LOS of 11 days and total cost of $34,210. Conclusions: Patients with HSCT or SOT have high IRs of COVID-19 with substantial associated costs. These findings show high burden of COVID-19 and unmet need, highlighting opportunities to improve COVID-19 prevention and care for this population. CITATION INFORMATION: Pizzicato L., Willey V., Pollack M., Wenziger C., Glasser L., Teng C., Hirpara S., Dube C., Verduzco-Gutierrez M., Cunningham D. Real-World Healthcare Resource Utilization (HCRU) and Costs Among Patients with Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant (SOT) with Covid-19 in a Commercially Insured or Medicare Advantage (MA) Population AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: [Figure presented]

Internal Medicine

Cunningham A, Mueller A, Getzinger J, **Obri M**, **Kerr H**, and **Jafri S**. Dermatologic Manifestations and Outcomes of Patients with Graft vs Host Disease Following Liver Transplant in a Real World Setting. *Am J Transplant* 2023; 23(6):S1180. Full Text

Purpose: The objective is to evaluate cutaneous manifestations and outcomes of patients with Graft Vs Host Disease (GVHD) following liver transplant. Methods: A retrospective review was conducted at an urban academic center to track cutaneous and multi-organ manifestations of GVHD s/p liver transplant. We analyzed the indication for liver transplant, cutaneous symptoms at initial presentation, 6 months, and 1 year, treatments, and survival rates. We compared outcomes in patients with cutaneous GVHD (cGVHD), cutaneous GVHD with additional organ involvement (AOI), and non-cutaneous GVHD. Results: 13 patients were diagnosed with GVHD s/p liver transplant. 30.8% developed cGVHD, 46.2% developed cGVHD with AOI, and 23.1% developed non-cutaneous GVHD. Mean age was 66.1 years. 76.9% were male. Indications for liver transplant were HCV cirrhosis (15.4%), familial amyloidosis (7.7%), NASH cirrhosis (53.8%), and alcoholic cirrhosis (23.1%). 100% of patients were treated with triamcinolone 0.1% and corticosteroids. Following liver transplant, the mean onset of cGVHD was 31.6 days (range 2-64). At initial presentation, 90% of patients had a diffuse, erythematous maculopapular rash on the chest, abdomen, and back. 60% of patients reported pruritus. Regarding multi-organ involvement, 69.2% developed GVHD with AOI. 11.1% of patients developed bilateral non-granulomatous uveitis (mean onset 7 months). 44.4% of patients developed colitis (mean onset 39.7 days). 88.9% of patients developed pancytopenia (mean onset 42.6 days). At both 6 and 12 months, 66.6% of patients had complete resolution of cGVHD. The mean duration until complete cutaneous resolution in patients with cGVHD vs cGVHD with AOI was 7.6 and 1.9 months, respectively. At both 6 and 12 months, 100% of patients had improvement of pruritus and degree of regional spread. A non-pruritic maculopapular rash remained in 33.3% of patients at 1 year. Common complications s/p liver transplant were bacteremia (69.2%), pneumonia (46.2%), UTIs (46.2%). The incidence of bacteremia in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 83.3, and 100%. The incidence of pneumonia in cGVHD, cGVHD with AOI, and non-cutaneous GVHD was 25, 50, and 66.7%. The incidence of UTIs in cGVHD, cGVHD with AOI,

and non-cutaneous GVHD was 25, 66.6, and 33.3%. Regarding survival, 53.8% of our GVHD patients are deceased. The mean survival duration s/p liver transplant was 86.4 days (range 39-167). 41.7% of all patients survived at the 6 months, 1 year, and 3 years. 100% of cGVHD patients survived to 6 months, 1 year, and 3 years. Notably, only 12.5% of cGVHD with AOI patients survived to 6 months, 1 year, and 3 years. Conclusions: The incidence of GVHD s/p liver transplant is approximately 0.5-2%. Based on our results, mortality is significantly increased at 6 months, 1 year, and 3 years in patients with cGVHD with AOI. Early recognition and treatment is crucial for patient prognosis. CITATION INFORMATION: Mueller A., Getzinger J., Obri M., Kerr H., Jafri S. Dermatologic Manifestations and Outcomes of Patients with Graft vs Host Disease Following Liver Transplant in a Real World Setting AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: A.Mueller: None. J.Getzinger: n/a. M.Obri: None. H.Kerr: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Internal Medicine

Faber A, **Lam H**, and **Simon R**. Metastatic Insulinoma Diagnosed Postpartum. *J Endocr Soc* 2023; 7:A1165-A1166. Full Text

A. Faber, Henry Ford Health System, Detroit, MI, United States

Introduction: Insulinomas are rare neuroendocrine tumors derived from the beta cells of the pancreas. These tumors generally occur at a rate of four cases per million per year, and they are seen across all demographics. Affected patients present with symptoms of hypoglycemia, including confusion, diaphoresis, and palpitations. Insulinomas occur as single or multiple tumors, and can be benign or malignant. Insulinomas with metastases are defined as malignant. The primary treatment is surgical resection. However, in the case of metastatic insulinomas prognosis can be quite poor with limited treatment options. Case Presentation: A 24-year-old female employed as a nurse with otherwise negative medical history originally presented around 3 months postpartum with epigastric pain which was attributed to gas. Symptoms progressed to include lightheadedness, palpitations, and sweating. She checked her blood glucose during these events and noted it to be consistently in the 30s-40s. She would treat these episodes with food and had short-term improvement in symptoms. She presented to an outside hospital where imaging revealed: hepatomegaly with innumerable hypodense liver lesions, hypo-enhancing pancreatic head lesion, sclerotic focus in T4 vertebral body, as well as multiple enlarged upper abdominal lymph nodes including peripancreatic, porta hepatis, and gastrohepatic. Liver biopsy revealed well-differentiated neuroendocrine tumor, WHO grade 3 likely from a pancreatic primary and chemotherapy was initiated with carboplatin and paclitaxel with some response. However, hypoglycemia became refractory to management with 5% dextrose drip, so she was transferred to our facility for escalation of care. TPN was initiated and dextrose drip was escalated eventually to 40% dextrose. She was also given octreotide, hydrocortisone, and eventually diazoxide. Given degree of tumor burden as well as abdominal ascites and clinical condition, surgery was deemed high risk and not recommended. Tumor board meeting was held and her chemotherapy regimen was changed to Carboplatin/Etoposide/Atezolizumab. She subsequently underwent hepatic artery embolization twice with improvement of hypoglycemia. Despite decreasing dextrose drip requirements by over 50%, patient was unable to be liberated from dextrose infusion and had multiple discussions about management options and prognosis. The patient eventually elected to go home with home hospice. Discussion: Insulinoma diagnosed in pregnancy or shortly after pregnancy is extremely rare. There are only three case reports of malignant insulinoma diagnosed in or after pregnancy. Given the degree of extensive metastases at time of presentation, we expect our patient's insulinoma was present prior to delivery. Hypoglycemia may have only manifested in the postpartum period when there was decreased levels of placenta-derived counterregulatory hormones.

Internal Medicine

Faber A, and **Levy S**. Hyperosmolar Hyperglycemic State Presenting As Seizures. *J Endocr Soc* 2023; 7:A497. Full Text

A. Faber, Henry Ford Health System, Detroit, MI, United States

Introduction: Hyperosmolar hyperglycemic state (HHS), also known as hyperosmotic hyperglycemic nonketotic state (HHNK), is one of the most severe complications of diabetes mellitus. HHS is a medical emergency defined by high serum osmolality and hyperglycemia as well as the absence of ketoacidosis in most cases. Wepresent an unusual case of a young man presenting with seizures who on further investigation was found to have HHS. Case Description: A 44-year-old man presented to the hospital for a possible seizure at home. His medical history is significant for EBV+ B-cell lymphoma receiving chemotherapy, HIV on HAART therapy, and prior history of cryptococcus meningitis in 2019. He did not have history of seizures or diabetes mellitus. He reported that five days prior to admission, he began experiencing polydipsia and polyuria, which later progressed to lethargy. The day of admission his mother found him on the floor with generalized body shaking with significant shaking of the right arm, urinary incontinence, and blood in his mouth from tongue biting. He was taken to the hospital due to concern for seizure. Workup revealed elevated blood glucose of 972 and elevated serum osmolality of 322. He did not present with overwhelming ketosis; his beta-hydroxybutyrate was 0.57, he did not have an anion gap, and ketones were not present in his urine. His A1c was elevated at 9.9%. The differential diagnosis for this patient's seizure included chemotherapy side effect, intracranial pathology, infectious etiology in the setting of known HIV, or HHS. Hematology evaluated the chemotherapy regimen and stated it was not likely the cause of his seizures. Neurology assessed the patient with a CT head, MRI brain, EEG, and lumbar puncture, all of which were negative. The CSF from the lumbar puncture underwent intensive testing, which was negative for HSV, VDRL, CMV, EBV, VZV, Lyme disease, and JC virus. Neurology initially started the patient on anti-seizure medication, however later stated his seizure was likely provoked from hyperglycemia and discontinued the medication. Infectious workup included chest X-ray, blood cultures, and urinalysis, all of which were negative. Endocrinology was consulted and recommended initiating basal and bolus insulin as well as testing for GAD antibodies. Unfortunately, the patient left the hospital against medical advice and GAD antibody testing was not completed. Discussion: The most common symptoms of HSS include hyperglycemia, polyuria, and polydipsia. Though neurological symptoms can occur, they are not common. The neurologic symptoms are typically not seen until the serum osmolality reaches 320 - 330 mOs/kg, and this patient's serum osmolality was elevated at 322 mOs/kg. Though seizure is not well understood in hyperglycemia, treatment for HHS-induced seizures focuses on aggressive management of the underlying hyperglycemic state.

Internal Medicine

Finotti M, **Jesse M**, Pillai A, Liapakis A, **Venkat D**, **Salgia R**, Kumar V, **Manivannan A**, **Lu M**, **Zhang T**, Verna E, and Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation. *Am J Transplant* 2023; 23(6):S864-S865. Full Text

Purpose: Living donor liver transplantation (LDLT) is a viable option to increase access to liver transplantation (LT). However, there are well-documented racial and gender-based inequities in access to deceased donor LT. Very little is empirically known about living liver donor (LLD) characteristics in relation to their recipients. Therefore, we aimed to explore the odds of receiving LDLT across LLD and recipient characteristics. Methods: We explored gender, interactions between LLD-recipient race/ethnicity, and other relevant factors on LDLT utilizing national data from the United Network for Organ Sharing (UNOS) for all adult LLD and their recipients who underwent LDLT from 1/1/2012 through 10/1/2022. Results: 3469 LDLTs occurred (5.46% of all LTs). A majority of LLDs were female (n 1864, 54%), mean 37.16 years of age (SD 10.41), and White race (n 2791, 81%), followed by Hispanic (n 423, 12%), Black (n 116, 3%), Asian (n 85, 2%), and Other (n 47, 1%). LDLT recipients were predominantly male (n 1843, 53%), mean 53.35 years of age (SD 13.22), and White race (n 2787, 80%), followed by Hispanic (n 437, 13%), Black (n 118, 3%), Asian (n 92, 3%), and Other (n 35, 1%). Of note, 42.9% (n 1487) of LLDs were not biologically related to their recipient. As reported in Table 1, men are both less likely to receive or be a LLD than women. Examining the donor by recipient race interactions, LDLT is more likely to occur between LLD and recipients with the same racial/ethnic category than differing race/ethnicity (regardless of comparator). When race/ethnicity is different between LLD-recipient, four significant interactions occurred indicating that White LLDs are less likely to donate to Black recipients than Hispanic or Others/Unknown and Asian donors are more likely to donate to Others/Unknown than either Hispanic or White recipients. Conclusions: While biological relatives are assumed to be the same race/ethnicity, nearly half of LLDs are not biologically related to their recipient and yet all racial groups were more likely to donate within their own racial category, adjusting for liver disease category and functional status. Also,

despite representing the majority of waitlisted and transplanted patients, men were less likely to receive LDLT, but men are also less likely to be a LLD. These results provide a starting point to foster efforts towards diversifying the LLD population. CITATION INFORMATION: Jesse M., Pillai A., Liapakis A., Venkat D., Salgia R., Kumar V., Manivannan A., Lu M., Zhang T., Verna E., Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.Jesse: None. E.Verna: None. N.Parikh: Consultant;; Eisai, Eli Lilly, Research Grant Site Overall Principal Investigator;; Genentech. A.Pillai: n/a. A.Liapakis: None. D.Venkat: n/a. R.Salgia: n/a. V.Kumar: None. A.Manivannan: n/a. M.Lu: n/a. T.Zhang: n/a. [Figure presented]

Internal Medicine

Mittal A, **Beidoun MH**, **Valdes JL**, **Peleman A**, **Reddy S**, and **Patel AK**. Hypercalcemia as a Rare Manifestation of Pneumocystis jirovecii Pneumonia. *J Am Soc Nephrol* 2023; 34:329. Full Text

A. Mittal, Henry Ford Hospital, Detroit, MI, United States

Introduction: Pneumocystis Jirovecii pneumonia (PJP) is a fungal infection which disproportionally affects immunocompromised individuals. We present two cases of PJP associated with hypercalcemia and acute kidney injury (AKI) in renal transplant recipients (RTR). Case Description: Case 1: A 40-year-old male RTR patient presented with oneweek of fever, cough, and shortness of breath. CT Chest showed peripheral groundglass opacities. Patient remained febrile, tachycardic, and hypoxic. Given the clinical presentation and Fungitell > 500 pg/mL, treatment for PJP was started with Atovaquone and steroids. Hypercalcemia (ionized calcium 1.62 mmol/L) was reported with routine workup insignificant for pharmacological or alternate underlying conditions. PTH was suppressed at 6 pg/mL and 1,25 DiHydroxyvitamin D was elevated above 200 pg/mL. 25-Hydroxy Vitamin D levels were within normal limits. Due to lack of improvement in hypercalcemia with IV hydration, Denosumab was prescribed with improvement in serum calcium levels. Bisphosphonates were contraindicated with renal dysfunction. Case 2: A 63-year-old male RTR patient presented with a three-week history of fatigue, cough, and chills. Workup similarly revealed PJP, hypercalcemia, and AKI with an elevated 1,25 DiHydroxyvitamin D. Due to failed treatment with IV Saline, Miacalcin, and Ketoconazole, Denosumab was used with improvement in Hypercalcemia. Clinical improvement of PJP reported with Primaquine and Clindamycin. Discussion: Two renal transplant patients, on immunosuppressive medications, presented with AKI, hypercalcemia, and PJP. This hypercalcemia is believed to be due to an alveolar macrophage mediated process, increasing 1-a-hydroxylase activity and elevating 1,25-DiHydroxyvitamin D. Both patients responded favorably to denosumab, a RANK-L inhibitor which prevents osteoclast activation. PJP was suspected based on bilateral ground-glass opacities on imaging, elevated fungitell, and presence of dry cough in an immunocompromised patient. LDH was not elevated in Case 1, as sensitivity of LDH elevation in non-HIV patients with PJP is as low as 63%. Clinical improvement noted with treatment of PJP. Hypercalcemia is a unique presentation of PJP in renal transplant recipients. Early intervention is recommended given the potential for continued alveolar macrophage mediated Hypercalcemia and AKI.

Internal Medicine

Obri MS, **Kamran W**, **Almajed M**, and **Obri M**. Interventional Radiology-Guided Splenic Artery Embolism in Liver Transplant Patients: A 10-Year Experience. *Am J Transplant* 2023; 23(6):S1187. Full Text

Purpose: This study aims to evaluate the efficacy and safety of splenic artery embolism (SAE) for the management of portal hypertension in patients who have had liver transplants Methods: A retrospective analysis was conducted on liver transplant patients who had underwent interventional radiology (IR) guided SAE post-transplant at a single tertiary transplant center from 2012 to 2022. The primary outcome of intervention efficacy was quantified by peak hepatic artery resistive indices and main portal vein velocities. Ultrasound with doppler obtained before and after the intervention were reviewed for these parameters. The average changes were calculated at a 95% confidence interval. Adverse events were also recorded at the time of the procedure and within one year of the procedure. Secondary outcomes that were measured included platelet count before and 1 month after procedure, spleen size, and need for subsequent splenectomy. Results: All 28 of the patients were white and 18 were males. The mean age of patient was 52.5 years (21-71 years) and time after transplant was 149.5 Days (2-1588 days).

96.4% of SAE were technically successful (n=27). 21 patients had main portal vein (MPV) velocities available and 24 had peak hepatic artery resistive indices (RI) available. In these patients, hepatic artery RI decreased by an average of 0.063 (95% CI 0.014-0.112) after SAE. MPV velocity decreased by an average of 47.2 cm/s (95% CI 27.3-67.1) after SAE. Absolute platelet count increased by an average of 60.0 K/uL (95% CI 36.7-83.3) with a 115.6% increase (95% CI 64.9- 166.3). 10.4% of patients (n=3) developed a procedure-related complication, all of which were femoral access site aneurysms. 0% of patients (n=0) patients suffered from bleeding, infections, or abscesses after the procedure. 10.7% of patients (n=3) required splenectomy after SAE. 1 splenectomy was due to technical failure and 2 were due to refractory symptoms. The change in spleen size was available in 26 patients and the average decrease is size was 1.07 cm (0.78-1.36) or 7% (5-9%) at a 95% confidence interval. Conclusions: IR-guided splenic artery embolism in liver transplant patients is a safe and effective procedure that carries an acceptable complication risk. Patients saw an improvement in both the hepatic artery resistive indices and main portal vein velocity post-embolization. CITATION INFORMATION: Obri M., Kamran W., Almajed M., Obri M. Interventional Radiology-Guided Splenic Artery Embolism in Liver Transplant Patients: A 10-Year Experience AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.S.Obri: None. W.Kamran: n/a. M.Almajed: n/a. M.Obri: n/a.

Internal Medicine

Obri MS, **Samad M**, **Alluri S**, **Alhaj Ali S**, **Almajed MR**, **Ichkhanian Y**, and **Jafri S**. Pulmonary Complications of Everolimus in Liver Transplant Patients: A 10-year Experience. *Am J Transplant* 2023; 23(6):S1007-S1008. Full Text

Purpose: The study aims to evaluate the safety of everolimus as part of the immunosuppression regimen in liver transplant patients. Methods: A retrospective study was conducted at a single, tertiary liver transplant center and was comprised of patients who had undergone liver transplant from 2009 to 2019. Patients were divided into two group depending on whether or not they had received everolimus during their post-transplant course. The primary outcome measured was the development of new pulmonary complications that have been associated with everolimus use. These complications include chronic obstructive pulmonary disease, pulmonary interstitial fibrosis, and pulmonary hypertension. The complications were measured by comparing pre- and post-transplant pulmonary function tests (PFTs) or by evaluating lung anatomy on computerized tomography (CT) scans. Secondary outcomes measured included everolimus discontinuation rates, re-transplant rates, and the rate of rejection between the two groups. Results: 450 patients were included in the study. 64% of the patients were male (n=288) and 83.6% of the patients were white. 65% (n=294) of the patients were never prescribed everolimus and 35% (n=156) of patients were prescribed everolimus throughout their transplant course. On average, patients were prescribed everolimus 208 days (range 35-2261 days) after transplant and the mean last known followup of the patients after everolimus initiation was 1529 days (2-2631). In regards to the primary outcome, 4% (n=6) of patients had a new pulmonary complication after everolimus initiation (n=6) and 6.3% of the control group patients had a new pulmonary complication (n=19). A chi-square statistic was used to calculate and the value was 1.33 with a p-value of 0.249. The result is not significant at p <.05. Of note, 51.3% (n=80) of the everolimus patients had to discontinue the medication throughout their use, with non-pulmonary adverse effects being the primary cause of discontinuation. The most common stand-alone causes of discontinuation were proteinuria, oral ulcers, and cost. 76.3% of the patients had multiple reasons for discontinuation. Secondary outcomes such as re-transplant rates and rejection rates had no significant difference between the everolimus and control group Conclusions: Everolimus appears to be safe from a pulmonary toxicity stand point, with no significant difference between patients who are taking everolimus and patients who are not. Furthermore, there was no significant difference in rejection and re-transplant rates. Of note, there was a significant amount of patients discontinuing the medication, primarily due to side effects. Larger multi-center studies would be needed to evaluate the side effects of everolimus and the tolerability of patients who had undergone liver transplant. CITATION INFORMATION: Obri M., Samad M., Alluri S., Alhaj Ali S., Almajed M., Ichkhanian Y., Jafri S. Pulmonary Complications of Everolimus in Liver Transplant Patients: A 10-year Experience AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.S.Obri: None. M.Samad: n/a. S.Alluri: n/a. S.Alhaj ali: n/a. M.R.Almajed: n/a. Y.Ichkhanian: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Internal Medicine

Rajagopal A, **Goleniak R**, and **Kumbar LM**. Point-of-Care Ultrasound (POCUS) in Metastatic Ovarian Carcinoma: Kidney Injury and Inferior Vena Cava (IVC) Compression. *J Am Soc Nephrol* 2023; 34:465. Full Text

A. Rajagopal, Henry Ford Hospital, Detroit, MI, United States

Introduction: Acute renal failure in metastatic cancer is common, with various causes. Point-of-care ultrasound (POCUS) aids in identifying complications like pleural effusions, edema, and thrombosis. Its utilization is validated both inpatient and outpatient, enhancing diagnostic capabilities at the bedside. Case Description: A 65-year-old female with active metastatic serous ovarian carcinoma of Müllerian origin presented with progressive dyspnea on exertion and lower extremity edema over one month. Her treatment history included Doxil/Bevacizumab with partial response, followed by Carboplatin/Taxol/Avastin and Niraparib with disease progression. Surgical intervention was not an option. Vital signs were significant for tachycardia. Physical examination findings included diminished lung sounds in the left base, distended abdomen, and 3+ pitting edema up to the knees bilaterally. Laboratory workup showed acute kidney injury with creatinine 2.11 mg/dL (baseline 0.9-1.0 mg/ dL) that had been gradually increasing over 6 months. Urinalysis revealed >300 mg/dL protein with a urine protein-to-creatinine ratio of 1.44 g/g. CT chest ruled out pulmonary embolism but revealed a moderate to large left pleural effusion. Intravenous diuretic therapy initially improved symptoms, but renal function subsequently worsened. POCUS demonstrated a patent but collapsible inferior vena cava (IVC) and an abdominal mass compressing the IVC. MRI confirmed flattening of the IVC throughout the abdomen with slit-like narrowing at the level of renal veins, attributed to mass effect from a large left hemiabdominal mass displacing bowel loops. Creatinine stabilized at 1.9 mg/dL, and the patient was discharged with daily furosemide for symptom management and volume status optimization. Discussion: Acute kidney injury due to metastatic mass compression of the IVC is an uncommon but important complication to consider. Compression of the IVC by an abdominal mass can contribute to renal impairment and venous congestion. POCUS is a valuable tool for assessing the IVC and identifying IVC compression, CT or MRI can provide further confirmation. In such cases, diuretic therapy should be used judiciously, with careful consideration of the patient's renal function and overall clinical status. Management of edema and venous congestion in such cases should focus on optimizing volume status and providing symptomatic relief.

Internal Medicine

Yoon Y, **Obri MS**, Sarowar A, **Almajed MR**, and **Jafri S**. Is Alkaline Phosphatase a Predictor of Mortality in Liver Transplant Patients? *Am J Transplant* 2023; 23(6):S1182-S1183. Full Text

Purpose: We aim to evaluate the association between alkaline phosphatase (ALP) and rejection and mortality rates in patients who underwent liver transplantation at 1 and 3 years. Methods: A retrospective study was performed. Patients who received a liver transplant from 2015-2019 were included in the study. Patients' indication of transplant and date of transplant and death were recorded. ALP was measured at the time of transplant, 3 months, 6 months, and 1 year after transplant when available. Mortality rates at 1 and 3 years were measured for patients with an ALP greater than 130 and with an ALP greater than 200 at the respective time periods. ALP values were stratified based on the available literature that suggests that a value great that 130 IU/L is abnormal. Patients who had evidence of rejection were excluded to not have a confounding variable affecting mortality and were analyzed separately. A chi-square was calculated to compare the relationships. Results: 220 patients met the study criteria and were included. A significant positive correlation was demonstrated between ALP level at the time of transplant and death at 1 and 3 years; the chi-square statistic at 1 year was 9.65 (p=0.008) and at 3 years was 6.55 (p=0.04). ALP level at 3 months after transplant had no statistical significance with mortality. ALP level at 6 months after transplant had a statistically significant positive correlation with mortality at 1 year with a chi-square of 7.67 (p=0.022) but did not have a statistically significant correlation at 3 years (p=0.089). ALP level at 12 months after transplant had a statistically significant positive correlation with mortality at 3 years with chi-square 15.17 (p=0.005). Rates of death per group are listed in Table 1. Of the 383 total transplant patients, 41% (n=157), developed transplant rejection. Of these patients, 28.7% (n=45), had an ALP of greater than 130 at the time of transplant; however, there was no statistically significant correlation between ALP level and rejection as the chi-square was 1.25 (p=0.264). Conclusions: ALP level measured at the time of liver transplant has a statistically significant positive correlation with mortality at 1 and 3

years. ALP level measured at 3, 6, and 12 months had varying levels of statistical significance, although they demonstrated a similar positive correlation. ALP appears to be a promising prognostic marker for post-transplant complications. Further data is necessary to understand the identified correlation. CITATION INFORMATION: Obri M., Sarowar A., Almajed M., Jafri S. Is Alkaline Phosphatase a Predictor of Mortality in Liver Transplant Patients? AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.S.Obri: None. A.Sarowar: n/a. M.R.Almajed: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie. [Figure presented]

Nephrology

Hermez K, **Rajagopal A**, **Soman SS**, and **Umanath K**. A Unique Presentation of Lupus Podocytopathy with Collapsing FSGS Variant. *J Am Soc Nephrol* 2023; 34:1133. Full Text

K. Hermez, Henry Ford Hospital, Detroit, MI, United States

Introduction: Lupus podocytopathy is a rare subset of lupus nephritis seen with nephrotic range proteinuria that presents with findings on kidney biopsy mimicking that of minimal change disease or focal segmental glomerular sclerosis (FSGS). A rare subset of collapsing glomerulopathy can also be seen. This condition has also been linked to the pathologic APOL-1 gene variant. We report a rare case of lupus podocytopathy with collapsing FSGS. Case Description: A 42-year-old African American male with a history of hypertension and systemic lupus erythematosus (on mycophenolate mofetil (MMF) 1.5 g twice daily for non-renal manifestations) presented after outpatient labs showed dramatically increased serum creatinine and BUN. His only reported symptoms were shortness of breath and fatigue. In the ED, blood pressure was 148/84 mmHg. Labs showed serum creatinine of 10.23 mg/dL (baseline of 2.0 mg/dL), BUN of 111, bicarbonate of 9 mmol/L, and hemoglobin of 7.4 g/dL. The urine albumin to creatinine ratio was 1,463.5 mg/g with a urine protein to creatinine ratio of 2.91 g/g. COVID-19, flu A/B, hepatitis panel, EBV, CMV, HIV, blood cultures, and parvovirus were all negative. Kidney biopsy demonstrated acute tubular injury, WHO class II lupus nephritis, and collapsing FSGS in the setting of lupus podocytopathy. APOL-1 gene testing is pending. He was initiated on pulse dose steroids for 3 days, and hemodialysis was initiated due to worsening acidosis. He was continued on his home dose of MMF. He currently remains hemodialysis dependent (declared ESRD). Discussion: Patients with SLE podocytopathy represent less than one percent of all SLE flares, with collapsing FSGS variant even more rare and associated with poor prognosis. In recent years the literature started defining non-HIV-related collapsing glomerulopathy, but no unified data regarding treatment guidelines exist. This patient was treated with a combination of steroids and MMF without success, highlighting a unique presentation of a rarely seen syndrome in lupus nephritis.

Nephrology

Hermez K, and **Sohaney R**. An Atypical Case of Immune Complex-Mediated Glomerulonephritis. *J Am Soc Nephrol* 2023; 34:1117. Full Text

K. Hermez, Henry Ford Hospital, Detroit, MI, United States

Introduction: Rapidly progressive crescentic glomerulonephritis is an aggressive clinical syndrome characterized by massive loss in kidney function in a relatively short period of time, days to weeks. The etiology of this disease is varied, with subtypes including anti-glomerular membrane disease, immune complex-mediated injury, or pauci-immune. We report a rare case of acute exudative and crescentic glomerulonephritis leading to end-stage renal disease due to an unknown infection. Case Description: A 28-year-old African American male with a medical history only remarkable for asthma presents with nausea, vomiting, diarrhea, and severe abdominal pain for 3-4 days. On admission, the patient's lab data showed a serum creatinine level of 12.28 mg/dL, BUN of 71, and WBC of 23,000. Renal ultrasound showed increased echogenicity of bilateral kidneys suggestive of medical renal disease. Non-emergent HD and kidney biopsy were ordered. COVID-19, flu A/B, hepatitis panel, ANA, c-ANCA, p-ANCA, and anti-GBM were all negative. Serum protein electrophoresis showed mildly elevated IgG lambda. C3 was mildly decreased, and C4 was normal. Blood cultures were negative. The patient was initiated on vancomycin/Cefepime/Metronidazole. Kidney biopsy demonstrated 14/16 glomeruli with necrotizing crescents, C3 predominant mesangial and capillary loop staining, and numerous mesangial and

segmental endothelial humps. Discussion: Patients with postinfectious glomerulonephritis and <50% glomerular involvement have a higher chance of mild disease and potential recovery, with >80% glomerular involvement documented as severe disease requiring therapy. This case represents ~87% glomerular exudative crescents due to an unknown cause, likely post-infectious. The patient was treated with pulse steroids x3 days, but no other immunosuppression was started as data is lacking in severe post-infectious GN as well as idiopathic immune complex RPGN. Initiation of oral or IV cyclophosphamide or rituximab was considered, however, was deferred and the patient was treated with steroid monotherapy. The patient remains on hemodialysis with no evidence of renal recovery. This case highlights the need for further studies in immunosuppression guidelines for patients with this debilitating disease.

Nephrology
Jung H, **Samaniego-Picota M**, Demko Z, Fehringer G, Marshall K, Armer M, Tabriziani H, Bhorade S, Gauthier P, and Cooper M. Performance of Donor-Derived Cell-Free Dna in Repeat Kidney Transplant Recipients. *Am J Transplant* 2023; 23(6):S972. Full Text

Purpose: Repeat kidney transplant recipients (RKTR) typically have two allografts in their abdomen, suggesting that there may be elevated levels of dd-cfDNA compared to single kidney transplant recipients (SKTR); however, initial reports have indicated minimal differences in dd-cfDNA levels between the two. We compared dd-cfDNA fractions between RKTR and SKTR in a large cohort of patients. Methods: Patients with either a SKTR or RKTR from the ProActive registry study (ClinicalTrials.gov NCT04091984) were included in this analysis. In a low-risk subcohort, which excluded patients with a rejection episode, dd-cfDNA fractions (%) (the ProsperaTMtest) were compared between SKTR and RKTR. Histology was used as the standard for determining rejection. Results: The full cohort included 9,091 blood draws from 930 patients. There were 46 biopsy matched blood draws from RKTR, including four showing rejection. The low-risk subcohort included 8,382 blood draws (866 patients; 60% male, 45% white), including 7,645 draws from 785 SKTR and 737 draws from 81 RKTR. In the low-risk subcohort, the distribution of dd-cfDNA fractions was higher in RKTR vs. SKTR ($p<0.001$). The 25th, 50th, 75th and 90th %ile dd-cfDNA fractions in RKTR were 36%, 55%, 108% and 166% higher than in SKTR, respectively (See Table). In the biopsy matched samples from the full cohort, 75% of RKTR with rejection (3/4) had dd-cfDNA% elevated above the 1% risk assessment threshold, while 67.7% (28/42) of non-rejections were <1%. Conclusions: The data in this study suggest that dd-cfDNA% in RKTR are higher compared to SKTR; the difference seems to be greater with higher dd-cfDNA%. More data is required to understand whether the dd-cfDNA% differences between SKTR and RKTR have a meaningful impact on clinical interpretation of dd-cfDNA. CITATION INFORMATION: Samaniego-Picota M., Demko Z., Fehringer G., Marshall K., Armer M., Tabriziani H., Bhorade S., Gauthier P., Cooper M. Performance of Donor-Derived Cell-Free Dna in Repeat Kidney Transplant Recipients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.Samaniego-picota: None. Z.Demko: n/a. G.Fehringer: n/a. K.Marshall: n/a. M.Armer: n/a. H.Tabriziani: n/a. S.Bhorade: n/a. P.Gauthier: n/a. M.Cooper: None. [Figure presented]

Nephrology
Kumar V, and **Patel AK**. The Increased Burden of CKD in Young Adults with Questionable Levels of Education and Health Literacy. *J Am Soc Nephrol* 2023; 34:376. Full Text

V. Kumar, Wayne State University, School of Medicine, Detroit, MI, United States

Introduction: This case highlights the harmful effects of unsatisfactory healthcare education that may contribute to poor patient insight in certain communities across the United States. Case Description: This patient is a 29-year-old G4P2113 black female with a past medical history of uncontrolled hypertension(HTN), chronic kidney disease(CKD), and morbid obesity. Her health insurance is managed by Medicaid. At age 17, she had her 1st spontaneous vaginal delivery(SVD) in the emergency department(ED) with no prenatal care(PNC). Urinalysis(UA) during her 3rd trimester was significant for 3+ proteinuria. She was discharged with normal blood pressure(BP). The patient was noncompliant with post-partum follow-up. Her 2nd term SVD was at age 18 with limited PNC(2 ED visits were for severe HTN and proteinuria was noted). BP at discharge was normal but she had proteinuria. In the next 5 years, she lost her 3rd pregnancy. At age 25, she presented for an annual GYN exam where she was diagnosed

with HTN and given NifedipineCC. ED visits documented that she had no primary care provider(PCP) and showed CKD stage 3A. A year later, she returned to the ED with uncontrolled HTN to confirm her 4th pregnancy. She had CKD stage 3B with 2+ proteinuria and a GFR of 43mL/min. She was admitted to labor and delivery and had a preterm SVD. When seen post-partum, the patient was in denial about her diagnosis of CKD. She did not comply with a renal diet and refused anti-hypertensives. To date, she does not have a PCP or nephrologist although she was referred and told about the gravity of the diagnosis. Discussion: Many factors contributed to the progression of this patient's illness: individual, interpersonal, societal and institutional factors. This patient lacked insight into the consequences of proteinuria and HTN that progressed to CKD. She had 3 children without family support. Her early pregnancies interfered with her high school education. We believe that her low socioeconomic status(SES) and domicile negatively impacted her access to a healthy diet. Her race, gender and SES predispose her to poorer health outcomes(HO). The effect of her education and health literacy highlights the impact of healthcare on young adults: It must be further studied to provide focused upstream interventions. An education program incorporating health literacy in high school may help prevent adverse HO.

Nephrology

Mittal A, **Beidoun MH**, **Valdes JL**, **Peleman A**, **Reddy S**, and **Patel AK**. Hypercalcemia as a Rare Manifestation of Pneumocystis jirovecii Pneumonia. *J Am Soc Nephrol* 2023; 34:329. Full Text

A. Mittal, Henry Ford Hospital, Detroit, MI, United States

Introduction: Pneumocystis Jirovecii pneumonia (PJP) is a fungal infection which disproportionally affects immunocompromised individuals. We present two cases of PJP associated with hypercalcemia and acute kidney injury (AKI) in renal transplant recipients (RTR). Case Description: Case 1: A 40-year-old male RTR patient presented with oneweek of fever, cough, and shortness of breath. CT Chest showed peripheral groundglass opacities. Patient remained febrile, tachycardic, and hypoxic. Given the clinical presentation and Fungitell > 500 pg/mL, treatment for PJP was started with Atovaquone and steroids. Hypercalcemia (ionized calcium 1.62 mmol/L) was reported with routine workup insignificant for pharmacological or alternate underlying conditions. PTH was suppressed at 6 pg/mL and 1,25 DiHydroxyvitamin D was elevated above 200 pg/mL. 25-Hydroxy Vitamin D levels were within normal limits. Due to lack of improvement in hypercalcemia with IV hydration, Denosumab was prescribed with improvement in serum calcium levels. Bisphosphonates were contraindicated with renal dysfunction. Case 2: A 63-year-old male RTR patient presented with a three-week history of fatigue, cough, and chills. Workup similarly revealed PJP, hypercalcemia, and AKI with an elevated 1,25 DiHydroxyvitamin D. Due to failed treatment with IV Saline, Miacalcin, and Ketoconazole, Denosumab was used with improvement in Hypercalcemia. Clinical improvement of PJP reported with Primaquine and Clindamycin. Discussion: Two renal transplant patients, on immunosuppressive medications, presented with AKI, hypercalcemia, and PJP. This hypercalcemia is believed to be due to an alveolar macrophage mediated process, increasing 1-a-hydroxylase activity and elevating 1,25-DiHydroxyvitamin D. Both patients responded favorably to denosumab, a RANK-L inhibitor which prevents osteoclast activation. PJP was suspected based on bilateral ground-glass opacities on imaging, elevated fungitell, and presence of dry cough in an immunocompromised patient. LDH was not elevated in Case 1, as sensitivity of LDH elevation in non-HIV patients with PJP is as low as 63%. Clinical improvement noted with treatment of PJP. Hypercalcemia is a unique presentation of PJP in renal transplant recipients. Early intervention is recommended given the potential for continued alveolar macrophage mediated Hypercalcemia and AKI.

Nephrology

Rajagopal A, **Goleniak R**, and **Kumbar LM**. Point-of-Care Ultrasound (POCUS) in Metastatic Ovarian Carcinoma: Kidney Injury and Inferior Vena Cava (IVC) Compression. *J Am Soc Nephrol* 2023; 34:465. Full Text

A. Rajagopal, Henry Ford Hospital, Detroit, MI, United States

Introduction: Acute renal failure in metastatic cancer is common, with various causes. Point-of-care ultrasound (POCUS) aids in identifying complications like pleural effusions, edema, and thrombosis. Its utilization is validated both inpatient and outpatient, enhancing diagnostic capabilities at the bedside.

Case Description: A 65-year-old female with active metastatic serous ovarian carcinoma of Müllerian origin presented with progressive dyspnea on exertion and lower extremity edema over one month. Her treatment history included Doxil/Bevacizumab with partial response, followed by Carboplatin/Taxol/Avastin and Niraparib with disease progression. Surgical intervention was not an option. Vital signs were significant for tachycardia. Physical examination findings included diminished lung sounds in the left base, distended abdomen, and 3+ pitting edema up to the knees bilaterally. Laboratory workup showed acute kidney injury with creatinine 2.11 mg/dL (baseline 0.9-1.0 mg/ dL) that had been gradually increasing over 6 months. Urinalysis revealed >300 mg/dL protein with a urine protein-to-creatinine ratio of 1.44 g/g. CT chest ruled out pulmonary embolism but revealed a moderate to large left pleural effusion. Intravenous diuretic therapy initially improved symptoms, but renal function subsequently worsened. POCUS demonstrated a patent but collapsible inferior vena cava (IVC) and an abdominal mass compressing the IVC. MRI confirmed flattening of the IVC throughout the abdomen with slit-like narrowing at the level of renal veins, attributed to mass effect from a large left hemiabdominal mass displacing bowel loops. Creatinine stabilized at 1.9 mg/dL, and the patient was discharged with daily furosemide for symptom management and volume status optimization. Discussion: Acute kidney injury due to metastatic mass compression of the IVC is an uncommon but important complication to consider. Compression of the IVC by an abdominal mass can contribute to renal impairment and venous congestion. POCUS is a valuable tool for assessing the IVC and identifying IVC compression, CT or MRI can provide further confirmation. In such cases, diuretic therapy should be used judiciously, with careful consideration of the patient's renal function and overall clinical status. Management of edema and venous congestion in such cases should focus on optimizing volume status and providing symptomatic relief.

Nephrology

Rajagopal A, **Sahota RJ**, **Hanna J**, **Soi V**, **Faber MD**, and **Kumbar LM**. Renal Riddles: Acute Interstitial Nephritis in Newly Diagnosed HIV. *J Am Soc Nephrol* 2023; 34:967-968. Full Text

A. Rajagopal, Henry Ford Hospital, Detroit, MI, United States

Introduction: Acute interstitial nephritis (AIN) is an inflammatory process often triggered by medications, infections, autoimmune diseases, or idiopathic factors. Interstitial nephritis can occur as a direct consequence of HIV infection, but cases demonstrating this through exclusion of other etiologies are rare. We present a case of acute interstitial nephritis overlying non-collapsing focal segmental glomerulosclerosis (FSGS) in a patient with newly diagnosed HIV. Case Description: A 51 year old African American male presented with hypertensive emergency along with 3 days of lower extremity edema, cough, dyspnea, and fatigue. Significant labs included: Cr 4.80 mg/dl (unclear baseline), UA with blood and > 500 protein, UPCR 9.9 g/g. Serology workup of nephrotic syndrome revealed ANA 1:640, ds-DNA 1:20, C3 low. Hepatitis panel was negative. HIV-1 positive, with viral load < 30 copies/mL, CD4 547, and Treponemal IgG with nonreactive RPR. Renal ultrasound showed bilateral increased renal echogenicity. Renal biopsy revealed primary FSGS non-collapsing variant and AIN with plasma cell rich infiltrate. Treatment with highly active antiretroviral therapy (HAART) was initiated. One month later, patient was readmitted with right cranial nerve (CN) III and VI palsy. MRI brain revealed possible new meningioma or inflammatory process. Repeat serology showed C3 improved, elevated IgG4, normal SSA/Ro and SSB/La, elevated rheumatoid factor, cerebrospinal fluid pleocytosis of mononuclear cells, and elevated IgG index and oligoclonal bands. Restaining of prior renal biopsy was negative for IgG4-related disease. Patient was started on corticosteroids for possible inflammatory neurologic process. Follow-up visits noted improvement in Cr < 1.0 mg/dl with continued nephrotic range proteinuria despite treatment. Discussion: This case underscores the complexity of diagnosis in the presence of, autoimmune markers, HIV infection, and overlapping clinical features. The diagnosis of AIN occurred prior to initiation of HAART or any other medications. The patient's renal function showed initial improvement with HAART, but a more significant improvement was observed upon the initiation of corticosteroid treatment. The recommended treatment for HIV-associated interstitial nephritis involves initiating HAART, while the efficacy of corticosteroids in this condition remains uncertain.

Nephrology

Raynaud M, **Khoury N**, Jittirat A, Fu Y, Gulbahce N, Woodward R, and Sulejmani N. Clinical Management of Pregnant Transplant Recipients: Utilization of Fetal Fraction and dd-cfDNA. *Am J Transplant* 2023; 23(6):S977-S978. Full Text

Purpose: One of many benefits of kidney transplant (KT) is restoration of fertility in women allowing the option to conceive. However, pregnancy in this population poses significant maternal and fetal challenges. Tools to accurately monitor for allograft rejection during pregnancy are non-specific and biopsy of the allograft can in some cases lead to unintended complications. Immunosuppression management is also complicated due to vast physiologic changes during pregnancy. Utilization of fetal and donor-derived cell-free DNA (dd-cfDNA) may provide better insights for management. Methods: This is a prospective, multi-center, observational study of KT patients undergoing dd-cfDNA (AlloSure, CareDx) monitoring monthly during pregnancy. All KT patients undergo dd-cfDNA surveillance as standard of care. The samples were interrogated for different genomes to quantify fetal fraction (FF) and ddcfDNA. The Kruskal-Wallis test was performed to analyze the dd-cfDNA and FF across time points. Results: Total of 7 KT recipients were included in this analysis. Of those, 5 had live births, 1 had a miscarriage, and 1 is ongoing. Complications during pregnancy included pre-eclampsia (2), post-partum bleeding (2), and allograft rejection (1). One patient was treated for clinical rejection during pregnancy due to rise in serum creatinine (1.3 to 1.7), however, the correlating dd-cfDNA remained stable at 0.23% indicating lack of rejection. Overall, FF significantly increased from 1stto 3rdtrimester ($p<0.0003$ (figure1a)) as expected due to increase in fetal mass. The dd-cfDNA did not differ across 3 trimesters (Figure 1b) indicating lack of injury to kidney allograft. The evolution of FF and dd-cfDNA from pre- to post-pregnancy is described in figure 1c. Clinical parameters correlated with pregnancy related changes in transplant population rather than allograft health (figure 1d). Conclusions: Utilization of dd-cfDNA and fetal fraction provides specific insights into kidney allograft function. This can lead to optimized noninvasive monitoring and management of pregnancy in this patient population. CITATION INFORMATION: Khoury N., Jittirat A., Fu Y., Gulbahce N., Woodward R., Sulejmani N. Clinical Management of Pregnant Transplant Recipients: Utilization of Fetal Fraction and dd-cfDNA AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: N.Khoury: n/a. A.Jittirat: n/a. Y.Fu: n/a. N.Gulbahce: Employee;; CareDX. R.Woodward: Employee;; CareDx, Stock Shareholder;; CareDx. N.Sulejmani: Employee;; CareDx. [Figure presented]

Nephrology

Wheeler M, **Baik I**, **Gonzalez H**, **Jantz A**, **Poparad-Stezar A**, **Summers B**, **Venkat D**, **Samaniego-Picota M**, and **Fitzmaurice M**. Evaluating the Use of Glucagon-Like Peptide 1 Receptor Agonists (GLP1 RA) in a Matched Cohort of Kidney and Liver Transplant Recipients. *Am J Transplant* 2023; 23(6):S947. Full Text

Purpose: To assess the safety and efficacy of GLP1 RA in a matched cohort of kidney transplant (KT) and liver transplant (LT) recipients who received these agents compared to patients who did not Methods: This single-center, retrospective analysis evaluated KT and LT recipients who were initiated on a GLP1 RA for at least 3 months (mo) matched to a nonintervention comparator group (non-GLP1 RA) based on organ type and diagnosis of diabetes mellitus present at time of transplant. The primary endpoint was change in hemoglobin A1C (HbA1c) at 6 mo. Secondary endpoints included weight (kg), BMI (kg/m2), insulin requirements, and number of oral diabetic agents (ODAs). Safety outcomes included incidence of adverse events (AEs), biopsy-proven acute rejection (BPAR), graft loss, and mortality. Results: Of the 74 patients included, 37 received GLP1 RA matched to 37 patients who did not. Baseline characteristics shown in Table 1. More patients in the GLP1 RA group were on ODAs and 10 patients (27%) initiated on an agent <1 year from transplant. Change in median HbA1c in GLP1 RA group from baseline to 6 mo was -0.5% [(7.0% (6.4-8.9); 6.5% (5.6-7.3)] compared to +0.6% in the non-GLP1 RA group [(5.8% (5.5-6.8); 6.6% (5.8-7.6)], p=0.53. Median change in total daily insulin units was -13 units vs +15 units in the GLP1 RA vs non-GLP1 RA group (p=0.16). GLP1 RA group median change in weight was -7.4 kg vs -0.3 kg in non-GLP1 RA group (p=0.02). BMI change was -3.1 kg/m2 in GLP1 RA vs +0.7 kg/m2 in non-GLP1 RA, p=0.02. In GLP1 RA group, 7 patients (38.9%) experienced an AEs related to drug with 4 (10.8%) leading to discontinuation. Common AE being abdominal pain. One patient (2.7%) discontinued drug due to cost, 3 patients (8.1%) found it ineffective, and 1 (2.7%) had a drug-unrelated discontinuation. Eight patients

(21.6%) in each group experienced BPAR. In the GLP1 RA group, 1 patient had graft loss compared to 2 patients in the non-GLP1 RA. No patient deaths occurred with GLP1 RA while 2 patient deaths in the comparator group. Conclusions: GLP1 RA lowered median HbA1c after 6 mo with subsequent clinically and statistically significant reductions in weight, BMI, and insulin requirements in both KT and LT recipients. AE rates are similar to reported literature. GLP1 RAs are safe and effective at all time points of initiation, including <1 year posttransplant, making them useful agents for management of metabolic complications in this patient population. CITATION INFORMATION: Baik I., Gonzalez H., Jantz A., Poparad-Stezar A., Summers B., Venkat D., Samaniego-Picota M., Fitzmaurice M. Evaluating the Use of Glucagon-Like Peptide 1 Receptor Agonists (GLP1 RA) in a Matched Cohort of Kidney and Liver Transplant Recipients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: I.Baik: None. H.Gonzalez: n/a. A.Jantz: n/a. A.Poparadstezar: n/a. B.Summers: n/a. D.Venkat: n/a. M.Samaniego-picota: None. M.Fitzmaurice: n/a. [Figure presented]

Neurology

Lu Y, Marigi E, Alder K, Mickley J, Camp C, Levy B, Krych A, and **Okoroha K**. Identifying Racial Disparity in Utilization and Outcomes of Hip Arthroscopy using Machine Learning. *Orthop J Sports Med* 2023; 11(7). Full Text

Y. Lu

Objectives: Background: Arthroscopic diagnosis and treatment of femoroacetabular pathology has been increasingly used in the past thirty years with interventions resulting in improved hip function and ultimate delay of hip arthroplasty in a minimally invasive manner. Unfortunately, previous investigations have observed decreased rates of access, utilization of, and outcomes following orthopedic interventions such as hip arthroplasty in underrepresented patients. The purpose of this study is to examine racial differences in procedural rates, outcomes, and complications in patients undergoing hip arthroscopy. Methods: Methods: The State Ambulatory Surgery and Services Database (SASD) and State Emergency Department Database (SEDD) of New York were queried for patients undergoing hip arthroscopy from 2011 to 2017. The primary outcomes investigated were utilization over time, total charges billed per encounter, 90-day emergency department visits, and revision hip arthroscopy. Patients were stratified into White and non-White race, and intergroup differences were evaluated with descriptive statistics. Subgroup analysis was performed with linear mixedeffects models to identify significant interactions between race and individual variables that contributed to any differences in the outcomes of interest. Temporal trends in utilization of hip arthroscopy and concomitant procedures between the two groups were analyzed with Poisson regression modeling. Finally, targeted maximum likelihood estimation (TMLE) was performed to provide nonparametric estimates of the specific differences in the outcomes studied using machine learning ensembles while controlling for patient risk factors. Results: Results: A total of 9,745 patients underwent hip arthroscopy during the study period, with 1,081 patients of non-White race (11.9%). Results of Poisson regression demonstrated an annual increase of 1.11 in the incidence rate of hip arthroscopy among White patients, compared to 1.03 for non-White patients ($p<0.001$), with this disparity projected to increase by 2040. Based on TMLE utilizing an ensemble of machine learning models, non-White patients were significantly more likely to incur higher costs (OR: 1.30, 95% CI: 1.24-1.37, $p<0.001$) and visit the emergency department within 90-days (OR: 1.09, 95% CI: 1.01, 1.18, $p=0.05$), but had negligible differences in reoperation rates at 90 days to 2 years (OR: 1.13, 95% CI: 0.78-1.63, $p=0.53$). Subgroup analysis identified higher likelihood for 90-day emergency department admissions among non-White patients compared to White patients, which were significantly compounded by Medicare insurance (OR: 2.95, 95% CI 1.46-5.95, $p=0.002$), median income in the lowest quartile (OR: 1.84, 95% CI: 1.2-2.61, $p=0.012$), and residence in low-income neighborhoods (OR: 2.05, 95% CI: 1.31-3.2, $p=0.006$). Subgroup analysis for charges billed and reoperation did not identify significant findings. Conclusions: Conclusion: Hip arthroscopy remains an increasingly utilized surgical technique for the treatment of a myriad of hip disorders. Unfortunately, racial disparities exist and are worsening over time. Irrespective of insurance status, non-white patients undergo hip arthroscopy at a lower rate, incur higher costs, and more frequently experience unexpected returns to the emergency department. Improved initiatives to improve the disparity in access to and outcomes following hip arthroscopy must be addressed to further its utility for all patients. (Figure Presented).

Neurology

Mohamed G, Noguiera R, Essibayi M, Nour HA, Mohammaden M, Haussen D, Ruiz M, Gross B, Kuybu O, Salem M, Burkhardt JK, Jankowitz B, Siegler J, Patel P, Hester T, Ortega-Gutierrez S, Farooqi M, Galecio-Castillo M, Nguyen TN, Abdalkader M, Klein P, Charles JH, Yavagal DY, Sinai V, **Jumah A**, Alaraj A, Peng S, Hafeez M, Tanweer O, Kan P, Scaggiante J, Matsoukas S, Fifi J, and **Chebl A**. TISSUE CLOCK BEYOND TIME CLOCK: ENDOVASCULAR THROMBECTOMY FOR PATIENTS WITH LARGE VESSEL OCCLUSION STROKE BEYOND 24-HOURS. *Eur Stroke J* 2023; 8(2):6. Full Text

A. Chebl, Henry Ford Health, Department of Neurology, Detroit, United States

Background and aims: Randomized trials proved the benefits of mechanical thrombectomy (MT) for select patients with large vessel occlusion (LVO) within 24-hours of last-known-well (LKW). Recent data suggest that LVO patients may benefit from MT beyond 24-hours. This study reports the safety and outcomes of MT beyond 24-hours of LKW compared to standard medical therapy (SMT). Methods: This is a retrospective analysis of LVO patients presented to eleven comprehensive stroke centers in the US beyond 24-hours from LKW between 01/2015-12/2021.We assessed 90-days outcomes using the modified Rankin Scale (mRS). Results: Of 334 patients presented with LVO beyond 24-hours, 64% received MT and 36% received SMT only. Patients who received MT were older (66±15 vs. 62±55 years, p= 0.047) and had a higher baseline NIHSS (16±7 vs.10±9, p=<0.001). Successful recanalization (TICI 2b-3) was achieved in 83%, and 5.6% had symptomatic ICH compared to 2.5% in the SMT group (p=0.19). MT was associated with mRS (0-2) at 90-days (aOR 5.73, p=0.02), less mortality 34 vs. 63% (p<0.001), and better discharge NIHSS (p=0.001) compared to SMT in patients with baseline NIHSS≥6. This treatment benefit remained after matching both groups. Age (aOR 0.94, p<0.001), baseline NIHSS (aOR 0.91, p 0.01), ASPECTS score ≥8 (aOR 3.06, p=0.04) and collaterals scores aOR (1.41, p=0.027) were associated with 90-day functional independence. Conclusions: MT for LVO beyond 24-hours appears to improve outcomes compared to SMT, especially in patients with severe strokes. Patients' age, ASPECTS, collaterals, and baseline NIHSS score should be considered before discounting MT merely based on LKW.

Neurology

Rascol O, Albanese A, Ellenbogen A, Ferreira JJ, Gurevich T, Hassin S, Hernandez-Vara J, Isaacson S, Kieburtz K, **LeWitt P**, Manzanares LL, Olanow CW, Pahwa R, Poewe W, Sarva H, Stocchi F, Yardeni T, Adar L, Salin L, Lopes N, Sasson N, Case R, Espay AJ, and Giladi N. Enrollment characteristics for patients entering a Phase 3 study of subcutaneous levodopa/carbidopa infusion with ND0612. *J Parkinsons Dis* 2023; 13:291-292. Full Text

A.J. Espay, James J and Joan A Gardner Center for Parkinson's disease and Movement Disorders, University of Cincinnati, Cincinnati, OH, United States

Introduction: The BouNDless study (NCT04006210) compared the efficacy, safety, and tolerability of subcutaneous levodopa/carbidopa (LD/CD) as an investigational ND0612 24-hour infusion versus oral immediate-release (IR)-LD/CD in patients with Parkinson's disease (PwP) experiencing motor fluctuations. Here we report patient enrollment characteristics; primary results will be available in 2023. Methods: Following screening, PwP on ≥4 doses/day of oral LD/dopa-decarboxylase inhibitor (LD ≥400mg/day) and experiencing ≥2.5h daily OFF-time were consented and enrolled. They entered a 4-6 week open-label adjustment period during which oral LD formulations and COMT inhibitor doses were converted to equivalent doses of IR-LD/CD and then adjusted to optimal clinical effect. Patients then entered an 4-6 week open-label ND0612 conversion period in which IR-LD/CD was replaced by ND0612 (LD/CD dose up to 720/90mg/day) with adjunct IR-LD/CD, as required, and adjusted until this combination regimen was optimal. Patients then entered a 12-week, double-blind, double-dummy period, during which they were randomized (1:1) either to their optimized regimen of ND0612 infusion (plus IR-LD/CD), or to the optimized IR-LD/CD-only regimen. Results: Enrollment characteristics of randomized patients (N=259) were similar to other clinical trials in PwP experiencing motor fluctuations refractory

(mean±SD age: 63.5±9.0y; 63.7% male; diagnosed 9.6±4.3y; motor fluctuations 4.5±3.3y, mean OFF time 6.1±1.7h). Levodopa equivalent daily doses at enrollment were 1029mg; 86% patient were receiving adjunct Parkinson's medications, mainly dopamine agonists (63%). Conclusions: Enrollment characteristics of patients randomized in the BouNDless trial are consistent with those observed in other clinical studies in PwP experiencing motor fluctuations.

Neurology

Zahoor I, **Nematullah M**, **Mir S**, **Waters J**, **Datta I**, **Cerghet M**, **Poisson LM**, **Rattan R**, and **Giri S**. Maresin-1 Ameliorates Inflammation and Prevents Disease Progression in Preclinical Model of Multiple Sclerosis. *Mult Scler J* 2023; 29(2):108-109. Full Text

I. Zahoor, Neurology, Henry Ford Health, Detroit, MI, United States

Background: Multiple sclerosis (MS) is one of the most common inflammatory and neurodegenerative diseases in young adults leading to a build-up of neurological defects with an irreversible disability. Unresolved inflammation represents the pathological hallmark of MS and several other autoimmune diseases, however current therapeutic options fail to adequately suppress the ongoing inflammation, resulting in inflammatory attacks that gradually increase in severity. Studies suggest that the endogenous mechanisms to resolve inflammation are intact but become defective in patients which result in deficiency of downstream metabolites, pro-resolving lipid mediators, leading to unresolved inflammation and a delay in the healing/repair process, thus resulting in disease progression and continued neuronal damage. Objectives: Docosahexaenoic acid (DHA) metabolism being defective in MS, we hypothesize that supplementation of downstream metabolite of DHA, maresin 1 (MaR1) will resolve inflammation and demyelination in preclinical animal model of MS, experimental allergic encephalomyelitis (EAE). Methods: We performed a comparative metabolite profiling using targeted metabolipidomics in serum samples from 29 relapsing-remitting (RRMS) patients and 29 age and gendermatched healthy controls (HC). For therapeutic effect of MaR1, we induced EAE in SJL mice, followed by intraperitoneal treatment with 300ng of MaR1 from day1 post-disease induction. We evaluated the effect on disease severity and inflammation by monitoring disease course of EAE, recall response by ELISA, cytokine expression analysis by qPCR and western blotting, and immune profiling by flow cytometry. Also, the neuroprotective effect of MaR1 through myelination was assessed by single molecule array (SIMOA) assay and histopathology. Statistical analysis was done using Graph-Pad Prism. Results: Metabolite profiling revealed significant imbalance ($p<0.05$) between inflammatory response and resolution process in MS, confirming the metabolic dysfunction of lipid mediators including MaR1. Restoration of MaR1 prevented disease progression and reduced disease severity in EAE by inhibiting the infiltration of immune cells (CD4+IL17+ and CD4+FNγ+) in CNS as shown by intracellular staining ($P<0.001$). Recall response showed that MaR1 significantly inhibited pro-inflammatory cytokine IL17 ($P<0.01$) and promoted IL10 and IL4 production ($P<0.001$). Also, MaR1 exerted neuroprotective effects as we found lower levels of NFL ($P<0.01$) in the serum of treated mice compared to untreated which was further confirmed by higher expression of MBP in brain from MaR1 treated group. Conclusions: Overall, our targeted metabolipidomics in MS patients identified MaR1 deficiency, whose supplementation exerts anti-inflammatory and neuroprotective effects in preclinical animal model, suggesting MaR1 could be a new therapeutic molecule in MS.

Neurosurgery

Herrgott GA, **Asmaro KP**, **Wells M**, **Nelson K**, **Thomas B**, **Hasselbach LA**, **Transou A**, **Cazacu S**, **Tundo KM**, **Nadimidla S**, **Scarpace L**, Barnholtz-Sloan J, Sloan AE, Selman WR, **DeCarvalho AC**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Craig J**, **Kalkanis S**, **Snyder J**, **Walbert T**, **Rock J**, **Noushmehr H**, and **Castro AVB**. Methylation-based Machine Learning Classifiers Discriminate Sellar Tumors By Lobe Origin Using Liquid Biopsy Or Surgical Specimens. *J Endocr Soc* 2023; 7:A705. Full Text

G.A. Herrgott, Henry Ford Health, Detroit, MI, United States

Background: The differential diagnosis of challenging sellar tumor cases can be inconclusive through imaging features and could benefit from noninvasive diagnostic approaches, such as liquid biopsy (LB). Similar to tissue, LB specimens carry tumor-specific DNA methylation signatures amenable to the

construction of accurate machine learning models able to discriminate CNS tumors. We aimed to develop methylation-based classifiers which classify sellar tumors by lobe of origin, using either LB or tumor tissue specimens. Methodology: We analyzed the DNA methylome (EPIC array) of tumor tissue (T) and LB specimens from adult patients with tumors representing each of the three pituitary lobes (Anterior: T=177; LB=37; Intermediate: T= 7; LB: 10 and Posterior: T=44, LB=2 cases). Using the most variably methylated CpG probes derived from the unsupervised variance-based analyses across tumors from different lobes, we applied multi-class linear discriminant analysis to constructmachine learningmodels to classify sellar tumor tissue and/or LB specimens. Results: We generated classifiers based on lobe-specific methylation signatures that were able to discriminate across sellar tumors either using tissue and/or LB specimens (500 and 600 CpGs, respectively) with observed accuracies of ~99% across independent validation. DISCUSSION/CONCLUSION: Our findings suggest that methylation-based classifiers constitute an accurate diagnostic approach to discriminate sellar tumors according to the lobe origin, either pre-surgically through a blood draw or through surgical tumor specimens. These classifiers are objective approaches that could complement imaging and pathology reports for an accurate diagnosis of inconclusive cases, ultimately leading to optimal management of the patients with these diseases.

Neurosurgery
Kirk J, Berg A, York M, **Schwalb J**, Siddiqui M, McInerney J, and Jimenez-Shahed J. Evidence-based correlates and predictors of medication reduction after DBS in PD. *J Parkinsons Dis* 2023; 13:284. Full Text

J. Kirk, Patient advocate, Boston, MA, United States

Objective: To explore predictors and correlates of LEDD reduction after DBS in a multi-center real-word registry of PD patients undergoing DBS. Methods: RAD-PD systematically characterizes PD patients undergoing DBS through patient-reported outcomes and clinicianadministered scales assessing disease features, medical/surgical treatments, motor/non-motor symptoms, quality of life, social determinants of health, stimulation parameters, and adverse effects. We analyzed 6-month outcomes according to LEDD change (decreased <75%/remained stable, decreased >/=75%, and increased LEDD). DBS outcomes, correlates of LEDD change at 6mos and predictors of LEDD change were investigated. Results: Amongst N=32 with 6mo outcomes (N=29 STN, N=3 GPi), mean baseline LEDD=1268mg (SD 659.7) and mean 6mo LEDD reduction = 565mg (SD 855). 27/32 (84.4%) had reduced/unchanged LEDD at 6mos, of which N=10 (37.0%) reduced >/=75% [mean reduction 87% (SD 8%)] and N=17 (62.9%) reduced <75%/remained stable [mean reduction 27% (SD 21%)]. 5/32 (15.6%) increased LEDD by mean 200% (SD 147%). 6mos post- DBS, MDS-UDPRS part 3, EQ5D, PDQ39 summary index, MDSUPDRS part 2, BDI, GAD-7, and NMSS significantly improved amongst all patients (Exact Wilcoxon signed rank test, $p<0.05$). When analyzed by degree of LEDD change, there were no statistically significant differences in PD motor phenotype or DBS target, but those who increased LEDD had significantly lower baseline LEDD (Table 1). Those who reduced LEDD>75% had significantly greater reductions in MDS-UPDRS 2, MoCA, and GAD- 7 (Fisher's exact test, Kruskal-Wallis rank sum test, Table 1). Correlates of LEDD change at 6mos included starting amantadine after DBS, and the %changes in MDS-UPDRS 3 OFF, PDQ39 summary index, MDS-UPDRS 2, GAD-7, and NMSS (linear regression, $p<0.05$). Amongst pre-op features, only baseline MoCA correlated with LEDD change ($p=0.02$) at 6mos. Patient satisfaction and QoL at 6mos were not influenced by LEDD change. Conclusions: A majority of patients reduced their LEDD 6mos after DBS with 31% reducing >/=75%, and 15% increasing. Motor phenotype and DBS target did not influence LEDD change. Those who increased had lower baseline LEDD but no clear baseline predictors of LEDD change were found. LEDD change at 6mos correlates with multiple motor and non-motor improvements, but does not influence patient satisfaction or quality of life. Long term follow-up and imaging are required.

Neurosurgery
Nagaraja T, and **Lee I**. A translational, preclinical model of image-guided laser interstitial thermal therapy for glioma cytoreduction with implications for testing therapies. *J Cereb Blood Flow Metab* 2023; 43(1):S158. Full Text

T. Nagaraja, Henry Ford Hospital, United States

Background: In vivo models of glioblastoma (GBM) are necessary for preclinical therapy testing. Animal models that parallel the clinical scenario of image-guided GBM cytoablation are presently unavailable. Aim: We have adapted image-guided, laser interstitial thermal therapy (LITT) for a preclinical GBM model with the aim of measuring tumor status and its vascular kinetics, acutely as surrogate biomarkers for ablation efficacy and longitudinally to assess GBM recurrence. Method: Athymic female rats were implanted with U251N tumor cells (n=20). When tumors reached ~4mm in diameter, they were ablated using a Visualase LITT system under diffusion-weighted MRI guidance. Five unablated tumor-bearing rats served as controls. MRI data were acquired at 24 h, and 2 and 4 weeks post-LITT. Rats were sacrificed for histopathology at 24 h, 2 and 4 weeks and the brain sections stained for hematoxylin and eosin (H&E) and human major histocompatibility complex (MHC) to measure the extent of tumor and to identify U251 tumor cells that are of human origin. Results: Sham controls were euthanized due to increased tumor burden by 2 weeks. LITT group showed little tumor tissue at post-LITT 24 h, evidence of recurrence at 2 weeks and significant regrowth at 4 weeks. MRI parameters showed elevated tumoral vascular permeability, Ktrans, values at pre-LITT imaging, that significantly decreased at 24 h and continued to be very low for the next 2 weeks. However, peri-ablation regions showed elevated Ktrans values at post-LITT 24 h suggesting increased bloodbrain barrier (BBB) permeability in ablation periphery (Fig. 1). A significant increase in Ktrans at 2 and 4 weeks coincided with glioma recurrence. Conclusions: A new preclinical image-guided GBM ablation model is presented. MRI was efficient in evaluating GBM cytoreduction and its subsequent recurrence. The recurrent tumor presented with radiological and histological features that were similar to recurrent human GBM.

Neurosurgery

Peterson D, Van Poppel M, Boling W, Santos P, **Schwalb J**, Eisenberg H, Mehta A, Spader H, Botros J, Vrionis F, Ko A, Adelson D, Lega B, Konrad P, Levine Y, Chernoff D, and Richardson M. CLINICAL SAFETY AND FEASIBILITY OF A NOVEL IMPLANTABLE NEUROIMMUNE MODULATION DEVICE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS. *Ann Rheum Dis* 2023; 82:1435. Full Text

D. Peterson, Austin Neurosurgeons (Arise Medical Center), Neurosurgery, Austin, United States

Background: An urgent need exists for differentiated RA therapies that are safer and cost-effective to expand treatment approaches for non-responders to disease-modifying anti-rheumatic drugs (DMARDs). Electrical stimulation of the vagus nerve activates the inflammatory reflex and has been shown to inhibit the production and release of inflammatory cytokines and decrease clinical signs and symptoms in chronic inflammatory diseases, including rheumatoid arthritis [1]. Objectives: The RESET-RA Study (NCT04539964) was designed to determine the safety and efficacy of a novel neuroimmune modulation device for treating rheumatoid arthritis. Presented here are data on the safety of the surgical implantation and use of this device in the first 60 human subjects enrolled in the study. Methods: The RESET-RA study is a randomized, double-blind, sham-controlled, multi-center, two-stage pivotal study to evaluate the safety and efficacy of a novel neuroimmune modulation device in patients with moderate-to-severe RA who are incomplete responders or are intolerant to one or more biologic or targeted synthetic DMARDs. The device system (SetPoint Medical, Valencia, CA) consists of 2 implanted components: a miniature, rechargeable, leadless pulse generator that is surgically implanted in the neck on the left vagus nerve and a silicon sleeve referred to as a positioning and orientation device (POD) that holds the generator in close approximation to the nerve; and two external components: a wireless charger and an iPad application for programming the pulse generation. All subjects were implanted with the study device. One to three weeks after the implant procedure, subjects were randomly assigned (1:1) to receive either active or sham stimulation (control). The safety of the surgical procedure, device, and device stimulation was blindly assessed after 12 weeks of stimulation therapy. Results: All device implant procedures were completed with no intraoperative complications, infections, or surgical revisions. No unanticipated adverse events (AEs) were reported during the perioperative period and at the end of 12 weeks of follow-up. No study discontinuations were due to AEs, and no subjects died during the study. There were no serious AEs related to the device, stimulation, or explant procedures. There were two serious AEs related to the implant procedure: vocal cord paresis and prolonged hoarseness were reported in two subjects and are known risks of implanting a device on the vagus nerve. The vocal cord paresis resolved following vocal cord augmentation with injectable filler and speech therapy; the other SAE is ongoing and improving with

speech therapy. Conclusion: Initial results demonstrated that implantation and programming of the novel neuroimmune modulation device was safe, and the surgical procedure and device were well tolerated. Full results from this study, including the clinical efficacy, will be presented after the study is fully enrolled and data is analyzed to determine potential of neuroimmune modulation for treating rheumatoid arthritis.

Nursing

Koro S, Balagamwala EH, Sahgal A, **Chapman D**, **Schaff EM**, **Siddiqui F**, Lo SS, Wei W, Tseng CL, Tsai J, Schaub SK, Angelov L, Billena C, Bommireddy A, Mayo ZS, Suh JH, and Chao ST. Multi-Institutional Validation of the Recursive Partitioning Analysis for Overall Survival in Patients Undergoing Spine Radiosurgery for Spine Metastasis. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S59-S60. Full Text

S. Koro, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, United States

Purpose/Objective(s): The recently published spine radiosurgery (sSRS) recursive partitioning analysis (RPA) for overall survival (OS) separated patients into 3 distinct prognostic groups. We sought to externally validate this RPA using 3 separate multi-institutional datasets. Materials/Methods: A total of 444 patients were utilized to develop the recently published sSRS RPA predictive of OS in patients with spine metastases. The RPA identified three distinct prognostic classes. RPA Class 1 was defined as KPS >70 and controlled systemic disease (n = 142); RPA Class 2 was defined as KPS>70 with uncontrolled systemic disease or KPS ≤70, age ≥54 and absence of visceral metastases (n = 207); RPA Class 3 was defined as KPS ≤70 and age <54 years or KPS≤70, age ≥54 years and presence of visceral metastases (n = 95). We utilized data from 3 large tertiary care centers to independently validate this RPA. Data from each institution was utilized independently to validate the RPA to minimize confounding based on institutional differences in patient selection. A total of 1,184 patients (221 patients from institution A, 749 institution B, and 214 from institution C) were in the validation cohort and were divided based on their RPA Class. Kaplan-Meier method was used to estimate OS and log-rank test was used to compare OS between RPA classes. Results: In each of the validation cohorts, the median OS was 19.9 months (institution A), 11.0 months (institution B), and 24.4 months (institution C). The patient distribution into RPA classification based on Institution A/B/C was, Class 1 (19.4%, 15.1%, 50.5%), Class 2 (74.7%, 57.7%%, 37.9%), and Class 3 (5.9%, 27.2%%, 11.2%), respectively. The median OS for patients in the validation cohort at Institution A/B/C based on RPA class was Class 1 (54 months, 27.1 months, 50.0 months), Class 2 (15.9 months, 13.0 months, 15.1 months) and Class 3 (6.9 months, 3.5 months, 6.1 months), respectively. Patients in RPA Class 1 had a significantly better OS compared to those in Class 2 of the each of the three external institution validation cohorts ($p<0.01$). Similarly, patients in RPA Class 2 had a significantly better OS compared to those in Class 3 ($p<0.01$). Conclusion: The external datasets from three large institutions independently validated the spine SRS RPA successfully for OS in patients undergoing sSRS for spinal metastases. This is the first RPA for OS to have been externally validated using multiple large datasets. Based on this validation, upfront spine SRS is strongly supported for patients in RPA Class 1 and Class 2 and is also cost effective with median OS >11 months for these patients. Patients in RPA Class 3 would benefit most from upfront conventional radiotherapy given their poor expected survival. Given successful external validation, this RPA helps guide physicians to identify those patients with spinal metastases who most benefit from sSRS.

Obstetrics, Gynecology and Women's Health Services

Koro S, Balagamwala EH, Sahgal A, **Chapman D**, **Schaff EM**, **Siddiqui F**, Lo SS, Wei W, Tseng CL, Tsai J, Schaub SK, Angelov L, Billena C, Bommireddy A, Mayo ZS, Suh JH, and Chao ST. Multi-Institutional Validation of the Recursive Partitioning Analysis for Overall Survival in Patients Undergoing Spine Radiosurgery for Spine Metastasis. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S59-S60. Full Text

S. Koro, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, United States

Purpose/Objective(s): The recently published spine radiosurgery (sSRS) recursive partitioning analysis (RPA) for overall survival (OS) separated patients into 3 distinct prognostic groups. We sought to externally validate this RPA using 3 separate multi-institutional datasets. Materials/Methods: A total of

444 patients were utilized to develop the recently published sSRS RPA predictive of OS in patients with spine metastases. The RPA identified three distinct prognostic classes. RPA Class 1 was defined as KPS >70 and controlled systemic disease (n = 142); RPA Class 2 was defined as KPS>70 with uncontrolled systemic disease or KPS ≤70, age ≥54 and absence of visceral metastases (n = 207); RPA Class 3 was defined as KPS ≤70 and age <54 years or KPS≤70, age ≥54 years and presence of visceral metastases (n = 95). We utilized data from 3 large tertiary care centers to independently validate this RPA. Data from each institution was utilized independently to validate the RPA to minimize confounding based on institutional differences in patient selection. A total of 1,184 patients (221 patients from institution A, 749 institution B, and 214 from institution C) were in the validation cohort and were divided based on their RPA Class. Kaplan-Meier method was used to estimate OS and log-rank test was used to compare OS between RPA classes. Results: In each of the validation cohorts, the median OS was 19.9 months (institution A), 11.0 months (institution B), and 24.4 months (institution C). The patient distribution into RPA classification based on Institution A/B/C was, Class 1 (19.4%, 15.1%, 50.5%), Class 2 (74.7%, 57.7%%, 37.9%), and Class 3 (5.9%, 27.2%%, 11.2%), respectively. The median OS for patients in the validation cohort at Institution A/B/C based on RPA class was Class 1 (54 months, 27.1 months, 50.0 months), Class 2 (15.9 months, 13.0 months, 15.1 months) and Class 3 (6.9 months, 3.5 months, 6.1 months), respectively. Patients in RPA Class 1 had a significantly better OS compared to those in Class 2 of the each of the three external institution validation cohorts ($p<0.01$). Similarly, patients in RPA Class 2 had a significantly better OS compared to those in Class 3 ($p<0.01$). Conclusion: The external datasets from three large institutions independently validated the spine SRS RPA successfully for OS in patients undergoing sSRS for spinal metastases. This is the first RPA for OS to have been externally validated using multiple large datasets. Based on this validation, upfront spine SRS is strongly supported for patients in RPA Class 1 and Class 2 and is also cost effective with median OS >11 months for these patients. Patients in RPA Class 3 would benefit most from upfront conventional radiotherapy given their poor expected survival. Given successful external validation, this RPA helps guide physicians to identify those patients with spinal metastases who most benefit from sSRS.

Obstetrics, Gynecology and Women's Health Services
McNitt M, **Ayyash M**, **Gear G**, and **Swain M**. Gender and Race Discrepancies in Resident Research Output at a Tertiary Care Center. *Obstet Gynecol* 2023; 141(5):94S. Full Text

M. McNitt, Henry Ford Health, Detroit, MI, United States

INTRODUCTION: The Accreditation Council for Graduate Medical Education requires residents to complete scholarly activity prior to graduation, but this does not necessarily translate into peer-reviewed publications. However, level of scholarly activity has been directly linked to successful fellowship match, and those who identify as women, African American, Hispanic, or Native American (underrep-resented in medicine [URiM]) are not well represented in fellowship positions. We therefore evaluated for race and gender-based discrepancy in scholarly activity as it relates to research involvement. METHODS: An IRB-approved (#15746) survey was sent to all residents at a tertiary hospital. This survey asked residents to share demographic information, when they got involved with research, number of first-author articles, and experience with presentations. Chi-square analysis was used. RESULTS: Analysis demonstrated that women began researching earlier than men (P 5.0027). However, this did not translate to a significant increase in poster presentations (P 5.270), oral presentations (P 5.0522), or number of first-author publications (P 5.492). When broken down by race, URiM men were exposed to research later than White men, White women, and URiM women (P,.005). There was no difference in poster presentations (P 5.350) or first-author publications (P 5.718), but White and URiM men had more experience giving oral presentations at conferences compared to their female colleagues (P,.005). CONCLUSION: The responses demonstrate that there is not a lack of involvement in research leading to less research output. In fact, despite earlier introduction to research, women have similar research outcomes as their peers. Therefore, effort needs to be placed on ensuring access to resources that assist with publishing research.

Obstetrics, Gynecology and Women's Health Services
Miller M, **Bensenhaver J**, **Cannella C**, **Petersen L**, and **Swain M**. Lessons Learned from the Integration of Reproductive Health Specialists in the Multidisciplinary Care of Women with Locally Advanced Breast Cancers. *Obstet Gynecol* 2023; 141(5):92S. Full Text

M. Miller, Henry Ford Health, Plymouth, MI, United States

INTRODUCTION: The objective of this study was to investigate whether a multidisciplinary approach to breast cancer care with the inclusion of a reproductive health specialist improves referral rates for fertility counseling and/or preservation. METHODS: An IRB-approved retrospective study including women of reproductive age diagnosed with locally advanced breast cancer and treated at a health system before and after the advent of a comprehensive, multidisciplinary tumor board (cMTB) with a reproductive health specialist was conducted. Rates of referral for fertility counseling and utilization of fertility preservation methods were compared between the cMTB and non-cMTB groups using t tests. Secondary analyses comparing baseline group characteristics and rates of referral/fertility preservation by age, insurance type, and race were performed using x2 tests. RESULTS: Of 306 study participants, 117 were cared for by a non-cMTB and 189 by a cMTB. The groups did not differ in average age, parity, breast cancer subtype, insurance type (public versus private), or treatment site (urban versus suburban); however, the distribution of race was significantly different (P 5.003). Overall, a greater percentage of women in the cMTB group received referrals for fertility counseling compared to those in the non-cMTB group (23.3% versus 0.9%, P,.001). Of the patients in the cMTB group who were referred for counseling, 20.5% underwent fertility preservation. Within the cMTB group, women younger than 30 were significantly more likely to be referred for fertility counseling (41.7% versus 20.6%, P 5.043) and undergo a fertility preservation procedure (16.7% versus 3.0%, P 5.016) than those aged 31-40. No significant differences in rates of referral or fertility preservation by race or insurance type were noted within each group. CONCLUSION: The inclusion of a reproductive health specialist in a multidisciplinary breast cancer tumor board increased rates of referral for fertility counseling for women of reproductive age. A similar, comprehensive approach to the care of reproductive-aged women with gynecologic malignancies should be considered.

Obstetrics, Gynecology and Women's Health Services

Zahoor I, **Nematullah M**, **Mir S**, **Waters J**, **Datta I**, **Cerghet M**, **Poisson LM**, **Rattan R**, and **Giri S**. Maresin-1 Ameliorates Inflammation and Prevents Disease Progression in Preclinical Model of Multiple Sclerosis. *Mult Scler J* 2023; 29(2):108-109. Full Text

I. Zahoor, Neurology, Henry Ford Health, Detroit, MI, United States

Background: Multiple sclerosis (MS) is one of the most common inflammatory and neurodegenerative diseases in young adults leading to a build-up of neurological defects with an irreversible disability. Unresolved inflammation represents the pathological hallmark of MS and several other autoimmune diseases, however current therapeutic options fail to adequately suppress the ongoing inflammation, resulting in inflammatory attacks that gradually increase in severity. Studies suggest that the endogenous mechanisms to resolve inflammation are intact but become defective in patients which result in deficiency of downstream metabolites, pro-resolving lipid mediators, leading to unresolved inflammation and a delay in the healing/repair process, thus resulting in disease progression and continued neuronal damage. Objectives: Docosahexaenoic acid (DHA) metabolism being defective in MS, we hypothesize that supplementation of downstream metabolite of DHA, maresin 1 (MaR1) will resolve inflammation and demyelination in preclinical animal model of MS, experimental allergic encephalomyelitis (EAE). Methods: We performed a comparative metabolite profiling using targeted metabolipidomics in serum samples from 29 relapsing-remitting (RRMS) patients and 29 age and gendermatched healthy controls (HC). For therapeutic effect of MaR1, we induced EAE in SJL mice, followed by intraperitoneal treatment with 300ng of MaR1 from day1 post-disease induction. We evaluated the effect on disease severity and inflammation by monitoring disease course of EAE, recall response by ELISA, cytokine expression analysis by qPCR and western blotting, and immune profiling by flow cytometry. Also, the neuroprotective effect of MaR1 through myelination was assessed by single molecule array (SIMOA) assay and histopathology. Statistical analysis was done using Graph-Pad Prism. Results: Metabolite profiling revealed significant imbalance ($p<0.05$) between inflammatory response and resolution process in MS, confirming the metabolic dysfunction of lipid mediators including MaR1. Restoration of MaR1 prevented disease progression and reduced disease severity in EAE by inhibiting the infiltration of immune cells (CD4+IL17+ and CD4+FNγ+) in CNS as shown by intracellular staining ($P<0.001$). Recall response

showed that MaR1 significantly inhibited pro-inflammatory cytokine IL17 (P<0.01) and promoted IL10 and IL4 production (P<0.001). Also, MaR1 exerted neuroprotective effects as we found lower levels of NFL (P<0.01) in the serum of treated mice compared to untreated which was further confirmed by higher expression of MBP in brain from MaR1 treated group. Conclusions: Overall, our targeted metabolipidomics in MS patients identified MaR1 deficiency, whose supplementation exerts anti-inflammatory and neuroprotective effects in preclinical animal model, suggesting MaR1 could be a new therapeutic molecule in MS.

Ophthalmology and Eye Care Services

Dossantos J, Choudhry H, Ndjonko LM, **Riddering A**, and Kaleem M. Assessing Eye Clinic Design and Accessibility Features. *Invest Ophthalmol Vis Sci* 2023; 64(8):862. Full Text

J. Dossantos, Ophthalmology, George Washington University, School of Medicine and Health Sciences, Washington, DC, United States

Purpose : Navigating healthcare facilities can be difficult for vulnerable populations such as the visually impaired and elderly who are at high risk for functional disability, falls, and injury. Currently, the Americans with Disabilities Act does not require buildings to increase accessibility by persons who are blind or visually impaired. To address this limitation, a team of vision rehabilitation specialists and occupational therapists at the Henry Ford Health Systems created a survey to assess the design features of medical centers. The purpose of our study is to validate the survey and use the survey to assess the eye clinics of a major academic institution. Methods : The SiteWise checklist was used to assess the Wilmer Eye Institute at the Johns Hopkins Hospital. Two graders were trained in the survey methods and performed their assessments independently. Eighty-three items from 8 spaces were evaluated. Two-way agreements between graders were analyzed at the item and location level. Items were graded as positive, negative, or not applicable and the total grades were averaged. Results : Of the total 83 items in the SiteWise Questionnaire, the Johns Hopkins Hospital Reviewer 1 assessed 56 positives (67.5%), 14 negatives (16.9%), and 13 items were deemed as Not applicable? (15.7%). Reviewer 2 similarly assessed 57 positives (68.7%), 13 negatives (15.7%), and 13 items were deemed as Not applicable? (15.7%). Percent concordance between both reviewers was 98.8% and one instance of disagreement was observed in the parking lot/sidewalks setting. Excluding not applicable cases there were 70 total items. The hallways (100.0%), waiting area (100.0%), and customer service area (88.2%) accounted for the areas with the highest percentage of positive responses, while restrooms (55.6%), entrances/exits (66.7%), and exam rooms (72.7%) were associated with the lowest percentage of positive responses. Between the two reviewers, the Johns Hopkins Hospital scored an average of 80.7% on the SiteWise questionnaire. Conclusions : Our results indicate that the SiteWise survey can be used reliably to assess eye clinic design and accessibility. Overall, hallways, waiting areas, and customer service areas were the most accessible while restrooms, entrances, and exam rooms were the least accessible, making them important areas for improvement.

Ophthalmology and Eye Care Services

Hicks PM, Woodward MA, Niziol LM, Lu MC, Darnley-Fisch D, Heisler M, Resnicow K, Musch DC, Mitchell J, **Imami NR**, and Newman-Casey PA. Neighborhood-Level Social Risk Factors Associated with Presenting Glaucoma Severity at a Tertiary Eye Care Center. *Invest Ophthalmol Vis Sci* 2023; 64(8):2478. Full Text

P.M. Hicks, University of Michigan, Department of Ophthalmology and Visual Sciences, Ann Arbor, MI, United States

Purpose : Social risk factors such as food and housing insecurity, transportation accessibility, residential inequality, and insurance access can impact eye health outcomes. These social risk factors change at a neighborhood-level depending on resource availability. We hypothesize that glaucoma patients with worse neighborhoodlevel social risk factors will present with more visual field (VF) loss from glaucoma. Methods : Patients with a glaucoma diagnosis were identified from the University of Michigan's electronic health record database, and data including demographics, address, and presenting mean deviation (MD) of the worse eye were obtained. Addresses were mapped to neighborhood-level measures of food and

housing insecurity, transportation accessibility, economic inequality (Gini Index), area deprivation, socioeconomic status, and insurance access using PolicyMap and Neighborhood Atlas. Age and gender adjusted linear regression models were used to estimate the effect (β) of neighborhood-level factors on worse eye MD, and results were adjusted for multiple comparisons. Results : 5,976 glaucoma patients were analyzed. Patients were an average of 69.3 years old (standard deviation [SD]=12.7) and 52.4% were female. Average MD in the worse eye was -8.04 decibels (SD=7.99). A 10-percentage point increase in neighborhood-level social risk factor measures was associated with significant worsening of MD, including percentage of supplemental nutrition assistance program recipients (β=-0.65, p<0.001), renters who are cost burdened (β=-0.15, p=0.003), households with no cars (β=-1.29, p<0.001), residents with Medicaid (β=-1.24, p<0.001), and residents who identified as a racial minority (β=-0.41, p<0.001). Further, worse area deprivation index (β=-0.52 per 0.1- unit increase, p<0.001), higher percentage of income spent on energy costs (β=-0.92 per 1% increase, p<0.001), worse Gini index (β=-0.47 per 0.1-unit increase, p=0.045), and lower neighborhood income (β=-0.77 per $10,000 decrease, p<0.001) were associated with significantly worse presenting MD. Conclusions : Patients presenting to a tertiary eye care center with more VF loss from glaucoma came from neighborhoods with higher levels of poverty. Additional research is needed to untangle how personal level socioeconomic factors and neighborhood level socioeconomic factors impact presenting disease severity.

Ophthalmology and Eye Care Services

Kasetty VM, **Sethi D**, **Patel N**, **Kumar N**, **Hessburg T**, **Desai UR**, and **Hamad AE**. Cataract Progression after Surgical Intervention for Uncomplicated Rhegmatogenous Retinal Detachments in Young Adults. *Invest Ophthalmol Vis Sci* 2023; 64(8):OD84. Full Text

V.M. Kasetty, Department of Ophthalmology, Henry Ford Health System, Detroit, MI, United States

Purpose : To determine the rates and risk factors for cataract progression after surgical intervention for uncomplicated rhegmatogenous retinal detachment (RRD) in young eyes. Methods : Retrospective cohort study of patients between the ages of 15 to 45 without prior retinal surgery undergoing pars plana vitrectomy (PPV), scleral buckling (SB), or combined PPV+SB for uncomplicated RRD between 2014 and 2020. Exclusion criteria included pseudophakic or aphakic eyes, eyes requiring multiple surgeries for RRD repair, eyes without at least 3 months of follow-up, eyes requiring lensectomy at the time of initial RRD repair, and combined detachments. Results : Thirty-six eyes from 34 patients met inclusion criteria with 28, 5, and 3 eyes undergoing PPV, PPV+SB, SB, respectively. The mean age at initial surgery was 35, 30, and 27 years with an average follow-up length of 859, 446, 452 days in PPV, PPV+SB, and SB eyes, respectively. Cataracts developed in 20/28, 5/5, and 1/3 eyes after PPV, PPV+SB, and SB, respectively with 17/20, 5/5, and 1/1 developing within 1 year. Cataract extraction was performed in 11/20, 1/5, and 0/1 PPV, PPV+SB, and SB eyes, respectively. After PPV, posterior subcapsular cataract rates were higher in patients below 35 (6/11 eyes) compared to above 35 years (7/17 eyes)(p=0.329) and nuclear sclerotic cataract (NSC) rates were higher in patients above 35 (11/17 eyes) compared to below 35 years (2/11 eyes) (p=0.022). Cataracts developed more frequently after macula-off RRD (14/16 eyes) compared to macula-on RRDs (6/12 eyes) (p=0.044) with NSC being more common in macula-off detachments (p=0.02). No other significant association between age, refractive status, vitreous status, and surgical time and cataract rate was observed. Conclusions : Cataract formation was common and frequent after PPV and PPV+SB but rare after SB in young patients undergoing RRD repair. Majority of cataracts after RRD repair develop within 1 year. PPV eyes were more likely to require cataract extraction compared to other repair methods. As majority of the studies analyzing cataract formation after retinal surgeries in young eyes are limited by small cohorts, further prospective studies or big-data retrospective studies should be performed to better assess the risk of cataract formation in these eyes.

Ophthalmology and Eye Care Services

Najafi A. Deep learning method to predict original RNFL thickness contour using anatomical parameters and OCT imaging. *Invest Ophthalmol Vis Sci* 2023; 64(8):2388. Full Text

A. Najafi, Ophthalmology, Henry Ford Health System, Detroit, MI, United States

Purpose : This is a proof-of-concept study. The concept is that a contour (retinal nerve fiber layer (RNFL)) can be predicted using relevant paramerts (anatomical parameters (APs) of peripapillary vessel diameter, number of vessels, and vessel location) that make the contour. This can be done using deep learning algorithms of generative adversarial network (GAN). Methods : This is a study on simulated computer-generated images. All images used in this study are generated by a python-written-code program and analyzed by a GAN. We generated 1100 dimensionality-reduced optical coherence tomography (OCT) images of APs with their corresponding RNFL thickness contour using randomly chosen AP values (expected images). Next, we designed a GAN to predict the RNFL contour based on the APs (generated images). We used 1000 images for training with 100 epochs, and 100 unseen images for testing. Finally, we used the mean absolute error (MAE) for quantification of dissimilarity between the expected and generated images. MAE is a statistical measure of errors between paired observations on the same entity. In our study, each pixel of the RNFL contour was compared between the expected and the generated images. Results : MAE was 0.021 between the expected and the generated RNFL contours. In other words, our GAN model predicted the RNFL contour correctly in 97.9% of its entirety. Conclusions : Peripapillary vessel diameter, number of vessels, and the location of vessels collectively determine RNFL thickness contour, which can subsequently be predicted accurately (97.9%) using a GAN.

Ophthalmology and Eye Care Services

Nixon A, Xu J, Brennan NA, **Morlock R**, and Cheng X. Subjective vision differences with soft contact lenses for myopia control in children and teenagers. *Invest Ophthalmol Vis Sci* 2023; 64(8):4936. Full Text

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Purpose : Soft contact lenses for myopia control (MC) are often evaluated in younger children (≤12 years), but meaningful myopia progression can occur during the teenage years. We performed post-hoc analysis of a prospective clinical study in myopic children to learn about subjective vision experience in soft contact lenses for MC by age. Methods : This was a multi-site, single-masked, 3x3 crossover study with a run-in period. Healthy myopic children from 7 and 17 years old were recruited, balancing the number of children 7-12 years old with those 13-17 years. Subjects initially used a daily disposable (DD) soft contact lens (SCL) with conventional optics (1DAM) for one week, then lens wear sequence was randomized and subjects were fit with one of three MC SCLs for each of three, 2-week periods. There were two senofilcon A prototype MC SCLs with noncoaxial ring-focus designs (for enhancing efficacy [EE] and enhancing vision [EV]) and one omafilcon A dual-focus (DF) design. Subjective vision was assessed using the Pediatric Myopia Control Questionnaire (PMCQ) at the 2-week follow-up. An overall vision item was analyzed using the Pearson chi-square test to assess differences in top two box (T2B, excellent and very good) proportions between the two age groups for each lens type separately. Results : The intent-to-treat population included 75 participants, with 38 from 7-12 years (mean 10.6 ± 1.05 years) and 37 from 13-17 years (mean 14.7 ± 1.31 years). Patientreported overall vision by lens type and age is shown in Figure 1. A significant difference in T2B proportions by age was detected for EE (p=0.032) and approached for DF (p=0.053), but there was no significant difference for 1DAM (p=0.252) or EV (p=0.502). Two subjects discontinued due to unsatisfactory vision with a test article, both from the 13-17 age group. Conclusions : The subjective visual impact of MC SCLs may be perceived differently in younger versus older children, with older children more judgmental of their vision experience, at least during the early period of wear. The subjective visual impact by age was design dependent, and a different balance of vision quality and myopia control efficacy may be prudent in older children to better fit their more critical assessment of vision quality and decreasing average annual rate of myopia progression.

Orthopedics/Bone and Joint Center

Castle J, **Jiang E**, **Wager S**, **Brown S**, **Kasto J**, **Gasparro M**, **Muh S**, **Makhni E**, **Moutzouros V**, and **Gaudiani M**. Worse Postoperative Outcomes and Higher Reoperation in Smokers Compared to Nonsmokers for Arthroscopic Rotator Cuff Repair. *Orthop J Sports Med* 2023; 11(7). Full Text

J. Castle

Objectives: Smoking significantly impairs healing potential and is a significant risk factor for complications after various orthopaedic surgeries. The purpose of this study was to determine if a cohort of former or current smokers at time of surgery met the minimally clinical important difference (MCID) for Patient-Reported Outcomes Measurement Information System Upper Extremity (PROMIS- UE), Depression (PROMIS-D), and Pain Interference (PROMIS-PI) scores in comparison to nonsmoking patients. Methods: A retrospective review of a prospectively collected database of patients undergoing arthroscopic rotator cuff was performed. Patients who completed preoperative and 6-month postoperative PROMIS scores were included. The MCID was calculated using a distribution technique with a threshold of 0.5 standard deviations above the mean. A cohort of nonsmokers was compared to a cohort of patients currently or former smokers at time of surgery in terms of their clinical outcomes and PROMIS scores. A sub-analysis was also performed where a cohort of nonsmokers were propensity matched 1:1 to a cohort of current/former smokers via age, body mass index (BMI), and tear size. Results: A total of 182 patients, 80 current or former smokers and 102 nonsmokers, who underwent rotator cuff repair were included in the study. Smokers had statistically different sized tears with more rated massive and more reoperations (16.3% vs 5.9%, P=0.02). No differences were found in preoperative PROMIS scores, change in PROMIS scores, proportion meeting MCID for PROMIS scores, and retear rate. In the sub-analysis, 74 current or former smokers were matched to 74 nonsmokers. Smokers had a lower change in PROMIS-UE (8.6 ± 9.8 vs 12.3 ± 10.0, P=0.007) and PROMIS-PI (-9.1 ± 8.5 vs -12.8 ± 10.1, P=0.03) postoperatively. Fewer met MCID for PROMIS UE postoperatively (60.3% vs 82.4%, P=0.003) and more had reoperations (16.2% vs 4.1%, P=0.02). Conclusions: Patients who smoke currently or had a history of smoking preoperatively demonstrated smaller improvements in function, pain scores, and were less likely to meet MCID for PROMIS-UE when compared to nonsmokers after arthroscopic rotator cuff repair. Smokers were more likely to undergo reoperations within 6 months.

Orthopedics/Bone and Joint Center

Castle J, **Jiang E**, **Wager S**, **Brown S**, **Kasto J**, **Gasparro M**, **Muh S**, **Makhni E**, **Moutzouros V**, and **Gaudiani M**. Similar Clinical and Patient Recorded Outcomes Amongst Older Patients over 65 Years of Age Compared to Younger Patients undergoing Arthroscopic Rotator Cuff Repair. *Orthop J Sports Med* 2023; 11(7). Full Text

J. Castle

Objectives: The purpose of our study was to determine if patients 65 years and over meet the minimally clinical important difference (MCID) for Patient-Reported Outcomes Measurement Information System Upper Extremity (PROMIS-UE), Depression (PROMIS-D), and Pain Interference (PROMIS-PI) at similar rates compared to a cohort of younger patients. Methods: A retrospective review of a prospectively collected database of patients undergoing RCR was performed. Patients with completed preoperative and 6-month follow up postoperative PROMIS scores were included. A cohort of 65 years and older (65<) was compared to a cohort of 64 years and younger (64>=) in terms of their clinical outcomes and PROMIS scores. A propensity matched analysis was then performed, which matched patients 65+ years old 1:1 to a cohort of 50 years or younger via tear size and body mass index (BMI). Results: A total of 318 patients were included with 79 patients ≥ 65 years (69.2 ± 3.4 years, mean ± SD) and 239 patients <65 years (55.1 ± 3.4 years). No significant differences were found in terms of gender, tear thickness, tear size, reoperation rate, retear rate, preoperative PROMIS-UE, PROMIS-PI, and PROMIS D scores, or change in postoperative PROMIS-UE, PROMIS-PI, and PROMIS D after 6 months. In the sub-analysis, 44 patients over 65 years of age were propensity matched to 44 under 50 years of age. No differences were found in PROMIS-UE change, PROMISD change, proportion meeting MCID PROMIS UE, and proportion meeting MCID of PROMIS PI after 6 months. Patients in the 65+ years group experienced larger changes in PROMIS PI scores (12.5 ± 9.6 vs 7.2 ± 7.5, p=0.005) while fewer patients experienced significant declines in PROMIS D scores (26% vs 47%, p=0.03). Conclusions: Patients ≥ 65 years experience no differences in reoperation or retear rate when compared to younger patients. Older patients undergoing RCR were more likely to have a larger improvement in pain scores but were less likely to have significant clinical change in their depression scores. With proper patient selection, patients ≥ 65 years can achieve clinically significant improvements 6 months after RCR that is similar to their younger counterparts.

Orthopedics/Bone and Joint Center

Lu Y, Marigi E, Alder K, Mickley J, Camp C, Levy B, Krych A, and **Okoroha K**. Identifying Racial Disparity in Utilization and Outcomes of Hip Arthroscopy using Machine Learning. *Orthop J Sports Med* 2023; 11(7). Full Text

Y. Lu

Objectives: Background: Arthroscopic diagnosis and treatment of femoroacetabular pathology has been increasingly used in the past thirty years with interventions resulting in improved hip function and ultimate delay of hip arthroplasty in a minimally invasive manner. Unfortunately, previous investigations have observed decreased rates of access, utilization of, and outcomes following orthopedic interventions such as hip arthroplasty in underrepresented patients. The purpose of this study is to examine racial differences in procedural rates, outcomes, and complications in patients undergoing hip arthroscopy. Methods: Methods: The State Ambulatory Surgery and Services Database (SASD) and State Emergency Department Database (SEDD) of New York were queried for patients undergoing hip arthroscopy from 2011 to 2017. The primary outcomes investigated were utilization over time, total charges billed per encounter, 90-day emergency department visits, and revision hip arthroscopy. Patients were stratified into White and non-White race, and intergroup differences were evaluated with descriptive statistics. Subgroup analysis was performed with linear mixedeffects models to identify significant interactions between race and individual variables that contributed to any differences in the outcomes of interest. Temporal trends in utilization of hip arthroscopy and concomitant procedures between the two groups were analyzed with Poisson regression modeling. Finally, targeted maximum likelihood estimation (TMLE) was performed to provide nonparametric estimates of the specific differences in the outcomes studied using machine learning ensembles while controlling for patient risk factors. Results: Results: A total of 9,745 patients underwent hip arthroscopy during the study period, with 1,081 patients of non-White race (11.9%). Results of Poisson regression demonstrated an annual increase of 1.11 in the incidence rate of hip arthroscopy among White patients, compared to 1.03 for non-White patients ($p<0.001$), with this disparity projected to increase by 2040. Based on TMLE utilizing an ensemble of machine learning models, non-White patients were significantly more likely to incur higher costs (OR: 1.30, 95% CI: 1.24-1.37, $p<0.001$) and visit the emergency department within 90-days (OR: 1.09, 95% CI: 1.01, 1.18, $p=0.05$), but had negligible differences in reoperation rates at 90 days to 2 years (OR: 1.13, 95% CI: 0.78-1.63, $p=0.53$). Subgroup analysis identified higher likelihood for 90-day emergency department admissions among non-White patients compared to White patients, which were significantly compounded by Medicare insurance (OR: 2.95, 95% CI 1.46-5.95, $p=0.002$), median income in the lowest quartile (OR: 1.84, 95% CI: 1.2-2.61, $p=0.012$), and residence in low-income neighborhoods (OR: 2.05, 95% CI: 1.31-3.2, $p=0.006$). Subgroup analysis for charges billed and reoperation did not identify significant findings. Conclusions: Conclusion: Hip arthroscopy remains an increasingly utilized surgical technique for the treatment of a myriad of hip disorders. Unfortunately, racial disparities exist and are worsening over time. Irrespective of insurance status, non-white patients undergo hip arthroscopy at a lower rate, incur higher costs, and more frequently experience unexpected returns to the emergency department. Improved initiatives to improve the disparity in access to and outcomes following hip arthroscopy must be addressed to further its utility for all patients. (Figure Presented).

Orthopedics/Bone and Joint Center

Patel H, Berlinberg E, Forlenza E, Gamsarian V, Mirle V, **Okoroha K**, Williams B, Yanke A, Cole B, and Verma N. A Radiostereometric Analysis of Tendon Migration following Arthroscopic and Mini- Open Biceps Tenodesis: Interference Screw confers Greater Construct Stability than All-Suture Suture Anchor Fixation, with No Difference in Patient-Reported Outcomes. *Orthop J Sports Med* 2023; 11(7). Full Text

H. Patel

Objectives: To quantify the postoperative migration of the BT construct between arthroscopic suprapectoral (ASPBT) and open subpectoral (OSPBT) techniques via interference screw (IS) or allsuture anchor with a single suture (SSSA) fixation with radiostereometric analysis (RSA). Methods: Distal migration of the biceps tendon following OSPBT with a Polyetheretherketone (PEEK) IS, OSPBT with one SSSA, ASPBT with PEEK IS, and ASPBT with two SSSAs was measured prospectively. Patients with symptomatic biceps tendinopathy and preoperative Patient-Reported Outcome Measures (PROMs)

including CMS, SANE, or PROMIS-UE scores were included. A tantalum bead was sutured on the proximal end of the long head biceps tendon before fixation. AP radiographs were performed immediately postoperatively, 1 week, and 3 months. Bead migration was measured, and PROMs were compared. Results: Of 115 patients, 94 were available for final follow-up (82%). Average age was 52.1±10.5 years, and BMI was 30.8±5.4 kg/m2. There was no difference in tendon migration between OSPBT and ASPBT performed with an IS (P=0.70). OSPBT performed with one SSSA (21.70 mm) demonstrated significantly greater migration than ASPBT with IS (4.31mm, P<0.001) and OSPBT with IS (5.04 mm, P<0.001). Three patients (9.4%) who had OSPBT with one SSSA and one who had ASPBT with two SSSAs (3.8%), developed a Popeye deformity; none occurred in the IS groups. Mean 12-week bead migration in patients with versus without Popeye deformity was 60.8 mm and 11.2 mm, respectively (P<0.0001). PROMs did not differ at final follow-up. Conclusions: ASPBT and OSPBT with IS fixation demonstrated the least tendon migration, while OSPBT with one SSSA yielded the most. Compared to IS, fixation with one, but not two, SSSAs resulted in significantly greater migration. Average bead migration following a Popeye deformity was 6.1cm. To minimize migration when using SSSAs, at least 2 sutures should be used with an interlocking pattern within the tendon.

Otolaryngology – Head and Neck Surgery

Ghanem AI, **Gilbert M**, **Li P**, **Vance S**, **Tam S**, **Ghanem T**, and **Siddiqui F**. Disease Characteristics, Treatment and Survival for Oropharyngeal Squamous Cell Carcinoma of Elderly. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Incidence of oropharyngeal cancers (OP) has been increasing over the past few decades, mainly driven by human papilloma virus (HPV) associated cancers in younger men. However, a large number of OP patients in recent years are ≥65 years of age. We wanted to determine if there is a difference in outcomes in elderly patients with OP as compared to younger patients. Materials/Methods: We queried our institutional prospectively maintained head and neck cancer database for patients with non-metastatic OP treated between 1/2009-6/2020. We excluded patients who did not receive any definitive treatment. We analyzed clinicopathological and treatment characteristics for elderly (age at diagnosis ≥65 years) compared to young (<65 years) across HPV subtypes. We also studied survival endpoints among age groups using Kaplan-Meier curves and log-rank test. Independent predictors were estimated using multivariate (MVA) Cox regression models for each HPV subtype. Results: We identified 340 patients who met our inclusion criteria: elderly 123 (36%) and young 213 (64%). The proportion of elderly HPV+ve patients showed an increasing trend over the years studied. Median age was 70 years (range 65-91) in elderly and 56 years (38-64) in young (p<0.001); and HPV+ve/-ve were 73.2/26.8% vs 74.6/25.3% for both age groups respectively (p = 0.86). Elderly patients had higher Charlson Comorbidity Index (CCI) and included more divorcees (p<0.05). There were more elderly current/former smokers (97% vs 82%; p = 0.007) within HPV-ve cases. Definitive radiotherapy (RT) +/- systemic therapy (CRT) was utilized in 73.2% (n = 249), while the remainder had surgery +/- adjuvant RT/CRT. There was no difference with age for OP subsite, 8th edition AJCC stage and treatment received except for more use of cetuximab (22.5% vs 10.2%; p<0.001) and weekly cisplatin (32.4% vs 25.8%; p<0.001) among elderly patients. After a median follow up of 5.24 years (IQR: 3.53), 3-year overall (OS) (HPV+ve: 85 vs 81%; HPV-ve: 39 vs 52%), locoregional free (LRFS) (HPV+ve: 86 vs 90%; HPV-ve: 67 vs 69%) and distant metastasis free (DMFS) survival (HPV+ve: 91 vs 90%; HPV-ve: 79 vs 81%) were all non-significant for elderly vs young respectively. On MVA, CCI and AJCC stage for HPV+ve; and smoking, T-stage and lymphovascular space invasion for HPV- were associated with OS. For HPV+ve, AJCC stage, adjuvant vs definitive RT and treatment in later years were predictive of better LRFS, whereas smoking index and extracapsular space invasion were deterministic for DMFS. Interestingly, outcomes among those who received cetuximab was similar to those who received concurrent cisplatin for all endpoints. Conclusion: We did not note any significant difference in outcomes among elderly patients treated for OP when compared to the younger patients when multi-disciplinary head and neck cancer care is provided. This was noted even though a significantly larger proportion of elderly patients received cetuximab concurrent with RT as opposed to standard of care cisplatin.

Otolaryngology – Head and Neck Surgery

Ghanem AI, **Gilbert M**, **Lin CH**, **Khalil-Moawad R**, **Momin S**, **Chang S**, **Ali H**, and **Siddiqui F**. Treatment Tolerance and Toxicity in Elderly Oropharyngeal Cancer Patients and Implication on Outcomes. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): To investigate the tolerance level and toxicity for standard of care treatment for oropharyngeal cancer (OP) in elderly patients and their impact on outcomes. Materials/Methods: Using our in-house head and neck cancer database, we looked for non-metastatic OP cases that received definitive treatment between 1/2009-6/2020. All patients received either definitive radiation therapy (RT) +/- concomitant systemic therapy (ST), or surgery followed by adjuvant RT or RT-ST. For the elderly (age at diagnosis ≥65 years) and young (<65 years) patients, we compared treatment package time (TPT) (time from surgery to RT conclusion) for adjuvant RT, total RT duration and unplanned RT interruptions. ST details and dose/protocol modifications were also compared. We evaluated worst grade of pain and mucositis, hospitalization for non-hydration causes and febrile neutropenia (FN) during RT. Feeding tube (FT) use and weight loss were compared. The independent effect of these indicators on locoregional (LRFS), distant (DRFS) recurrence free and overall (OS) survival was assessed using multivariate analyses (MVA). Results: A cohort of 326 patients was included: 36% elderly (n = 118) and 64% young (n = 208), with no differences in AJCC stage distribution (8th), treatment received and HPV status (HPV+ve: 73% vs 74.6%; p = 0.86). In 23.6 % who received adjuvant RT, median TPT was 86 (range 72-128) and 81 (65-137) days for elderly vs young (p = 0.27); whereas in the definitive RT cases 76.4%, total RT duration was 49 days for both age groups. Overall, prescribed RT course was not completed in 4% and unplanned RT interruptions occurred in 22.8% and both were non-significant between age groups. Among the 261 patients that received ST, elderly utilized more cetuximab (26 vs 12%; p = 0.007). For those who received cisplatin, 20% of elderly had cumulative dose <200 mg/m2 compared to 6% among the younger age group (p = 0.006); and cisplatin was changed to carboplatin or cetuximab in 18% vs 8% (p = 0.019). Delayed/cancelled cycles and dose reductions were similar. There were more hospitalizations (47% vs 27%; p<0.001) and a trend for more FN (9% vs 3%; p = 0.09) with older age, while worst pain and mucositis was similar. FTs were used more in elderly patients (64% vs 50%; p = 0.02), for a median of 97 vs 64 days (p = 0.31); of which 19.5% vs 11% (p = 0.28) were inserted before RT start. However, % weight loss was non-significant. On MVA, longer RT duration, FT use and hospitalizations predicted worse LRFS and DRFS; and they were prognostic for OS in addition to TPT >90 days (p<0.05 for all). Nevertheless, elderly vs young had non-significant 3-year LRFS (91% vs 90% and 67% vs 69%), DRFS (86% vs 90% and 79% vs 81%) & OS (85% vs 81% and 39% vs 52%) for HPV+ve and HPV-ve respectively (p>0.05). Conclusion: Elderly patients with OP need more multi-disciplinary supportive care when receiving RT and concurrent ST. However, survival outcomes are equivalent to younger patients. Ongoing studies should enroll more elderly candidates and stratify endpoints with age.

Otolaryngology – Head and Neck Surgery

Herrgott GA, **Asmaro KP**, **Wells M**, **Nelson K**, **Thomas B**, **Hasselbach LA**, **Transou A**, **Cazacu S**, **Tundo KM**, **Nadimidla S**, **Scarpace L**, Barnholtz-Sloan J, Sloan AE, Selman WR, **DeCarvalho AC**, **Mukherjee A**, **Robin AM**, **Lee IY**, **Craig J**, **Kalkanis S**, **Snyder J**, **Walbert T**, **Rock J**, **Noushmehr H**, and **Castro AVB**. Methylation-based Machine Learning Classifiers Discriminate Sellar Tumors By Lobe Origin Using Liquid Biopsy Or Surgical Specimens. *J Endocr Soc* 2023; 7:A705. Full Text

G.A. Herrgott, Henry Ford Health, Detroit, MI, United States

Background: The differential diagnosis of challenging sellar tumor cases can be inconclusive through imaging features and could benefit from noninvasive diagnostic approaches, such as liquid biopsy (LB). Similar to tissue, LB specimens carry tumor-specific DNA methylation signatures amenable to the construction of accurate machine learning models able to discriminate CNS tumors. We aimed to develop methylation-based classifiers which classify sellar tumors by lobe of origin, using either LB or tumor tissue specimens. Methodology: We analyzed the DNA methylome (EPIC array) of tumor tissue (T) and LB specimens from adult patients with tumors representing each of the three pituitary lobes (Anterior: T=177; LB=37; Intermediate: T= 7; LB: 10 and Posterior: T=44, LB=2 cases). Using the most variably methylated

CpG probes derived from the unsupervised variance-based analyses across tumors from different lobes, we applied multi-class linear discriminant analysis to constructmachine learningmodels to classify sellar tumor tissue and/or LB specimens. Results: We generated classifiers based on lobe-specific methylation signatures that were able to discriminate across sellar tumors either using tissue and/or LB specimens (500 and 600 CpGs, respectively) with observed accuracies of ~99% across independent validation. DISCUSSION/CONCLUSION: Our findings suggest that methylation-based classifiers constitute an accurate diagnostic approach to discriminate sellar tumors according to the lobe origin, either pre-surgically through a blood draw or through surgical tumor specimens. These classifiers are objective approaches that could complement imaging and pathology reports for an accurate diagnosis of inconclusive cases, ultimately leading to optimal management of the patients with these diseases.

Pharmacy

Baik I, **Fitzmaurice M**, **Hanke P**, **Jantz A**, **Spaillari F**, **Summers B**, **Kim D**, and **Poparad-Stezar A**. Evaluation of the Safety and Benefits of Peripherally Administered Anti-Thymocyte Globulin (p-ratg) in Kidney Transplant (kt) Recipients. *Am J Transplant* 2023; 23(6):S834. Full Text

Purpose: Due to risk of infusion-associated reactions, the recommended route of administration of rabbit anti-thymocyte globulin is through a high flow vein. Historically, central line access is preferred, but data suggests peripheral administration is a safe alternative. This study aims to better understand the safety, tolerability, and implications of p-rATG administration after institutional practice change from central line administration (Table 1). Methods: This single-center, retrospective analysis evaluated use of p-rATG in KT recipients between August 1st, 2021 and September 30th, 2022. Adult patients who received p-rATG induction were included. The primary outcome was occurrence of local and systemic adverse reactions (ADE). Secondary outcomes evaluated benefits of p-rATG use, like decrease in use of central line placement, time in operative room (OR), and effect on length of stay. Results: There were 41 patients included, with baseline characteristics shown in Table 2. No anaphylaxis, flash pulmonary edema, extravasation, or thrombosis observed. Fourteen patients (34%) experienced minor ADEs, with the majority experiencing hypertension (71%). Of the patients who experienced minor ADEs, 71% received all pre-medications, but only 21% received them within one hour of the start of infusion. Decrease in average bicarbonate levels after first dose from 23.4mmol/L to 19.2mmol/L occurred. No patients required central line placement. Average time in the OR was 3:13 hours (hr) (2:59hr in deceased donor recipients (DDR) and 4:56hr in living donor recipients (LDR)). Median length of stay 5.9 days for DDR and 4.2 days for LDR compared to 5.2 days for DDR and 4.4 days for LDR based on historical institutional data. Conclusions: p-rATG is overall safe and well tolerated, without incidence of major adverse events. Expected infusion reactions occurred mainly due to deviations from protocol, however increased sustained acidosis observed, likely due to volume of infusion. Administration of p-rATG allowed for reduced use of central lines and did not negatively impact stay length. P-rATG administration is a safe strategy for induction administration in KT CITATION INFORMATION: Baik I., Fitzmaurice M., Hanke P., Jantz A., Spaillari F., Summers B., Kim D., Poparad-Stezar A. Evaluation of the Safety and Benefits of Peripherally Administered Anti-Thymocyte Globulin (p-ratg) in Kidney Transplant (kt) Recipients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: I.Baik: None. M.Fitzmaurice: n/a. P.Hanke: n/a. A.Jantz: n/a. F.Spaillari: n/a. B.Summers: n/a. D.Kim: n/a. A.Poparad-stezar: None. [Figure presented]

Pharmacy

Wheeler M, **Baik I**, **Gonzalez H**, **Jantz A**, **Poparad-Stezar A**, **Summers B**, **Venkat D**, **Samaniego-Picota M**, and **Fitzmaurice M**. Evaluating the Use of Glucagon-Like Peptide 1 Receptor Agonists (GLP1 RA) in a Matched Cohort of Kidney and Liver Transplant Recipients. *Am J Transplant* 2023; 23(6):S947. Full Text

Purpose: To assess the safety and efficacy of GLP1 RA in a matched cohort of kidney transplant (KT) and liver transplant (LT) recipients who received these agents compared to patients who did not Methods: This single-center, retrospective analysis evaluated KT and LT recipients who were initiated on a GLP1 RA for at least 3 months (mo) matched to a nonintervention comparator group (non-GLP1 RA) based on organ type and diagnosis of diabetes mellitus present at time of transplant. The primary endpoint was change in hemoglobin A1C (HbA1c) at 6 mo. Secondary endpoints included weight (kg), BMI (kg/m2), insulin requirements, and number of oral diabetic agents (ODAs). Safety outcomes included incidence of

adverse events (AEs), biopsy-proven acute rejection (BPAR), graft loss, and mortality. Results: Of the 74 patients included, 37 received GLP1 RA matched to 37 patients who did not. Baseline characteristics shown in Table 1. More patients in the GLP1 RA group were on ODAs and 10 patients (27%) initiated on an agent <1 year from transplant. Change in median HbA1c in GLP1 RA group from baseline to 6 mo was -0.5% [(7.0% (6.4-8.9); 6.5% (5.6-7.3)] compared to +0.6% in the non-GLP1 RA group [(5.8% (5.5-6.8); 6.6% (5.8-7.6)], p=0.53. Median change in total daily insulin units was -13 units vs +15 units in the GLP1 RA vs non-GLP1 RA group (p=0.16). GLP1 RA group median change in weight was -7.4 kg vs -0.3 kg in non-GLP1 RA group (p=0.02). BMI change was -3.1 kg/m2 in GLP1 RA vs +0.7 kg/m2 in non-GLP1 RA, p=0.02. In GLP1 RA group, 7 patients (38.9%) experienced an AEs related to drug with 4 (10.8%) leading to discontinuation. Common AE being abdominal pain. One patient (2.7%) discontinued drug due to cost, 3 patients (8.1%) found it ineffective, and 1 (2.7%) had a drug-unrelated discontinuation. Eight patients (21.6%) in each group experienced BPAR. In the GLP1 RA group, 1 patient had graft loss compared to 2 patients in the non-GLP1 RA. No patient deaths occurred with GLP1 RA while 2 patient deaths in the comparator group. Conclusions: GLP1 RA lowered median HbA1c after 6 mo with subsequent clinically and statistically significant reductions in weight, BMI, and insulin requirements in both KT and LT recipients. AE rates are similar to reported literature. GLP1 RAs are safe and effective at all time points of initiation, including <1 year posttransplant, making them useful agents for management of metabolic complications in this patient population. CITATION INFORMATION: Baik I., Gonzalez H., Jantz A., Poparad-Stezar A., Summers B., Venkat D., Samaniego-Picota M., Fitzmaurice M. Evaluating the Use of Glucagon-Like Peptide 1 Receptor Agonists (GLP1 RA) in a Matched Cohort of Kidney and Liver Transplant Recipients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: I.Baik: None. H.Gonzalez: n/a. A.Jantz: n/a. A.Poparadstezar: n/a. B.Summers: n/a. D.Venkat: n/a. M.Samaniego-picota: None. M.Fitzmaurice: n/a. [Figure presented]

Public Health Sciences

Abu Jawdeh BG, **Sreedhar S**, **Lu M**, **Moonka D**, and **Jafri S**. The Efficacy of Everolimus in Liver Transplant Patients. *Am J Transplant* 2023; 23(6):S855. Full Text

Purpose: The objective of our study is to illuminate the long term impact of everolimus on renal function in liver transplant patients in a real world setting. Methods: We completed a single institution, retrospective chart review of patients who had a liver transplant from 2013-2020. 774 patients were included and everolimus status was noted. Everolimus use was classified as: “never used”, “ongoing use”, and “short-term use”. Additionally, glomerular filtration rates (GFR) and creatinine values were noted for 2 months, 1 year, and 3 years post-transplant. Patient outcomes including survival were evaluated. A logistic regression was performed for discrete time to event (death) model with varying covariates (GFR <60 and everolimus status). We also calculated means, hazard ratios (HR), and odds ratios (OR) for comparisons. Results: Of 774 patients, 496 were never on everolimus, 162 were briefly on the medication, and 116 were actively taking it. 277 patients were female. The average time patients were on the medication was 3.32 months with a standard deviation (SD) of 0.40, ranging from 0-69.08 months. Race was categorized into African American (85 patients), White (570 patients), Asian (13 patients), and other (106 patients). The average age was 55.51 years for patients who were never on everolimus, 58.99 years for short-term use, and 57.66 years for ongoing everolimus use. The use of everolimus had a marginal effect on GFR <60 (P=0.07). The status of ongoing use was trending towards renal protection against a GFR <60 when compared with never on everolimus (HR=0.372, 95%CI=0.139- 0.999, P=0.08). Everolimus status had no impact on survival. One year survival for the ongoing treatment group compared to the never on group was not significantly different (HR=1.951, 95%CI=1.103-3.452, P=0.06). The three-year hazard ratio was 1.474 (95%CI=0.838-2.594, P=0.34) and the five-year hazard ratio was 1.37 (95%CI=0.752-2.496, P=0.44). Individuals that were not African American had an increased likelihood of survival (HR=0.544, 95%CI=0.355- 0.834, P <0.05). Finally, female sex increased the risk of a posttransplant GFR <60 (OR=2.87, 95%CI=1.78-4.68, P<0.05). Conclusions: Everolimus treatment status had no impact on survival. Ongoing everolimus treatment trended towards renal protection against GFR <60 compared to never using the medication. However, African American race decreased the likelihood of survival. Finally, female sex increased the risk of a GFR <60. Future studies evaluating everolimus over a longer period of time would be valuable. CITATION INFORMATION: Sreedhar S., Lu M., Moonka D., Jafri S. The Efficacy of Everolimus in Liver Transplant Patients AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: S.Sreedhar: None. M.Lu: n/a. D.Moonka: None. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Public Health Sciences

Benitz S, **Nasser M**, Steep A, **Loveless I**, **Wen HJ**, **Long D**, **Davis E**, **Rempinski D**, **Louw M**, **Moore J**, **Steele N**, Mahajan U, Regel I, Bednar F, and **Crawford H**. Single-cell epigenomic analysis reveals an important role of the receptor kinase Ror2 in the erosion of cellular identity during pancreatic carcinogenesis. *Pancreatology* 2023; 23:e126. Full Text

Abstract Background: The major driver for pancreatic ductal adenocarcinoma (PDAC) is oncogenic KRAS. However, adult acinar cells, a probable origin of PDAC, are largely refractory to KrasG12D-mediated oncogenic transformation. With the concomitant loss of transcription factors that regulate acinar cell differentiation, such as Pdx1 (Pancreatic and Duodenal Homeobox 1), acinar cells undergo a rapid cell identity switch, known as acinar-to-ductal metaplasia (ADM). How loss of cell identity cooperates with oncogenic Kras to induce pancreatic transformation is largely unclear. Methods: To elucidate mechanisms responsible for the accelerated cellular reprogramming in KrasG12D;Pdx1f/f animals, single-cell ATAC-seq (Assay for Transposase-Accessible Chromatin using sequencing) from frozen pancreatic bulk tissue was performed. Chromatin accessibility states were captured at early stages of carcinogenesis and correlated to RNA-seq data. Differentially regulated genes were validated by multiplex RNAscope and immunohistochemistry staining and functionally studied in pancreatic cancer cell lines. Results: Single-cell ATAC-seq proved a powerful tool for defining cell-type identity, cellular reprogramming and target genes in early metaplastic transformation of pancreatic tissue. Notably, acinar cells of KrasG12D;Pdx1f/f animals as well as a proportion of metaplastic lesions in both, KrasG12D and KrasG12D;Pdx1f/f mice, showed elevated accessibility and expression of the Ror2 gene. As a receptor tyrosine kinase, Ror2 controls essential signalling pathways, such as Ras-MAPK signalling. By analysing Ror2 knockout mice, we found that the receptor kinase regulates the identity of metaplastic epithelia. Moreover, Ror2 expression highly correlates with the more aggressive basal-like subtype in mouse and human PDAC. Overexpression of ROR2 in pancreatic cancer cell lines with a classical differentiation induced epithelial-to-mesenchymal transition, characterised by the downregulation of multiple epithelial markers and upregulation of mesenchymal genes. In addition, ROR2-overexpressing cells proliferated much more rapidly, while knockout of ROR2 in pancreatic cancer cells significantly decreased cell proliferation. Conclusion: Our in-depth sequencing data revealed that expression of KrasG12D with the concomitant loss of Pdx1 leads to vast alterations of acinar cell identity. We identified the receptor kinase Ror2 as a regulator of pancreatic cancer initiation and driver of pancreatic cancer cell aggressiveness.

Public Health Sciences

Bhan A, **Simon R**, **Jacobsen G**, **Yaseen A**, **Navaratnarajah P**, **Sweidan A**, and **Rao SD**. Clinical Relevance Of 24-hour Urine Calcium Measurement In Patients With Primary Hyperparathyroidism (PHPT). *J Endocr Soc* 2023; 7:A246-A247. Full Text

A. Bhan, Henry Ford Hospital, Bloomfield Hills, MI, United States

Introduction: PHPT is the third most common endocrine disease and the most common cause of hypercalcemia in outpatient setting, presents with mild to moderate hypercalcemia with unsuppressed or elevated serum PTH levels, and most patients are asymptomatic. A 24-hour urine Ca measurement to exclude both hypo-and hypercalciuria is used to recommend parathyroidectomy. The purpose of our study is to evaluate the clinical relevance of urine Ca measurement in evaluating patients with PHPT. Methods: A retrospective electronic medical record review was performed on all adult patients with PHPT in whom a 24-hour urine Ca was measured between 2015-2019. Patients with secondary HPT, those without a 24-hour urine Ca measurement, and patients with serum Cr >1.5 mg/dl were excluded. Results: 393 patients met inclusion criteria for subsequent analyses. For the entire cohort, mean serum Ca was 10.9 ± 0.6 mg/dl, Cr 0.9 ± 0.2 mg/dl and PTH 111± 65 pg/ml with no significant difference between groups by gender, race, or stone history. Mean urine Ca for the entire cohort was 254 ± 170 mg/day. 46% and 35% had urine Ca >250 or >300 mg/d respectively. Multiple linear regression results indicated that higher serum Ca ($p=0.004$), lower serum Cr ($p<0.001$), white race ($p<0.001$), and higher urine sodium ($p<0.001$) were all significantly predictive of higher UCa. However, the mean urine Ca did not differ between patients with and without nephrolithiasis (276 ± 182 Vs. 280 ± 247 mg/d; $p=0.174$). Discussion: The most recent guidelines for the management of asymptomatic PHPT recommend measurement of 24-hour urine

Ca in all PHPT patients. However, the validity, sensitivity and specificity of such an approach has never been formally evaluated, considering wide variability of urine Ca excretion in the population and lack of difference in urine Ca between patients with and without nephrolithiasis. Previous guidelines discussed this issue and determined that measurement of a 24-hour urine collection is cumbersome and adds very little to patient management. Our study questions the clinical relevance of re-including 24-hour urine Ca in the latest guidelines. Conclusions: Our study suggests that measurement of 24-hour urine Ca in the routine evaluation of patients with PHPT is unhelpful.

Public Health Sciences

Finotti M, **Jesse M**, Pillai A, Liapakis A, **Venkat D**, **Salgia R**, Kumar V, **Manivannan A**, **Lu M**, **Zhang T**, Verna E, and Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation. *Am J Transplant* 2023; 23(6):S864-S865. Full Text

Purpose: Living donor liver transplantation (LDLT) is a viable option to increase access to liver transplantation (LT). However, there are well-documented racial and gender-based inequities in access to deceased donor LT. Very little is empirically known about living liver donor (LLD) characteristics in relation to their recipients. Therefore, we aimed to explore the odds of receiving LDLT across LLD and recipient characteristics. Methods: We explored gender, interactions between LLD-recipient race/ethnicity, and other relevant factors on LDLT utilizing national data from the United Network for Organ Sharing (UNOS) for all adult LLD and their recipients who underwent LDLT from 1/1/2012 through 10/1/2022. Results: 3469 LDLTs occurred (5.46% of all LTs). A majority of LLDs were female (n 1864, 54%), mean 37.16 years of age (SD 10.41), and White race (n 2791, 81%), followed by Hispanic (n 423, 12%), Black (n 116, 3%), Asian (n 85, 2%), and Other (n 47, 1%). LDLT recipients were predominantly male (n 1843, 53%), mean 53.35 years of age (SD 13.22), and White race (n 2787, 80%), followed by Hispanic (n 437, 13%), Black (n 118, 3%), Asian (n 92, 3%), and Other (n 35, 1%). Of note, 42.9% (n 1487) of LLDs were not biologically related to their recipient. As reported in Table 1, men are both less likely to receive or be a LLD than women. Examining the donor by recipient race interactions, LDLT is more likely to occur between LLD and recipients with the same racial/ethnic category than differing race/ethnicity (regardless of comparator). When race/ethnicity is different between LLD-recipient, four significant interactions occurred indicating that White LLDs are less likely to donate to Black recipients than Hispanic or Others/Unknown and Asian donors are more likely to donate to Others/Unknown than either Hispanic or White recipients. Conclusions: While biological relatives are assumed to be the same race/ethnicity, nearly half of LLDs are not biologically related to their recipient and yet all racial groups were more likely to donate within their own racial category, adjusting for liver disease category and functional status. Also, despite representing the majority of waitlisted and transplanted patients, men were less likely to receive LDLT, but men are also less likely to be a LLD. These results provide a starting point to foster efforts towards diversifying the LLD population. CITATION INFORMATION: Jesse M., Pillai A., Liapakis A., Venkat D., Salgia R., Kumar V., Manivannan A., Lu M., Zhang T., Verna E., Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.Jesse: None. E.Verna: None. N.Parikh: Consultant;; Eisai, Eli Lilly, Research Grant Site Overall Principal Investigator;; Genentech. A.Pillai: n/a. A.Liapakis: None. D.Venkat: n/a. R.Salgia: n/a. V.Kumar: None. A.Manivannan: n/a. M.Lu: n/a. T.Zhang: n/a. [Figure presented]

Public Health Sciences

Ghanem AI, **Gilbert M**, **Li P**, **Vance S**, **Tam S**, **Ghanem T**, and **Siddiqui F**. Disease Characteristics, Treatment and Survival for Oropharyngeal Squamous Cell Carcinoma of Elderly. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Incidence of oropharyngeal cancers (OP) has been increasing over the past few decades, mainly driven by human papilloma virus (HPV) associated cancers in younger men. However, a large number of OP patients in recent years are ≥65 years of age. We wanted to determine if there is a difference in outcomes in elderly patients with OP as compared to younger patients. Materials/Methods: We queried our institutional prospectively maintained head and neck cancer database for patients with

non-metastatic OP treated between 1/2009-6/2020. We excluded patients who did not receive any definitive treatment. We analyzed clinicopathological and treatment characteristics for elderly (age at diagnosis ≥65 years) compared to young (<65 years) across HPV subtypes. We also studied survival endpoints among age groups using Kaplan-Meier curves and log-rank test. Independent predictors were estimated using multivariate (MVA) Cox regression models for each HPV subtype. Results: We identified 340 patients who met our inclusion criteria: elderly 123 (36%) and young 213 (64%). The proportion of elderly HPV+ve patients showed an increasing trend over the years studied. Median age was 70 years (range 65-91) in elderly and 56 years (38-64) in young (p<0.001); and HPV+ve/-ve were 73.2/26.8% vs 74.6/25.3% for both age groups respectively (p = 0.86). Elderly patients had higher Charlson Comorbidity Index (CCI) and included more divorcees (p<0.05). There were more elderly current/former smokers (97% vs 82%; p = 0.007) within HPV-ve cases. Definitive radiotherapy (RT) +/- systemic therapy (CRT) was utilized in 73.2% (n = 249), while the remainder had surgery +/- adjuvant RT/CRT. There was no difference with age for OP subsite, 8th edition AJCC stage and treatment received except for more use of cetuximab (22.5% vs 10.2%; p<0.001) and weekly cisplatin (32.4% vs 25.8%; p<0.001) among elderly patients. After a median follow up of 5.24 years (IQR: 3.53), 3-year overall (OS) (HPV+ve: 85 vs 81%; HPV-ve: 39 vs 52%), locoregional free (LRFS) (HPV+ve: 86 vs 90%; HPV-ve: 67 vs 69%) and distant metastasis free (DMFS) survival (HPV+ve: 91 vs 90%; HPV-ve: 79 vs 81%) were all non-significant for elderly vs young respectively. On MVA, CCI and AJCC stage for HPV+ve; and smoking, T-stage and lymphovascular space invasion for HPV- were associated with OS. For HPV+ve, AJCC stage, adjuvant vs definitive RT and treatment in later years were predictive of better LRFS, whereas smoking index and extracapsular space invasion were deterministic for DMFS. Interestingly, outcomes among those who received cetuximab was similar to those who received concurrent cisplatin for all endpoints. Conclusion: We did not note any significant difference in outcomes among elderly patients treated for OP when compared to the younger patients when multi-disciplinary head and neck cancer care is provided. This was noted even though a significantly larger proportion of elderly patients received cetuximab concurrent with RT as opposed to standard of care cisplatin.

Public Health Sciences

Ghanem AI, **Gilbert M**, **Lin CH**, **Khalil-Moawad R**, **Momin S**, **Chang S**, **Ali H**, and **Siddiqui F**. Treatment Tolerance and Toxicity in Elderly Oropharyngeal Cancer Patients and Implication on Outcomes. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): To investigate the tolerance level and toxicity for standard of care treatment for oropharyngeal cancer (OP) in elderly patients and their impact on outcomes. Materials/Methods: Using our in-house head and neck cancer database, we looked for non-metastatic OP cases that received definitive treatment between 1/2009-6/2020. All patients received either definitive radiation therapy (RT) +/- concomitant systemic therapy (ST), or surgery followed by adjuvant RT or RT-ST. For the elderly (age at diagnosis ≥65 years) and young (<65 years) patients, we compared treatment package time (TPT) (time from surgery to RT conclusion) for adjuvant RT, total RT duration and unplanned RT interruptions. ST details and dose/protocol modifications were also compared. We evaluated worst grade of pain and mucositis, hospitalization for non-hydration causes and febrile neutropenia (FN) during RT. Feeding tube (FT) use and weight loss were compared. The independent effect of these indicators on locoregional (LRFS), distant (DRFS) recurrence free and overall (OS) survival was assessed using multivariate analyses (MVA). Results: A cohort of 326 patients was included: 36% elderly (n = 118) and 64% young (n = 208), with no differences in AJCC stage distribution (8th), treatment received and HPV status (HPV+ve: 73% vs 74.6%; p = 0.86). In 23.6 % who received adjuvant RT, median TPT was 86 (range 72-128) and 81 (65-137) days for elderly vs young (p = 0.27); whereas in the definitive RT cases 76.4%, total RT duration was 49 days for both age groups. Overall, prescribed RT course was not completed in 4% and unplanned RT interruptions occurred in 22.8% and both were non-significant between age groups. Among the 261 patients that received ST, elderly utilized more cetuximab (26 vs 12%; p = 0.007). For those who received cisplatin, 20% of elderly had cumulative dose <200 mg/m2 compared to 6% among the younger age group (p = 0.006); and cisplatin was changed to carboplatin or cetuximab in 18% vs 8% (p = 0.019). Delayed/cancelled cycles and dose reductions were similar. There were more hospitalizations (47% vs 27%; p<0.001) and a trend for more FN (9% vs 3%; p = 0.09) with older age,

while worst pain and mucositis was similar. FTs were used more in elderly patients (64% vs 50%; p = 0.02), for a median of 97 vs 64 days (p = 0.31); of which 19.5% vs 11% (p = 0.28) were inserted before RT start. However, % weight loss was non-significant. On MVA, longer RT duration, FT use and hospitalizations predicted worse LRFS and DRFS; and they were prognostic for OS in addition to TPT >90 days (p<0.05 for all). Nevertheless, elderly vs young had non-significant 3-year LRFS (91% vs 90% and 67% vs 69%), DRFS (86% vs 90% and 79% vs 81%) & OS (85% vs 81% and 39% vs 52%) for HPV+ve and HPV-ve respectively (p>0.05). Conclusion: Elderly patients with OP need more multi-disciplinary supportive care when receiving RT and concurrent ST. However, survival outcomes are equivalent to younger patients. Ongoing studies should enroll more elderly candidates and stratify endpoints with age.

Public Health Sciences

Gunaga S, **Al-Hage A**, **Buchheister A**, **Welchans M**, **Awada M**, **Smiles B**, **Savage A**, **Latack K**, **Schultz L**, and **Miller J**. 365 Trends in Hospice and Palliative Medicine Consults Initiated in the Emergency Department: A Seven-Year Utilization Analysis. *Ann Emerg Med* 2023; 82(4):S161-S162. Full Text

Objectives: Emergency departments (EDs) play a central role in end-of-life care, yet early integration of high-quality palliative care and hospice services is often under-utilized. Studies have shown that early access to these services improves patient outcomes, goal-concordant care and reduces health care costs. Translation of this evidence into clinical practice remains inconsistent, and the extent to which these services are utilized remains unclear. This retrospective cross-sectional cohort study aimed to describe the clinical prevalence and trends of ED ordered hospice and palliative medicine consults over a seven-year period in a large metropolitan health system. Methods: We conducted a retrospective cohort study of electronic health records (EHR) from five EDs within a large, integrated urban and suburban health system. The study period spanned from January 1st, 2016, to December 31st, 2022, and included data from all ED visits by patients > 18 years old who had a hospice and/or palliative medicine consult ordered in the ED. A variety of patient specific demographic, clinical, and outcome variables were collected. The yearly number of hospice and palliative medicine consults ordered in each ED were also obtained and compared by year and by site. Across years, we compared incident rates of hospice and palliative consults per 1,000 ED patients who were over 50 years old, had an ESI ≤ 3, and were admitted. Data analysis included descriptive statistics, chi-square testing, and regression analysis to examine trends over time. Results: A total of 6,097 hospice and palliative medicine consults were ordered in the ED for 5,687 ED encounters, and 5,345 unique patients meeting the inclusion criteria. The mean age of participants was 77.9 years ±13.7, with 57.2% being female and 74.7% identifying as White. Of the total cohort, 90.6% (5,152) were admitted to the hospital, 7.2% (410) were discharged home, 2.0% (112) died in the ED, and 55.2% (2,843) died during their hospital stay. Hospice and palliative medicine consults initiated in the ED showed a significant annual increase from 324 in 2016 to 1,328 in 2022, representing a 410% overall increase (p < 0.001). This seven-year trend is detailed in Figure 1. ED-ordered hospice consults outnumbered palliative consults 1.68 to 1 in 2016; however, in 2022 that ratio flipped to where ED palliative consults were 1.66 times more common. After the onset of the COVID-19 pandemic, there was a significant 188% increase in daily ED hospice and palliative consults when compared to pre-pandemic levels (p < 0.001). The calculated prevalence of hospice and palliative medicine consults in the ED for patients who were over 50 years old, had an ESI ≤ 3, and were admitted was 5.9 consults for every 1,000 visits (0.59%) in 2016. This prevalence significantly increased to 19.7 consults (1.97%) for every 1,000 visits in 2022 (p < 0.001). Conclusions: This study reveals an increasing trend of ED initiated hospice and palliative consults in our health system. Though promising, this effort likely only touches the surface of the unmet palliative needs of our ED patients and families. Further research is required to examine if these trends are observed across other healthcare facilities nationwide and to identify potential obstacles to implementation. [Formula presented] No, authors do not have interests to disclose

Public Health Sciences

Pavlov TS, **Arkhipov SN**, **Wu A**, **Meng Z**, **Adrianto I**, and **Ortiz PA**. Transcriptomics Analysis of ADPKD Cysts Shows Remodeling of Purinergic Receptors in Pkd1RC/RC Mice. *J Am Soc Nephrol* 2023; 34:556. Full Text

T.S. Pavlov, Henry Ford Hospital, Detroit, MI, United States

Background: Polycystic kidney diseases (PKD) are characterized by development of multiple cysts, dilations of nephron segments, which replace normal tissues and lead to kidney insufficiency. Methods: To identify new gene pathways affected by cyst development in collecting ducts, we used a bulk RNAseq approach comparing gene expression of normal microdissected cortical collecting ducts (n=3) vs cysts (n=4) microdissected from the same Pkd1RC/RC mice. Results: Bulk-RNA analysis identified 18,000 genes and allowed statistical comparison of over 15,000 genes. Our data reveals that although cysts originate from normal collecting ducts, cystic epithelium show 2692 down-regulated and 2278 upregulated genes ($p<0.05$ pAdj. FDR). Ingenuity Pathways Analysis identifies the following intracellular mechanisms mostly affected by transition: Rac and Rho signaling, fibrosis signaling, epithelial-to-mesenchymal transition, cytoskeleton rearrangement and ERK/MAPK signaling. Our previous publication reported that development of cysts in an autosomal recessive model of PKD is associated with a shift of P2Y to P2X receptor abundance. In the current study we found that in the autosomal dominant Pkd1RC/RC mice model purinergic signaling undergoes similar remodeling. The most abundant ionotropic receptors with reduced expression were P2ry2 and P2ry4, whereas ionotropic receptors P2rx5 and P2rx7 increased expression (2.88 and 1.53, log2). Additionally, analysis detected elevated abundance of P2ry6, P2ry12 and P2ry13 RNA level. We hypothesize that the physiological significance of the predominant P2X signaling in the cysts include their role in regulation of ATP release via pannexin-1 channels. Abnormal ATP accumulation in the cyst space was shown earlier to contribute in cystogenesis and we previously showed that pannexin-1 mediates ATP release to the cyst lumen. In the presented study, RNAscope confirms hyperexpression of P2rx7 mRNA in cysts. In a heterologous CHO cells system, interaction of P2X7 with pannexin-1 upregulates channel activity and both proteins co-immuno precipitate. Conclusions: Development and establishment of ADPKD cysts involves massive transcriptome remodeling of collecting ducts which include a shift in purinergic signaling that facilitates pathogenic pannexin-1 hyperactivity.

Public Health Sciences

Zahoor I, **Nematullah M**, **Mir S**, **Waters J**, **Datta I**, **Cerghet M**, **Poisson LM**, **Rattan R**, and **Giri S**. Maresin-1 Ameliorates Inflammation and Prevents Disease Progression in Preclinical Model of Multiple Sclerosis. *Mult Scler J* 2023; 29(2):108-109. Full Text

I. Zahoor, Neurology, Henry Ford Health, Detroit, MI, United States

Background: Multiple sclerosis (MS) is one of the most common inflammatory and neurodegenerative diseases in young adults leading to a build-up of neurological defects with an irreversible disability. Unresolved inflammation represents the pathological hallmark of MS and several other autoimmune diseases, however current therapeutic options fail to adequately suppress the ongoing inflammation, resulting in inflammatory attacks that gradually increase in severity. Studies suggest that the endogenous mechanisms to resolve inflammation are intact but become defective in patients which result in deficiency of downstream metabolites, pro-resolving lipid mediators, leading to unresolved inflammation and a delay in the healing/repair process, thus resulting in disease progression and continued neuronal damage. Objectives: Docosahexaenoic acid (DHA) metabolism being defective in MS, we hypothesize that supplementation of downstream metabolite of DHA, maresin 1 (MaR1) will resolve inflammation and demyelination in preclinical animal model of MS, experimental allergic encephalomyelitis (EAE). Methods: We performed a comparative metabolite profiling using targeted metabolipidomics in serum samples from 29 relapsing-remitting (RRMS) patients and 29 age and gendermatched healthy controls (HC). For therapeutic effect of MaR1, we induced EAE in SJL mice, followed by intraperitoneal treatment with 300ng of MaR1 from day1 post-disease induction. We evaluated the effect on disease severity and inflammation by monitoring disease course of EAE, recall response by ELISA, cytokine expression analysis by qPCR and western blotting, and immune profiling by flow cytometry. Also, the neuroprotective effect of MaR1 through myelination was assessed by single molecule array (SIMOA) assay and histopathology. Statistical analysis was done using Graph-Pad Prism. Results: Metabolite profiling revealed significant imbalance ($p<0.05$) between inflammatory response and resolution process in MS, confirming the metabolic dysfunction of lipid mediators including MaR1. Restoration of MaR1 prevented disease progression and reduced disease severity in EAE by inhibiting the infiltration of immune cells (CD4+IL17+ and CD4+FNγ+) in CNS as shown by intracellular staining ($P<0.001$). Recall response

showed that MaR1 significantly inhibited pro-inflammatory cytokine IL17 (P<0.01) and promoted IL10 and IL4 production (P<0.001). Also, MaR1 exerted neuroprotective effects as we found lower levels of NFL (P<0.01) in the serum of treated mice compared to untreated which was further confirmed by higher expression of MBP in brain from MaR1 treated group. Conclusions: Overall, our targeted metabolipidomics in MS patients identified MaR1 deficiency, whose supplementation exerts anti-inflammatory and neuroprotective effects in preclinical animal model, suggesting MaR1 could be a new therapeutic molecule in MS.

Radiation Oncology
Chuong M, **Parikh P**, Low D, **Kim J**, Mittauer K, Bassetti M, Glide-Hurst C, Raldow A, Yang Y, Portelance L, Zaki B, Kim H, Mancias J, Ng J, Pfeffer R, Mueller A, Kelly P, Boldrini L, Fuss M, and Lee P. Quality of life after ablative 5-fraction radiation therapy from the phase II SMART pancreas trial. *Radiother Oncol* 2023; 182:S61. Full Text

Purpose or Objective Prospective trials have demonstrated that patient-reported quality of life (QoL) does not significantly change after non-ablative pancreas stereotactic body radiation therapy (SBRT). However, QoL outcomes after ablative SBRT are unknown. Acute grade 3+ toxicity from the phase II SMART pancreas trial (NCT03621644) for borderline resectable (BRPC) and locally advanced pancreas cancer (LAPC) was uncommon, as previously reported. We present QoL outcomes from the SMART pancreas trial, which were assessed as a secondary endpoint. Materials and Methods 136 patients completed study therapy. Eligibility criteria included adenocarcinoma or adenosquamous histology, absence of distant metastatic disease on re-staging after completing 3+ months of induction chemotherapy, CA19-9 <500 U/mL, and no prior pancreas surgery. The prescription dose was 50 Gy in 5 fractions (BED10=100 Gy). SMART was delivered on a 0.35T MR-guided device with intrafraction cine-MRI, soft tissue tracking, and automatic beam gating. On-table adaptive replanning using an isotoxicity approach was performed prior to each fraction as needed. Surgery was performed in 39 patients (28.7%) within 90 days of SMART. QoL assessments using the NCCN-FACT FHSI-18 survey instrument were acquired at 3 time points (TP): prior to SMART (TP1), 3 months after SMART (TP2), and 12 months after SMART (TP3). Median follow-up after SMART was 8.8 months and therefore evaluation of QoL in this analysis was limited to TP1 and TP2. Results QoL assessment was completed at TP1 and TP2 by 133 (97.8%) and 106 (77.9%) patients, respectively. There was no difference in mean total FACT FHSI-18 scores at TP1 vs. TP2 (25.1 vs. 25.2; p=0.629). No significant differences were observed in mean subscale scores: physical (13.6 vs. 14.1; p=0.535), emotional (2.5 vs. 2.5; p=0.449), treatment side effects (1.5 vs. 1.2; p=0.071), or function/well-being (7.5 vs. 7.4; p=0.408). Mean scores for the 18 individual survey questions were not significantly different over time except for an increase in pain (0.8 vs. 1.1; p=0.002) and discomfort in the stomach area (1.0 vs. 1.3; p=0.013). No significant increase in mean pain score was noted among unresected patients (1.0 vs. 1.1; p=0.076) in contrast to resected patients (0.4 vs. 1.0; p=0.003). Likewise, no significant increase in mean score related to discomfort in the stomach area was observed among unresected patients (1.2 vs. 1.4; p=0.297) in contrast to resected patients (0.4 vs. 1.2; p<0.001). Conclusion This is the first analysis of prospectively evaluated patient-reported QoL outcomes following 5-fraction SMART for BRPC/LAPC. Despite the ablative prescription dose, we observed no significant overall QoL change within the first 3 months after SMART for unresected patients. Additional follow-up is planned to evaluate long-term QoL within 12 months after SMART.

Radiation Oncology
Felter M, Krause M⊘ller P, Josipovic M, Bekke S, Bernchou U, Serup-Hansen E, **Parikh P**, **Joshua K**, Geertsen P, Behrens C, Vogelius I, P⊘hl M, Schytte T, and Persson G. MR-guided SBRT of infra-diaphragmatic soft tissue metastases – early toxicity and dosimetric results. *Radiother Oncol* 2023; 182:S214-S215. Full Text

Purpose or Objective The recommended biologically effective dose (BED10) of at least 100 Gy in stereotactic body radiotherapy (SBRT) is challenging to achieve for metastases close to radiosensitive organs at risk (OAR) without risking unacceptable toxicity. The MR linac may help overcome this challenge by offering online adaption and real-time imaging during treatment. We present early toxicity and dosimetric results from a prospective multicenter phase-2 study (SOFT), where the safety and efficacy of risk-adapted MR-guided SBRT of infra-diaphragmatic soft tissue metastases in patients with

OMD were investigated (clinicaltrials.gov ID NCT04407897). Materials and Methods A risk-adapted strategy was applied, and prespecified OAR constraints were prioritized over target coverage. Fractionation schemes were 45 Gy/3 fractions (f), 50 Gy/5 f, and 60 Gy/8 f, depending on proximity to OAR. PTV margins followed institutional practice. Inhomogeneous dose prescription aimed at gross tumor volume (GTV) D99% >95%, mean GTV dose ≥ 100% and planning target volume (PTV) D99% >67%. All dose plans were exported for central dosimetric analysis. To account for the different dose levels prescribed, the achieved dose to the target (GTV D99%) was recalculated into BED10. Early toxicity was assessed according to the Common Terminology Criteria for Adverse Events v.5.0 at baseline and 2, 6, and 12 weeks after the end of treatment. Results The study closed in February 2022 after the inclusion of 121 patients with 147 metastatic targets. Most patients had prostate, colorectal, lung, or kidney cancer. Targets were mainly located in the liver (41%), lymph nodes (35%), or adrenal glands (14%). Almost half of the targets (48%) were located less than 10 mm from radiosensitive OARs. Normal tissue constraints to visceral organs were respected in all plans. Figure 1 shows the achieved GTV coverage. The prescription, GTV D99% >95% was achieved for 63% of the targets (median = 96% isodose, range 45.8%-108.0%). Mean GTV dose > 100% was achieved for 91% of the targets (median=105.4% isodose, range 76.8%-124.2%). The prescription, PTV D99% > 67% was achieved for 67 % of the targets (median=70.2% isodose, range 20.4%-94.8 %). The closer the target was to the OAR, the harder it was to reach the desired BED10 > 100 Gy for GTV D99%, but it was still achievable in some cases, as illustrated in Figure 2. Overall, the most common treatment-related adverse events (TRAE) were fatigue (n=70), nausea (n=35), and pain from the irradiated site (n=34). No patients experienced early grade (G) 4-5 TRAE. Only two patients had G3 TRAE, and both were fatigue. Forty-eight patients (40%) had G2, and 68 (56%) had G1 TRAE. Conclusion With MR-guided risk-adapted SBRT, ablative doses can be achieved for high-risk infra-diaphragmatic targets with an acceptable early toxicity rate. [Figure presented]

Radiation Oncology

Ghanem AI, **Gilbert M**, **Li P**, **Vance S**, **Tam S**, **Ghanem T**, and **Siddiqui F**. Disease Characteristics, Treatment and Survival for Oropharyngeal Squamous Cell Carcinoma of Elderly. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Incidence of oropharyngeal cancers (OP) has been increasing over the past few decades, mainly driven by human papilloma virus (HPV) associated cancers in younger men. However, a large number of OP patients in recent years are ≥65 years of age. We wanted to determine if there is a difference in outcomes in elderly patients with OP as compared to younger patients. Materials/Methods: We queried our institutional prospectively maintained head and neck cancer database for patients with non-metastatic OP treated between 1/2009-6/2020. We excluded patients who did not receive any definitive treatment. We analyzed clinicopathological and treatment characteristics for elderly (age at diagnosis ≥65 years) compared to young (<65 years) across HPV subtypes. We also studied survival endpoints among age groups using Kaplan-Meier curves and log-rank test. Independent predictors were estimated using multivariate (MVA) Cox regression models for each HPV subtype. Results: We identified 340 patients who met our inclusion criteria: elderly 123 (36%) and young 213 (64%). The proportion of elderly HPV+ve patients showed an increasing trend over the years studied. Median age was 70 years (range 65-91) in elderly and 56 years (38-64) in young (p<0.001); and HPV+ve/-ve were 73.2/26.8% vs 74.6/25.3% for both age groups respectively (p = 0.86). Elderly patients had higher Charlson Comorbidity Index (CCI) and included more divorcees (p<0.05). There were more elderly current/former smokers (97% vs 82%; p = 0.007) within HPV-ve cases. Definitive radiotherapy (RT) +/- systemic therapy (CRT) was utilized in 73.2% (n = 249), while the remainder had surgery +/- adjuvant RT/CRT. There was no difference with age for OP subsite, 8th edition AJCC stage and treatment received except for more use of cetuximab (22.5% vs 10.2%; p<0.001) and weekly cisplatin (32.4% vs 25.8%; p<0.001) among elderly patients. After a median follow up of 5.24 years (IQR: 3.53), 3-year overall (OS) (HPV+ve: 85 vs 81%; HPV-ve: 39 vs 52%), locoregional free (LRFS) (HPV+ve: 86 vs 90%; HPV-ve: 67 vs 69%) and distant metastasis free (DMFS) survival (HPV+ve: 91 vs 90%; HPV-ve: 79 vs 81%) were all non-significant for elderly vs young respectively. On MVA, CCI and AJCC stage for HPV+ve; and smoking, T-stage and lymphovascular space invasion for HPV- were associated with OS. For HPV+ve, AJCC stage, adjuvant vs

definitive RT and treatment in later years were predictive of better LRFS, whereas smoking index and extracapsular space invasion were deterministic for DMFS. Interestingly, outcomes among those who received cetuximab was similar to those who received concurrent cisplatin for all endpoints. Conclusion: We did not note any significant difference in outcomes among elderly patients treated for OP when compared to the younger patients when multi-disciplinary head and neck cancer care is provided. This was noted even though a significantly larger proportion of elderly patients received cetuximab concurrent with RT as opposed to standard of care cisplatin.

Radiation Oncology
Ghanem AI, **Gilbert M**, **Lin CH**, **Khalil-Moawad R**, **Momin S**, **Chang S**, **Ali H**, and **Siddiqui F**. Treatment Tolerance and Toxicity in Elderly Oropharyngeal Cancer Patients and Implication on Outcomes. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e584. Full Text

A.I. Ghanem, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): To investigate the tolerance level and toxicity for standard of care treatment for oropharyngeal cancer (OP) in elderly patients and their impact on outcomes. Materials/Methods: Using our in-house head and neck cancer database, we looked for non-metastatic OP cases that received definitive treatment between 1/2009-6/2020. All patients received either definitive radiation therapy (RT) +/- concomitant systemic therapy (ST), or surgery followed by adjuvant RT or RT-ST. For the elderly (age at diagnosis ≥65 years) and young (<65 years) patients, we compared treatment package time (TPT) (time from surgery to RT conclusion) for adjuvant RT, total RT duration and unplanned RT interruptions. ST details and dose/protocol modifications were also compared. We evaluated worst grade of pain and mucositis, hospitalization for non-hydration causes and febrile neutropenia (FN) during RT. Feeding tube (FT) use and weight loss were compared. The independent effect of these indicators on locoregional (LRFS), distant (DRFS) recurrence free and overall (OS) survival was assessed using multivariate analyses (MVA). Results: A cohort of 326 patients was included: 36% elderly (n = 118) and 64% young (n = 208), with no differences in AJCC stage distribution (8th), treatment received and HPV status (HPV+ve: 73% vs 74.6%; p = 0.86). In 23.6 % who received adjuvant RT, median TPT was 86 (range 72-128) and 81 (65-137) days for elderly vs young (p = 0.27); whereas in the definitive RT cases 76.4%, total RT duration was 49 days for both age groups. Overall, prescribed RT course was not completed in 4% and unplanned RT interruptions occurred in 22.8% and both were non-significant between age groups. Among the 261 patients that received ST, elderly utilized more cetuximab (26 vs 12%; p = 0.007). For those who received cisplatin, 20% of elderly had cumulative dose <200 mg/m2 compared to 6% among the younger age group (p = 0.006); and cisplatin was changed to carboplatin or cetuximab in 18% vs 8% (p = 0.019). Delayed/cancelled cycles and dose reductions were similar. There were more hospitalizations (47% vs 27%; p<0.001) and a trend for more FN (9% vs 3%; p = 0.09) with older age, while worst pain and mucositis was similar. FTs were used more in elderly patients (64% vs 50%; p = 0.02), for a median of 97 vs 64 days (p = 0.31); of which 19.5% vs 11% (p = 0.28) were inserted before RT start. However, % weight loss was non-significant. On MVA, longer RT duration, FT use and hospitalizations predicted worse LRFS and DRFS; and they were prognostic for OS in addition to TPT >90 days (p<0.05 for all). Nevertheless, elderly vs young had non-significant 3-year LRFS (91% vs 90% and 67% vs 69%), DRFS (86% vs 90% and 79% vs 81%) & OS (85% vs 81% and 39% vs 52%) for HPV+ve and HPV-ve respectively (p>0.05). Conclusion: Elderly patients with OP need more multi-disciplinary supportive care when receiving RT and concurrent ST. However, survival outcomes are equivalent to younger patients. Ongoing studies should enroll more elderly candidates and stratify endpoints with age.

Radiation Oncology
Herr DJ, Moncion A, Griffith K, Marsh R, Grubb M, Bhatt AK, Dominello MM, **Walker EM**, Narayana V, Abu-Isa EI, Vicini FA, Hayman JA, and Pierce LJ. Factors Associated with Cardiac Radiation Dose Reduction Following Hypofractionated Radiation Therapy for Localized, Left-Sided Breast Cancer in a Large Statewide Quality Consortium. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S138. Full Text

D.J. Herr, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Purpose/Objective(s): Limiting radiation dose to the heart is important for minimizing the risk of long-term cardiac toxicity in patients with left-sided early-stage breast cancer. Materials/Methods: Prospectively collected dosimetric data were analyzed for patients undergoing hypofractionated radiation therapy to the left breast for localized node-negative breast cancer within the Michigan Radiation Oncology Quality Consortium (MROQC) from 2016-2022. Goals for limiting cardiac dose were adjusted over time. From 2016-2020, the cardiac quality metric focused on total mean heart dose (MHD) from the composite whole breast and boost plans, tightening from a goal of MHD ≤2 Gy to MHD ≤1.2 Gy by 2020. In 2021-2022, the cardiac metric transitioned to a combined goal of MHD ≤1.0 Gy from the whole breast plan and ≥95% lumpectomy cavity planning target volume (PTV) receiving 95% of the prescription dose. Separate multivariate logistic regression models were developed to assess for covariates associated with meeting the MHD goal in 2016-2020 and combined MHD/PTV coverage goal in 2021-2022. Results: In total, 4,165 patients were analyzed with a median age of 64 years. Most patients (86%) had either Tis or T1 disease, and 66% received hormone therapy. Baseline demographic and disease characteristics did not change substantially between treatment periods. Use of breath-hold or motion gating increased from 42% in 2016-2020 to 46% in 2021-2022. Similarly, use of prone positioning increased from 12% to 20%. From 2016-2020, 90.9% of plans achieved the MHD goal, compared to 93.6% of plans achieving the composite MHD/PTV goal from 2021-2022. On multivariate analysis in the 2016-2020 cohort, treatment with motion management (OR 5.20, 95% CI [3.59-7.54], p<0.0001) or prone positioning (OR 3.21, 95% CI [1.85-5.57], p < 0.0001) were associated with meeting the MHD goal, while receipt of boost (OR 0.25, 95% CI [0.17-0.39], p<0.0001) and omission of hormone therapy (OR 0.65, 95% CI [0.49-0.88], p = 0.0047), were associated with not meeting the MHD goal. During the era including composite heart dose and PTV coverage goals (2021-2022), treatment with motion management (OR 1.89, 95% CI [1.12-3.21], p = 0.018) or prone positioning (OR 3.71, 95% CI [1.73-7.95], p = 0.0008) were associated with meeting the combined goal, while larger breast volume (≥1440 cc, OR 0.34, 95% CI [0.13 – 0.91], p = 0.031) and treatment at an academic center (OR 0.36, 95% CI [0.22-0.67], p = 0.0009) were associated with not meeting the combined goal. Conclusion: In our statewide consortium, rates of compliance with aggressive targets for limiting cardiac dose remain high, despite tightening of these goals to include lower mean heart doses and inclusion of a concurrent PTV coverage goal. Treatment using motion management or prone positioning is associated with achieving the cardiac dose goals.

Radiation Oncology

Herr DJ, Yin H, Bergsma DP, Dragovic AF, Matuszak MM, Grubb M, Dominello MM, **Movsas B**, Kestin LL, Boike TP, Bhatt AK, Hayman JA, Jolly S, Schipper M, and Paximadis PA. Dosimetric Predictors for Acute Esophagitis during Radiation Therapy for Lung Cancer: An Update of a Large Statewide Observational Study. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e24. Full Text

D.J. Herr, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Purpose/Objective(s): Acute esophagitis remains a clinical challenge during the treatment of locally advanced non-small cell lung cancer (NSCLC). Here, we analyze the dosimetric and patient-level characteristics associated with acute grade 2+ and 3+ esophagitis in patients undergoing radiation therapy for NSCLC across a statewide consortium. Materials/Methods: Demographic, dosimetric, and acute toxicity data were prospectively collected for patients undergoing definitive radiation therapy +/- chemotherapy for stage II-III NSCLC from 2012-2022 across the Michigan Radiation Oncology Quality Consortium (MROQC). Logistic regression models were used to characterize the risk of grade 2+ and 3+ esophagitis as a function of dosimetric and clinical covariates. Multivariate regression models were fitted to predict the 50% risk of grade 2 esophagitis or 3% risk of grade 3 esophagitis at each dose value. Results: Of 1760 patients evaluated, 84.2% had stage III disease and 85.3% received concurrent chemotherapy. 79.2% of patients had an ECOG performance status ≤1. Rates of acute grade 2+ and 3+ esophagitis were 48.4% and 2.2%, respectively. On multivariate analyses, performance status, mean esophageal dose and esophageal D2cc were significantly associated with grade 2+ and 3+ esophagitis. Concurrent chemotherapy was associated with grade 2+ but not grade 3+ esophagitis. Dose-response relationships were modeled for grade 2+ and 3+ esophagitis by mean esophageal dose and esophageal D2cc, stratified by performance status and/or receipt of concurrent chemotherapy. For all patients, mean

esophageal dose of 29 Gy and esophageal D2cc of 61 Gy corresponded to a 3% risk of acute grade 3+ esophagitis. For patients receiving chemotherapy, mean esophageal dose of 22 Gy and esophageal D2cc of 49.5 Gy corresponded to a 50% risk of acute grade 2+ esophagitis. Conclusion: Performance status, concurrent chemotherapy, mean esophageal dose and esophageal D2cc are associated with acute esophagitis during definitive treatment of NSCLC. Models that quantitatively account for these factors can be useful in individualizing radiation plans. Mean esophageal dose of 29 Gy and esophageal D2cc of 61 Gy corresponded to a 3% risk of acute grade 3+ esophagitis and merit consideration as contemporary treatment planning constraints.

Radiation Oncology
Koro S, Balagamwala EH, Sahgal A, **Chapman D**, **Schaff EM**, **Siddiqui F**, Lo SS, Wei W, Tseng CL, Tsai J, Schaub SK, Angelov L, Billena C, Bommireddy A, Mayo ZS, Suh JH, and Chao ST. Multi-Institutional Validation of the Recursive Partitioning Analysis for Overall Survival in Patients Undergoing Spine Radiosurgery for Spine Metastasis. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S59-S60. Full Text

S. Koro, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, United States

Purpose/Objective(s): The recently published spine radiosurgery (sSRS) recursive partitioning analysis (RPA) for overall survival (OS) separated patients into 3 distinct prognostic groups. We sought to externally validate this RPA using 3 separate multi-institutional datasets. Materials/Methods: A total of 444 patients were utilized to develop the recently published sSRS RPA predictive of OS in patients with spine metastases. The RPA identified three distinct prognostic classes. RPA Class 1 was defined as KPS >70 and controlled systemic disease (n = 142); RPA Class 2 was defined as KPS>70 with uncontrolled systemic disease or KPS ≤70, age ≥54 and absence of visceral metastases (n = 207); RPA Class 3 was defined as KPS ≤70 and age <54 years or KPS≤70, age ≥54 years and presence of visceral metastases (n = 95). We utilized data from 3 large tertiary care centers to independently validate this RPA. Data from each institution was utilized independently to validate the RPA to minimize confounding based on institutional differences in patient selection. A total of 1,184 patients (221 patients from institution A, 749 institution B, and 214 from institution C) were in the validation cohort and were divided based on their RPA Class. Kaplan-Meier method was used to estimate OS and log-rank test was used to compare OS between RPA classes. Results: In each of the validation cohorts, the median OS was 19.9 months (institution A), 11.0 months (institution B), and 24.4 months (institution C). The patient distribution into RPA classification based on Institution A/B/C was, Class 1 (19.4%, 15.1%, 50.5%), Class 2 (74.7%, 57.7%%, 37.9%), and Class 3 (5.9%, 27.2%%, 11.2%), respectively. The median OS for patients in the validation cohort at Institution A/B/C based on RPA class was Class 1 (54 months, 27.1 months, 50.0 months), Class 2 (15.9 months, 13.0 months, 15.1 months) and Class 3 (6.9 months, 3.5 months, 6.1 months), respectively. Patients in RPA Class 1 had a significantly better OS compared to those in Class 2 of the each of the three external institution validation cohorts ($p<0.01$). Similarly, patients in RPA Class 2 had a significantly better OS compared to those in Class 3 ($p<0.01$). Conclusion: The external datasets from three large institutions independently validated the spine SRS RPA successfully for OS in patients undergoing sSRS for spinal metastases. This is the first RPA for OS to have been externally validated using multiple large datasets. Based on this validation, upfront spine SRS is strongly supported for patients in RPA Class 1 and Class 2 and is also cost effective with median OS >11 months for these patients. Patients in RPA Class 3 would benefit most from upfront conventional radiotherapy given their poor expected survival. Given successful external validation, this RPA helps guide physicians to identify those patients with spinal metastases who most benefit from sSRS.

Radiation Oncology
Lombardo J, Castillo E, Castillo R, Miller RC, Jones BL, Miften M, Kavanagh BD, Dicker AP, Boyle C, Simone NL, **Movsas B**, Grills IS, Guerrero TM, Rusthoven CG, and Vinogradskiy Y. Comprehensive Quality of Life Report from a Prospective Clinical Trial of 4DCT-Ventilation Functional Lung Avoidance Radiation Therapy. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S67-S68. Full Text

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Purpose/Objective(s): Functional imaging has been developed that uses 4DCT images and image processing to generate lung ventilation maps (4DCT-ventilation). 4DCT-ventilation functional avoidance uses 4DCT-images to generate plans that avoid functional regions of the lung with the goal of reducing pulmonary toxicity. A 4DCT-ventilation functional avoidance, phase II, multi-center clinical trial was completed, and patient reported outcomes (PRO) measured. PROs are an essential measure of quality-of-life following radiotherapy. The purpose of this work is to quantify PRO changes for lung cancer patients treated with functional avoidance and to compare PROs against clinical pneumonitis. Materials/Methods: Patients with locally advanced lung cancer receiving curative intent radiotherapy (prescriptions of 45-75 Gy) and chemotherapy were accrued. Each patient had a 4DCT-ventilation image generated using 4DCT data. Favorable arc geometry and optimization techniques were used to generate functional avoidance plans. PRO instruments included the Functional Assessment of Cancer Therapy Lung (FACT-L) questionnaire and the Visual Analog Scale (VAS) administered pre-treatment and 3-, 6-, and 12-months post-treatment to gather data on physical, social, emotional, functional, and pulmonary well-being. The percentage of patients with clinically significant decline was calculated using the FACT-TOI (Trial Outcome Index), FACT-LCS (Lung Cancer Subscale), and VAS instruments. To evaluate the correlation between PROs and clinical toxicity, the percentage of clinically significant FACT-LCS decline was compared (Chi-square test) for patients who did or did not experience grade 2+ pneumonitis. Results: Fifty-nine patients completed baseline PRO surveys. Median age was 65, 83% of patients had non-small-cell lung cancer, with 75% having stage III disease. Clinically significant FACT-TOI decline at, 3, 6, and 12 months was 46.3%, 38.5%, and 26.8%, respectively. The percentage of patients with clinically significant FACT-LCS decline was 33.3%, 33.3%, and 29.3%, at 3 months, 6 months, and 12 months, respectively. The percentage of patients with clinically significant VAS decline at 3, 6, and 12 months was 18.9%, 20.0%, and 18.6%, respectively. Patients who experienced grade 2+ pneumonitis had a greater percentage of clinically significant decline at all time-points with the results reaching significance ($p = 0.045$) at 6 months. Conclusion: The study presents the first comprehensive evaluation of PROs for patients treated with 4DCT-ventilation functional avoidance. The data show that 20-40% of patients had clinically significant decline and that PROs had a strong correlation with pneumonitis. The PRO data demonstrate that functional avoidance results in low rates of patient reported outcome clinical decline and provide seminal results to be used in phase III studies.

Radiation Oncology

Moncion A, Griffith K, **Walker EM**, Jagsi R, Dominello MM, Wilson M, Mietzel M, Grubb M, Marsh R, Vicini FA, and Pierce LJ. Impact of Breast Volume on Achieving a Conservative Heart and Target Coverage Metric for Patients Receiving Whole Breast Radiotherapy in a Statewide Consortium. *Int J Radiat Oncol Biol Phys* 2023; 117(2):e193-e194. Full Text

A. Moncion, Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

Purpose/Objective(s): Radiation to large breast volumes (BV) has been associated with increased dose inhomogeneities, breast fibrosis, and induration. Radiation exposure to the heart during breast radiotherapy has been associated with late cardiovascular morbidity and mortality. This study, therefore, investigates the impact of BV on achieving optimal lumpectomy cavity target coverage (V95% [%] >95) while maintaining mean heart dose constraints (MHD, mean [Gy] <1) across a range of BV from patients enrolled in a statewide consortium. Materials/Methods: A retrospective analysis was conducted for 2,506 patients receiving left-sided whole breast moderately-hypofractionated (2.5-2.8 Gy/fx) radiotherapy without nodal fields between 2018-2022. The BV was calculated for each patient from contours in the treatment planning system, and the volume distribution partitioned into quartiles. Dosimetric parameters were calculated from dose-volume histograms. The percentage of patients in which the metrics were achieved was calculated for each BV quartile for different treatment positions: all positions, supine, supine with breathing motion management, and prone. Results: The BV ranges within the quartiles (~620 patients/quartile) were ≤720.0 cc, 720.1 to ≤1065.0 cc, 1065.1 to ≤1500.0 cc, and >1500.0 cc for quartiles Q1-Q4, respectively. Of the 2,506 patients, 76% were treated supine (of which 41.6% were treated using breathing motion management techniques), 23.5% were treated prone, and 0.5% were treated decubitus. Discrete percentages of patients able to meet the metrics are provided in the table. An increase in BV

from Q1 to Q4 correlated with lower percentages of patients meeting the MHD metric, however no correlation was observed between BV and target coverage. Treating supine with breathing motion management resulted in a higher percentage of patients meeting the MHD metric (odds ratio (OR) = 1.96 relative to supine without motion management, p<0.0001), while the prone setup proved to be the superior technique across all quartiles (OR = 3.95 relative to supine, p<0.0001). Conclusion: Increasing BVs resulted in lower percentages of patients receiving MHD≤1 Gy. Thus, cardiac sparing may be more difficult to achieve in patients with larger BV. Utilization of alternate treatment positions, such as supine with breathing motion management and prone, greatly improved the percentage of patients able to meet the MHD metric without sacrificing target coverage in all quartiles. Prone positioning was the technique least susceptible to BV effects in meeting the MHD≤1 Gy goal.

Radiation Oncology

Nyati S, **Stricker H**, **Barton KN**, **Li P**, **Elshaikh M**, **Ali H**, **Brown SL**, **Hwang C**, **Peabody J**, **Freytag SO**, **Movsas B**, and **Siddiqui F**. Replication Competent Adenovirus-Mediated Cytotoxic and Interleukin-12 Gene Therapy in Prostate Cancer: 36-month Follow-Up Data from a Phase I Clinical Trial. *Mol Ther* 2023; 31(4):297. Full Text

Introduction: Men with locally recurrent prostate cancer, after definitive radiotherapy, have few therapeutic options. Oncolytic adenovirus-mediated cytotoxic gene therapy is an investigational cancer therapy. Delivery of the suicide gene to the tumor is by direct intratumoral or systemic injection of a viral vector containing the suicide gene. Our approach incorporates yeast cytosine deaminase (yCD) and herpes simplex virus thymidine kinase (HSV-1 TK), to confer sensitivity to 5-fluorocytosine (5-FC) and Valganciclovir (vGCV), respectively. The pro-drugs are converted into active drugs that inhibit DNA damage repair. Here we report the safety of oncolytic adenovirus-mediated suicide gene therapy that incorporates an interleukin-12 (IL12) gene for treatment of recurrent prostate cancer. Methods: In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 15 subjects with recurrent prostate cancer (T1c-T2) at escalating doses (1 × 1010, 3 × 1010, 1 × 1011, 3 × 1011, or 1 × 1012 viral particles). Subjects received 5-FC and vGCV for 7 days. The study endpoint was toxicity through day 30. Experimental endpoints included measurements of serum IL12, interferon gamma (IFNγ), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells (PBMC) and proliferation markers were analyzed by flow cytometry. Results and conclusions: Fifteen patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC and vGCV. Approximately 92% of the 115 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of only two patients. Elevated serum IL12, IFNγ, and CXCL10 levels were detected in 57%, 93%, and 79% of subjects, respectively. Serum cytokines demonstrated viral dose dependency, especially apparent in the highest-dose cohorts. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration in cohort 5. The study did not detect a significant difference in the PSA doubling time (PSADT) between pre and post treatment by paired Wilcoxon rank test (p=0.17). There was no correlation between adenoviral dose and PSADT in each cohort separately or pooled (cohorts1-3 and cohorts 4-5). The study maximum tolerated dose (MTD) was not reached indicating 1012 viral particles was safe. This trial confirmed that replication-competent Ad5-IL-12 adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) was well tolerated when administered locally to prostate tumors.

Radiation Oncology

Schrader M, Garcia Schüler H, Kishan A, Atalar B, Boldrini L, Ehrbar S, Igaki H, Leeman J, Mak R, Mellon E, Nilo I, Nagar H, Pedersen A, Ozyar E, **Parikh P**, **Dolan J**, Perryck S, Placidi L, Steinberg M, Marchesano M, Maingon P, Tanadini-Lang S, Wilke L, and Andratschke N. Patients with cardiac implantable electronic devices: A Patterns of Care Survey for low-field MRgRT. *Radiother Oncol* 2023; 182:S1595. Full Text

Purpose or Objective Patients with cardiac implantable electronic devices (CIEDs) represent a critical cohort concerning radiotherapy and MR safety challenges. CIEDs experiences in an MRI environment are described in the literature. Yet, with the advent of Magnetic Resonance guided Radiotherapy (MRgRT) using hybrid MR and linear accelerators (MR linac) only case reports exist, and clinical experience is

lacking. The intent of this survey was to capture the pattern of practice in institutions employing a low-field MR linac in patients with CIEDs and to derive cautious practice recommendations. Materials and Methods The survey consisted of 9 multiple choice and open questions regarding treatment of patients with MRgRT and experiences with different devices with follow-up inquiries and was sent to all worldwide active low-field MR linac centers (n=53). The participants gave information about patients until the end of 2021. Results We received replies from 13 centers worldwide (response rate 25%) which provided data on their decision making process of CIED patients in an MR environment. 54% of the centers had been treating 41 CIED patients in total, while 46% had not yet treated CIED patients but would consider treatment if specific requirements were met. 62% of the centers with CIED experience would allow MR conditional devices, the remaining centers (23%) would also allow non-conditional devices. 2 centers (15%) did not allow any CIED. 95% of the patients had conditional CIEDs and two patients had nonconditional devices. 28 % of all reported devices were CIEDs with cardioverter, defibrillator function (ICDs). The focus of all centers was the benefit of MRgRT vs the risk of device damage or failure. Some centers would only treat if a) the patient was not CIED dependent (15%), b) the device could be turned off (8%), or c) if a continuous heart and O2 monitoring was not needed (8%). The centers developed individual workflows based mainly on technical data sheets, national guidelines and cardiologist's recommendation and cardiologists periprocedural check. Yet, only one third of the centers implemented a CIED physics specific checklist. Monitoring was in most cases continuous visual and verbal monitoring besides common emergency precautions. Pulse oximetry was the most frequent reported monitoring modality. No CIED related incident has been reported so far. Conclusion Despite missing MRgRT recommendations on the management of CIEDs, half of the responding centers allowed patient treatment with CIED after following safety procedures and weighting benefit risk of MRgRT. No clinical incidence, device damage or change with the 41 patients treated was reported, indicating that MRgRT in CIED patients could be considered safe, given pre—treatment checklists, protocols, and close collaborations with cardiologists. We recommend center-manufacturer collaboration and experience expansion of all participating centers in further surveys.

Radiation Oncology

Siddiqui F, **Nyati S**, **Elshaikh M**, Barton K, **Ali H**, **Brown S**, **Hwang C**, **Peabody J**, **Freytag S**, **Movsas B**, and **Stricker H**. Replication Competent Adenovirus-mediated Cytotoxic and Interleukin-12 Gene Therapy in Prostate Cancer: 36 Month Follow-Up Data from a Phase I Clinical Trial. *Cancer Clin Trials* 2023; 46(6):S13-S14. Full Text

F. Siddiqui, Henry Ford Health Cancer, United States

Background: Men with locally recurrent prostate cancer, after definitive radiotherapy, have few therapeutic options that have a high likelihood of eradicating the tumor with a reasonable degree of safety. Oncolytic adenovirus-mediated cytotoxic gene therapy is an investigational cancer therapy that is currently being evaluated in clinical trials. Delivery of the suicide gene to the tumor is usually accomplished by direct intratumoral or systemic injection of a viral vector containing the suicide gene. Two suicide genes that have been evaluated in preclinical models and in the clinic are the E. Coli coli cytosine deaminase (CD) and herpes simplex virus thymidine kinase (HSV-1 TK), which confer sensitivity to 5-fluorocytosine (5-FC) and ganciclovir (GCV), respectively. The pro-drugs are converted into active drugs that block DNA synthesis. In the past we have evaluated the toxicity and efficacy of oncolytic adenovirus-mediated cytotoxic gene therapy in five different clinical trials in prostate cancer, including a prospective randomized phase 2 study. In this Phase I trial we evaluated the safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL12) gene therapy in recurrent prostate cancer patients. Objectives: Phase I dose-escalation trial to evaluate the maximum tolerated dose (MTD) of replication competent adenovirus type 5 gene therapy with interleukin-12 delivered using ultrasound guided intraprostatic injection. Methods: Replication-competent adenovirus (Ad5-yCD/mutTKSR39- rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/ mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 15 subjects with recurrent prostate cancer (T1c-T2) at escalating doses (1 × 1010, 3 × 1010, 1 × 1011, 3 × 1011, or 1×1012 viral particles). Subjects received oral prodrugs, 5-fluorocytosine (5-FC) and Valganciclovir (vGCV) therapy for 7 days. The study endpoint was toxicity through day 30. Experimental endpoints included measurements of serum IL12, interferon gamma (IFN-gamma), and CXCL10 to assess immune system activation. Peripheral blood mononuclear

cells (PBMC) and proliferation markers were analyzed by flow cytometry. Results: Fifteen patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC and vGCV. Approximately 92% of the 115 adverse events observed were grade 1/2 requiring no medical intervention. Ad5- yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of only two patients. Elevated serum IL12, IFN-gamma, and CXCL10 levels were detected in 57%, 93%, and 79% of subjects, respectively. Serum cytokines demonstrated viral dose dependency, especially apparent in cohorts 4 and 5. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration in cohort 5. There was no correlation between adenoviral dose and PSA doubling time (PSADT). Conclusions: Ultrasound guided intraprostatic injection of replication competent adenovirus type 5 containing wo suicides genes and interleukin- 12 is well tolerated up to a dose of 1 × 1012 viral particles. The study maximum tolerated dose (MTD) was not reached. Further studies will be done to evaluate efficacy of this therapeutic approach in patients with locally recurrent prostate cancer.

Radiation Oncology

Zhu S, Cordero-Marcos M, Czeizler E, Bose S, Magliari A, and **Chetty IJ**. Predicting Prostate VMAT 3D Radiation Doses of Continuously Varying Organ Dose Trade-Offs Using a Conditional Variational Autoencoder. *Int J Radiat Oncol Biol Phys* 2023; 117(2):S164-S165. Full Text

S. Zhu, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI, United States

Purpose/Objective(s): Predicting 3D radiation doses from planning structures is a promising method of knowledge-based treatment planning. However, most models are designed to predict only one 3D dose distribution per patient, based on historical organ dose trade-offs. To allow customizable plan generation, in this study, we aim to show the feasibility of dose prediction in which the degrees of organ dose trade-off could be explicitly specified. Specifically, the bladder vs. rectum dose trade-off in prostate cancer was investigated. Materials/Methods: In an IRB-approved study, we obtained imaging and structure contours for 167 patients with prostate cancer who received definitive radiotherapy. Training data was generated by automatically creating 3 different plans for each patient: while keeping target dose patterns constant, 1 base plan was generated with optimization objectives directly based on the output of a custom RapidPlan model prediction (S = 0), 1 plan with the goal to significantly lower bladder dose relative to the rectum (S = -1), and 1 plan with the goal to significantly lower rectum dose relative to the bladder (S = 1). This process was achieved by adjusting priority values during optimization. S is a scalar indicating the degree of bladder vs. rectum dose trade-off (higher S = higher dose to the bladder relative to the rectum). A conditional variational autoencoder (cVAE) was constructed as the generative model. Training, validation, and testing sets consist of 124, 10, and 33 patients, respectively. During training, the inputs to the model were 3D structure masks with voxel values modified based on S, and the output was the corresponding 3D dose. For model testing, we selected 7 equispaced values of S in the range [-1, +1] for each of the 33 test patients, generated the 3D doses for each S value (normalized to D2% = 110%), and calculated the differences of key dosimetric parameters (for S levels other than 0) compared to the predicted base plan (S = 0). The mean and standard deviations for these differences were reported. Results: The cVAE model converged after training for 800 epochs. As the value of S increased from -1 to +1, the target coverage remained similar, while the doses to the bladder and rectum increased and decreased, respectively, as expected (Table 1). This pattern was also confirmed by qualitative examination of dose-volume histograms for additional S values. Conclusion: We demonstrated the feasibility of predicting 3D radiation dose distributions for prostate cancer where the degrees of organ dose trade-off could be explicitly specified.

Sleep Medicine

Cheng P, **Kalmbach D**, **Sagong C**, **Fellman-Couture C**, and **Drake C**. Digital CBT-I versus stepped-care CBT-I to prevent depression one year later. *Eur Psychiatry* 2023; 66:S110. Full Text

P. Cheng, Sleep Research, Henry Ford Health, Novi, United States

Introduction: Insomnia is a robust risk factor for depression. Treating insomnia with digital CBT-I (dCBT-I) has been shown to prevent future episodes of depression; however, remission rate of insomnia following dCBT-I is lower compared to face-to-face CBTI (fCBT-I), which may reduce the effect on depression

prevention. A stepped-care model can optimize care by starting with a least resource intensive intervention (step 1: dCBT-I) and stepping-up non-remitters to specialized treatment (step 2: face-to-face CBT-I). Objectives: This study examined the efficacy of a stepped-care approach to prevent depression. Methods: 1018 individuals with DSM-5 insomnia and no depression were randomized into two conditions at step 1: dCBT-I (n=613), or an online sleep education control (n=624). Participants in the dCBT-I condition who did not show remission for insomnia (ISI>9) were further randomized to either face-to-face CBT-I (n=103) or sleep education (n=104). Rates of clinically significant depression (moderate severity and above) was assessed at one-year follow-up. Results: Insomnia remission rates were higher in the dCBT-I group (40%) compared to the control group (22%). Those who did not remit following step-1 dCBT-I showed step-2 insomnia remission rates of 75% following fCBT-I compared to 38% following the step 2 control. At one year follow-up, the incident rate of clinically significant depression was 2.4 times higher in those who received control (13.2%) compared to fCBT-I (5.5%) at step 2. Depression rate was 10.1% in those who did not receive dCBT-I at step-1. Conclusions: Preliminary evidence from this study provide supported that a stepped-care approach may produce greater protection against incident depression than dCBT-I alone.

Surgery

Chau L, **Lu Z**, **Miyake K**, **Kitajima T**, **Wickramaratne N**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Creation of Machine Learning Based Models Predicting Donation After Circulatory Death Liver Transplantation Survival and Length of Stay. *Am J Transplant* 2023; 23(6):S856-S857. Full Text

Purpose: Machine learning techniques allow for complex modeling of associations with iterative cloud-based model tuning and deployment. We aim to apply these methods to estimate DCD liver transplantation outcomes. Methods: All adult DCD liver transplant recipients in the UNOS STAR file from Feb 1, 2003, to Sept 14, 2021 were included. Pediatric and simultaneous transplantation were excluded. Study cohort was divided into 80% training, 10% validation, and 10% testing sub-groups with more recent transplantations weighted for testing. Python and TensorFlow based feed-forward neural networks and gradient boosting decision tree models hosted on Google Cloud platform were deployed to predict 1-year patient survival, 1-year liver graft survival, and length of index hospitalization (LOS). Performance of the models was assessed using area under the receiver operating curve (AUC-ROC) and root mean square error (RMSE) with confidence intervals constructed using bootstrapping with 2000 resamples. Results: 8074 DCD liver transplant recipients were included in the study with 791 recipients in the testing cohort. 142 donor, recipient, and waitlist characteristics available at time of transplantation were used for model construction. The model was predictive of 1-year patient survival with AUC-ROC 0.794 (95% C.I. 0.659-0.929), 1-year liver graft survival with AUC-ROC 0.825 (95% C.I. 0.716-0.934), and index LOS with RMSE 16.9. Conclusions: We demonstrate a cloud-based machine learning model that robustly predicts DCD liver transplantation index hospitalization length of stay, as well as 1-year patient and graft survival. Further hyperparameter tuning with future iterations of registry data will allow for continuous improvement. CITATION INFORMATION: Chau L., Lu Z., Miyake K., Kitajima T., Wickramaratne N., Rizzari M., Yoshida A., Abouljoud M., Nagai S. Creation of Machine Learning Based Models Predicting Donation After Circulatory Death Liver Transplantation Survival and Length of Stay AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: L. Chau: None. [Figure presented]

Surgery

Chau L, **MacLean EK**, **Kathawate RG**, **Abdallah Y**, **Wickramaratne N**, **Kitajima T**, **Miyake K**, **Nagai S**, **Yoshida A**, **Abouljoud M**, and **Rizzari M**. Early Experience of Normothermic Liver Perfusion Pump in Liver Transplantation. *Am J Transplant* 2023; 23(6):S721. Full Text

Purpose: Normothermic machine-based liver perfusion (NMP) has demonstrated improved outcomes versus cold ischemic storage in liver-alone transplantation. Methods: This study includes adult liver-alone transplantation recipients at our center from 1/16/2016 to 7/1/2022. Liver transplantation delivered on pump were identified with retrospective chart review. 1-to-2 propensity score matched models adjusting for donor and recipient characteristics were fitted to estimate the treatment effect of NMP on post-reperfusion syndrome, index hospital length of stay (LOS), 3-month biliary complications, biopsy proven rejection, graft survival, and patient survival compared to conventional ischemic cold storage. Results: 593 liver transplantations were included with 42 delivered on NMP. The NMP group had higher DCD liver

transplantation (35.7% vs 17.4%, P=0.001), fewer reoperations (9.1% vs. 19.2%, P=0.04), trend towards shorter LOS (9 [IQR: 7-16] vs 10 [IQR:7-18] days, P=0.42), trend towards less post-reperfusion syndrome (11.3% vs 20%, P=0.06). On propensity score matched analysis, OCS livers had non-inferior 3-month biliary complications (HR = 1.34, P = 0.78, [95% C.I. = 0.47-2.78]), biopsy proven rejection (HR = 1.58, P = 0.77, [95% C.I. = 0.49-5.15]), graft failure (HR = 0.42, P = 0.78, [95% C.I. = 0.56-2.62]), and patient death (HR = 0.39, P = 0.66, [95% C.I. = 0.30-2.81]). Conclusions: The use of NMP in liver-alone transplantation in our center is associated with significantly higher proportion of DCD liver transplantation and fewer reoperations, trend towards shorter LOS and post-reperfusion syndrome, as well as non-inferior 3-month biliary complications, graft survival, and patient survival compared to livers delivered on conventional cold ischemic storage. CITATION INFORMATION: Chau L., MacLean E., Kathawate R., Abdallah Y., Wickramaratne N., Kitajima T., Miyake K., Nagai S., Yoshida A., Abouljoud M., Rizzari M. Early Experience of Normothermic Liver Perfusion Pump in Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: L.Chau: None. M.Abouljoud: None. M.Rizzari: None. E.K.Maclean: n/a. R.G.Kathawate: n/a. Y.Abdallah: n/a. N.Wickramaratne: n/a. T.Kitajima: n/a. K.Miyake: None. S.Nagai: None. A.Yoshida: n/a. [Figure presented]

Surgery
Ciria R, **Ivanics T**, Aliseda D, Claasen M, Alconchel F, Briceño J, Berardi G, Rotellar F, and Sapisochin G. Transplant Oncology for Primary and Secondary Liver Tumors: A Patient-level Metaanalysis Compared to Standard and Non-standard Indications for Liver Transplantation. *HPB* 2023; 25:S233-S234. Full Text

Background: Concerns about the safety of Transplant Oncology have been raised. However, some other controversial indications (such as re-transplants, combined organs or high-risk recipients), are been currently performed with no questioning. The main aim of our research is to put all the indications of liver transplantation (LT) for malignancies in the context of standard and controversial wide-accepted indications considering overall reported outcomes. Methods: PubMed, Embase and WoS were screened selecting studies that included transplanted patients for intrahepatic and hilar cholangiocarcinoma (iCC-hCC), metastatic neuroendocrine tumors (NET) and liver metastases from colorectal cancer (CRLM). Pooled and patient-level survival data meta-analyses were performed and comparative analyses were made with OS outcomes of patients transplanted for standard (n = 66924), standard+HCC (n=19804) and unusual but accepted (n = 53754) indications collected from the UNOS database between 2005 and 2020 (PROSPERO CRD4202022268510). Results: An initial set of 1205, 1951, 3302 and 2461 manuscripts were identified from which 23, 17, 16 and 11 manuscripts including 484, 796, 751 and 103 patients were finally analyzed from series in which LT has been performed for iCC, hCC, NET, CRLNM, respectively. Secondary patient-level survival data meta-analyses were performed including 345, 721, 494 and 103 patients, respectively. By merging survival data obtained from UNOS database and the 4 meta-analyses, TrOncol indications have lower survival than Standard Indications. However, when compared with “non-standard” indications, 5-year overall survival was significantly better than 4thredo-transplant, combined liver and pancreas and similar to 3 redo transplant and LT on recipients >70yo. Five-year OS rates for Transplant Oncology indications were above 50% except for pCC which was 47.4%. Conclusions: Outcomes of Transplant Oncology indications are beyond the minimal requirement of 50% 5y OS and higher than other indications performed during routine practice. Liver transplant teams and National Organizations should ensure protocols to incorporate Transplant Oncology indications within routine LT indications under strict selection criteria.

Surgery
Finotti M, **Jesse M**, Pillai A, Liapakis A, **Venkat D**, **Salgia R**, Kumar V, **Manivannan A**, **Lu M**, **Zhang T**, Verna E, and Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation. *Am J Transplant* 2023; 23(6):S864-S865. Full Text

Purpose: Living donor liver transplantation (LDLT) is a viable option to increase access to liver transplantation (LT). However, there are well-documented racial and gender-based inequities in access to deceased donor LT. Very little is empirically known about living liver donor (LLD) characteristics in relation to their recipients. Therefore, we aimed to explore the odds of receiving LDLT across LLD and recipient characteristics. Methods: We explored gender, interactions between LLD-recipient race/ethnicity, and

other relevant factors on LDLT utilizing national data from the United Network for Organ Sharing (UNOS) for all adult LLD and their recipients who underwent LDLT from 1/1/2012 through 10/1/2022. Results: 3469 LDLTs occurred (5.46% of all LTs). A majority of LLDs were female (n 1864, 54%), mean 37.16 years of age (SD 10.41), and White race (n 2791, 81%), followed by Hispanic (n 423, 12%), Black (n 116, 3%), Asian (n 85, 2%), and Other (n 47, 1%). LDLT recipients were predominantly male (n 1843, 53%), mean 53.35 years of age (SD 13.22), and White race (n 2787, 80%), followed by Hispanic (n 437, 13%), Black (n 118, 3%), Asian (n 92, 3%), and Other (n 35, 1%). Of note, 42.9% (n 1487) of LLDs were not biologically related to their recipient. As reported in Table 1, men are both less likely to receive or be a LLD than women. Examining the donor by recipient race interactions, LDLT is more likely to occur between LLD and recipients with the same racial/ethnic category than differing race/ethnicity (regardless of comparator). When race/ethnicity is different between LLD-recipient, four significant interactions occurred indicating that White LLDs are less likely to donate to Black recipients than Hispanic or Others/Unknown and Asian donors are more likely to donate to Others/Unknown than either Hispanic or White recipients. Conclusions: While biological relatives are assumed to be the same race/ethnicity, nearly half of LLDs are not biologically related to their recipient and yet all racial groups were more likely to donate within their own racial category, adjusting for liver disease category and functional status. Also, despite representing the majority of waitlisted and transplanted patients, men were less likely to receive LDLT, but men are also less likely to be a LLD. These results provide a starting point to foster efforts towards diversifying the LLD population. CITATION INFORMATION: Jesse M., Pillai A., Liapakis A., Venkat D., Salgia R., Kumar V., Manivannan A., Lu M., Zhang T., Verna E., Parikh N. Interaction Between Donor and Recipient Race/Ethnicity in Living Donor Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: M.Jesse: None. E.Verna: None. N.Parikh: Consultant;; Eisai, Eli Lilly, Research Grant Site Overall Principal Investigator;; Genentech. A.Pillai: n/a. A.Liapakis: None. D.Venkat: n/a. R.Salgia: n/a. V.Kumar: None. A.Manivannan: n/a. M.Lu: n/a. T.Zhang: n/a. [Figure presented]

Surgery

Gouchoe DA, **Shamaa TM**, Mohamed A, **Bajjoka I**, **Crombez C**, **Nagai S**, **Yoshida A**, **Abouljoud M**, and **Rizzari M**. The 24-Hour Normothermic Machine Perfusion of Discarded Human Liver Grafts. *Am J Transplant* 2023; 23(6):S920-S921. Full Text

Purpose: The persistent shortage of liver allografts contributes to significant waitlist mortality. Normothermic machine perfusion (NMP) has the potential to extend viability and allow liver function evaluation in discarded organs. The main aim of the study was to evaluate the recovery of non-usable human livers utilizing NMP. Methods: 6 high-risk human liver grafts that were discarded underwent normothermic liver preservation for an extended period of 24 hours. Transmedics Organ Care System™ liver perfusion device was used to preserve a donor liver in a functioning, near physiologic state. Parameters of biochemical and synthetic liver function were collected periodically and subsequently analyzed. Liver parenchyma and bile duct biopsies were obtained pre- and 24 hours post-NMP. Results: 4/6 (67%) grafts were DCDs with a median age of 54 (IQR: 42-61) years and a median CIT of 262 (IQR: 209-1024) minutes [Table 1]. 5/6 (83%) livers produced a median of 75 ml of bile (Range 55-100) after 24 hrs of NMP. Lactate dropped to normal levels (<2 mmol/L) for all livers after around 4 hrs on NMP [Figure 1]. There was a positive correlation between the 24 hr ALT level and pre-NMP CIT (r=0.9; p=0.02). Biopsies showed improvement of liver architecture with reduced inflammation for 2/6 (33%) at the end of the perfusion Conclusions: Using NMP for discarded liver grafts might identify certain grafts that are suitable for transplantation. Further studies utilizing NMP with subsequent transplantation would validate this strategy. CITATION INFORMATION: Shamaa T., Mohamed A., Bajjoka I., Crombez C., Nagai S., Yoshida A., Abouljoud M., Rizzari M. The 24-Hour Normothermic Machine Perfusion of Discarded Human Liver Grafts AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: T.M.Shamaa: None. A.Mohamed: n/a. I.Bajjoka: n/a. C.Crombez: n/a. S.Nagai: None. A.Yoshida: n/a. M.Abouljoud: None. M.Rizzari: None. [Figure presented]

Surgery

Hider A, Bonham A, **Carlin A**, Finks J, Ghaferi A, **Varban O**, and Ehlers A. Differences in Post-Surgical Outcomes and Complications Among Males and Females Undergoing Bariatric Surgery: A State-wide Analysis. *Surg Endosc* 2023; 37:S392-S393. Full Text

A. Hider, University of Michigan Medical School, United States

Introduction: Sex as a biologic variable remains largely understudied, even for the most commonly performed operations. Bariatric surgery is one of the most commonly performed operations in the USA and is the most effective treatment for obesity and obesityassociated comorbidities. However, there is scant data to describe potential differences in outcomes between male and female patients, particularly with regards to weight loss. Within this context, we examined weight loss and complications up to one year following sleeve gastrectomy or gastric bypass within a state-wide bariatric quality improvement collaborative. Methods and Procedures: We performed a retrospective cohort study among patients who had bariatric surgery. Using a state-wide bariatric-specific data registry, all patients who underwent gastric bypass or sleeve gastrectomy between June 2006 and June 2022 were identified. The primary outcome was total body weight loss, percent total body weight loss, and body mass index at one year. The secondary outcome was the adjusted risk of 30-day complications. We used multivariable linear regression models to estimate weight loss and BMI, and multivariable logistic regression models to estimate overall risk of complications. Results: Among 107,504 patients, the majority (n = 85,135; 79.2%) were female and most patients (n = 49,731; 58%) underwent sleeve gastrectomy. Compared to female patients, male patients were older (47.6 yrs vs 44.8 yrs; p<0.0001), had higher baseline weight (346.6 lbs vs 279.9 lbs; p<0.0001), had higher preoperative BMI (49.9 kg/m2 vs 47.2 kg/m2; p<0.0001), and higher prevalence of most comorbid conditions, including hypertension, hyperlipidemia, diabetes, and sleep apnea (p<0.0001). Compared to females patients, male patients experienced greater total body weight loss (105.1 lbs vs 84.9 lbs; p<0.0001) and higher excess body weight loss (60.0% vs 58.8%; p<0.0001) but had higher BMI overall (34.0 kg/m2 vs 32.8 kg/m2; p<0.0001) at one year of follow-up. Compared to females, males had higher rates of 30-day complications, including serious complications (2.5% vs 1.9%; p<0.0001). Conclusion: In this study we found that both males and females experienced excellent weight loss with a low risk of complications following bariatric surgery. However, male sex was associated with slightly greater weight loss and slightly higher incidence of complications. Providers should consider referring males earlier for bariatric surgery which may improve outcomes for this population.

Surgery

Jarman A, **Ching Chau L**, **Soheim R**, **Dix M**, **McFarlin K**, and **Stanton C**. Effect of Neuromuscular Blockade Reversal on Post-operative Urinary Retention Following Inguinal Herniorrhaphy. *Surg Endosc* 2023; 37:S307-S308. Full Text

A. Jarman, Henry Ford Hospital, United States

Introduction: Within the United States, reversal of nondepolarizing neuromuscular blockade is routinely accomplished by anticholinesterases such as neostigmine combined with glycopyrrolate or edrophonium combined with atropine. Sugammadex, a selective antagonist for rocuronium, is commonly utilized due to rapid onset of action and decreased side effect profile. Sugammadex was previously associated with reduced rates of post operative urinary retention (POUR) compared to anticholinesterases. This study aims to define the risk of POUR following inguinal herniorrhaphy in those that received sugammadex compared to anticholinesterases in a single tertiary referral center. Methods: All adults undergoing inguinal herniorrhaphy from 1/1/ 2019 to 7/1/2022 with at least 30 days of follow up were identified. Inclusion criteria include those who received aminosteroid non-depolarizing muscle relaxants rocuronium or edrophonium and were reversed with an anticholinesterase or sugammadex. Patients who did not receive a neuromuscular blocking agent were excluded. The 30-day incidence of new onset POUR was identified through chart review. 1 to 2 propensity score matched models were fitted to evaluate the treatment of effect of sugammadex vs. anticholinesterase on POUR adjusting for patient comorbidities, ASA class, wound class, operative laterality, urgency of case, and open vs. minimally invasive repair. Results: 3345 patients were included in this study with 1101 receiving sugammadex and 2244 receiving anticholinesterase for neuromuscular blockade reversal. The 30-day rate of new POUR was 2.8%, 1.4% in the sugammadex and 4.4% in the anticholinesterase groups respectively. 61% of the cohort received elective herniorrhaphy, 73.6% were unilateral repairs, 0.75% were repeat herniorrhaphy on the same side, 3.2% required inpatient stay post-operatively with average length of stay of 1.5 days [IQR: 1-2]. After propensity score matching, patients receiving sugammadex had significantly lower risk of POUR

compared to anticholinesterase overall (OR: 0.340, P<0.001, 95% C.I. = 0.198-0.585), in open cases (OR: 0.296, P = 0.013, 95% C.I. = 0.113-0.775), minimally invasive cases (OR: 0.36, P = 0.002, 95% C.I. = 0.188-0.693), unilateral repairs (OR: 0.371, P = 0.001, 95% C.I. = 0.203-0.681), bilateral repairs (OR: 0.25, P = 0.025, 95% C.I. = 0.074-0.838), elective cases (OR: 0.329, P<0.001, 95% C.I. = 0.185-0.584), and clean cases (OR: 0.312, P<0.001, 95% C.I. = 0.176-0.553). Conclusions: The incidence of 30-day new onset post-operative urinary retention in our cohort was 2.8%. Sugammadex for neuromuscular blockade was associated with significantly lower risk of 30-day new onset POUR compared to anticholinesterase overall and when stratifying by operative modality, laterality, and wound class. (Figure Presented).

Surgery
Knobbe TJ, Ryan RJ, Merzkani M, **Kim D**, Mai M, Heilman R, Smith B, Everly M, and Stegall M. Patient Recorded Outcomes (PROs) After Kidney Transplantation: Envarsus vs Tacrolimus (Multicenter Transplant Alliance Cohort). *American Journal of Transplantation* 2023; 23(6):S1167. Full Text

Purpose: The goal of this study was to compare Patient Reported Outcomes (PROs) after kidney transplantation in patients receiving either Envarsus (once daily longacting tacrolimus) or conventional twice daily tacrolimus (BID Tac). Methods: In this prospective, non-randomized clinical trial at 5 centers in the US, patients transplanted between 8/23/2019 and 3/7/2022 were given either Envarsus or BID Tac primarily based on their insurance coverage for the drugs. At 4 and 12 months after transplantation, patients answered 2 questionnaires: The Calcineurin Inhibitor-Related Symptoms (CIRS) survey (5 common side effects) and The Transplant Related Symptoms (TRS) survey (15 common post-transplant symptoms). The primary endpoint was number of patients with one or more symptoms scored as moderate/severe/very severe (Mod/Sev/VSev) at 12 months analyzed using multivariable models adjusted for age, race, sex, and transplant center. Results: Of the 274 patients enrolled, 2 died, 69 withdrew from the study before 12 months or failed to complete their 12-month survey, and 203 completed both surveys at 12 months. Ten patients originally on Envarsus converted to BID Tac for insurance reasons and were analyzed in the BID Tac group at 12 months. Of the 203, 17% were African American, 39% female, and the mean age was 55. At 1 year, 60 (29.6%) patients had at least one Mod/Sev/VSev CIRS with the most common being hand trembling (27), muscle weakness (26), and muscle cramps (20). Fourteen (7%) patients reported at least 1 Sev/VSev CIRS. For TRS, 125 (61.6%) had at least one Mod/Sev/VSev symptom including: fatigue (47), diarrhea (45), and insomnia (43). Sixty-two (30%) reported at least one Sev/VSev and 33 had multiple symptoms. In multivariable analysis, there were no significant predictors of Mod/Sev/VSev CIRS symptoms. For TRS surveys, recipient female gender was associated with increased Mod/Sev/VSev symptoms (2.15 (1.11, 4.28) p = 0.0252) and recipient age trended toward significance (1.03, p = 0.0615). There were no differences in eGFR between Envarsus and tacrolimus at 4 or 12 months. Conclusions: One year after kidney transplantation, a Mod/Sev/VSev CIRS and TRS are common, but Sev/VSev CRS were rare. In a multivariable model for TRS, female recipients reported more severe symptoms. The type of tacrolimus drug (Envarsus vs BID Tac) did not affect symptoms. These data suggest the need for specific management approaches to address PROs after kidney transplantation. CITATION INFORMATION: Ryan R., Merzkani M., Kim D., Mai M., Heilman R., Smith B., Everly M., Stegall M. Patient Recorded Outcomes (PROs) After Kidney Transplantation: Envarsus vs Tacrolimus (Multicenter Transplant Alliance Cohort) AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: R.J.Ryan: None. M.Merzkani: None. D.Kim: n/a. M.Mai: n/a. R.Heilman: None. B.Smith: None. M.Everly: n/a. M.Stegall: n/a.

Surgery
Maheshwari R, **Gupta D**, **Nagai S**, **Muszkat Y**, **Beltran N**, and **Jafri S**. Management of Graft vs Host Disease Following Intestinal Transplantation. *Am J Transplant* 2023; 23(6):S733. Full Text

Purpose: We present four patients with multi-visceral transplant (MVT) complicated by graft-versus-host disease (GvHD). Methods: We reviewed 26 cases following MVT for incidence of GvHD. Four patients that received MVT between 2011-2022 were evaluated for outcomes following surgery, including patient characteristics, diagnosis, organs involved, treatment, complications, and outcomes. Results: Four patients receiving MVT developed GvHD. 75% were male, median age at transplant was 45.75 (range 39-54), three were white, and one was black. Three patients presented for MVT due to pancreatic

neuroendocrine tumor with liver metastasis and had GvHD which affected the skin. The other patient presented for MVT due to alcoholic cirrhosis complicated by portal and splenic thrombosis and chronic pancreatitis and had GvHD which affected the skin and bone marrow. All four patients had liver, pancreas, and small bowel transplants and received steroids. One patient with skin involvement also received photopheresis and etanercept. The patient with bone marrow involvement also received etanercept. Graft and patient survival at one and three years for those with skin involvement was 100% (3/3) and 50% (1/2) and for bone marrow involvement was 0% (0/1) and 0% (0/1) respectively. Infection within one month of GvHD diagnosis occurred in 33% (1/3) of patients with skin involvement (acute bacterial pneumonia) and 100% (1/1) with bone marrow involvement (septic shock). There were no signs of CMV or transplant rejection within one month of GvHD diagnosis. In patients where induction agents were noted, three received thymoglobulin and one also received rituximab. At GvHD diagnosis, all four patients were on prednisone. Of those with skin involvement, two were on tacrolimus with one also on solumedrol, and a third was on everolimus. The patient with bone marrow involvement initially had a blood STR of <1% donor and 99% recipient and a skin STR of 17% donor and 83% recipient. Retesting showed only recipient DNA two weeks after. Two patients with skin involvement had STR available. One had a blood STR of <1% donor and 99% recipient and a skin STR of 6% donor and 94% recipient while the second had a skin STR of 18% donor and 82% recipient. In patient one, retesting showed only recipient DNA two weeks after. Patient two was not retested. The patient with bone marrow involvement expired due to septic shock from E.coli, Klebsiella pneumoniae and Candida. Conclusions: GvHD occurs when the primary T cells of the allogenic grafted tissue recognize the host's proteins as foreign resulting in an immune response against the host. Biopsy and pathologic evaluation are required for diagnosis. High clinical suspicion for GvHD in MVT is necessary as early recognition and treatment improve outcomes. CITATION INFORMATION: Gupta D., Nagai S., Muszkat Y., Beltran N., Jafri S. Management of Graft vs Host Disease Following Intestinal Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: D.Gupta: None. S.Nagai: None. Y.Muszkat: n/a. N.Beltran: n/a. S.Jafri: Speakers Bureau;; Gilead, Takeda, Abbvie.

Surgery

Potti C, **Chau LC**, **Ferguson R**, **Rakitin I**, **Obeid N**, and **Stanton C**. Development and validation of an open pancreatic necrosectomy risk score in acute pancreatitis. *Surg Endosc* 2023; 37:S535-S536. Full Text

C. Potti, Henry Ford Hospital, United States

Introduction: There are a paucity of literature describing risk factors for requirement of open pancreatic necrosectomy. This study aims to develop a risk model predictive of progression to open necrosectomy amongst patients with acute pancreatitis in a tertiary center. Methods: Adult patients admitted with acute pancreatitis from 7/1/ 2013 to 7/1/2022 were included. Variables of interest were selected using backward stepwise selection with criteria for entry P = 0.1 and exit P = 0.2. Variables available for selection include patient demographics, cause of pancreatitis, comorbidities, prior 30-day readmission, number of computed tomography (CT) imaging, and serum laboratory values within 72 h of admission. Logistic regression models and corresponding nomogram were fitted based on selected variables to predict requirement for open pancreatic necrosectomy during the same admission. Performance of the model was assessed by computing the area under the receiver operating characteristic curve (AUROC) after tenfold stratified cross-validation. 95% confidence intervals were calculated with 200 bootstrap replications. Results: 3493 admissions with 3022 patients admitted for pancreatitis were included. Most common etiologies of pancreatitis included alcohol (61.6%) and gallstones (29.2%). 3% of the cohort progressed to open pancreatic necrosectomy with 1% requiring repeat operative intervention. The model identified 8 clinical factors predictive of progression to open pancreatic necrosectomy during the same admission: male sex, race, etiology, ICU admission, organ failure on admission, number of prior CTs, presence of pancreatic necrosis on CT, and prior 30-day readmission. The model AUROC was 0.855 (95% C.I. = 0.79-0.92). Conclusion: We demonstrate a risk score using 8 clinical factors that predict progression to open pancreatic necrosectomy during the same admission among patients admitted with acute pancreatitis.

Surgery

Reddy R, Mollberg N, Adams K, **Popoff A**, Lam G, Lall S, and Lagisetty K. STATEWIDE TRENDS EM ESOPHAGECTOMY APPROACH: DATA FROM A REGIONAL THORACIC QUALITY COLLABORATIVE. *Dis Esophagus* 2023; 36:84-85. Full Text

R. Reddy, University of Michigan, Ann Arbor, United States

Background: Esophagectomy patients continue to have high morbidity and mortality. Regional quality collaboratives have been shown to improve care around cardiac surgery. Our statewide cardiac surgery collaborative (33 programs) created thoracic surgery collaborative 10 years ago, sharing data to improve care at all locations. There were 17 programs participating in sharing lung cancer surgery data, and 10 programs sharing esophageal cancer surgery data. We reviewed trends in esophagectomy approach and perioperative outcomes from the quality collaborative. Methods: Prospectively collected data from patients with loco-regional esophageal cancer who underwent esophagectomy between 2014 to 2022 were analyzed. We evaluated 3 separate 3-year cohorts. Pre-operative assessment, surgical approach lymph node harvest, post-operative outcomes, and length of stay (LOS) were analyzed using linear regression and chi squared tests. Results: Annual esophagectomy volume ranged from 114 to 14S cases per year. There was significant increase in use of preoperative CT scans ($p = 0.02$) and a trend towards higher use of endoscopic resection as part of the staging paradigm ($p = NS$). There was a notable shift towards more minimally invasive esophagectomy approaches ($p < 0.0001$) with robotic assisted minimally invasive esophagectomy being the most common in the recent cohort (Figure). Lymph node harvest trended towards higher yield over time, but was only significant with the open trans-thoracic approaches ($p < 0.01$). There were no significant differences noted in rates of positive margin or in length of stay. Conclusion: Regional quality collaboratives allow for tracking of esophageal cancer care at a broader level than single institutions. We noted increased use of minimally invasive techniques, specifically robotic assisted over the past decade with trends towards improved lymph node dissection. Despite the increase use of minimally invasive surgery, length of stay did not change.

Surgery

Soheim R, **Ching Chau L**, and **McFarlin K**. Combined Robotic and Endoscopic Assisted Gastric Lipoma Excision. *Surg Endosc* 2023; 37:S572. Full Text

R. Soheim, Henry Ford Hospital, United States

This is a video case presentation of removal of a gastric lipoma. 54 year old woman with an enlarging gastric lipoma who underwent a combined robotic and endoscopic approach to excision. Patient did well post-operatively.

Surgery

Soheim R, **Chung S**, **Chau LC**, **Dix M**, **Bowman M**, **Obeid N**, **Gupta AH**, and **Stanton C**. Risk Factors and Natural History of Bedside Percutaneous Endoscopic Versus Fluoroscopic Guided Gastrostomy Tubes in Intensive Care Unit Patients. *Surg Endosc* 2023; 37:S229. Full Text

R. Soheim, Henry Ford Hospital, United States

Introduction: There is a paucity of literature comparing patients receiving bedside placed percutaneous endoscopic gastrostomy (PEG) versus fluoroscopic guided percutaneous gastrostomy tubes (G-tube) in an intensive care unit (ICU) setting. This study aims to investigate and compare the natural history and complications associated with PEG versus fluoroscopic G-tube placement in ICU patients. Methods: All adult patients admitted in the ICU requiring feeding tube placement at our center from 1/1/2017 to 1/1/2022 were identified through retrospective chart review. Patients with at least 6-months follow-up were included in this study. Descriptive statistics were used to illustrate the cohort's natural history. Adjusting for patient comorbidities, hospital factors, and indications for enteral access, a 1-to-2 propensity score matched cox proportional hazards model was fitted evaluate the treatment effect of bedside PEG tube placement versus G-tube placement on patient complications, 6-month readmission, and 6-month death. Major complications were defined as the need for operative or procedural intervention. Results:

This study included 740 patients, with 178 bedside PEG (mean age 59.9 [IQR: 47-68.3] years; 55.9% black race; 63.5% male sex) and 562 fluoroscopic G-tube (62.9 [IQR: 51.1-71.1] years; 42.6% black race; 58.5% male sex) placements. Indication for enteral access was predominantly trauma (23.7%) or respiratory (33.7%) in nature for PEG recipients and neurologic (59.6%) for G-tube recipients. The overall rate of complication was 22.3% (13% PEG, 25.2% G-tube, P = 0.003). The major complication rate was 11.2% (8.5% PEG, 12.1% G-tube, P = 0.09). Most common complications were tube dysfunction (16.7% PEG; 39.4% G-tube; p = 0.04) or dislodgement (58.3% PEG; 40.8% G-tube). The average hospital stay was 30.9 days (IQR: 22.3-45.3) for PEG and 24.7 days (IQR: 17.6-36.9) for G-tube recipients (P<0.001). 55.9% PEG and 45.7% G-tube recipients were discharged to long-term care whereas 5% PEG and 9.6% G-tube recipients were discharged home (p<0.001). After propensity score matching, G-tube recipients had significantly increased risk for all-cause (HR: 2.7, 95% C.I.: 1.56-4.87, P<0.001) and major complications (HR: 2.11, 95% C.I.: 1.05-4.23, P = 0.035). There were no significant differences in 6-month rates of readmission (HR: 0.90, 95% C.I.: 0.58-1.38, P = 0.62) or death (HR: 1.00, 95% C.I.: 0.70-1.44, P = 0.7). Conclusions: The overall rate of complications for ICU patients requiring feeding tube in our cohort was 22.3%. ICU patients receiving fluoroscopic guided percutaneous gastrostomy tube placement had significantly elevated risk of 6-month all-cause and major complications compared to those undergoing bedside percutaneous endoscopic gastrostomy. (Figure Presented).

Surgery

Vo E, **Shimada S**, **Miyake K**, **Venkat D**, **Gonzalez H**, **Moonka D**, **Rizzari M**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. Adverse Effects of New-Onset Diabetes After Liver Transplantation. *Am J Transplant* 2023; 23(6):S1006-S1007. Full Text

Purpose: While diabetes is considered as a risk factor for poor outcomes after liver transplantation (LT), the impact of new-onset diabetes after LT (NODAT) on post-transplant outcomes remains to be elucidated. The aims of this study are to identify the clinical characteristics of NODAT and to investigate its impacts on post-transplant outcomes. Methods: Adult patients underwent LT at our center between 2014 and 2020 were evaluated. Inclusion criteria include use of tacrolimus as initial immunosuppression regimen and those who survived 3 months at least post-LT. To evaluate possible impact of NODAT on post-LT outcomes, those who developed NODAT within 3 months after LT were classified as NODAT group. In addition, patients were further classified into the following 2 groups; prior history of diabetes before LT (PHDBT) and non-diabetes (ND) groups. Patient characteristics of NODAT and post-LT conditional outcomes after 3 months, and cardiovascular and/or pulmonary complications, were compared. Results: A total of 83 and 225 and 263 patients were classified into NODAT, PHDBT, and ND groups. The proportion of cholestatic liver disease (21.7, 5.3, and 12.9%, P<0.001) and rejection within 30 days (42.2, 7.1, and 4.6%, P<0.001) in NODAT, PHDBT, and ND, respectively. Mean serum tacrolimus concentration trough level in the first week after LT was 7.12, 6.12, and 6.12 ng/ml in these 3 groups, respectively (P<0.001). Duration of corticosteroids were significantly longer in NODAT (416 days) compared to PHDBD (289 days) or ND (228 days) (P<0.001). (Table 1). Three-year graft and patient survival after 3 months were significantly worse in NODAT than in ND (Graft: 80.5% vs. 95.0%, P<0.001, Patient: 82.0% vs. 95.4%, P<0.001) but similar to PHDBT (Figures 1 and 2). Adjusted risk of 3-year graft loss and patient death were significantly higher in NODAT compared to ND (Graft; adjusted hazard ratio [aHR] 3.41, p=0.004, Patient; aHR 3.61, p=0.004). Incidence rates of cardiovascular or pulmonary complications after LT in NODAT were significantly higher than in ND (Cardiovascular; 16.9% vs. 3.8%, P<0.001; Pulmonary; 20.5% vs. 11.0%, P=0.04,) but similar to PHDBT (Cardiovascular vs. 16.9%, P=0.99; Pulmonary vs. 20.0%, P=0.99). Conclusions: Cholestatic liver disease, high tacrolimus concentration, and early rejection might be risk factors for NODAT. NODAT was associated with the worse long-term outcomes and increases risk of cardiovascular and/or pulmonary complications. CITATION INFORMATION: Shimada S., Miyake K., Venkat D., Gonzalez H., Moonka D., Rizzari M., Yoshida A., Abouljoud M., Nagai S. Adverse Effects of New-Onset Diabetes After Liver Transplantation AJT, Volume 23, Issue 6, Supplement 1. DISCLOSURES: S.Shimada: None. K.Miyake: None. D.Venkat: n/a. H.Gonzalez: n/a. D.Moonka: None. M.Rizzari: None. A.Yoshida: n/a. M.Abouljoud: None. S.Nagai: None. [Figure presented]

Urology

Becker R, Dibianco JM, Moncaleano GF, Higgins A, Kleer E, **Leavitt D**, King A, **Kachroo N**, **Majdalany S**, Gandham D, Conrado B, Daignault-Newton S, Dauw C, and Ghani K. The Dynamic Patient Experience of Pain and Ability to Work after Ureteroscopy and Stenting. *J Endourol* 2023; 37:A136-A137. Full Text

R. Becker, University of Michigan Medicine, United States

Introduction: Ureteral stents can cause significant patient discomfort, yet the temporal dynamics of symptoms and impact on social activities remain poorly characterized. We employed an automated text message tool to collect daily ecological momentary assessments (EMA) following ureteroscopy with stenting regarding pain and ability to work. Our aim was to assess the feasibility of capturing EMA data, and better characterize the postoperative patient experience. Methods: As an exploratory endpoint within an ongoing pragmatic clinical trial (NCT05026710), patients undergoing ureteroscopy and stone intervention with stenting (without a tether) were asked to complete daily EMAs for 10 days postoperatively, or until the stent was removed, whichever was longer. Stents were removed in the office. Questionnaires were distributed via text message and included a numeric pain scale (0- 10) and a single item from the validated PROMIS Ability to Participate in Social Roles and Activities instrument, as well as days missed from work or school. Responses from postoperative day (POD) 1 through the day of stent removal (up to POD10) were analyzed for the first 59 participants in EMAs. Results: Median patient age was 58 years (interquartile range [IQR] 50-67), 56% were female. Stones were 54% renal and 46% ureteric, with median stone diameter 9mm (IQR 7-10). Median stent dwell time was 7 days (IQR 6-8). Pain scores were highest on POD1 (median score 4/10) and declined with each subsequent day, reaching median score 2/10 on POD5. 63% of patients on POD1 reported they had trouble performing their usual work at least sometimes, but by POD5 this was < 50% of patients. Patients who work or attend school reported a median of 1 day missed (IQR 0-2). Conclusions: An automated daily text message EMA system for capturing patient reported outcomes was demonstrated to be feasible with sustained excellent engagement. Patients with stents reported the worst pain and interference with work on POD1 with steady improvements thereafter, and by POD5 the majority of patients had minimal pain or trouble performing their usual work.

Urology

Ditonno F, Pandolfo SD, Franco A, Derweesh IH, Margulis V, **Abdollah F**, Ferro M, Djaladat H, Guruli G, Simone G, Mehrazin R, Gonzalgo ML, Wu Z, Porpiglia F, Eun DD, Correas A, Minervini A, Sundaram CP, and Autorino R. Robotic Distal Ureterectomy for High-Risk Distal Ureteral Urothelial Carcinoma: A Retrospective Multicenter Comparative Analysis (ROBUUST Collaborative Analysis). *J Endourol* 2023; 37:A89-A90. Full Text

F. Ditonno, Department of Urology, Rush University, Chicago, IL, United States

Introduction: The role of kidney-sparing surgery (KSS) in patients with high-risk upper urinary tract urothelial carcinoma (UTUC) is controversial. The aim of this study was to assess the outcomes of robotic distal ureterectomy in patients with highrisk distal ureteral tumours. Methods: Three hundred and sixty-five patients with high-risk UTUC of the distal ureter were retrieved from the ROBUUST (ROBotic surgery for Upper Tract Urothelial Cancer Study) multicenter international (2006- 2019). The study population was divided in two subgroups according to the type of surgical approach: 38 patients treated with robotic distal ureterectomy and 135 treated with robotic nephroureterectomy (RNU). Time to recurrence, defined by urinary cytology, CT scan or cystoscopy at last follow-up, was the primary endpoint. Secondary endpoint was the post-operative renal function, calculated as eGFR at last follow- up. A Mann-Whitney U test was performed to compare mean (± SD) of each outcome between the two populations. Results: In the overall population, mean age was 70.4 years (±9.3), with a mean preoperative Cr of 1.2 (±0.8) mg/dL and a mean tumour size of 3.3 (±2.1) cm. No significant difference was observed in terms of time to recurrence (13.3 months vs 14.3 months, p = 0.8) between patients treated with distal ureterectomy and RNU. Post-operative eGFR, instead, was significantly better in patients treated with distal ureterectomy (63.4 mL/min/1.73m2vs 51 mL/min/1.73m2,p = 0.01). Conclusions: Within the limitations related to the retrospective study design, our findings suggest comparable outcomes in terms of time to recurrence between distal ureterectomy and RNU, and an advantage of in terms of post-operative renal function preservation. KSS might be considered as a potential option for selected high-risk patients.

Urology

González Martínez J, Ramirez-Dominguez LB, Jimenez Medina I, Matamoros-Volante A, Villar-Muñoz LG, **Rambhatla A**, Agarwal A, and Maldonado I. Constant antioxidant supplementation increases blastocyst formation from oocyte donors. *Hum Reprod* 2023; 38:i143. Full Text

J. González Martínez, CITMER-Reproductive Medicine, IVF Laboratory, Puebla, Mexico

Study question: Does constant supplementation of antioxidants to the culture media increase blastocyst formation from oocyte donors? Summary answer: The constant supplementation of antioxidants to the culture media increases blastocyst formation from oocyte donors What is known already: The use of a combination of various antioxidants in embryo culture media has recently been investigated to explore the potential benefit for embryo development and clinical outcomes. However, the concentration of antioxidants added to the culture has only been determined by its effect. In this study, we performed a repeated antioxidants supplementation to resemble a physiological oxidation reduction environment. Therefore, we investigated the effect of antioxidants added every 12 hours to the culture media on blastocyst formation and expansion in oocyte donors. Study design, size, duration: This prospective study was conducted at CITMER, Mexico from April 2020 to November 2022.We included a total of 258 recipients from oocyte donors undergoing IVF/ICSI. Participants/materials, setting, methods: A total of 2403 zygotes were divided into 4 groups and cultured in the following conditions until blastocyst stage: Group 1A: 563 zygotes 20% O2 with antioxidants every 12 hours, Group 1B: 1109 zygotes 20% O2 with antioxidants at the beginning, Group 2A: 339 zygotes 5% O2 with antioxidants every 12 hours, Group 2B: 392 zygotes 5% O2 with antioxidants at the beginning. Embryo development was assessed. Odds ratio and Fisher test were performed. $p<0.05$=significant Main results and the role of chance: For both oxygen tensions, we found a significant increase in the total blastocyst formation rate (day 5+day 6) when antioxidants were added repeatedly (1A: 54.7% vs 1B: 45.9%, $p=0.0007*$; 2A: 58.7% vs 2A: 46.9%, $p=0.001*$). In addition, the rate of expansion at days 5 + 6 was also significantly higher than in the groups where the antioxidants were added only at the beginning of the culture (1A: 35.9% vs 1B: 29.9%, $p=0.01*$; 2A: 41.3% vs 2A: 31.6%, $p=0.006*$). Limitations, reasons for caution: Given this is a sibling zygotes study, patients are their own controls. Wider implications of the findings: Constant supplementation of antioxidants to the culture media increases blastocyst formation from oocyte donors as well as the expansion rate, which may significantly improve clinical outcomes.

Urology

Miller A, Suryavanshi M, Khooblall P, Adler A, Mukherjee S, Agudelo J, De S, and **Kachroo N**. The Kidney Stone Microbiome is Comprised of Antibiotic-Resistant, Biofilm-Forming Bacteria, Which Has Implications for the Etiology of Lithogenesis. *J Endourol* 2023; 37:A24-A25. Full Text

A. Miller, Cleveland Clinic Foundation, United States

Introduction: Evidence suggests that urinary stone disease (USD) is associated with the urinary tract microbiome, termed urobiome. We and others have shown a strong association between USD and past antibiotic use. Furthermore, there is increasing evidence that active biofilm formation is present in calcium- based stones. These data present the hypothesis that antibiotic resistant, biofilm-forming bacteria promote the lithogenesis of calcium-based stones. Methods: To test our hypothesis, we obtained calcium oxalate or calcium phosphate stones surgically extracted through percutaneous nephrolithotomy or ureteroscopy. Stone fragments were rinsed with sterile PBS to remove non-adherent surface bacteria, crushed aseptically, serially diluted, and inoculated onto five different culture media. Resulting colony-forming units were isolated for identification and plate-based assays to quantify biofilm formation and antibiotic resistance. Eleven antibiotics were chosen for testing, which included common surgical prophylaxes and colistin, considered an antibiotic of last resort. Results: From five calcium oxalate and five calcium phosphate stones, we obtained 75 bacterial isolates comprised of Kocuria, Escherichia, Micrococcus, Staphylococcus, Bacillus, Actinomyces, Brevibacterium, Rothia, and Dermacoccus genera. Out of 44 isolates tested, 42 exhibited strong biofilm formation, with one each exhibiting moderate or no biofilm formation. The strongest biofilms were from K. rhizophila, Bacillus spp. and M. luteus. Most isolates (38 out of 44) exhibited complete resistance at least one antibiotic. Thirteen isolates exhibited

complete resistance to four different antibiotics. A total of 6 of the 11 antibiotics exhibited at least moderate effectiveness against all isolates, which included amoxycillin-clavulanic acid, ciprofloxacin, gentamicin, cefazolin, levofloxacin, and vancomycin. Colistin was the least effective, with only nine of 44 isolates exhibiting susceptibility. Conclusions: Our study presents strong evidence for biofilm formation in stone-associated bacteria and moderate evidence for antibiotic resistance. Unexpectedly, most isolates were resistant to colistin, which suggests that this antibiotic is not effective as a last resort. More work is needed to understand the mechanisms of how biofilm formation promotes lithogenesis. (Figure Presented).

Urology

Nyati S, **Stricker H**, **Barton KN**, **Li P**, **Elshaikh M**, **Ali H**, **Brown SL**, **Hwang C**, **Peabody J**, **Freytag SO**, **Movsas B**, and **Siddiqui F**. Replication Competent Adenovirus-Mediated Cytotoxic and Interleukin-12 Gene Therapy in Prostate Cancer: 36-month Follow-Up Data from a Phase I Clinical Trial. *Mol Ther* 2023; 31(4):297. Full Text

Introduction: Men with locally recurrent prostate cancer, after definitive radiotherapy, have few therapeutic options. Oncolytic adenovirus-mediated cytotoxic gene therapy is an investigational cancer therapy. Delivery of the suicide gene to the tumor is by direct intratumoral or systemic injection of a viral vector containing the suicide gene. Our approach incorporates yeast cytosine deaminase (yCD) and herpes simplex virus thymidine kinase (HSV-1 TK), to confer sensitivity to 5-fluorocytosine (5-FC) and Valganciclovir (vGCV), respectively. The pro-drugs are converted into active drugs that inhibit DNA damage repair. Here we report the safety of oncolytic adenovirus-mediated suicide gene therapy that incorporates an interleukin-12 (IL12) gene for treatment of recurrent prostate cancer. Methods: In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 15 subjects with recurrent prostate cancer (T1c-T2) at escalating doses (1 × 1010, 3 × 1010, 1 × 1011, 3 × 1011, or 1 × 1012 viral particles). Subjects received 5-FC and vGCV for 7 days. The study endpoint was toxicity through day 30. Experimental endpoints included measurements of serum IL12, interferon gamma (IFNγ), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells (PBMC) and proliferation markers were analyzed by flow cytometry. Results and conclusions: Fifteen patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC and vGCV. Approximately 92% of the 115 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of only two patients. Elevated serum IL12, IFNγ, and CXCL10 levels were detected in 57%, 93%, and 79% of subjects, respectively. Serum cytokines demonstrated viral dose dependency, especially apparent in the highest-dose cohorts. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration in cohort 5. The study did not detect a significant difference in the PSA doubling time (PSADT) between pre and post treatment by paired Wilcoxon rank test (p=0.17). There was no correlation between adenoviral dose and PSADT in each cohort separately or pooled (cohorts1-3 and cohorts 4-5). The study maximum tolerated dose (MTD) was not reached indicating 1012 viral particles was safe. This trial confirmed that replication-competent Ad5-IL-12 adenovirus (Ad5-yCD/mutTKSR39rep-hIL-12) was well tolerated when administered locally to prostate tumors.

Urology

Siddiqui F, **Nyati S**, **Elshaikh M**, Barton K, **Ali H**, **Brown S**, **Hwang C**, **Peabody J**, **Freytag S**, **Movsas B**, and **Stricker H**. Replication Competent Adenovirus-mediated Cytotoxic and Interleukin-12 Gene Therapy in Prostate Cancer: 36 Month Follow-Up Data from a Phase I Clinical Trial. *Cancer Clin Trials* 2023; 46(6):S13-S14. Full Text

F. Siddiqui, Henry Ford Health Cancer, United States

Background: Men with locally recurrent prostate cancer, after definitive radiotherapy, have few therapeutic options that have a high likelihood of eradicating the tumor with a reasonable degree of safety. Oncolytic adenovirus-mediated cytotoxic gene therapy is an investigational cancer therapy that is currently being evaluated in clinical trials. Delivery of the suicide gene to the tumor is usually accomplished by direct intratumoral or systemic injection of a viral vector containing the suicide gene.

Two suicide genes that have been evaluated in preclinical models and in the clinic are the E. Coli coli cytosine deaminase (CD) and herpes simplex virus thymidine kinase (HSV-1 TK), which confer sensitivity to 5-fluorocytosine (5-FC) and ganciclovir (GCV), respectively. The pro-drugs are converted into active drugs that block DNA synthesis. In the past we have evaluated the toxicity and efficacy of oncolytic adenovirus-mediated cytotoxic gene therapy in five different clinical trials in prostate cancer, including a prospective randomized phase 2 study. In this Phase I trial we evaluated the safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL12) gene therapy in recurrent prostate cancer patients. Objectives: Phase I dose-escalation trial to evaluate the maximum tolerated dose (MTD) of replication competent adenovirus type 5 gene therapy with interleukin-12 delivered using ultrasound guided intraprostatic injection. Methods: Replication-competent adenovirus (Ad5-yCD/mutTKSR39- rep-hIL-12) expressing yCD/mutTKSR39 (yeast cytidine deaminase/ mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL12) was injected into tumors of 15 subjects with recurrent prostate cancer (T1c-T2) at escalating doses (1 × 1010, 3 × 1010, 1 × 1011, 3 × 1011, or 1×1012 viral particles). Subjects received oral prodrugs, 5-fluorocytosine (5-FC) and Valganciclovir (vGCV) therapy for 7 days. The study endpoint was toxicity through day 30. Experimental endpoints included measurements of serum IL12, interferon gamma (IFN-gamma), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells (PBMC) and proliferation markers were analyzed by flow cytometry. Results: Fifteen patients received Ad5-yCD/mutTKSR39rep-hIL-12 and oral 5-FC and vGCV. Approximately 92% of the 115 adverse events observed were grade 1/2 requiring no medical intervention. Ad5- yCD/mutTKSR39rep-hIL-12 DNA was detected in the blood of only two patients. Elevated serum IL12, IFN-gamma, and CXCL10 levels were detected in 57%, 93%, and 79% of subjects, respectively. Serum cytokines demonstrated viral dose dependency, especially apparent in cohorts 4 and 5. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTKSR39rep-hIL-12 administration in cohort 5. There was no correlation between adenoviral dose and PSA doubling time (PSADT). Conclusions: Ultrasound guided intraprostatic injection of replication competent adenovirus type 5 containing wo suicides genes and interleukin- 12 is well tolerated up to a dose of 1 × 1012 viral particles. The study maximum tolerated dose (MTD) was not reached. Further studies will be done to evaluate efficacy of this therapeutic approach in patients with locally recurrent prostate cancer.

Urology

Wilder S, **Butaney M**, **Wang Y**, Hijazi M, Gandham D, Van Til M, Goldman B, Qi J, Mirza M, Johnson A, Rudoff M, Wenzler D, **Rogers CG**, and Lane BR. Decision-Making Regarding Conversion from Partial to Radical Nephrectomy in MUSICKIDNEY. *J Endourol* 2023; 37:A163-A164. Full Text

S. Wilder, Henry Ford Health, United States

Introduction: Partial nephrectomy (PN) has emerged as the standard of care for localized small renal masses. Its use has expanded to include larger and more complex masses, with increasing potential for conversion to radical nephrectomy (RN). Limited data exists regarding specific reasons for conversion to RN. We evaluated incidence and reason for conversion in patients undergoing robotic PN (RPN) using data from a statewide quality improvement (QI) collaborative. Methods: MUSIC-KIDNEY maintains a prospective statewide registry of newly diagnosed T1RM. All patients with a plan to undergo RPN at initial visit with the urologic surgeon were queried and then stratified based on actual procedure performed (RPN vs. RN). Pre-operative and intra-operative records were obtained for each patient to confirm conversion from RPN to RN, determine preoperative assessment of PN difficulty, and assess reason for conversion. Patient, tumor, and practice variables were obtained via the MUSIC registry and compared between cohorts via Wilcoxon rank sum test. Pathologic data and postoperative renal function were assessed. Results: A total of 650 patients were identified with an initial plan to undergo RPN. The rate of conversion from RPN to RN was 4.7% (27/650). No open conversions were documented. Patients undergoing conversion had larger (4.4 cm vs 2.8 cm) and higher complexity (63.0% with intermediate/high RENL score vs 51.6%) tumors. Patients who underwent conversion had significantly higher rates of pT3/T4 disease (28% vs 8.7%, $p = 0.006$) and lower postoperative renal function (Cr 1.3 vs 1.0, $p < 0.001$). Review of the 27 cases that underwent conversion found that 24 conversions were performed due to tumor complexity and/or oncologic concerns for locally-advanced disease, with only 5 (0.9%) conversions secondary to intraoperative bleeding. Only 63.0% (17/27) of converted cases had preoperative documentation regarding assessment of PN difficulty and/or likelihood of conversion. 88%

(15/17) of converted cases with preoperative documentation available indicated increased surgical complexity ('PN vs. RN', 'complicated PN, etc.). Conclusions: MUSIC-KIDNEY has identified a low rate of conversion (< 5%) from RPN to RN within the collaborative that likely reflects the increased proportion of surgeries for tumors with increased oncologic risk, in which the plan may better be termed PN vs. RN. The rate of intraoperative conversion for uncontrolled bleeding was < 1%. These findings provide further data to justify the safety of PN, even in higher complexity tumors. We have identified QI opportunities to standardize preoperative documentation regarding PN difficulty, and multiple initiatives within MUSIC-KIDNEY exist to improve this and other aspects of surgical care for patients with renal masses.

Urology
Wilder S, May A, Vaishampayan N, Qi J, Mirza M, Johnson A, Noyes SL, **Butaney M**, **Wang Y**, **Rogers CG**, Levin M, Morgan T, and Lane BR. Surveillance of cT1 Renal Masses is Common in Patients with CKD. *J Endourol* 2023; 37:A159-A160. Full Text

S. Wilder, Henry Ford Health, United States

Introduction: Patients with chronic kidney disease (CKD) and T1 renal masses (T1RM) represent a difficult group to treat. Most published data support the important role of partial nephrectomy (PN) in this context, however real-world decision making is complex and most published series use intervention as the trigger for inclusion. This selection bias has likely led to under-reporting of surveillance. We aim to describe GFR outcomes and treatment trends in patients with CKD and T1RM within practices participating in MUSIC- KIDNEY. Methods: We reviewed the MUSIC-KIDNEY registry for patients undergoing urologic evaluation for T1RM from 9/2017 to 1/2022. Patients were categorized as having CKD if pre-existing GFR was < 60 ml/min/1.73m2, or without CKD when GFR ≥60. Inclusion criteria mandated that GFR data was available at ≥6 months post-diagnosis. The primary outcome was “substantial GFR decline,” defined as a drop of > 15% and to GFR< 45. Trends in treatment and GFR outcomes were compared between patients with or without CKD and between treatment categories. Results: We identified 3,036 patients evaluated for T1RM. 839 (28%) had pre-existing CKD. Similar rates of ablation and RN were seen between the CKD and no-CKD groups. Interestingly, rather than an increase in rate of PN in the CKD group, a decline was seen (17% in CKD vs. 34% in no-CKD). A concomitant increase in rate of surveillance was observed (61% in CKD vs. 47% in no-CKD) (Figure 1a). Among CKD patients, active surveillance was more likely to be used in older patients (76 yr vs. 67 yr) with greater comorbidity (48 with CCI ≥2 vs. 47% with CCI = 0) and smaller masses (2.3 cm vs. 3.2 cm) when compared to PN. Of the 822 patients with 6 month follow up, 102 (12%) had a substantial decline in GFR: 27% of those with pre-existing CKD and 7% without CKD. PN and RN led to notably higher rates of GFR decline in those with pre-existing CKD compared to those without (Figure 1b). Conclusions: Despite the long-held notion that patients with T1RM and CKD have an imperative indication for nephronsparing interventions, predominately PN, our study suggests urologists and patients commonly choose to avoid intervention altogether. This may reflect an under-recognition or shift towards non-operative management of T1RM, particularly in patients at high risk for significant renal functional decline.

Urology
Wilder S, **Wang Y**, Hijazi M, Mirza M, Van Til M, Ghani KR, Maatman T, Semerjian A, Rosenberg B, Seifman B, Lane BR, and **Rogers CG**. Technical Skill of Partial Nephrectomy on Patient Outcomes: A Video Review Project. *J Endourol* 2023; 37:A160-A161. Full Text

S. Wilder, Henry Ford Health, United States

Introduction: It is unknown if technical skills of surgeons performing robotic partial nephrectomy (RPN) are linked to patient outcomes. We conducted a peer surgeon video review exercise in a surgical collaborative to understand if aspects of the procedure could be identified for improving patient outcomes. Methods: RPN surgeons participating in a statewide quality improvement collaborative (MUSIC-KIDNEY) were invited to submit and review RPN videos. Videos were segmented into 6 steps: exposure of kidney, identification of ureter and gonadal, hilar dissection, tumor localization, clamping and resection, and renorrhaphy. Video clips were deidentified and distributed to blinded peer reviewer surgeons who provided written feedback and scores using a previously published evaluation tool: Scoring for Partial

Nephrectomy (SPaN), 1 = lowest and 5 = highest. Outcomes from MUSIC registry for all submitting surgeons were assessed for length of stay (LOS), estimated blood loss (EBL) > 500, warm ischemia time (WIT) > 30 min, positive surgical margin (PSM), and readmission. Surgeons were stratified into low scoring (score ≤ median score) and high scoring (score > median). Outcomes were compared between cohorts through Chi squared and Fisher's exact test with p-value < 0.05. Score card and written comments were provided to all participants. Participant survey results were collected 2 months after video review. Results: 11 surgeons submitted a total of 127 video clips; 379 total reviews were performed by 24 reviewers over the span of 2 months. The average score for reviewed clips was 4.1, with surgeon averages ranging between 3.6 and 4.7. Low-scores overall as well as in tumor resection and renorrhaphy were significantly associated with several outcomes including PSM, 30 day readmissions, EBL, and LOS (Figure). Surveys indicated submitters and reviewers found the process and score card valuable for identifying areas of improvement, learning different RPN techniques, and educating trainees. Conclusions: Video review of RPN demonstrated that surgeons with higher technical skill had a significantly lower frequency of intraoperative and post-operative complications. Given these results, the MUSIC- KIDNEY collaborative are in the process of developing interventions to address technical aspects of RPN with the goal to reassess and improve outcomes.

Books and Book Chapters

Surgery
Balli S, **Shumway KR**, and Sharan S. Physiology, Fever. *StatPearls*; 2023. Full Text

Ochsner LSU Monroe
Henry Ford Health
LSU Health Sciences, Shreveport, LA

Fever, or pyrexia, is the elevation of an individual's core body temperature above a 'set-point' regulated by the body's thermoregulatory center in the hypothalamus. This increase in the body's 'set-point' temperature is often due to a physiological process brought about by infectious causes or non-infectious causes such as inflammation, malignancy, or autoimmune processes. These processes involve the release of immunological mediators, which trigger the thermoregulatory center of the hypothalamus, leading to an increase in the body's core temperature. The normal temperature of the human body is approximately 37 degrees Celsius (C), or 98.6 degrees Fahrenheit (F), and varies by about 0.5 C throughout the day. This variation in the core body temperature results from normal physiological processes throughout the human body, including metabolic changes, sleep/wake cycles, hormone variability, and changing activity levels. However, in the case of a fever, the increase in the core body temperature is often greater than 0.5 C and is attributed to a fever-inducing substance (pyrogen). While these numbers may vary slightly based on the source, below is a summary of how to categorize fever. Low-grade: 37.3 to 38.0 C (99.1 to 100.4 F). Moderate-grade: 38.1 to 39.0 C (100.6 to 102.2 F). High-grade: 39.1 to 41 C (102.4 to 105.8 F). Hyperthermia: Greater than 41 C (105.8 F). It is essential to understand that the definition of fever is not the same as that of hyperthermia (hyperpyrexia). In fever, there is an increase in the 'set-point' temperature brought about by the hypothalamus, enabling the body to maintain a controlled increase in the core temperature and general functionality of all organ systems. In hyperthermia, however, the rise in the body's core temperature is beyond the confines of the set-point temperature and regulation of the hypothalamus.

Surgery
Campbell M, Sultan A, **Shumway KR**, and Pillarisetty LS. Physiology, Korotkoff Sound. *StatPearls;* 2023. Full Text

Cusom
Tulane School of Medicine
Henry Ford Health
Midland Memorial / Texas Tech University

In 1905, Nikolai Korotkov, a Russian military surgeon, wrote a 281-word report for the imperial medical military academy detailing his auscultatory technique for determining systolic and diastolic blood pressure. This technique requires only a sphygmomanometer (blood pressure cuff) and a stethoscope to listen to what is now known as Korotkoff sounds. Korotkoff sounds are pulsatile circulatory sounds heard upon auscultation of the brachial artery. While advancements in technology have allowed for the use of electronic blood pressure machines, this non-invasive method of acquiring blood pressure measurements has proven accurate and easy to perform, making it the "gold standard" for blood pressure measurement, even today. Understanding the underlying physiology and proper measurement techniques are essential for quality patient care and appropriate medical therapy.

Surgery
Casale J, **Shumway KR**, and Hatcher JD. Physiology, Eustachian Tube Function. *StatPearls*; 2023. Full Text

Campbell University School of Osteopathic Medicine
Henry Ford Health
Mercer University Med. Sch./Coliseum MC

The Eustachian tube (ET), named after Italian anatomist Bartolomeo Eustachio, is a fibrocartilaginous duct connecting the middle ear (posterior to the eardrum) to the nasopharynx. Also known as the pharyngotympanic tube, the Eustachian tube is approximately 36 mm long, 2-3 mm wide, and functions primarily in optimizing middle ear sound transmission and equalizing pressures within the ear. Normally a closed structure, the Eustachian tube opens in response to movement of the mandible and pharynx, such as during chewing or swallowing. Structurally, the Eustachian tube has osseous (anteroinferior) and cartilaginous (posterosuperior) portions, is comprised of cartilage and mucosa, and is supported by surrounding soft tissue, the sphenoid sulcus, and peritubal muscles (tensor veli palatini, levator veli palatini, salpingopharyngeus, and tensor tympani).

Surgery
Dave HD, **Shumway KR**, and Al Obaidi NM. Physiology, Biliary. *StatPearls;* 2023. Full Text

Tver State Medical University, Tver, Russian Federation
Henry Ford Health
Kamc

The biliary system refers to bile production, storage, and secretion via the liver, gallbladder, and bile ducts. Bile ducts are categorized into intrahepatic and extrahepatic bile ducts. Intrahepatic bile ducts include the left and right hepatic ducts, which join to form the common hepatic duct (CHD), while extrahepatic bile ducts include the common bile duct (CBD), which is formed from the CHD and cystic duct. The CBD and pancreatic duct converge to form the ampulla of Vater, which bile travels through before passing through the sphincter of Oddi and into the second portion of the duodenum. Initially, bile is a unique alkaline (7.5 to 8.1 pH) fluid secreted by hepatocytes (600-1000 mL/day), further altered and refined by the epithelial cells lining the biliary tract, and becoming acidic in the gallbladder (5.2 to 6.0 pH). The gallbladder stores this fluid, where it gets concentrated and subsequently released into the digestive tract via the CBD. On receiving stimulation via the hormone cholecystokinin (CCK) from the intestinal tract due to the presence of food in the intestinal lumen, the gallbladder contracts and secretes bile into the duodenum. The composition of bile is predominantly water with multiple dissolved substances, including cholesterol, amino acids, enzymes, vitamins, heavy metals, bile salts, bilirubin, and phospholipids.

Surgery
Derderian C, **Shumway KR**, and Tadi P. Physiology, Withdrawal Response. *StatPearls*; 2023. Full Text

Creighton University School of Medicine
Henry Ford Health
Asram Medical College, Eluru, India

The withdrawal response (reflex), also known as the nociceptive flexion reflex, is an automatic response of the spinal cord that is critical in protecting the body from harmful stimuli. The first known definition of a reflex dates back to 1649 when René Descartes noted that specific bodily movements occurred instantaneously and independent of the process of thought. Modern definitions state that a reflex is an involuntary response of effector tissue caused by the stimulation of specific receptors. The reflex arc is the basic unit of a reflex, which involves neural pathways acting on an impulse before that impulse has reached the brain. Instead of directly traveling to the brain, sensory neurons of a reflex arc synapse in the spinal cord. This is an important evolutionary adaptation for survival, which allows faster actions by activating spinal motor neurons instead of delaying reaction time by signals first having to go to the brain. The withdrawal reflex can occur in either the upper or lower limbs and is a polysynaptic reflex, which means that interneurons mediate the reflex between the afferent (sensory) and efferent (motor) signals. In contrast, the deep tendon reflex is monosynaptic and does not utilize interneurons to transmit information. Additionally, the withdrawal response is an intersegmental reflex arc, meaning that the outcomes of the reflex are mediated by the stimulation or inhibition of motor neurons from multiple levels of the same spinal cord.

Surgery
Elshazzly M, Anekar AA, **Shumway KR**, and Caban O. Physiology, Newborn. *StatPearls*; 2023. Full Text

Campbell University School of OM
Mysore Medical College
Henry Ford Health
Campbell University

The physiology of a newborn is unique and complex in that it changes over a period of minutes, hours, days, and months. Once a human reaches adulthood, our physiology typically remains stable and predictable, with any deviation potentially leading to pathology and disease. However, a newborn's rapid and ever-changing physiology is essential in adapting to a world outside the womb. This article aims to discuss the important physiology associated with the newborn period to allow a deeper understanding of the complexities of this stage of life.

Surgery
Gawdi R, **Shumway KR**, and Emmady PD. Physiology, Blood Brain Barrier. *StatPearls*; 2023. Full Text

Wake Forest School of Medicine
Henry Ford Health
UNC school of Medicine, Atrium Health

The blood-brain barrier (BBB), first described by Paul Ehlrich (1885), is a highly selective semi-permeable membrane between the blood and brain interstitium. This unique barrier allows cerebral blood vessels to regulate the movement of molecules and ions between the blood and the brain. The BBB is composed of cerebral capillary wall endothelial cells (ECs) held together via tight junctions (TJs). These TJs, surrounded by pericytes, astrocytes, and the basal lamina, contribute to the highly selective nature of the BBB, limiting the passage of substances from the blood to the brain more so than any other capillaries in the body.

Surgery
Lacroix AE, Gondal H, **Shumway KR**, and Langaker MD. Physiology, Menarche. *StatPearls*; 2023. Full Text

University of Nebraska Medical Center
Henry Ford Health
Campbell University

Menarche is defined as the first menstrual period in a female adolescent. Menarche typically occurs between the ages of 10 and 16, with the average age of onset being 12.4 years. The determinants of menarcheal age are continuously being researched; socioeconomic conditions, genetics, general health, nutritional status, exercise, seasonality, and family size are thought to play a role. Menarche tends to be painless and occurs without warning. The first cycles are usually anovulatory with varied lengths and flow. Menarche signals the beginning of reproductive abilities and is closely associated with the ongoing development of secondary sexual characteristics.

Surgery
Muse ME, **Shumway KR**, and Crane JS. Physiology, Epithelialization. *StatPearls*; 2023. Full Text

Henry Ford Health
Sampson Regional Med Ctr / Campbell Univ

Epithelial tissue comprises sheets of cells bound tightly together found in the skin, GI, urinary, reproductive, and respiratory tracts. The epithelium serves as a barrier to protect the body from pathogens and functions to maintain homeostasis. When epithelial tissue is damaged, the body responds via four phases of wound healing: hemostasis, inflammation, proliferation, and remodeling (maturation). Epithelialization is the process of repairing epithelial surface defects via keratinocytes during the proliferative phase of wound healing.

Surgery
Oberman R, **Shumway KR**, and Bhardwaj A. Physiology, Cardiac. *StatPearls*; 2023. Full Text

Acom
Henry Ford Health
University of Pennsylvania

Clinical personnel must understand how cardiac physiology is intertwined with other organ systems and how pathophysiology relates to simple gross physiology. Cardiac physiology is one of healthcare's most important aspects of medical knowledge. The cardiovascular system constantly adapts to maintain homeostasis in the body, specifically to maintain oxygen perfusion of tissues. The heart will adapt via multiple variables such as heart rate, stroke volume, preload, afterload, diastole, and systole. This article defines these terms and extrapolates them into a working model of cardiac physiology.

Surgery
Ogobuiro I, Gonzales J, **Shumway KR**, and Tuma F. Physiology, Gastrointestinal. *StatPearls*; 2023. Full Text

University of the East Ramon Magsaysay
Henry Ford Health
Central Michigan University

The gastrointestinal (GI) system comprises the GI tract and accessory organs. The GI tract consists of the oral cavity, pharynx, esophagus, stomach, small intestine, large intestine, and anal canal. The accessory organs include the teeth, tongue, and glandular organs such as salivary glands, liver, gallbladder, and pancreas. The main functions of the GI system include ingestion and digestion of food, nutrient absorption, secretion of water and enzymes, and excretion of waste products.

Surgery
Osilla EV, Marsidi JL, **Shumway KR**, and Sharma S. Physiology, Temperature Regulation. *StatPearls*; 2023. Full Text

University of South Alabama, DeBusk COM
Henry Ford Health

Mery Fitzgerald Hospital

Thermoregulation is the maintenance of physiologic core body temperature by balancing heat generation with heat loss. A healthy individual will have a core body temperature of 37 +/- 0.5°C (98.6 +/- 0.9°F), the temperature range needed for the body's metabolic processes to function correctly. The human body's thermostat is the hypothalamic thermoregulatory center, which, more specifically, is located in the preoptic area of the hypothalamus. This center sets the body's set point and regulates temperature homeostasis. The hypothalamus contains temperature sensors, which receive information via nerve cells called thermoreceptors. The body has peripheral and central thermoreceptors. The peripheral thermoreceptors are located in the skin and sense surface temperatures, while central thermoreceptors are found in the viscera, spinal cord, and hypothalamus and sense the core temperature. Variations in body temperature activate these thermoreceptors, which inform the preoptic area of the hypothalamus. This area then activates heat regulation mechanisms to increase or decrease body temperature and return it to baseline.

Surgery
Patel AK, Reddy V, **Shumway KR**, and Araujo JF. Physiology, Sleep Stages. *StatPearls*; 2023. Full Text

NYIT College of Osteopathic Medicine
McKinsey & Company
Henry Ford Health
Ufrn

The human body cycles through two phases of sleep, (1) rapid eye movement (REM) and (2) non-rapid eye movement (NREM) sleep, which is further divided into three stages, N1-N3. Each phase and stage of sleep includes variations in muscle tone, brain wave patterns, and eye movements. The body cycles through all of these stages approximately 4 to 6 times each night, averaging 90 minutes for each cycle. This article will discuss the progression of the sleep stages and the unique features associated with each.

Surgery
Ripa R, George T, **Shumway KR**, and Sattar Y. Physiology, Cardiac Muscle. *StatPearls*; 2023. Full Text

St. George's University, West Indies, Grenada
Creighton University School of Medicine
Henry Ford Health
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Cardiac muscle also called the myocardium, is one of three major categories of muscles found within the human body, along with smooth muscle and skeletal muscle. Cardiac muscle, like skeletal muscle, is made up of sarcomeres that allow for contractility. However, unlike skeletal muscle, cardiac muscle is under involuntary control. The heart is made up of three layers—pericardium, myocardium, and endocardium. The endocardium is not cardiac muscle and is comprised of simple squamous epithelial cells and forms the inner lining of the heart chambers and valves. The pericardium is a fibrous sac surrounding the heart, consisting of the epicardium, pericardial space, parietal pericardium, and fibrous pericardium. The cardiac muscle is responsible for the contractility of the heart and, therefore, the pumping action. The cardiac muscle must contract with enough force and enough blood to supply the metabolic demands of the entire body. This concept is termed cardiac output and is defined as heart rate x stroke volume, which is determined by the contractile forces of the cardiac muscle and the frequency at which they are activated. With a change in metabolic demand comes a change in the contractility of the heart.

Surgery
Shaikh FH, **Shumway KR**, and Soni A. Physiology, Taste. *StatPearls*; 2023. Full Text

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The human body is capable of perceiving five traditional senses: hearing, sight, smell, touch, and taste. Also known as gustation, the sense of taste is essential in discerning the characteristics of substances that one ingests. At a basic evolutionary level, taste allows one to assess whether ingested substances are nutritious or potentially hazardous. This sensation is primarily relayed via receptors located on the tongue. However, at a higher cortical level, taste is considered a multisensory experience as smell, texture, and activation of specific receptors (eg, pain receptors from spicy food) all play a role in determining how something "tastes." A fundamental working knowledge of the anatomy of the tongue is important in fully understanding the concept of taste. The human tongue is divided into an anterior two-thirds and a posterior one-third, separated by a v-shaped groove called the sulcus terminalis. The dorsal aspect of the tongue is covered with bumps known as papillae, of which there are four types: circumvallate, fungiform, foliate, and filiform. The circumvallate, fungiform, and foliate papillae contain taste buds known as gustatory papillae. Taste buds are found on the tongue and the pharynx, larynx, soft palate, and epiglottis. The circumvallate papillae are on the distal aspect of the anterior two-thirds of the tongue and are most sensitive to bitter tastes. The fungiform papillae are found on the tip of the tongue and are most sensitive to sweet and savory (umami) tastes. The foliate papillae are found on the sides of the tongue and are most sensitive to salty and sour tastes. Filiform papillae are found throughout the entire surface of the dorsal tongue and do not contain taste buds. The rough texture of the filiform papillae aid in the gripping of food and transfer down to the esophagus, as well as in the cleaning of the mouth and spreading of saliva.

Surgery
Zimmerman B, **Shumway KR**, and Jenzer AC. Physiology, Tooth. *StatPearls*; 2023. Full Text

Rhode Island Hospital/Brown
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Womack Army Hospital

Teeth serve multiple functions beyond mastication, including shaping the kinetics of phonation, breathing, maintaining a patent airway, and serving as a foundation for the vertical dimensions of the face. The maxilla and mandible, which together form the jaw, contain alveolar bone, a thick ridge of bone that forms the sockets of the teeth. Appropriate size and jaw positioning are critical in developing a proper bite (occlusion) and subsequent mastication. As will be discussed later in detail, certain teeth have specialized roles in chewing, with the entire group functioning as a dynamic entity.