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Henry Ford Health System

Henry Ford Health System Publication List – March 2020

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 System personnel. Searches were conducted in PubMed, Embase, and Google Scholar during the month, and then imported into EndNote for formatting. There are 127 unique citations listed this month; 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 System authors.

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Articles

Allergy and Immunology

Jackson DJ, Bacharier LB, Calatroni A, Gill MA, Hu J, Liu AH, Wheatley LM, Gern JE, Gruchalla RS, Khurana Hershey GK, Kattan M, Kercsmar CM, **Kim H**, O'Connor GT, Patel S, Pongracic JA, Wood RA, and Busse WW. Serum IL-6: A biomarker in childhood asthma? *J Allergy Clin Immunol* 2020. Epub ahead of print. PMID: 32004524. Full Text

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Washington University School of Medicine, St Louis, Mo.
Rho Inc, Chapel Hill, NC.
University of Texas Southwestern Medical Center, Dallas, Tex.
Children's Hospital of Colorado and University of Colorado School of Medicine, Denver, Colo.
National Institute of Allergy and Infectious Diseases, Bethesda, Md.
University of Wisconsin School of Medicine and Public Health, Madison, Wis.
Cincinnati Children's Hospital, Cincinnati, Ohio.
Columbia University College of Physicians and Surgeons, New York, NY.
Henry Ford Health System, Detroit, Mich.
Boston University School of Medicine, Boston, Mass.
Children's National Health System, Washington, DC.
Ann Robert H. Lurie Children's Hospital of Chicago, Chicago, Ill.
Johns Hopkins University School of Medicine, Baltimore, Md.

Cardiology/Cardiovascular Research

Ando T, **Villablanca PA**, Takagi H, and Briasoulis A. Meta-Analysis of Hospital-Volume Relationship in Transcatheter Aortic Valve Implantation. *Heart Lung Circ* 2019. Epub ahead of print. PMID: 32089491. Full Text

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BACKGROUND: Whether a volume-outcome relationship, that is, higher volume centres have better outcomes compared with lower volume hospitals, exists in transcatheter aortic valve implantation (TAVI) has not yet been systematically explored. METHODS: We performed a systematic review and meta-analysis to evaluate whether highest or intermediate annual TAVI volume hospitals has better short-term (in-hospital or 30-days) mortality compared with the lowest volume hospitals. Odds ratio (OR) and 95% confidence interval (CI) was calculated with the Mantel-Haenszel method. RESULTS: We identified 10 publications from nine different countries including TAVI performed between 2005-2017. Included patients were mainly high-risk cohorts. We included five and six studies to assess volume-outcome relationship in the highest and intermediate volume

hospitals compared with the lowest volume hospitals, respectively. Our results showed that in both the highest (OR 0.66, 95%CI 0.53-0.83, p=0.0003, I(2)=78%) and intermediate (OR 0.85, 95%CI 0.79-0.92, p<0.0001, I(2)=0%) volume hospitals, there was a statistically significant volume-outcome relationship for short-term mortality compared with the lowest volume hospitals. CONCLUSIONS: Our review suggests a significant volume-outcome relationship post-TAVI in both the highest and intermediate volume hospitals compared with the lowest volume hospitals mainly in high surgical risk patients. The high heterogeneity in this relationship between the highest and the lowest volume hospitals warrant cautious interpretation. Whether this relationship remains significant in low-risk cohort requires further study.

Cardiology/Cardiovascular Research
Cormican D, McHugh S, Boisen M, Winter D, **So CY**, **Villablanca PA**, and Ramakrishna H. The Low Risk Transcatheter Aortic Valve Replacement Trials-An Analysis. *J Cardiothorac Vasc Anesth* 2020. Epub ahead of print. PMID: 32144060. Full Text

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Cardiology/Cardiovascular Research
Edla S, Atti V, Kumar V, Tripathi B, **Neupane S**, Nalluri N, Abela G, Rosman H, and Mehta RH. Comparison of nationwide trends in 30-day readmission rates after carotid artery stenting and carotid endarterectomy. *J Vasc Surg* 2020; 71(4):1222-1232.e1229. PMID: 31564583. Full Text

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OBJECTIVE: Carotid revascularization procedures, carotid artery stenting (CAS) and carotid endarterectomy (CEA), are among the most common vascular interventions performed in the United States, with significant resource utilization. Whereas multiple studies have reported outcomes after these procedures, data regarding 30-day readmission rates after these interventions remain scant. METHODS: The U.S. Nationwide Readmission Database (2010-2014) was queried to identify all patients >/=18 years who were readmitted within 30 days after a hospital discharge for CEA or CAS. RESULTS: Among 476,260 patients included, 13.5% underwent CAS and 86.5% underwent CEA. The combined 30-day readmission rate for all carotid revascularization procedures was 9.2% (10.6% after CAS and 9.0% after CEA). After 1:3 propensity matching, CAS was associated with higher risk of readmission compared with CEA (10.4% vs 9.4%). Neurologic complications and cardiac conditions were the two most common causes of readmission after both CAS (29.7% and 23.7%, respectively) and CEA (28.2% and 21.7%, respectively). The 30-day readmission rates were higher in CAS patients across all age groups as well as in those with a low or high baseline burden of comorbidities. CONCLUSIONS: In this large nationwide study, CAS was associated with higher 30-day readmission rates compared with CEA irrespective of age or baseline burden of comorbidities. Neurologic or cardiac adverse events were responsible for >50% of readmissions after CAS and CEA.

Cardiology/Cardiovascular Research
Fernando RJ, Shah R, Yang Y, Goeddel LA, **Villablanca PA**, Gil IJN, and Ramakrishna H. Transcatheter Mitral Valve Repair and Replacement: Analysis of Recent Data and Outcomes. *J Cardiothorac Vasc Anesth* 2020. Epub ahead of print. PMID: 32151510. Full Text

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Cardiology/Cardiovascular Research
Guerrero M, Vemulapalli S, Xiang Q, **Wang DD**, Eleid M, Cabalka AK, Sandhu G, Salinger M, Russell H, Greenbaum A, Kodali S, George I, Dvir D, Whisenant B, Russo MJ, Pershad A, Fang K, Coylewright M, Shah P, Babaliaros V, Khan JM, Tommaso C, Saucedo J, Kar S, Makkar R, Mack M, Holmes D, Leon M, Bapat V, Thourani VH, Rihal C, **O'Neill W**, and Feldman T. Thirty-Day Outcomes of Transcatheter Mitral Valve Replacement for Degenerated Mitral Bioprostheses (Valve-in-Valve), Failed Surgical Rings (Valve-in-Ring), and Native Valve With Severe Mitral Annular Calcification (Valve-in-Mitral Annular Calcification) in the United States: Data From the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv* 2020; 13(3):e008425. PMID: 32138529. Full Text

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BACKGROUND: Transcatheter mitral valve replacement using aortic transcatheter heart valves has recently become an alternative for patients with degenerated mitral bioprostheses, failed surgical repairs with annuloplasty rings or severe mitral annular calcification who are poor surgical candidates. Outcomes of these procedures are collected in the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. A comprehensive analysis of mitral valve-in-valve (MViV), mitral valve-in-ring (MViR), and valve-in-mitral annular calcification (ViMAC) outcomes has not been performed. We sought to evaluate short-term outcomes of early experience with MViV, MViR, and ViMAC in the United States. METHODS: Retrospective analysis of data from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. RESULTS: Nine hundred three high-risk patients (median Society of Thoracic Surgeons score 10%) underwent MViV (n=680), MViR (n=123), or ViMAC (n=100) between March 2013 and June 2017 at 172 hospitals. Median age was 75 years, 59.2% female. Technical and procedural success were higher in MViV. Left ventricular outflow tract obstruction occurred more frequently with ViMAC (ViMAC=10%, MViR=4.9%, MViV=0.7%; P<0.001). In-hospital mortality (MViV=6.3%, MViR=9%, ViMAC=18%; P=0.004) and 30-day mortality (MViV=8.1%, MViR=11.5%, ViMAC=21.8%; P=0.003) were higher in ViMAC. At 30-day follow-up, median mean mitral valve gradient was 7 mm Hg, most patients (96.7%) had mitral regurgitation grade </=1 (+) and were in New York Heart Association class I to II (81.7%). CONCLUSIONS: MViV using aortic balloon-expandable transcatheter heart valves is associated with a low complication rate, a 30-day mortality lower than predicted by the Society of Thoracic Surgeons score, and superior short-term outcomes than MViR and ViMAC. At 30 days, patients in all groups experienced improvement of symptoms, and valve performance remained stable. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02245763.

Cardiology/Cardiovascular Research
Loehn T, **O'Neill WW**, Lange B, Pfluecke C, Schweigler T, Mierke J, Waessnig N, Mahlmann A, Youssef A, Speiser U, Strasser RH, and Ibrahim K. Long term survival after early unloading with Impella CP((R)) in acute myocardial infarction complicated by cardiogenic shock. *Eur Heart J Acute Cardiovasc Care* 2020; 9(2):149-157. PMID: 30456984. Full Text

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BACKGROUND: The use of percutaneous left ventricular assist devices in patients with acute myocardial infarction complicated by cardiogenic shock (AMICS) is evolving. The aim of the study was to assess the long-term outcome of patients with AMICS depending on early initiation of Impella CP((R)) support prior to a percutaneous coronary intervention (PCI). METHODS: We retrospectively reviewed all patients who underwent PCI and Impella CP((R)) support between 2014 and 2016 for AMICS at our institution. We compared survival to discharge between those with support initiation before (pre-PCI) and after (post-PCI) PCI. RESULTS: A total of 73 consecutive patients (69+/-12 years old, 27.4% female) were supported with Impella CP((R)) and underwent PCI for AMICS (34 pre-PCI vs. 39 post-PCI). All patients were admitted with cardiogenic shock, and 58.9% sustained cardiac arrest. Survival at discharge was 35.6%. Compared with the post-PCI group, patients in the pre-PCI group had more lesions treated (p=0.03), a higher device weaning rate (p=0.005) and higher survival to discharge as well as to 30 and 90 days after device implantation, respectively (50.0% vs. 23.1%, 48.5% vs. 23.1%, 46.9 vs. 20.5%, p < 0.05). Kaplan-Meier analysis showed a higher survival at one year (31.3% vs. 17.6%, log-rank p-value=0.03) in the pre-PCI group. Impella support initiation before PCI was an independent predictor of survival up to 180 days after device implantation. CONCLUSIONS: In this small, single-centre, non-randomized study Impella CP((R)) initiation prior to PCI was associated with higher survival rates at discharge and up to one year in AMICS patients presenting with high risk for in-hospital mortality.

Cardiology/Cardiovascular Research

Mentz RJ, DeVore AD, Tasissa G, Heitner JF, Pina IL, Lala A, Cole RT, **Lanfear D**, Patel CB, Ginwalla M, Old W, Salacata AS, Bigelow R, Fonarow GC, and Hernandez AF. PredischaRge initiation of Ivabradine in the ManagEment of Heart Failure: Results of the PRIME-HF Trial. *Am Heart J* 2020; 223:98-105. PMID: 32217365. Full Text

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Harrington Heart & Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, OH.
Sentara Cardiovascular Research Institute, Norfolk, VA.
Great Lakes Heart Center of Alpena, Alpena, MI.
Ahmanson-UCLA Cardiomyopathy Center, University of California, Los Angeles, Los Angeles, CA.

BACKGROUND: Ivabradine is guideline-recommended to reduce heart failure (HF) hospitalization in patients with stable chronic HF with reduced ejection fraction (EF). Ivabradine initiation following acute HF has had limited evaluation, and there are few randomized data in US patients. The PredischaRge initiation of Ivabradine in the ManagEment of Heart Failure (PRIME-HF) study was conducted to address predischarge ivabradine initiation in stabilized acute HF patients. METHODS: PRIME-HF was an investigator-initiated, randomized, open-label study of predischarge initiation of ivabradine versus usual care. Eligible patients were hospitalized for acute HF but stabilized, with EF </=35%, on maximally tolerated beta-blocker and in sinus rhythm with heart rate >/=70 beats/min. Ivabradine was acquired per routine care. The primary end point was the proportion of patients on ivabradine at 180 days. Additional end points included heart rate change, patient-reported outcomes, beta-blocker use/dose, and safety events (symptomatic bradycardia and hypotension). RESULTS: Overall, 104 patients (36% women, 64% African American) were randomized, and the study was terminated early because of funding limitations. At 180 days, 21 of 52 (40.4%) of patients randomized to predischarge initiation were treated with ivabradine compared with 6 of 52 (11.5%) randomized to usual care (odds ratio 5.19, 95% CI 1.88-14.33, P = .002). The predischarge initiation group experienced greater reduction in heart rate through 180 days (mean -10.0 beats/min, 95% CI -15.7 to -4.3 vs 0.7 beats/min, 95% CI -5.4 to 6.7, P = .011). Patient-reported outcomes, beta-blocker use/dose, and safety events were similar (all P > .05). CONCLUSIONS: Ivabradine initiation prior to discharge among stabilized HF patients increased ivabradine use at 180 days and lowered heart rates without reducing beta-blockers or increasing adverse events. As the trial did not achieve the planned enrollment, additional studies are needed.

Cardiology/Cardiovascular Research

Qureshi AM, Turner ME, **O'Neill W**, Denfield SW, Aghili N, Badiye A, Gandhi R, Tehrani B, Chang G, Oyama JK, Sinha S, Brozzi N, and Morray B. Percutaneous Impella RP use for refractory right heart failure in adolescents and young adults-A multicenter U.S. experience. *Catheter Cardiovasc Interv* 2020. Epub ahead of print. PMID: 32129576. Full Text

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Advanced Heart Failure, Heart Transplant and Interventional Cardiology, Jackson Memorial Hospital, Miami, Florida, USA.
Division of Cardiology, Hoag Memorial Hospital, Newport Beach, California, USA.
Inova Heart and Vascular Institute, Inova Fairfax Hospital, Annandale, Virginia, USA.
Emory Heart & Vascular Center, Emory, St. Joseph's Hospital, Atlanta, Georgia, USA.
Cardiovascular Disease, The Queen's Medical Center, Honolulu, Hawaii, USA.
Division of Pediatric Cardiology, Seattle Children's Hospital, University of Washington School of Medicine, Seattle, Washington, USA.

OBJECTIVE: To assess the outcomes of the use of the percutaneous Impella RP device (Abiomed, Danvers, MA) in adolescents and young adults. BACKGROUND: Results of the Impella RP device have been reported in adults, but a multicenter experience in adolescents and young adults has yet to be reported. METHODS: Patients </=21 years of age who underwent implantation of an Impella RP device for refractory right heart failure from June, 2016 to April, 2018 at nine U.S. Centers were included. RESULTS: A total of 12 adolescents, median age of 18 (14-21) years and median weight 74.4 (49-112.4) kg underwent Impella RP implantation (INTERMACS Profile 1 in nine and Profile 2 in three patients. The central venous pressure decreased from 20 (16-35) to 12 (7-17) mmHg, (p = .001). One patient was concomitantly supported with an intra-aortic balloon pump (IABP) and the rest with a percutaneous/surgically placed left ventricular assist device. There was one adverse event related to the Impella RP device (thrombosis requiring explant). The support duration was 6.5 days (4.8 hr-18.4 days) and survival to hospital discharge was 83%. At a median follow-up of 11 months (5 days-2.5 years), 8 of 12 (67%) patients are alive. CONCLUSIONS: In this multicenter experience, the Impella RP device was found to be efficacious and safe when used in adolescents and young adults. Further studies are warranted to identify suitable young/pediatric candidates for Impella RP therapy for right heart failure.

Cardiology/Cardiovascular Research
Sabbah HN, **Zhang K**, **Gupta RC**, and Emanuele M. Effects of Intravenous Infusion of Vepoloxamer on Left Ventricular Function in Dogs with Advanced Heart Failure. *Cardiovasc Drugs Ther* 2020. Epub ahead of print. PMID: 32146638. Full Text

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PURPOSE: Vepoloxamer (VEPO), a rheologic agent, repairs damaged cell membranes, thus inhibiting unregulated Ca(2+) entry into cardiomyocytes. This study examined the effects of i.v. infusion of VEPO on LV function in dogs with coronary microembolization-induced heart failure (HF) (LV ejection fraction, EF ~ 30%). METHODS: Thirty-five HF dogs were studied. Study 1: 21 of 35 dogs were randomized to 2-h infusion of VEPO at dose of 450 mg/kg (n = 7) or VEPO at 225 mg/kg (n = 7) or normal saline (control, n = 7). Hemodynamics were measured at 2 h, 24 h, 1 week, and 2 weeks after infusion. Study 2: 14 HF dogs were randomized to 2-h infusions of VEPO (450 mg/kg, n = 7) or normal saline (control, n = 7). Each dog received 2 infusions of VEPO or saline (pulsed therapy) 3 weeks apart and hemodynamics measured at 24 h, and 1, 2, and 3 weeks after each infusion. In both studies, the change between pre-infusion measures and measures at other time points (treatment effect, Delta) was calculated. RESULTS: Study 1: compared to pre-infusion, high dose VEPO increased LVEF by 11 +/- 2% at 2 h, 8 +/- 2% at 24 h ($p < 0.05$), 8 +/- 2% at 1 week ($p < 0.05$), and 4 +/- 2% at 2 weeks. LV EF also increased with low-dose VEPO but not with saline. Study 2: VEPO but not saline significantly increased LVEF by 6.0 +/- 0.7% at 2 h ($p < 0.05$); 7.0 +/- 0.7%% at 1 week ($p < 0.05$); 1.0 +/- 0.6% at 3 weeks; 6.0 +/- 1.3% at 4 weeks ($p < 0.05$); and 5.9 +/- 1.3% at 6 weeks ($p < 0.05$). CONCLUSIONS: Intravenous VEPO improves LV function for at least 1 week after infusion. The benefits can be extended with pulsed VEPO therapy. The results support development of VEPO for treating patients with acute on chronic HF.

Cardiology/Cardiovascular Research
So CY, **Kang G**, **Lee JC**, and **Eng MH**. The Retro-antegrade Approach to Paravalvular Leak Closure After Transcatheter Aortic Valve Replacement. *EuroIntervention* 2020. Epub ahead of print. PMID: 32176617. Request Article

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Cardiology/Cardiovascular Research

Tahhan AS, Vaduganathan M, Greene SJ, Alrohaibani A, **Raad M**, Gafeer M, Mehran R, Fonarow GC, Douglas PS, Bhatt DL, and Butler J. Enrollment of Older Patients, Women, and Racial/Ethnic Minority Groups in Contemporary Acute Coronary Syndrome Clinical Trials: A Systematic Review. *JAMA Cardiol* 2020. Epub ahead of print. PMID: 32211813. Full Text

Emory Clinical Cardiovascular Research Institute, Emory University School of Medicine, Atlanta, Georgia.
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Importance: Although age, sex, and race/ethnicity are important factors when generalizing the findings of clinical trials to routine practice, trends in the representation of these groups in contemporary acute coronary syndrome (ACS) trials are not well defined. Objective: To characterize the representation of older patients, women, and racial/ ethnic minorities in ACS randomized trials. Evidence Review: A systemic search was conducted of ACS trials published in 8 major medical journals between January 2001 and December 2018. Overall, 1067520 patients from 460 trials were included. Findings were compared with epidemiologic studies of patients with ACS. Findings: The median number of participants per trial was 711 (interquartile range, 324-2163) and the median number of sites per trial was 21 (interquartile range, 5-73). Overall, 207 trials (45.0%) studied drug therapy, and 210 (45.7%) evaluated procedural interventions. The mean (SD) age of trial participants was 62.9 (10.7) years and increased from 62.3 (11.2) years in 2001-2006 to 64.0 (10.4) years in 2013-2018 (P = .01). The corresponding mean (SD) age was 66.4 (14.8) years in US epidemiologic studies and 70.0 (13.5) years in European epidemiologic studies. The overall proportion of women enrolled was 26.8% and decreased over time, from 27.8% in 2001-2006 to 24.9% in 2013-2018 (P = .21 for trend). The corresponding weighted proportions of women were 38.0% in US epidemiologic studies and 32.0% in European studies. The distribution of racial/ethnic groups was reported in only 99 trials (21.5%). In trials with reported data, 15.0% of the trial participants were nonwhite, which increased from 12.0% in 2001-2006 to 14.0% in 2013-2018. Black patients represented 3.7% of all patients during the entire study time frame, Asian patients represented 9.6%, and Hispanic patients represented 7.8%. Trends in the representation of black patients remained unchanged from 2001-2006 (5.2%) to 2013-2018 (4.9%), while the enrollment of Asian and Hispanic patients increased from 2001-2006 to 2013-2018 (from 1.9% to 10.8% for Asian patients and from 5.4% to 14.5% for Hispanic patients). Conclusions and Relevance: Older patients and women are underrepresented in contemporary ACS trials compared with epidemiologic studies. Over time, there has been modest improvement in the representation of older patients but not women patients. More than three-quarters of trials did not report race/ethnicity data, with available data suggesting a modest increase in the enrollment of nonwhite patients owing to the enrollment of Asian and Hispanic patients. Enrollment of black patients remained low over time.

Cardiology/Cardiovascular Research

Teuteberg JJ, Cleveland JC, Jr., **Cowger J**, Higgins RS, Goldstein DJ, Keebler M, Kirklin JK, Myers SL, Salerno CT, Stehlik J, Fernandez F, Badhwar V, Pagani FD, and Atluri P. The Society of Thoracic Surgeons Intermacs 2019 Annual Report: The Changing Landscape of Devices and Indications. *Ann Thorac Surg* 2020; 109(3):649-660. PMID: 32115073. Full Text

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Department of Cardiovascular and Thoracic Surgery, West Virginia University, Morgantown, West Virginia.
Department of Cardiac Surgery, University of Michigan, Ann Arbor, Michigan.
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BACKGROUND: The field of mechanical circulatory support has been impacted by the approval of new continuous-flow left ventricular assist devices (LVADs) and changes to the United States heart allocation system. METHODS: Primary isolated

continuous-flow LVAD implants in The Society of Thoracic Surgeons Intermacs registry from January 2014 through September 2019 were evaluated. Survival and freedom from major adverse events were compared between axial-flow, centrifugal-flow with hybrid levitation (CF-HL), and centrifugal-flow with full magnetic levitation (CF-FML) devices. RESULTS: Of 2603 devices implanted in 2014, 1824 (70.1%) were axial flow and 1213 (46.6%) were destination therapy (DT); through September 2019, 1752 devices were implanted, but only 37 (2.1%) were axial flow and 1230 (70.2%) were DT. Implants were performed in 13,016 patients between 2014 and 2018. Patients receiving implants in 2017-2018 compared with 2014-2016 were more likely to be at Intermacs profile 1 (17.1% vs 14.3%, P < .001) and to have preimplant temporary mechanical circulatory support (34.8% vs 29.3%, P < .001). Overall survival and freedom from major adverse events were higher with CF-FML devices. In multivariable analysis of survival between CF-HL and CF-FML, device type was not a significant early hazard, but the use of CF-HL devices had a late hazard ratio for death of 3.01 (P < .001). CONCLUSIONS: Over the past 5 years, centrifugal-flow LVADs have become the dominant technology and DT the most common implant strategy. While outcomes with CF-FML devices are promising, comparisons with other devices from nonrandomized registry studies should be made with caution.

Cardiology/Cardiovascular Research

Villablanca PA, **Lemor A**, So CY, **Kang G**, **Jain T**, Gupta T, Ando T, Mohananey D, Ranka S, Hernandez-Suarez DF, Michel P, **Frisoli T**, **Wang DD**, **Eng M**, **O'Neill W**, and Ramakrishna H. Increased Risk of Perioperative Ischemic Stroke in Patients Who Undergo Noncardiac Surgery with Preexisting Atrial Septal Defect or Patent Foramen Ovale. *J Cardiothorac Vasc Anesth* 2020. Epub ahead of print. PMID: 32127264. Full Text

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OBJECTIVES: To evaluate whether a preoperative diagnosis of atrial septal defect (ASD) or patent foramen ovale (PFO) is associated with perioperative stroke in noncardiac surgery and their outcomes. DESIGN: Retrospective cohort analysis. SETTING: United States hospitals. PARTICIPANTS: Adults patients (>/=18 years old) who underwent major noncardiac surgery from 2010 to 2015 were identified using the Healthcare Cost and Utilization Project's National Readmission Database. INTERVENTIONS: Preoperative diagnosis of ASD or patent foramen ovale. MEASUREMENTS AND MAIN RESULTS: Among the 19,659,161 hospitalizations for major noncardiac surgery analyzed, 12,248 (0.06%) had a preoperative diagnosis of ASD/PFO. Perioperative ischemic stroke occurred in 723 (5.9%) of patients with ASD/PFO and 373,291 (0.02%) of those without ASD/PFO (adjusted odds ratio [aOR], 16.7; 95% confidence interval [CI]: 13.9-20.0). Amongst the different types of noncardiac surgeries, obstetric, endocrine, and skin and burn surgery were associated with higher risk of stroke in patients with pre-existing ASD/PFO. Moreover, patients with ASD/PFO also had an increased in-hospital mortality (aOR, 4.6, 95% CI: 3.6-6.0), 30-day readmission (aOR, 1.2, 95% CI: 1.04-1.38), and 30-day stroke (aOR, 7.2, 95% CI: 3.1-16.6). After adjusting for atrial fibrillation, ischemic stroke remained significantly high in the ASD/PFO group (aOR: 23.7, 95%CI 19.4-28.9), as well as in-hospital mortality (aOR: 5.6, 95% CI 4.1-7.7), 30-day readmission (aOR: 1.19, 95%CI 1.0-1.4), and 30-day stroke (aOR: 9.3, 95% CI 3.7-23.6). CONCLUSIONS: Among adult patients undergoing major noncardiac surgery, pre-existing ASD/PFO is associated with increased risk of perioperative ischemic stroke, in-hospital mortality, 30-day stroke, and 30-day readmission after surgery.

Center for Health Policy and Health Services Research

Boudreau DM, Lapham G, Johnson EA, Bobb JF, Matthews AG, McCormack J, Liu D, Campbell CI, Rossom RC, Binswanger IA, Yarborough BJ, Arnsten JH, Cunningham CO, Glass JE, Murphy MT, Zare M, Hechter RC, **Ahmedani B**, **Braciszewski JM**, Horigian VE, Szapocznik J, Samet JH, Saxon AJ, Schwartz RP, and Bradley KA. Documented opioid use disorder and its treatment in primary care patients across six U.S. health systems. *J Subst Abuse Treat* 2020; 112s:41-48. PMID: 32220410. Full Text

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BACKGROUND: The United States is in the middle of an opioid overdose epidemic, and experts are calling for improved detection of opioid use disorders (OUDs) and treatment with buprenorphine or extended release (XR) injectable naltrexone, which can be prescribed in general medical settings. To better understand the magnitude of opportunities for treatment among primary care (PC) patients, we estimated the prevalence of documented OUD and medication treatment of OUD among PC patients. METHODS: This cross-sectional study included patients with >/=2 visits to PC clinics across 6 healthcare delivery systems who were >/=16 years of age during the study period (fiscal years 2014-2016). Diagnoses, prescriptions, and healthcare utilization were ascertained from electronic health records and insurance claims (5 systems that also offer health insurance). Documented OUDs were defined as >/=1 International Classification of Diseases code for OUDs (active or remission), and OUD treatment was defined as >/=1 prescription(s) for buprenorphine formulations indicated for OUD or naltrexone XR, during the 3-year study period. The prevalence of documented OUD and treatment (95% confidence intervals) across health systems were estimated, and characteristics of patients by treatment status were compared. Prevalence of OUD and OUD treatment were adjusted for age, gender, and race/ethnicity. Combined results were also adjusted for site. RESULT: Among 1,403,327 eligible PC patients, 54-62% were female and mean age ranged from 46 to 51 years across health systems. The 3-year prevalence of documented OUD ranged from 0.7-1.4% across the health systems. Among patients with documented OUD, the prevalence of medication treatment (primarily buprenorphine) varied across health systems: 3%, 12%, 16%, 20%, 22%, and 36%. CONCLUSION: The prevalence of documented OUD and OUD treatment among PC patients varied widely across health systems. The majority of PC patients with OUD did not have evidence of treatment with buprenorphine or naltrexone XR, highlighting opportunities for improved identification and treatment in medical settings. These results can inform initiatives aimed at improving treatment of OUD in PC. Future research should focus on why there is such variation and how much of the variation can be addressed by improving access to medication treatment.

Center for Health Policy and Health Services Research
Maye M, Sanchez VE, Stone-MacDonald A, and Carter AS. Early Interventionists' Appraisals of Intervention Strategies for Toddlers with Autism Spectrum Disorder and Their Peers in Inclusive Childcare Classrooms. *J Autism Dev Disord* 2020. Epub ahead of print. PMID: 32193762. Full Text

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Mounting evidence supports several naturalistic developmental behavioral interventions (NDBI) for toddlers and preschoolers within inclusive childcare centers and preschools. However, these interventions pose many barriers to community implementation. As part of a larger project to create an adapted NDBI for early educators in childcare centers, we surveyed 101 early interventionists who had worked with a toddler with autism within the last 12 months. Early interventionists rated 22-of-31 NDBI strategies to be significantly more effective for All Toddlers versus Toddlers with Autism. However, when comparing the top 10 rated strategies between groups, there was a large degree of overlap. Moreover, many of these highly rated NDBI strategies are consistent with best practice accreditation and early education standards within the United States.

Dermatology
Abdel-Malek ZA, Jordan C, Ho T, Upadhyay PR, Fleischer A, and **Hamzavi I**. The Enigma and Challenges of Vitiligo Pathophysiology and Treatment. *Pigment Cell Melanoma Res* 2020. Epub ahead of print. PMID: 32198977. Full Text

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Vitiligo is the most common acquired pigmentary disorder, which afflicts 0.5-1% of the world population, and is characterized by depigmented skin patches resulting from melanocyte loss. Vitiligo has a complex etiology, and varies in its manifestations, progression, and response to treatment. It presents as an autoimmune disease, evidenced by circulating melanocyte-specific antibodies, and association with other autoimmune diseases. However, autoimmunity may be secondary to the high oxidative stress in vitiligo skin and to intrinsic defects in melanocytes and their microenvironment, which contribute to aberrant stress response, neo-antigenicity, and susceptibility of melanocytes to immune attack and apoptosis. There is also a genetic predisposition to vitiligo, which sensitizes melanocytes to environmental agents, such as phenolic compounds. Currently, there are different treatment modalities for re-pigmenting vitiligo skin. However, when repigmentation is achieved, the major challenge is maintaining the pigmentation, which is lost in 40% of cases. In this review, we present an overview of the clinical aspects of vitiligo, its pathophysiology, the intrinsic defects in melanocytes and their microenvironment, and treatment strategies. Based on lessons from the biology of human melanocytes, we present our perspective of how repigmentation of vitiligo skin can be achieved and sustained.

Dermatology
Chapman S, Adelman M, Sullivan A, Mancuso J, and **Lim HW**. Apremilast-associated drug reaction with eosinophilia and systemic symptoms. *JAAD Case Reports* 2020; 6(4):302-304. Full Text

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Dermatology
Menter A, Gelfand JM, Connor C, Armstrong AW, Cordoro KM, Davis DMR, Elewski BE, Gordon KB, Gottlieb AB, Kaplan DH, Kavanaugh A, Kiselica M, Kivelevitch D, Korman NJ, Kroshinsky D, Lebwohl M, Leonardi CL, Lichten J, **Lim HW**, Mehta NN, Paller AS, Parra SL, Pathy AL, Prater EF, Rahimi RS, Rupani RN, Siegel M, Stoff B, Strober BE, Tapper EB, Wong EB, Wu JJ, Hariharan V, and Elmets CA. Joint AAD-NPF Guidelines of Care for the Management of Psoriasis with Systemic Non-Biological Therapies. *J Am Acad Dermatol* 2020. Epub ahead of print. PMID: 32119894. Full Text

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Pediatric Dermatology Society Alliance.
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Michigan Medicine, University of Michigan, Ann Arbor, MI.
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Psoriasis is a chronic inflammatory disease involving multiple organ systems and affecting approximately 2% of the world's population. In this guideline, we focus the discussion on systemic, non-biologic medications for the treatment of this disease.

We provide a detailed discussion of efficacy and safety for the most commonly used medications-including methotrexate, cyclosporine, and acitretin-and provide recommendations to assist prescribers in initiating and managing patients on these treatments. Additionally, we discuss newer therapies, including tofacitinib and apremilast, and briefly touch upon a number of other medications, including fumaric acid esters (used outside the US) and therapies that are no longer widely used for the treatment of psoriasis, i.e. hydroxyurea, leflunomide, mycophenolate mofetil, thioguanine, and tacrolimus.

Dermatology
Robinson G, McMichael A, Wang SQ, and **Lim HW**. Sunscreen and frontal fibrosing alopecia: A review. *J Am Acad Dermatol* 2020; 82(3):723-728. Epub ahead of print. PMID: 31654665. Full Text

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Frontal fibrosing alopecia (FFA) is a cicatricial alopecia of unknown etiology. The incidence of FFA appears to be increasing with time, leading to suspicion of a possible environmental trigger. Observational studies have reported a positive correlation between facial sunscreen use and FFA. This finding raises the question of whether sunscreen use plays a role in disease development. In this article, we review the available literature on the association of sunscreen with FFA. There is insufficient evidence to establish a direct causal relationship between sunscreen and FFA. Further studies are required to better characterize the role of sunscreen and the environment in the pathogenesis of this unique disease.

Dermatology
Robinson G, Townsend S, and **Jahnke MN**. Molluscum Contagiosum: Review and Update on Clinical Presentation, Diagnosis, Risk, Prevention, and Treatment. *Current Dermatology Reports* 2020; 9(1):83-92. Request Article

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Purpose of Review: Molluscum contagiosum (MC) is a self-limited cutaneous viral infection that most commonly affects children and immunocompromised populations. This review provides an update on the clinical manifestations, risk, diagnosis, treatment, and prevention of this frequently encountered infection. Recent Findings: A recent Cochrane review concluded that there is insufficient evidence to establish the superiority of any specific treatment modality or to confirm that active intervention is superior to benign neglect (van der Wouden JC et al., Cochrane Database Syst Rev 5:CD004767, 2017). Interim pilot study data suggests that cantharidin outperforms placebo (Guzman AK et al., Int J Dermatol 57:1001–1006, 2018). Imiquimod is no longer recommended for treatment of MC (van der Wouden JC et al., Cochrane Database Syst Rev 5:CD004767, 2017; Papadopoulos EJ, https://www.fda.gov/files/drugs/published/N20-723S020-Imiquimod-Clinical-BPCA.pdf, 2006; Katz KA et al., Pediatr Dermatol 35:282–283, 2018). Summary: Optimal management strategies for MC remain unclear due to the multitude of proposed therapies, lack of high-quality evidence, and uncertain benefit of intervention for uncomplicated disease. Aside from watchful waiting, destructive therapies such as cantharidin and curettage are among the best studied methods and remain the treatment of choice for most patients.

Dermatology
Stein Gold L, Bagel J, Allenby K, and Sidgiddi S. Betamethasone dipropionate spray 0.05% alleviates troublesome symptoms of plaque psoriasis. *Cutis* 2020; 105(2):97-102;e101. PMID: 32186532. Request Article

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Patients consider pruritus and scaling to be the most bothersome symptoms of psoriasis. Psoriatic plaques on the knees and elbows are widely considered difficult to treat because of the thicker stratum corneum, which reduces skin hydration and topical absorption. Betamethasone dipropionate (BD) spray 0.05% is a topical steroid with demonstrated efficacy in treating plaque psoriasis. Post hoc analyses of 2 phase 3 trials were done to assess the efficacy of BD spray in relieving the symptom of itching and improving the signs of erythema, scaling, and plaque elevation on plaques located on the knees and elbows vs its vehicle and an augmented BD (AugBD) lotion 0.05%. Betamethasone dipropionate spray reduced the incidence of pruritus, with approximately half of patients who reported itching at baseline showing complete itch relief by day 4. Betamethasone dipropionate spray also reduced the signs of psoriasis on knee and elbow plaques in more patients than AugBD lotion at day 4, though the differences were not statistically significant. Efficacy was similar between the 2 formulations on days 8 and 15. Betamethasone dipropionate spray rapidly relieved2 of the most bothersome symptoms of psoriasis and improved psoriatic signs in hard-to-treat knee and elbow plaques.

Dermatology
Wright E, **Kurland E**, and **Lim HW**. Solar urticaria caused by visible light in a 33-year-old male refractory to treatment with omalizumab. *Photodermatol Photoimmunol Photomed* 2020. Epub ahead of print. PMID: 32141097. Full Text

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Diagnostic Radiology
Aggarwal A, Lazarow F, Anzai Y, Elsayed M, Ghobadi C, Dandan OA, **Griffith B**, Straus CM, and Kadom N. Maximizing Value While Volumes are Increasing. *Curr Probl Diagn Radiol* 2020. Epub ahead of print. PMID: 32222265. Full Text

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Radiologists are facing ever increasing volumes while trying to provide value-based care. There are several drivers of increasing volumes: increasing population size, aging population, increased utilization, gaps in evidence-based care, changes in the provider workforce, defensive medicine, and increasing case complexity. Higher volumes result in increased cognitive and systemic errors and contribute to radiologist fatigue and burnout. We discuss several strategies for mitigating high volumes including abbreviated MRI protocols, 24/7 radiologist coverage, reading room assistants, and other strategies to tackle radiologist burnout.

Diagnostic Radiology
Dai Z, **Carver E**, **Liu C**, **Lee J**, **Feldman A**, **Zong W**, **Pantelic M**, **Elshaikh M**, and **Wen N**. Segmentation of the Prostatic Gland and the Intraprostatic Lesions on Multiparametic Magnetic Resonance Imaging Using Mask Region-Based Convolutional Neural Networks. *Advances in Radiation Oncology* 2020. Epub ahead of print. Full Text

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Purpose: Accurate delineation of the prostate gland and intraprostatic lesions (ILs) is essential for prostate cancer dose-escalated radiation therapy. The aim of this study was to develop a sophisticated deep neural network approach to magnetic resonance image analysis that will help IL detection and delineation for clinicians. Methods and Materials: We trained and evaluated mask region-based convolutional neural networks to perform the prostate gland and IL segmentation. There were 2 cohorts in this study: 78 public patients (cohort 1) and 42 private patients from our institution (cohort 2). Prostate gland segmentation was performed using T2-weighted images (T2WIs), although IL segmentation was performed using T2WIs and coregistered apparent diffusion coefficient maps with prostate patches cropped out. The IL segmentation model was extended to select 5 highly suspicious volumetric lesions within the entire prostate. Results: The mask region-based convolutional neural networks model was able to segment the prostate with dice similarity coefficient (DSC) of 0.88 ± 0.04, 0.86 ± 0.04, and 0.82 ± 0.05; sensitivity (Sens.) of 0.93, 0.95, and 0.95; and specificity (Spec.) of 0.98, 0.85, and 0.90. However, ILs were segmented with DSC of 0.62 ± 0.17, 0.59 ± 0.14, and 0.38 ± 0.19; Sens. of 0.55 ± 0.30, 0.63 ± 0.28, and 0.22 ± 0.24; and Spec. of 0.974 ± 0.010, 0.964 ± 0.015, and 0.972 ± 0.015 in public validation/public testing/private testing patients when trained with patients from cohort 1 only. When trained with patients from both cohorts, the values were as follows: DSC of 0.64 ± 0.11, 0.56 ± 0.15, and 0.46 ± 0.15; Sens. of 0.57 ± 0.23, 0.50 ± 0.28, and 0.33 ± 0.17; and Spec. of 0.980 ± 0.009, 0.969 ± 0.016, and 0.977 ± 0.013. Conclusions: Our research framework is able to perform as an end-to-end system that automatically segmented the prostate gland and identified and delineated highly suspicious ILs within the entire prostate. Therefore, this system demonstrated the potential for assisting the clinicians in tumor delineation.

Diagnostic Radiology
Davatzikos C, Barnholtz-Sloan JS, Bakas S, Colen R, Mahajan A, Quintero CB, Font JC, Puig J, Jain R, Sloan AE, Badve C, Marcus DS, Choi YS, Lee SK, Chang JH, **Poisson LM**, **Griffith B**, Dicker AP, Flanders AE, Booth TC, Rathore S, Akbari H, Sako C, Bilello M, Shukla G, Kazerooni AF, Brem S, Lustig R, Mohan S, Bagley S, Nasrallah M, and O'Rourke DM. AI-based Prognostic Imaging Biomarkers for Precision Neurooncology: the ReSPOND Consortium. *Neuro Oncol* 2020. Epub ahead of print. PMID: 32152622. Full Text

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Diagnostic Radiology

Hosseini MP, Tran TX, Pompili D, Elisevich K, and **Soltanian-Zadeh H**. Multimodal data analysis of epileptic EEG and rs-fMRI via deep learning and edge computing. *Artificial Intelligence in Medicine* 2020; 104. PMID: Full Text

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Background and objective: Multimodal data analysis and large-scale computational capability is entering medicine in an accelerative fashion and has begun to influence investigational work in a variety of disciplines. It is also informing us of therapeutic interventions that will come about with such development. Epilepsy is a chronic brain disorder in which functional changes may precede structural ones and which may be detectable using existing modalities. Methods: Functional connectivity analysis using electroencephalography (EEG) and resting state-functional magnetic resonance imaging (rs-fMRI) has provided such meaningful input in cases of epilepsy. By leveraging the potential of autonomic edge computing in epilepsy, we develop and deploy both noninvasive and invasive methods for monitoring, evaluation, and regulation of the epileptic brain. First, an autonomic edge computing framework is proposed for the processing of big data as part of a decision support system for surgical candidacy. Second, a multimodal data analysis using independently acquired EEG and rs-fMRI is presented for estimation and prediction of the epileptogenic network. Third, an unsupervised feature extraction model is developed for EEG analysis and seizure prediction based on a Convolutional deep learning (CNN) structure for distinguishing preictal (pre-seizure) state from non-preictal periods by support vector machine (SVM) classifier. Results: Experimental and simulation results from actual patient data validate the effectiveness of the proposed methods. Conclusions: The combination of rs-fMRI and EEG/iEEG can reveal more information about dynamic functional connectivity. However, simultaneous fMRI and EEG data acquisition present challenges. We have proposed system models for leveraging and processing independently acquired fMRI and EEG data.

Emergency Medicine

Miller J, House S, Lovato L, Meltzer A, Hahn B, Avarello J, Plasse T, Kalfus I, Fathi R, and Silverman R. Absence of QT prolongation after administration of a 24-mg bimodal-release ondansetron pill (RHB-102). *Am J Emerg Med* 2020. Epub ahead of print. PMID: 32139212. Full Text

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OBJECTIVES: Prospective data evaluating the effect of ondansetron on the corrected QT (QTc) interval is lacking in emergency department clinical use. As part of a randomized trial of a 24-mg bimodal-release ondansetron (RHB-102) pill, we tested the effect of RHB-102 compared to placebo on QTc change. METHODS: This was a planned safety outcome analysis within a multicenter, double-blind, placebo-controlled trial. The trial compared the effects of RHB-102 among patients >/=12 years who presented to 21 centers with symptoms of acute gastroenteritis. Patients with an initial baseline electrocardiogram as well as a follow-up electrocardiogram 4 h later were included in the analysis. The safety endpoint for this analysis was the change from baseline in QTc interval at 4 h, the median time at which ondansetron serum level peaks. RESULTS: A total of 147 patients were included with a mean baseline QTc in the RHB-102 and placebo arms of 410 and 406 ms, respectively. There was no difference in the change in QTc at 4 h post-study drug administration between the RHB-102 (+4, 95% CI 1-8 ms) and placebo group (+5, 95% CI 1-9 ms). In the RHB-102 arm, 6.6% of patients had a QTc change >30 ms and in the placebo arm 3.6% (p = 0.48). No patient in either arm had a QTc change >60 ms after study drug administration. CONCLUSION: In patients with normal baseline QTc, 24-mg bimodal-release ondansetron did not prolong the QTc in comparison to placebo.

Emergency Medicine

Peacock WF, Christenson R, Diercks DB, Fromm C, Headden GF, Hogan CJ, Kulstad EB, LoVecchio F, **Nowak RM**, Schrock JW, Singer AJ, Storrow AB, Straseski J, Wu AHB, and Zelinski DP. Myocardial Infarction Can Be Safely Excluded by High-sensitivity Troponin I Testing 3 Hours After Emergency Department Presentation. *Acad Emerg Med* 2020. Epub ahead of print. PMID: 32220124. Full Text

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BACKGROUND: The accuracy and speed by which acute myocardial infarction (AMI) is excluded are an important determinant of emergency department (ED) length of stay and resource utilization. While high-sensitivity troponin I (hsTnI) >99th percentile (upper reference level [URL]) represents a "rule-in" cutpoint, our purpose was to evaluate the ability of the Beckman Coulter hsTnI assay, using various level-of-quantification (LoQ) cutpoints, to rule out AMI within 3 hours of ED presentation in suspected acute coronary syndrome (ACS) patients. METHODS: This multicenter evaluation enrolled adults with >5 minutes of ACS symptoms and an electrocardiogram obtained per standard care. Exclusions were ST-segment elevation or chronic hemodialysis. After informed consent was obtained, blood samples were collected in heparin at ED admission (baseline), >/=1 to 3, >/=3 to 6, and >/=6 to 9 hours postadmission. Samples were processed and stored at -20 degrees C within 1 hour and were tested at three independent clinical laboratories on an immunoassay system (DxI 800, Beckman Coulter). Analytic cutpoints were the URL of 17.9 ng/L and two LoQ cutpoints, defined as the 10 and 20% coefficient of variation (5.6 and 2.3 ng/L, respectively). A criterion standard MI diagnosis was adjudicated by an independent endpoint committee, blinded to hsTnI, and using the universal definition of MI. RESULTS: Of 1,049 patients meeting the entry criteria, and with baseline and 1- to 3-hour hsTnI results, 117 (11.2%) had an adjudicated final diagnosis of AMI. AMI patients were typically older, with more cardiovascular risk factors. Median (IQR) presentation time was 4 (1.6-16.0) hours after symptom onset, although AMI patients presented ~0.5 hour earlier than non-AMI. Enrollment and first blood draw occurred at a mean of ~1 hour after arrival. To evaluate the assay's rule-out performance, patients with any hsTnI > URL were considered high risk and were excluded. The remaining population (n = 829) was divided into four LoQ relative categories: both hsTnI < LoQ (Lo-Lo cohort); first hsTnI < LoQ and 2nd > LoQ (Lo-Hi cohort); first > LoQ and second < LoQ (Hi-Lo cohort); or both > LoQ (Hi-Hi cohort). In patients with any hsTnI result <20% CV LoQ (Groups 1-3), n = 231 (23.9% ruled out), AMI negative predictive value (NPV) was 100% (95% confidence interval [CI] = 98.9% to 100%). In patients with any hsTnI below the 10% LoQ, n = 611 (58% rule out), AMI NPV was 100% (95% CI = 99.5% to 100%). Of the Hi-Hi cohort (i.e., no hsTnI below the 10% LoQ, but both < URL), there were four AMI patients, NPV was 98.2% (95% CI = 95.4% to 99.3%), and sensitivity was 96.6. CONCLUSIONS: Patients presenting >3 hours after the onset of suspected ACS symptoms, with at least two Beckman

Coulter Access hsTnI < URL and at least one of which is below either the 10 or the 20% LoQ, had a 100% NPV for AMI. Two hsTnI values 1 to 3 hours apart with both < URL, but also >LoQ had inadequate sensitivity and NPV.

Emergency Medicine

Peacock WF, Rafique Z, Vishnevskiy K, Michelson E, Vishneva E, Zvereva T, Nahra R, Li D, and **Miller J**. Emergency Potassium Normalization Treatment Including Sodium Zirconium Cyclosilicate: A Phase II, Randomized, Double-blind, Placebo-controlled Study (ENERGIZE). *Acad Emerg Med* 2020. Epub ahead of print. PMID: 32149451. Full Text

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OBJECTIVES: Sodium zirconium cyclosilicate (SZC) is a novel, highly selective potassium binder currently approved in the United States and European Union for treatment of hyperkalemia. This pilot evaluation explored the efficacy of SZC with insulin and glucose as hyperkalemia treatment in the emergency department (ED). METHODS: This exploratory, phase II, multicenter, randomized, double-blind, placebo-controlled study (NCT03337477) enrolled adult ED patients with blood potassium >/= 5.8 mmol/L. Patients were randomized 1:1 to receive SZC 10 g or placebo, up to three times during a 10-hour period, with insulin and glucose. The primary efficacy outcome was the mean change in serum potassium (sK(+)) from baseline until 4 hours after start of dosing. RESULTS: Overall, 70 patients were randomized (SZC n = 33, placebo n = 37), of whom 50.0% were male. Their mean (+/- standard deviation [+/-SD]) age was 59.0 (+/-13.8) years and mean initial sK(+) was similar between groups (SZC 6.4 mmol/L, placebo 6.5 mmol/L). The least squares mean (+/-SD) sK(+) change from baseline to 4 hours was -0.41 (+/-0.11) mmol/L and -0.27 (+/-0.10) mmol/L with SZC and placebo, respectively (difference = -0.13 mmol/L, 95% confidence interval [CI] = -0.44 to 0.17). A greater reduction in mean (+/-SD) sK(+) from baseline occurred with SZC compared with placebo at 2 hours: -0.72 (+/-0.12) versus -0.36 (+/-0.11) mmol/L (LSM difference = -0.35 mmol/L, 95% CI = -0.68 to -0.02), respectively. A numerically lower proportion of patients in the SZC group required additional potassium-lowering therapy due to hyperkalemia at 0 to 4 hours versus placebo (15.6% vs. 30.6%, respectively; odds ratio = 0.40, 95% CI = 0.09 to 1.77). Comparable proportions of patients experienced adverse events in both treatment groups at 0 to 24 hours. CONCLUSIONS: This pilot study suggested that SZC with insulin and glucose may provide an incremental benefit in the emergency treatment of hyperkalemia over insulin and glucose alone.

Emergency Medicine

Sawaya RD, El Zahran T, Mrad S, Abdul Massih C, **Shaya S**, Makki M, Tamim H, and Majdalani M. Comparing febrile children presenting on and off antibiotics to the emergency department: a retrospective cohort study. *BMC Pediatr* 2020; 20(1):117. PMID: 32164611. Full Text

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BACKGROUND: It is not yet known how antibiotics may affect Serious Bacterial Infections (SBI). Our aim is to describe the presentation, management, and serious bacterial infections (SBI) of febrile children on or off antibiotics. METHODS: Retrospective, cohort study of febrile Emergency Department patients, 0-36 months of age, at a single institution, between 2009and 2012. RESULTS: Seven hundred fifty-three patients were included: 584 in the No-Antibiotics group and 169 (22%) in the Antibiotics group. Age and abnormal lung sounds were predictors for being on antibiotics (OR 2.00 [95% CI 1.23-3.25] and OR 1.04 [95% CI 1.02-1.06] respectively) while female gender, and lower temperatures were negative predictors (OR 0.68 [95%0.47-0.98] and OR 0.47 [95% CI 0.32-0.67] respectively). Antibiotics were prescribed by a physician 89% of the time; the most common one being Amoxicillin/Clavulanic Acid (39%). The antibiotic group got more blood tests (57% vs 45%) and Chest X-Rays (37% vs 25%). Overall, the percent of SBIs (and pneumonias) was statistically the same in both groups (6.5% in the No-antibiotic group VS 3.6%). CONCLUSIONS: Children presenting on antibiotics and off antibiotics were significantly different in their presentation and management, although the overall percentages of SBI were similar in each group. Further investigations into this subgroup of febrile children are needed.

Gastroenterology
Alimirah M, **Sadiq O**, and **Gordon SC**. Novel Therapies in Hepatic Encephalopathy. *Clinics in Liver Disease* 2020. Epub ahead of print. Full Text

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Despite widespread use of lactulose and rifaximin for the treatment of hepatic encephalopathy, this complication of advanced liver disease remains a major burden on the health care system in the United States and continues to predispose to high morbidity and mortality. Several agents have surfaced over recent years with promise to treat hepatic encephalopathy and mitigate the cognitive impairment associated with this disease process. The purpose of this article is to highlight the leading emerging therapies in hepatic encephalopathy as well as their therapeutic targets.

Gastroenterology
Kitajima T, **Nagai S**, **Segal A**, **Magee M**, **Blackburn S**, **Ellithorpe D**, **Yeddula S**, **Qadeer Y**, **Yoshida A**, **Moonka D**, **Brown K**, and **Abouljoud MS**. Posttransplant Complications Predict Alcohol Relapse in Liver Transplant Recipients. *Liver Transpl* 2020; 26(3):379-389. PMID: 31872969. Full Text

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Alcohol relapse after liver transplantation (LT) in patients with alcohol-related liver disease (ALD) is a major challenge. Although its association with pretransplant psychosocial factors was extensively studied, the impacts of posttransplant courses on alcohol relapse have not been well investigated. The aim of this study is to analyze peritransplant factors associated with posttransplant alcohol relapse in patients with ALD. This study evaluated 190 adult LT patients with ALD from 2013 to 2019. Risk factors for alcohol relapse were analyzed, focusing on posttransplant chronic complications, which were classified as Clavien-Dindo classification 3a or higher that lasted over 30 days. The posttransplant alcohol relapse rate was 13.7% (26/190) with a median onset time of 18.6 months after transplant. Multivariate Cox regression analysis revealed that posttransplant chronic complications were an independent risk factor for posttransplant alcohol relapse (hazard ratio [HR], 5.40; P = 0.001), along with psychiatric comorbidity (HR, 3.93; P = 0.001), history of alcohol relapse before LT (HR, 3.00; P = 0.008), and an abstinence period <1.5 years (HR, 12.05; P = 0.001). A risk prediction model was created using 3 pretransplant risk factors (psychiatric comorbidity, alcohol relapse before LT, and abstinence period <1.5 years). This model clearly stratified the risk of alcohol relapse into high-, moderate-, and low-risk groups (P < 0.001). Of the 26 patients who relapsed, 11 (42.3%) continued drinking, of whom 3 died of severe alcoholic hepatitis, and 13 (50.0%) achieved sobriety (outcomes for 2 patients were unknown). In conclusion, posttransplant chronic complications increased the risk of alcohol relapse. Recognition of posttransplant chronic complications in conjunction with the risk stratification model by pretransplant psychosocial factors would help with the prediction of posttransplant alcohol relapse.

Gastroenterology
Nagai S, **Chau LC**, **Kitajima T**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, and **Moonka D**. A Share 21 Model in Liver Transplantation: Impact on Waitlist Outcomes. *Am J Transplant* 2020. Epub ahead of print. PMID: 32155314. Full Text

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With the introduction of MELD-Na based allocation, the score at which patients benefit from liver transplantation (LT) has shifted from a score of 15 to 21. This study aimed to evaluate waitlist outcomes in patients with MELD-Na scores <21 and explore the utility of replacing "Share 15" with "Share 21". The study uses data from the OPTN/UNOS registry. All adult patients registered for LT after implementation of the MELD-Na based allocation were evaluated. Waitlist patients with initial and final scores <21 were eligible. Patients with exception scores were excluded. To explore the potential impact of a Share 21 model, patients with an initial MELD-Na score of 6-14 (Group 1) and those with a score of 15-20 (Group 2) were compared for waitlist outcomes. There were 3,686 patients with an initial score of 6-14 (Group 1) and 3,282 with a score of 15-20 (Group 2). Group 2, when compared to Group 1, showed comparable risk of mortality (adjusted hazard ratio [aHR] 1.00, P=0.97), higher transplant probability (aHR 3.25, P<0.001), and lower likelihood of removal from listing because of improvement (aHR 0.74, P=0.011). Share 21 may enhance transplant opportunities and increase parity for patients with higher MELD-Na scores without compromising waitlist outcomes.

Gastroenterology

Nagai S, **Kitajima T**, **Yeddula S**, **Salgia R**, Schilke R, **Abouljoud MS**, and **Moonka D**. Effect of mandatory 6-month waiting period on waitlist and transplant outcomes in patients with hepatocellular carcinoma. *Hepatology* 2020. Epub ahead of print. PMID: 32157711. Full Text

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OPTN/UNOS policy mandates a 6-month waiting period before exception scores are granted to liver transplant candidates with hepatocellular carcinoma (HCC). This study aims to evaluate waitlist and post-transplant outcomes, in HCC patients, before and after implementation of the 6-month waiting rule. We examined two groups from the UNOS registry; Group 1 (pre 6-month rule) comprised patients registered as transplant candidates with HCC from Jan. 1, 2013 to Oct. 7, 2015 (n=4,814). Group 2 (post 6-month rule) comprised patients registered from Oct. 8, 2015 to Jun. 30, 2018 (n=3,287). As expected, the transplant probability was higher in the first six months after listing in Group 1 than Group 2 at 42.0% vs 6.3% (P<0.001). However, the 6-month waitlist mortality/dropout rate was lower in Group 2 at 1.2% than Group 1 at 4.1% (P<0.001). To assess regional parity of transplant, UNOS-regions were categorized into three groups based on MELD score at transplant; lower-score (regions 3,10&11), mid-score (1,2,6,8&9), and higher-score region groups (4,5&7). Outcomes were compared from the time exception points were given which we defined as conditional waitlist outcomes. Conditional waitlist mortality/dropout decreased, and transplant probability increased in all region groups, but the benefits of the policy were more pronounced in the higher and mid-score groups, compared to the lower-score group. The decline in waitlist mortality/dropout was only significant in the high MELD group (P<0.001). No effect was observed on post-transplant mortality or percent of patients within Milan criteria on explant. CONCLUSION: The HCC policy change was associated with decreased waitlist mortality/dropout and increased transplant probability. The policy helped decrease but did not eliminate regional disparities in transplant opportunity without an effect on post-transplant outcomes.

Global Health Initiative

Plum A, Tanniru M, and Khuntia J. An innovation platform for diffusing public health practices across a global network. *Health Policy and Technology* 2020. Epub ahead of print. Request Article

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Hospitals and health systems in high-income countries (HIC) develop the capacities of peer healthcare organizations around the world by diffusing clinical, quality, and public health improvement practices in lower and middle-income countries (LMIC). In turn, these HIC healthcare institutions are exposed to innovative approaches developed and used by global communities to advance care despite resource constraints in the LMIC contexts. Attention has been growing in recent years to the potential these innovations can have to improve care delivery, lower costs, and drive quality within resource-constrained communities in HIC. Often referred to as “reverse innovations,” the identification, adaptation, and diffusion of these practices face challenges in uptake related to limited evidence, perceptions of poor quality or irrelevance, and a complicated regulatory and policy environment. This paper suggests the development of an approach to improve the capacity of the healthcare organizations in the HIC as well, based on lessons learned from diffusing practices in LMIC. It concludes with the need for a knowledge platform to support innovation diffusion in both directions.

Global Health Initiative

Wagner JL, Carreno JJ, **Kenney RM, Kilgore PE**, and **Davis SL**. Antimicrobial Stewardship Metrics that Matter. *Infectious Diseases in Clinical Practice* 2020; 28(2):89-93. Full Text

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Background Guidelines for antimicrobial stewardship programs (ASPs) highlight the need for measuring quality metrics as surrogate markers for outcome. The objective of this study was to determine the relationship between ASP quality metrics and patient outcomes at an institution with an established ASP. Methods Retrospective cohort study including 442 patients receiving intravenous antibiotics for 72 hours or more in 1 of 3 designated inpatient units were assessed for compliance with ASP metrics and associated outcomes. Clinical success was defined as discharged alive, without adverse drug reaction and not readmitted within 30 days of discharge. Results The mean (SD) age was 62 (17) years with 205 males (46%) enrolled. A total of 422 patients (96%) had documented indication for therapy, 365 (83%) had appropriate cultures obtained at baseline, 354 (80%) had appropriate empiric therapy at baseline, and 166 (83%) of 199 had appropriate deescalation performed. All metrics were met in 58% of patients. Sixty-two percent of patients achieved clinical success; while, 14% died, 13% had an adverse drug reaction, and 21% were readmitted within 30 days. Completion of all ASP metrics was not associated with clinical success (odds ratio, 0.862; P = 0.46). Documentation of indication for therapy was a significant indicator for clinical success (97.8% vs 91.7%; P = 0.003); this remained associated after adjusting for infection type and severity. Conclusions

Documented indication showed strong association with clinical success, providing support for use of the Centers for Disease Control's Core Elements as a metric for quality of care.

Hematology-Oncology
Kaplan MH, Contreras-Galindo R, **Jiagge E**, Merajver SD, Newman L, Bigman G, Dosik MH, Palapattu GS, Siddiqui J, Chinnaiyan AM, Adebamowo S, and Adebamowo C. Is the HERV-K HML-2 Xq21.33, an endogenous retrovirus mutated by gene conversion of chromosome X in a subset of African populations, associated with human breast cancer? *Infect Agent Cancer* 2020; 15:19. PMID: 32165916. Full Text

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The human endogenous retroviruses HERV-K HML-2 have been considered a possible cause of human breast cancer (BrC). A HERV-K HML-2 fully intact provirus Xq21.33 was recently identified in some West African people. We used PCR technology to search for the Xq21.33 provirus in DNA from Nigerian women with BrC and controls. to see if Xq21.33 plays any role in predisposing to BrC. This provirus was detected in 27 of 216 (12.5%) women with BrC and in 22 of 219 (10.0%) controls. These results were not statistically significant. The prevalence of provirus in premenopausal control women 44 years or younger [18/157 (11.46%)} vs women with BrC [12/117 (10.26%)] showed no statistical difference. The prevalence of virus in postmenopausal control women > 45 yrs. was 7.4% (4/54) vs 15.31% (15/98) in postmenopausal women with BrC. These changes were not statistically significant at <.05, but the actual p value of <.0.079, suggests that Xq21.33 might play some role in predisposing to BrC in postmenopausal women. Provirus was present in Ghanaian women (6/87), in 1/6 Pygmy populations and in African American men (4/45) and women (6/68), but not in any Caucasian women (0/109). Two BrC cell lines (HCC 70 and DT22) from African American women had Xq21.33. Env regions of the virus which differed by 2-3 SNPs did not alter the protein sequence of the virus. SNP at 5730 and 8529 were seen in all persons with provirus, while 54% had an additional SNP at 7596.Two Nigerian women and 2 Ghanaian women had additional unusual SNPs. Homozygosity was seen in (5/27) BrC and (2/22) control women. The genetic variation and homozygosity patterns suggested that there was gene conversion of this X chromosome associated virus. The suggestive finding in this preliminary data of possible increased prevalence of Xq21.33 provirus in post-menopausal Nigerian women with BrC should be clarified by a more statistically powered study sample to see if postmenopausal African and/or African American women carriers of Xq21.33 might show increased risk of BrC. The implication of finding such a link would be the development of antiretroviral drugs that might aid in preventing BrC in Xq21.33+ women.

Hematology-Oncology
Kim MM, Parmar HA, Schipper M, Devasia T, Aryal MP, Kesari S, O'Day S, Morikawa A, Spratt DE, Junck L, Mammoser A, Hayman JA, Lawrence TS, Tsien CI, Aiken R, Goyal S, Abrouk N, **Trimble M**, Cao Y, and Lao CD. BRAINSTORM: A Multi-Institutional Phase I/II Study of RRx-001 in Combination with Whole Brain Radiation Therapy for Patients with Brain Metastases. *Int J Radiat Oncol Biol Phys* 2020. Epub ahead of print. PMID: 32169409. Request Article

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BACKGROUND: To determine the RP2D of RRx-001, a radiosensitizer with vascular normalizing properties, when used with whole-brain radiation therapy (WBRT) for brain metastases, and to assess whether quantitative changes in perfusion MRI after RRx-001 correlate with response. METHODS: Five centers participated in this phase I/II trial of RRx-001 given once pre-WBRT then twice weekly during WBRT. Four dose levels were planned (5 mg/m2, 8.4 mg/m2, 16.5 mg/m2, 27.5 mg/m2). Dose-escalation was managed by the TITE-CRM algorithm. Linear mixed models were used to correlate change in 24-hour T1, Ktrans (capillary permeability) and Vp (plasma volume) with change in tumor volume. RESULTS: Between 2015-2017, 31 patients were enrolled. Two patients dropped out prior to any therapy. Median age was 60 years (range, 30-76) and 12 were male. The most common tumor types were melanoma (59%) and non-small cell lung cancer (18%). No DLT's were observed. The most common severe adverse event was grade 3 asthenia (6.9%, 2/29). The median intracranial response rate was 46% (95%CI 24-68) and median OS was 5.2 months (95%CI 4.5-9.4). No neurologic deaths occurred. Among 10 patients undergoing DCE-MRI, a reduction in Vp 24 hours after RRx-001 was associated with reduced tumor volume at 1 and 4 months (p</=0.01). CONCLUSIONS: The addition of RRx-001 to WBRT is well-tolerated with favorable intracranial response rates. Because activity was observed across all dose levels, the RP2D is 10 mg twice weekly. A reduction in Vp by DCE-MRI 24 hours after RRx-001 suggests anti-angiogenic activity associated with longer-term tumor response.

Hypertension and Vascular Research
Bryson TD, **Pandrangi TS**, **Khan SZ**, **Xu J**, **Pavlov TS**, **Ortiz PA**, **Peterson E**, and **Harding P**. The deleterious role of the prostaglandin E2 EP3 receptor in angiotensin II hypertension. *Am J Physiol Heart Circ Physiol* 2020; 318(4):H867-h882. PMID: 32142358. Full Text

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Angiotensin II (ANG II) plays a key role in regulating blood pressure and inflammation. Prostaglandin E2 (PGE2) signals through four different G protein-coupled receptors, eliciting a variety of effects. We reported that activation of the EP3 receptor reduces cardiac contractility. More recently, we have shown that overexpression of the EP4 receptor is protective in a mouse myocardial infarction model. We hypothesize in this study that the relative abundance of EP3 and EP4 receptors is a major determinant of end-organ damage in the diseased heart. Thus EP3 is detrimental to cardiac function and promotes inflammation, whereas antagonism of the EP3 receptor is protective in an ANG II hypertension (HTN) model. To test our hypothesis, male 10- to 12-wk-old C57BL/6 mice were anesthetized with isoflurane and osmotic minipumps containing ANG II were implanted subcutaneously for 2 wk. We found that antagonism of the EP3 receptor using L798,106 significantly attenuated the increase in blood pressure with ANG II infusion. Moreover, antagonism of the EP3 receptor prevented a decline in cardiac function after ANG II treatment. We also found that 10- to 12-wk-old EP3-transgenic mice, which overexpress EP3 in the cardiomyocytes, have worsened cardiac function. In conclusion, activation or overexpression of EP3 exacerbates end-organ damage in ANG II HTN. In contrast, antagonism of the EP3 receptor is beneficial and reduces cardiac dysfunction, inflammation, and HTN.NEW & NOTEWORTHY This study is the first to show that systemic treatment with an EP3 receptor antagonist (L798,106) attenuates the angiotensin II-induced increase in blood pressure in mice. The results from this project could complement existing hypertension therapies by combining blockade of the EP3 receptor with antihypertensive drugs.

Hypertension and Vascular Research
Venkat P, **Cui C**, **Chen Z**, **Chopp M**, **Zacharek A**, **Landschoot-Ward J**, **Culmone L**, **Yang XP**, **Xu J**, and **Chen J**. CD133+Exosome Treatment Improves Cardiac Function after Stroke in Type 2 Diabetic Mice. *Transl Stroke Res* 2020. Epub ahead of print. PMID: 32198711. Request Article

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Cardiac complications post-stroke are common, and diabetes exacerbates post-stroke cardiac injury. In this study, we tested whether treatment with exosomes harvested from human umbilical cord blood derived CD133+ cells (CD133+Exo) improves cardiac function in type 2 diabetes mellitus (T2DM) stroke mice. Adult (3-4 m), male, BKS.Cg-m+/+Lepr(db)/J (db/db, T2DM) and non-DM (db+) mice were randomized to sham or photothrombotic stroke groups. T2DM-stroke mice were treated with phosphate-buffered saline (PBS) or CD133+Exo (20 mug, i.v.) at 3 days after stroke. T2DM sham and T2DM+CD133+Exo treatment groups were included as controls. Echocardiography was performed, and mice were sacrificed at 28 days after stroke. Cardiomyocyte hypertrophy, myocardial capillary density, interstitial fibrosis, and inflammatory factor expression were measured in the heart. MicroRNA-126 expression and its target gene expression were measured in the heart. T2DM mice exhibit significant cardiac deficits such as decreased left ventricular ejection fraction (LVEF) and shortening fraction (LVSF), increased left ventricular diastolic dimension (LVDD), and reduced heart rate compared to non-DM mice. Stroke in non-DM and T2DM mice significantly decreases LVEF compared to non-DM and T2DM-sham, respectively. Cardiac dysfunction is

worse in T2DM-stroke mice compared to non-DM-stroke mice. CD133+Exo treatment of T2DM-stroke mice significantly improves cardiac function identified by increased LVEF and decreased LVDD compared to PBS treated T2DM-stroke mice. In addition, CD133+Exo treatment significantly decreases body weight and blood glucose but does not decrease lesion volume in T2DM-stroke mice. CD133+Exo treatment of T2DM mice significantly decreases body weight and blood glucose but does not improve cardiac function. CD133+Exo treatment in T2DM-stroke mice significantly decreases myocardial cross-sectional area, interstitial fibrosis, transforming growth factor beta (TGF-beta), numbers of M1 macrophages, and oxidative stress markers 4-HNE (4-hydroxynonenal) and NADPH oxidase 2 (NOX2) in heart tissue. CD133+Exo treatment increases myocardial capillary density in T2DM-stroke mice as well as upregulates endothelial cell capillary tube formation in vitro. MiR-126 is highly expressed in CD133+Exo compared to exosomes derived from endothelial cells. Compared to PBS treatment, CD133+Exo treatment significantly increases miR-126 expression in the heart and decreases its target gene expression such as Sprouty-related, EVH1 domain-containing protein 1 (Spred-1), vascular cell adhesion protein (VCAM), and monocyte chemoattractant protein 1 (MCP1) in the heart of T2DM-stroke mice. CD133+Exo treatment significantly improves cardiac function in T2DM-stroke mice. The cardio-protective effects of CD133+Exo in T2DM-stroke mice may be attributed at least in part to increasing miR-126 expression and decreasing its target protein expression in the heart, increased myocardial capillary density and decreased cardiac inflammatory factor expression.

Hypertension and Vascular Research

Yang A, and **Mottillo EP**. Adipocyte lipolysis: from molecular mechanisms of regulation to disease and therapeutics. *Biochem J* 2020; 477(5):985-1008. PMID: 32168372. Full Text

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Fatty acids (FAs) are stored safely in the form of triacylglycerol (TAG) in lipid droplet (LD) organelles by professional storage cells called adipocytes. These lipids are mobilized during adipocyte lipolysis, the fundamental process of hydrolyzing TAG to FAs for internal or systemic energy use. Our understanding of adipocyte lipolysis has greatly increased over the past 50 years from a basic enzymatic process to a dynamic regulatory one, involving the assembly and disassembly of protein complexes on the surface of LDs. These dynamic interactions are regulated by hormonal signals such as catecholamines and insulin which have opposing effects on lipolysis. Upon stimulation, patatin-like phospholipase domain containing 2 (PNPLA2)/adipocyte triglyceride lipase (ATGL), the rate limiting enzyme for TAG hydrolysis, is activated by the interaction with its co-activator, alpha/beta hydrolase domain-containing protein 5 (ABHD5), which is normally bound to perilipin 1 (PLIN1). Recently identified negative regulators of lipolysis include G0/G1 switch gene 2 (G0S2) and PNPLA3 which interact with PNPLA2 and ABHD5, respectively. This review focuses on the dynamic protein-protein interactions involved in lipolysis and discusses some of the emerging concepts in the control of lipolysis that include allosteric regulation and protein turnover. Furthermore, recent research demonstrates that many of the proteins involved in adipocyte lipolysis are multifunctional enzymes and that lipolysis can mediate homeostatic metabolic signals at both the cellular and whole-body level to promote inter-organ communication. Finally, adipocyte lipolysis is involved in various diseases such as cancer, type 2 diabetes and fatty liver disease, and targeting adipocyte lipolysis is of therapeutic interest.

Infectious Diseases

Melia MT, Paez A, Reid G, Chirch LM, Luther VP, Blackburn BG, Perez F, Abdoler E, Kaul DR, Rehm S, Harik N, Barsoumian A, Person AK, Yun H, Beckham JD, Boruchoff S, Cariello PF, Cutrell JB, Graber CJ, Lee DH, Maziarz E, Paras ML, Razonable RR, Ressner R, **Chen A**, Chow B, Escota G, **Herc E**, Johnson A, Maves RC, Nnedu O, Clauss H, Kulkarni P, Pottinger PS, Serpa JA, Bhowmick T, Bittner M, Wooten D, Casanas B, Shnekendorf R, and Blumberg EA. The Struggling Infectious Diseases Fellow: Remediation Challenges and Opportunities. *Open Forum Infect Dis* 2020; 7(3):058. PMID: 32166097. Request Article

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Remediation of struggling learners is a challenge faced by all educators. In recognition of this reality, and in light of contemporary challenges facing infectious diseases (ID) fellowship program directors, the Infectious Diseases Society of America Training Program Directors' Committee focused the 2018 National Fellowship Program Directors' Meeting at IDWeek on "Remediation of the Struggling Fellow." Small group discussions addressed 7 core topics, including feedback and evaluations, performance management and remediation, knowledge deficits, fellow well-being, efficiency and time management, teaching skills, and career development. This manuscript synthesizes those discussions around a competency-based framework to provide program directors and other educators with a roadmap for addressing common contemporary remediation challenges.

Internal Medicine
Alimirah M, **Sadiq O**, and **Gordon SC**. Novel Therapies in Hepatic Encephalopathy. *Clinics in Liver Disease* 2020. Epub ahead of print. PMID: Full Text

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Despite widespread use of lactulose and rifaximin for the treatment of hepatic encephalopathy, this complication of advanced liver disease remains a major burden on the health care system in the United States and continues to predispose to high morbidity and mortality. Several agents have surfaced over recent years with promise to treat hepatic encephalopathy and mitigate the cognitive impairment associated with this disease process. The purpose of this article is to highlight the leading emerging therapies in hepatic encephalopathy as well as their therapeutic targets.

Internal Medicine
DeCamillo D, **Ellsworth S**, **Kaatz S**, and Barnes GD. Use of apixaban and rivaroxaban in young adults with acute venous thromboembolism: a multi-center retrospective case series. *J Thromb Thrombolysis* 2020. Epub ahead of print. PMID: 32219722. Full Text

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Since 2012 four direct oral anticoagulants (DOAC) have been approved by the US Food and Drug Administration (FDA) for treatment of acute venous thromboembolism (VTE). Clinical trials comparing DOACs to warfarin included more than 13,500 patients. However, included patients were all age 39 years or older. We sought to describe real-world use of DOACs among young adults with acute VTE. Multi-center retrospective case series of young adult patients (age 18-40 years) at two large academic medical centers who initiated any DOAC for VTE therapy in 2015 or 2016. Thrombotic and bleeding events as well

as off-label drug use were described using summary statistics. Fifty-seven patients were identified (63.2% female). One of the 57 patients (1.8%) had a thromboembolic event. Seven of the 57 patients (12.3%) experienced a bleeding event, one categorized as a major bleed and six being categorized as clinically relevant non-major bleeding. One of the ten (10%) patients receiving apixaban was not initiated on the FDA-recommended 10 mg twice daily for the first 7 days. Seven of the 47 (14.9%) patients receiving rivaroxaban were not initiated on the FDA-recommended 15 mg twice daily dosing for the first 21 days. Bleeding occurred in approximately 14% of young adult patients treated with DOAC therapy. However, only one patient had their DOAC discontinued due to a major bleeding event. Recurrence of DVT while on DOAC therapy was rare.

Internal Medicine

Kerndt CC, Balinski AM, and **Papukhyan HV**. Giant Pericardial Lipoma Inducing Cardiac Tamponade and New Onset Atrial Flutter. *Case Rep Cardiol* 2020. Epub ahead of print. PMID: 32190390. Request Article

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Although pericardial lipomas are both rare and benign, rapid or excessive growth can induce potentially fatal conditions such as pericarditis, arrhythmia, and cardiac tamponade. This case illustrates an example where a 65-year-old with atypical chest tightness unveiled a 10 x 15 cm anterior pericardial mass with circumferential effusion and progressive deterioration to cardiac tamponade. Initial transthoracic echocardiogram imaging was technically difficult in this patient due to habitus and body mass, which failed to illustrate underlying effusion. Recurrent bouts of refractory supraventricular tachycardia prompted further investigation of this patient's presentation with transesophageal echocardiogram, which showed evidence of an echogenic mass with cardiac tamponade. An urgent pericardial window and pericardial lipectomy immediately relieved this hemodynamically compromising condition. Subsequent atrial flutter resulted with the removal of the anterior fat pad during surgery, complicating recovery.

Nephrology

Agrawal V, Plantinga L, Abdel-Kader K, Pivert K, Provenzano A, **Soman S**, Choi MJ, and Jaar BG. Burnout and Emotional Well-Being among Nephrology Fellows-a National Online Survey. *J Am Soc Nephrol* 2020. Epub ahead of print. PMID: 32123052. Full Text

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BACKGROUND: Physician burnout and emotional distress are associated with work dissatisfaction and provision of suboptimal patient care. Little is known about burnout among nephrology fellows. METHODS: Validated items on burnout, depressive symptoms, and well being were included in the American Society of Nephrology annual survey emailed to US nephrology fellows in May to June 2018. Burnout was defined as an affirmative response to two single-item questions of experiencing emotional exhaustion or depersonalization. RESULTS: Responses from 347 of 808 eligible first- and second-year adult nephrology fellows were examined (response rate=42.9%). Most fellows were aged 30-34 years (56.8%), male (62.0%), married or partnered (72.6%), international medical graduates (62.5%), and pursuing a clinical nephrology fellowship (87.0%). Emotional exhaustion and depersonalization were reported by 28.0% and 14.4% of the fellows, respectively, with an overall burnout prevalence of 30.0%. Most fellows indicated having strong program leadership (75.2%), positive work-life balance (69.2%), presence of social support (89.3%), and career satisfaction (73.2%); 44.7% reported a disruptive work environment and 35.4% reported depressive symptoms. Multivariable logistic regression revealed a statistically significant association between female gender (odds ratio [OR], 1.90; 95% confidence interval [95% CI], 1.09 to 3.32), poor work-life balance (OR, 3.97; 95% CI, 2.22 to 7.07), or a disruptive work environment (OR, 2.63; 95% CI, 1.48 to 4.66) and burnout. CONCLUSIONS: About one third of US nephrology fellows surveyed reported experiencing burnout and depressive symptoms. Further exploration of burnout-especially that reported by female physicians, as well as burnout associated with poor work-life balance or a disruptive work environment-is warranted to develop targeted efforts that may enhance the educational experience and emotional well being of nephrology fellows.

Neurology

Carlson AP, Hanggi D, Wong GK, Etminan N, **Mayer SA**, Aldrich F, Diringer MN, Schmutzhard E, Faleck HJ, Ng D, Saville BR, Bleck T, Grubb R, Jr., Miller M, Suarez JI, Proskin HM, and Macdonald RL. Single-Dose Intraventricular Nimodipine Microparticles Versus Oral Nimodipine for Aneurysmal Subarachnoid Hemorrhage. *Stroke* 2020; 51(4):1142-1149. PMID: 32138631. Full Text

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Background and Purpose- EG-1962 is a sustained release formulation of nimodipine administered via external ventricular drain in patients with aneurysmal subarachnoid hemorrhage. A randomized, open-label, phase 1/2a, dose-escalation study provided impetus for this study to evaluate efficacy and safety of a single intraventricular 600 mg dose of EG-1962 to patients with aneurysmal subarachnoid hemorrhage, compared with standard of care oral nimodipine. Methods- Subjects were World Federation of Neurological Surgeons grades 2-4, modified Fisher grades 2-4 and had an external ventricular drain inserted as part of standard of care. The primary end point was the proportion of subjects with favorable outcome at day 90 after aneurysmal subarachnoid hemorrhage (extended Glasgow outcome scale 6-8). The proportion of subjects with favorable outcome at day 90 on the Montreal cognitive assessment, as well as the incidence of delayed cerebral ischemia and infarction, use of rescue therapy and safety were evaluated. Results- The study was halted by the independent data monitoring board after planned interim analysis of 210 subjects (289 randomized) with day 90 outcome found the study was unlikely to achieve its primary end point. After day 90 follow-up of all subjects, the proportion with favorable outcome on the extended Glasgow outcome scale was 45% (65/144) in the EG-1962 and 42% (62/145) in the placebo group (risk ratio, 1.01 [95% CI, 0.83-1.22], P=0.95). Consistent with its mechanism of action, EG-1962 significantly reduced vasospasm (50% [69/138] EG-1962 versus 63% [91/144], P=0.025) and hypotension (7% [9/138] versus 10% [14/144]). Analysis of prespecified subject strata suggested potential efficacy in World Federation of Neurological Surgeons 3-4 subjects (46% [32/69] EG-1962 versus 32% [24/75] placebo, odds ratio, 1.22 [95% CI, 0.94-1.58], P=0.13). No safety concerns were identified that halted the study or that preclude further development. Conclusions- There was no significant increase in favorable outcome for EG-1962 compared with standard of care in the overall study population. The safety profile was acceptable. Registration- URL: https://www.clinicaltrials.gov; Unique identifier: NCT02790632.

Neurology

Schefold JC, Backlund M, Ala-Kokko T, Zuercher P, Mukherjee R, Mistry S, **Mayer SA**, Dziewas R, Bakker J, and Jakob SM. The PhINEST study - Pharyngeal ICU Novel Electrical Stimulation Therapy: Study protocol of a prospective, multi-site, randomized, sham-controlled, single-blind (outcome assessor-blinded) study. *Medicine (Baltimore)* 2020; 99(11):e19503. PMID: 32176093. Full Text

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INTRODUCTION: Post-extubation dysphagia is commonly observed in ICU patients and associated with increased aspiration rates, delayed resumption of oral intake/ malnutrition, prolonged ICU and hospital length of stay, decreased quality of life, and increased mortality. Conventional therapeutic approaches are limited. Pharyngeal electrical stimulation (PES) was previously shown to improve swallowing function and airway safety in severely dysphagic tracheostomised stroke patients. METHODS: In a multi-center, single-blind, 1:1 randomized controlled study, up to 400 (360 evaluable) mixed emergency adult ICU patients with recent extubation following mechanical ventilation and confirmed oropharyngeal dysphagia will be enrolled at investigational academic ICUs. Primary objective is to evaluate the effectiveness of PES in reducing the severity of unsafe swallows. Patients will be randomized to receive PES (or sham) treatment on 3 consecutive days in addition to best supportive care. Primary endpoint is a composite of 2 endpoints with hierarchy based on clinical priorities: DISCUSSION:: This study will evaluate the effects of PES on swallowing safety in critically ill ICU patients post mechanical ventilation with oropharyngeal dysphagia.

Neurology

Siegler JE, Messe SR, Sucharew H, Kasner SE, Mehta T, Arora N, Starosciak AK, De Los Rios La Rosa F, Barnhill NR, Mistry AM, Patel K, Assad S, Tarboosh A, Dakay K, Wagner J, Bennett A, Jagadeesan B, Streib C, Weber SA, Chitale R, Volpi JJ, **Mayer SA**, Yaghi S, Jayaraman MV, Khatri P, and Mistry EA. Noncontrast CT versus Perfusion-Based Core Estimation in Large Vessel Occlusion: The Blood Pressure after Endovascular Stroke Therapy Study. *J Neuroimaging* 2020; 30(2):219-226. PMID: 31762108. Full Text

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BACKGROUND AND PURPOSE: The 2018 AHA guidelines recommend perfusion imaging to select patients with acute large vessel occlusion (LVO) for thrombectomy in the extended window. However, the relationship between noncontrast CT and CT perfusion imaging has not been sufficiently characterized >6 hours after last known normal (LKN). METHODS: From a multicenter prospective cohort of consecutive adults who underwent thrombectomy for anterior LVO 0-24 hours after LKN, we correlated baseline core volume (rCBF < 30%) and the Alberta Stroke Program Early CT Scale (ASPECTS) score. We compared perfusion findings between patients with an unfavorable ASPECTS (<6) against those with a favorable ASPECTS (>/=6), and assessed findings over time. RESULTS: Of 485 enrolled patients, 177 met inclusion criteria (median age: 69 years, interquartile range [IQR: 57-81], 49% female, median ASPECTS 8 [IQR: 6-9], median core 10 cc [IQR: 0-30]). ASPECTS and core volume moderately correlated (r = -.37). A 0 cc core was observed in 54 (31%) patients, 70% of whom had ASPECTS <10. Of the 28 patients with ASPECTS <6, 3 (11%) had a 0 cc core. After adjustment for age and stroke severity, there was a lower ASPECTS for every 1 hour delay from LKN (cOR: 0.95, 95% confidence of interval [CI]: 0.91-1.00, P = .04). There was no difference in core (P = .51) or penumbra volumes (P = .87) across patients over time. CONCLUSIONS: In this multicenter prospective cohort of patients who underwent thrombectomy, one-third of patients had normal CTP core volumes despite nearly three quarters of patients showing ischemic changes on CT. This finding emphasizes the need to carefully assess both noncontrast and perfusion imaging when considering thrombectomy eligibility.

Neurology

Tsivgoulis G, Goyal N, Katsanos AH, Malhotra K, Ishfaq MF, Pandhi A, Frohler MT, Spiotta AM, Anadani M, Psychogios M, Maus V, Siddiqui A, Waqas M, Schellinger PD, Groen M, Krogias C, Richter D, Saqqur M, Garcia-Bermejo P, Mokin M, Leker R, Cohen JE, Magoufis G, Psychogios K, Lioutas VA, Van Nostrand M, Sharma VK, Paciaroni M, Rentzos A, Shoirah H, Mocco J, Nickele C, **Mitsias PD**, Inoa V, Hoit D, Elijovich L, Arthur AS, and Alexandrov AV. Intravenous thrombolysis for large vessel or distal occlusions presenting with mild stroke severity. *Eur J Neurol* 2020. Epub ahead of print. PMID: 32149450. Full Text

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BACKGROUND AND PURPOSE: We investigated the effectiveness of intravenous thrombolysis (IVT) in acute ischaemic stroke (AIS) patients with large vessel or distal occlusions and mild neurological deficits, defined as National Institutes of Health Stroke Scale scores < 6 points. METHODS: The primary efficacy outcome was 3-month functional independence (FI) [modified Rankin Scale (mRS) scores 0-2] that was compared between patients with and without IVT treatment. Other efficacy outcomes of interest included 3-month favorable functional outcome (mRS scores 0-1) and mRS score distribution at discharge and at 3 months. The safety outcomes comprised all-cause 3-month mortality, symptomatic intracranial hemorrhage (ICH), asymptomatic ICH and severe systemic bleeding. RESULTS: We evaluated 336 AIS patients with large vessel or distal occlusions and mild stroke severity (mean age 63 +/- 15 years, 45% women). Patients treated with IVT (n = 162) had higher FI (85.6% vs. 74.8%, P = 0.027) with lower mRS scores at hospital discharge (P = 0.034) compared with the remaining patients. No differences were detected in any of the safety outcomes including symptomatic ICH, asymptomatic ICH, severe systemic bleeding and 3-month mortality. IVT was associated with higher likelihood of 3-month FI [odds ratio (OR), 2.19; 95% confidence intervals (CI), 1.09-4.42], 3-month favorable functional outcome (OR, 1.99; 95% CI, 1.10-3.57), functional improvement at discharge [common OR (per 1-point decrease in mRS score), 2.94; 95% CI, 1.67-5.26)] and at 3 months (common OR, 1.72; 95% CI, 1.06-2.86) on multivariable logistic regression models adjusting for potential confounders, including mechanical thrombectomy. CONCLUSIONS: Intravenous thrombolysis is independently associated with higher odds of improved discharge and 3-month functional outcomes in AIS patients with large vessel or distal occlusions and mild stroke severity. IVT appears not to increase the risk of systemic or symptomatic intracranial bleeding.

Neurology

Venkat P, **Cui C**, **Chen Z**, **Chopp M**, **Zacharek A**, **Landschoot-Ward J**, **Culmone L**, **Yang XP**, **Xu J**, and **Chen J**. CD133+Exosome Treatment Improves Cardiac Function after Stroke in Type 2 Diabetic Mice. *Transl Stroke Res* 2020. Epub ahead of print. PMID: 32198711. Request Article

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Cardiac complications post-stroke are common, and diabetes exacerbates post-stroke cardiac injury. In this study, we tested whether treatment with exosomes harvested from human umbilical cord blood derived CD133+ cells (CD133+Exo) improves cardiac function in type 2 diabetes mellitus (T2DM) stroke mice. Adult (3-4 m), male, BKS.Cg-m+/+Lepr(db)/J (db/db, T2DM) and non-DM (db+) mice were randomized to sham or photothrombotic stroke groups. T2DM-stroke mice were treated with phosphate-buffered saline (PBS) or CD133+Exo (20 mug, i.v.) at 3 days after stroke. T2DM sham and T2DM+CD133+Exo treatment groups were included as controls. Echocardiography was performed, and mice were sacrificed at 28 days after stroke. Cardiomyocyte hypertrophy, myocardial capillary density, interstitial fibrosis, and inflammatory factor expression were

measured in the heart. MicroRNA-126 expression and its target gene expression were measured in the heart. T2DM mice exhibit significant cardiac deficits such as decreased left ventricular ejection fraction (LVEF) and shortening fraction (LVSF), increased left ventricular diastolic dimension (LVDD), and reduced heart rate compared to non-DM mice. Stroke in non-DM and T2DM mice significantly decreases LVEF compared to non-DM and T2DM-sham, respectively. Cardiac dysfunction is worse in T2DM-stroke mice compared to non-DM-stroke mice. CD133+Exo treatment of T2DM-stroke mice significantly improves cardiac function identified by increased LVEF and decreased LVDD compared to PBS treated T2DM-stroke mice. In addition, CD133+Exo treatment significantly decreases body weight and blood glucose but does not decrease lesion volume in T2DM-stroke mice. CD133+Exo treatment of T2DM mice significantly decreases body weight and blood glucose but does not improve cardiac function. CD133+Exo treatment in T2DM-stroke mice significantly decreases myocardial cross-sectional area, interstitial fibrosis, transforming growth factor beta (TGF-beta), numbers of M1 macrophages, and oxidative stress markers 4-HNE (4-hydroxynonenal) and NADPH oxidase 2 (NOX2) in heart tissue. CD133+Exo treatment increases myocardial capillary density in T2DM-stroke mice as well as upregulates endothelial cell capillary tube formation in vitro. MiR-126 is highly expressed in CD133+Exo compared to exosomes derived from endothelial cells. Compared to PBS treatment, CD133+Exo treatment significantly increases miR-126 expression in the heart and decreases its target gene expression such as Sprouty-related, EVH1 domain-containing protein 1 (Spred-1), vascular cell adhesion protein (VCAM), and monocyte chemoattractant protein 1 (MCP1) in the heart of T2DM-stroke mice. CD133+Exo treatment significantly improves cardiac function in T2DM-stroke mice. The cardio-protective effects of CD133+Exo in T2DM-stroke mice may be attributed at least in part to increasing miR-126 expression and decreasing its target protein expression in the heart, increased myocardial capillary density and decreased cardiac inflammatory factor expression.

Neurology

Viarasilpa T, **Panyavachiraporn N**, **Marashi SM**, **Van Harn M**, **Kowalski RG**, and **Mayer SA**. Prediction of Symptomatic Venous Thromboembolism in Critically Ill Patients: The ICU-Venous Thromboembolism Score. *Crit Care Med* 2020. Epub ahead of print. PMID: 32187076. Full Text

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OBJECTIVES: To identify risk factors and develop a prediction score for in-hospital symptomatic venous thromboembolism in critically ill patients. DESIGN: Retrospective cohort study. SETTING: Henry Ford Health System, a five-hospital system including 18 ICUs. PATIENTS: We obtained data from the electronic medical record of all adult patients admitted to any ICU (total 264 beds) between January 2015 and March 2018. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Symptomatic venous thromboembolism was defined as deep vein thrombosis, pulmonary embolism, or both, diagnosed greater than 24 hours after ICU admission and confirmed by ultrasound, CT, or nuclear medicine imaging. A prediction score (the ICU-Venous Thromboembolism score) was derived from independent risk factors identified using multivariable logistic regression. Of 37,050 patients who met the eligibility criteria, 529 patients (1.4%) developed symptomatic venous thromboembolism. The ICU-Venous Thromboembolism score consists of six independent predictors: central venous catheterization (5 points), immobilization greater than or equal to 4 days (4 points), prior history of venous thromboembolism (4 points), mechanical ventilation (2 points), lowest hemoglobin during hospitalization greater than or equal to 9 g/dL (2 points), and platelet count at admission greater than 250,000/muL (1 point). Patients with a score of 0-8 (76% of the sample) had a low (0.3%) risk of venous thromboembolism; those with a score of 9-14 (22%) had an intermediate (3.6%) risk of venous thromboembolism (hazard ratio, 6.7; 95% CI, 5.3-8.4); and those with a score of 15-18 (2%) had a high (17.7%) risk of venous thromboembolism (hazard ratio, 28.1; 95% CI, 21.7-36.5). The overall C-statistic of the model was 0.87 (95% CI, 0.85-0.88). CONCLUSIONS: Clinically diagnosed symptomatic venous thromboembolism occurred in 1.4% of this large population of ICU patients with high adherence to chemoprophylaxis. Central venous catheterization and immobilization are potentially modifiable risk factors for venous thromboembolism. The ICU-Venous Thromboembolism score can identify patients at increased risk for venous thromboembolism.

Neurology

Williams AM, Wu Z, Bhatti UF, Biesterveld BE, Kemp MT, Wakam GK, Vercruysse CA, Chtraklin K, Siddiqui AZ, Pickell Z, Dekker SE, Tian Y, Liu B, Li Y, **Buller B**, and Alam HB. Early Single-Dose Exosome Treatment Improves Neurologic Outcomes in a 7-Day Swine Model of Traumatic Brain Injury and Hemorrhagic Shock. *J Trauma Acute Care Surg* 2020. Epub ahead of print. PMID: 32218019. Full Text

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BACKGROUND: Early single-dose treatment with human mesenchymal stem cell (MSC)-derived exosomes promotes neuroprotection and promotes blood-brain barrier (BBB) integrity in models of traumatic brain injury (TBI) and hemorrhagic shock (HS) in swine. The impact of an early single dose of exosomes on late survival (7-day), however, remains unknown. We sought to evaluate the impact of early single-dose exosome treatment on neurologic outcomes, brain lesion size, inflammatory cytokines, apoptotic markers, and mediators of neural plasticity in a 7-day survival model. METHODS: Yorkshire swine were subjected to a severe TBI (8-mm cortical impact) and HS (40% estimated total blood volume). After one hour of shock, animals were randomized (n=4/cohort) to receive either lactated Ringer's (LR; 5mL) or LR + exosomes (LR+EXO; 1 x 10 exosome particles). After an additional hour of shock, animals were resuscitated with normal saline. Daily neurologic severity scores (NSS) were compared. At 7 days following injury, lesion size, inflammatory markers, and mediators of inflammation (NF-kappaB), apoptosis (BAX), and neural plasticity (BDNF) in brain tissue were compared between groups. RESULTS: Exosome-treated animals had significantly lower NSS (first 4 days; $p < 0.05$) and faster neurologic recovery. At 7-days, exosome-treated animals had significantly smaller ($p < 0.05$) brain lesion sizes. Exosome-treated animals also had significantly lower levels of inflammatory markers (IL-1, IL-6, IL-8, and IL-18) and higher granulocyte-macrophage colony stimulating factor (GM-CSF) levels compared to the control animals, indicating specific impacts on various cytokines. BAX and NF-kappaB levels were significantly lower ($p < 0.05$) in exosome-treated animals, while BDNF levels were significantly higher ($p < 0.05$) in the exosome-treated animals. CONCLUSIONS: In a large animal model of TBI and HS, early single-dose exosome treatment attenuates neurologic injury, decreases brain lesion size, inhibits inflammation and apoptosis, and promotes neural plasticity over a seven-day period. LEVEL OF EVIDENCE: Not applicable (pre-clinical study).

Neurology
Zafar SF, Subramaniam T, **Osman G**, Herlopian A, and Struck AF. Electrographic seizures and ictal-interictal continuum (IIC) patterns in critically ill patients. *Epilepsy Behav* 2020; 106. Epub ahead of print. PMID: 32222672. Full Text

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Critical care long-term continuous electroencephalogram (cEEG) monitoring has expanded dramatically in the last several decades spurned by technological advances in EEG digitalization and several key clinical findings: 1-Seizures are relatively common in the critically ill-large recent observational studies suggest that around 20% of critically ill patients placed on cEEG have seizures. 2-The majority (~75%) of patients who have seizures have exclusively "electrographic seizures", that is, they have no overt ictal clinical signs. Along with the discovery of the unexpectedly high incidence of seizures was the high prevalence of EEG patterns that share some common features with archetypical electrographic seizures but are not uniformly considered to be "ictal". These EEG patterns include lateralized periodic discharges (LPDs) and generalized periodic discharges (GPDs)-patterns that at times exhibit ictal-like behavior and at other times behave more like an interictal finding. Dr. Hirsch and colleagues proposed a conceptual framework to describe this spectrum of patterns called the ictal-interictal continuum (IIC). In the following years, investigators began to answer some of the key pragmatic clinical concerns such as which patients are at risk of seizures and what is the optimal duration of cEEG use. At the same time, investigators have begun probing the core questions for critical care EEG-what is the underlying pathophysiology of these patterns, at what point do these patterns cause secondary brain injury, what are the optimal treatment strategies, and how do these patterns affect clinical outcomes such as neurological disability and the development of epilepsy. In this review, we cover recent advancements in both practical concerns regarding cEEG use, current treatment strategies, and review the evidence associating IIC/seizures with poor clinical outcomes.

Neurology
Zheng Z, **Chopp M**, and **Chen J**. Multifaceted roles of pericytes in central nervous system homeostasis and disease. *J Cereb Blood Flow Metab* 2020. Epub ahead of print. PMID: 32208803. Full Text

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Neurosurgery
Barzilai O, **Robin AM**, O'Toole JE, and Laufer I. Minimally Invasive Surgery Strategies: Changing the Treatment of Spine Tumors. *Neurosurg Clin N Am* 2020; 31(2):201-209. PMID: 32147011. Full Text

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Innovation in surgical technique and contemporary spinal instrumentation paired with intraoperative navigation/imaging concepts allows for safer and less-invasive surgical approaches. The combination of stereotactic body radiotherapy, contemporary surgical adjuncts, and less-invasive techniques serves to minimize blood loss, soft tissue injury, and length of hospital stay without compromising surgical efficacy, potentially enabling patients to begin adjuvant treatment sooner.

Neurosurgery

Puduvalli VK, Wu J, Yuan Y, Armstrong TS, Vera E, Wu J, Xu J, Giglio P, Colman H, **Walbert T**, Raizer J, Groves MD, Tran D, Iwamoto F, Avgeropoulos N, Paleologos N, Fink K, Peereboom D, Chamberlain M, Merrell R, Penas Prado M, Yung WKA, and Gilbert MR. A Bayesian Adaptive Randomized Phase II Multicenter Trial of Bevacizumab with or without Vorinostat in Adults with Recurrent Glioblastoma. *Neuro Oncol* 2020. Epub ahead of print. PMID: 32166308. Full Text

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BACKGROUND: Bevacizumab has promising activity against recurrent glioblastoma (GBM). However, acquired resistance to this agent results in tumor recurrence. We hypothesized that vorinostat, a histone deacetylase (HDAC) inhibitor with antiangiogenic effects, would prevent acquired resistance to bevacizumab. METHODS: This multicenter phase II trial used a Bayesian adaptive design to randomize patients with recurrent GBM to bevacizumab alone or bevacizumab plus vorinostat with the primary endpoint of progression-free survival (PFS) and secondary end points of overall survival (OS) and clinical outcomes assessment (MDASI-BT). Eligible patients were adults (>/=18 yrs) with histologically confirmed GBM recurrent after prior radiation therapy, with adequate organ function, KPS>/=60, and no prior bevacizumab or HDAC inhibitors. RESULTS: Ninety patients (bevacizumab+vorinostat:49, bevacizumab:41) were enrolled of whom 74 were evaluable for PFS (bevacizumab+vorinostat:44, bevacizumab:30). Median PFS (3.7 vs 3.9 months, p=0.94, HR 0.63 [95% CI 0.38, 1.06, p=0.08]), median OS (7.8 vs 9.3 months, p=0.64, HR 0.93 [95% CI 0.5, 1.6, p=0.79]) and clinical benefit were similar between the two arms. Toxicity (>/=grade 3) in 85 evaluable patients included hypertension (n=37), neurological changes (n=2), anorexia (n=2), infections (n=9), wound dehiscence (n=2), DVT/PE (n=2), and colonic perforation (n=1). CONCLUSIONS: Bevacizumab combined with vorinostat did not yield improvement in PFS, OS or clinical benefit compared with bevacizumab alone nor a clinical benefit in adults with recurrent GBM. This trial is the first to test a Bayesian adaptive design with adaptive randomization and Bayesian continuous monitoring in patients with primary brain tumor and demonstrates the feasibility of using complex Bayesian adaptive design in a multicenter setting.

Nursing

Kitajima T, **Nagai S**, **Segal A**, **Magee M**, **Blackburn S**, **Ellithorpe D**, **Yeddula S**, **Qadeer Y**, **Yoshida A**, **Moonka D**, **Brown K**, and **Abouljoud MS**. Posttransplant Complications Predict Alcohol Relapse in Liver Transplant Recipients. *Liver Transpl* 2020; 26(3):379-389. PMID: 31872969. Full Text

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Alcohol relapse after liver transplantation (LT) in patients with alcohol-related liver disease (ALD) is a major challenge. Although its association with pretransplant psychosocial factors was extensively studied, the impacts of posttransplant courses on alcohol relapse have not been well investigated. The aim of this study is to analyze peritransplant factors associated with

posttransplant alcohol relapse in patients with ALD. This study evaluated 190 adult LT patients with ALD from 2013 to 2019. Risk factors for alcohol relapse were analyzed, focusing on posttransplant chronic complications, which were classified as Clavien-Dindo classification 3a or higher that lasted over 30 days. The posttransplant alcohol relapse rate was 13.7% (26/190) with a median onset time of 18.6 months after transplant. Multivariate Cox regression analysis revealed that posttransplant chronic complications were an independent risk factor for posttransplant alcohol relapse (hazard ratio [HR], 5.40; P = 0.001), along with psychiatric comorbidity (HR, 3.93; P = 0.001), history of alcohol relapse before LT (HR, 3.00; P = 0.008), and an abstinence period <1.5 years (HR, 12.05; P = 0.001). A risk prediction model was created using 3 pretransplant risk factors (psychiatric comorbidity, alcohol relapse before LT, and abstinence period <1.5 years). This model clearly stratified the risk of alcohol relapse into high-, moderate-, and low-risk groups (P < 0.001). Of the 26 patients who relapsed, 11 (42.3%) continued drinking, of whom 3 died of severe alcoholic hepatitis, and 13 (50.0%) achieved sobriety (outcomes for 2 patients were unknown). In conclusion, posttransplant chronic complications increased the risk of alcohol relapse. Recognition of posttransplant chronic complications in conjunction with the risk stratification model by pretransplant psychosocial factors would help with the prediction of posttransplant alcohol relapse.

Obstetrics, Gynecology and Women's Health Services

Saad F, **Ayyash M**, Ayyash M, Elhage N, Ali I, Makki M, Hamade H, and Blackwood RA. Assessing Knowledge, Physician Interactions and Patient-Reported Barriers to Colorectal Cancer Screening Among Arab Americans in Dearborn, Michigan. *J Community Health* 2020. Epub ahead of print. PMID: 32189212. Full Text

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Colorectal cancer (CRC) is the second leading cause of cancer related deaths among men and women in the United States (Haggar and Boushey in Clin Colon Rectal Surg 22:191-197, 2009). Screening tests have shown to be successful at early detection of precancerous polyps. Between 2000 and 2010, there was a 72% growth in the population that identifies having an Arabic-speaking ancestry (Arab American Institute in https://www.aaiusa.org/demographics, 2011). Despite this, little research has been conducted to assess this unique community's knowledge regarding CRC. Given that low screening rates can be attributed to lack of knowledge, this study was designed to address CRC knowledge and screening barriers in an Arab American community. Between February 2016 and June 2017, an anonymous survey was conducted in English or Arabic among 131 patients from cancer programs at the Arab Community Center for Economic and Social Services (ACCESS) in Dearborn, MI. Program participants were expected to have greater insight and awareness about cancer risk than the general population. Knowledge deficiencies surrounding CRC and the screening process were identified. 70% of participants did not know what a colon polyp is and over 89% were not aware of their individual risk for CRC. 45.8% have never had a CRC screening and leading barriers included screening costs, lack of health insurance, and lack of advice by physicians. The goal of this study was to serve as a tool to healthcare providers by identifying evident gaps in medical knowledge surrounding CRC. In order to help better serve and educate patients, healthcare providers and community organizations are encouraged to fight the stigma and help to reduce misunderstandings.

Orthopedics/Bone and Joint

Georgiadis AG, **Muh SJ**, **Silverton CD**, **Weir RM**, and Laker MW. Response to Letter to the Editor on "A Prospective Double-Blind Placebo Controlled Trial of Topical Tranexamic Acid in Total Knee Arthroplasty". *J Arthroplasty* 2020; 35(4):1161-1162. PMID: 31902613. Full Text

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Orthopedics/Bone and Joint

Jildeh TR, **Taylor KA**, **Tramer JS**, **Khalil LS**, Hasan L, **Okoroha KR**, and **Moutzouros V**. Risk Factors for Postoperative Opioid Use in Arthroscopic Shoulder Labrum Surgery. *Arthroscopy* 2020. Epub ahead of print. PMID: 32200066. Full Text

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PURPOSE: The purpose of this study was to determine the correlation between pre- and postoperative opioid use in patients undergoing arthroscopic shoulder labral repair, as well as patient risk factors associated with increased postoperative opioid use following the procedure. METHODS: A retrospective review of all patients undergoing arthroscopic shoulder labral surgery at a single institution between August 2013 and November 2017 was performed. Patients were stratified as opioid nonusers, acute users, or chronic users based on preoperative consumption. Patient demographics, injury characteristics, surgical interventions, and postoperative opioid use for the first 12 months after surgery were then analyzed. RESULTS: A total of 340 patients were included in this study. The average age was 26.3 years old (range 13-68) and the average body mass index was 27.5 kg/m(2) (range 18.4-45.0). Preoperative opioid users (acute and chronic) were found to continue to receive opioid medications at extended time points beyond 2 months postoperatively compared to non-users (P < .001). Patients with intraoperatively identified SLAP tears experienced more preoperative pain, and required greater postoperative opioid prescriptions (P <.018). When stratifying for other common shoulder instability injury patterns, there were no differences between the number of postoperative opioid prescriptions filled and presence of Bankart, Hill Sachs, Reverse Hill Sachs, anterior labroligamentous periosteal sleeve avulsion, glenolabral articular disruption, or humeral avulsion of the glenohumeral ligament lesions, (P > .05). CONCLUSIONS: In patients undergoing arthroscopic labral surgery, the chronicity of preoperative opioid use, number of concomitant procedures at the time of initial surgery, and presence of biceps tenodesis were found to significantly increase postoperative opioid demand. Orthopaedic surgeons should recognize risk factors for increased opioid use postoperatively and adapt treatment strategies and patient counseling accordingly.

Orthopedics/Bone and Joint
Makhni EC, **Gulledge CM**, **Kuhlmann NA**, and **Muh SJ**. Open Acromioclavicular Joint Reconstruction With Semitendinosus Allograft Utilizing the Cerclage Technique. *Arthroscopy Techniques* 2020. Epub ahead of print. Full Text

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Acromioclavicular (AC) joint injuries most commonly occur in young males after a direct injury at the acromion. General consensus stresses nonoperative treatment for type I and II injuries and surgical treatment for types IV through VI, whereas management of type III injuries is more controversial. If surgery is indicated, there are multiple techniques including hook plate, screw fixation, coracoclavicular fixation, and anatomic and nonanatomic reconstruction. The overall complication rate is high (14%), regardless of technique. In this Technical Note, we outline a technique for open repair of a chronic AC joint separation using a semitendinosus allograft using the cerclage for enhanced fixation.

Orthopedics/Bone and Joint
Patel BH, **Okoroha KR**, **Jildeh TR**, Lu Y, Baker JD, Nwachukwu BU, Foster MG, Allen AA, and Forsythe B. Adductor injuries in the National Basketball Association: an analysis of return to play and player performance from 2010 to 2019. *Phys Sportsmed* 2020:1-8. PMID: 32202444. Request Article

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Objectives: 1) To evaluate return to play (RTP) timing in National Basketball Association (NBA) athletes following adductor injuries, and 2) to evaluate the effect of adductor injuries on player performance, game availability, and career longevity following RTP.Methods: Adductor injuries in NBA athletes from the 2009-2010 to 2018-2019 seasons were identified utilizing publicly available records via previously validated methodology. RTP time was calculated, and player performance and game availability were compared pre- vs. post-injury. Additionally, an injury-free control group matched for age, BMI, position, and experience was assembled to allow for comparisons in performance, availability, and career length.Results: In total, 79 adductor injuries across 65 NBA athletes were identified. The average injured player was 28.3 +/- 4.0 years of age, and had 6.5 +/- 4.2 seasons of NBA experience. Guards were injured more frequently than forwards or centers (49% vs 25% vs 25%, respectively). All players were able to RTP following first-time adductor injury after missing an average of 7.7 +/- 9.8 games (median [IQR]: 4 [1-9]) and 16.9 +/- 20.4 days (median [IQR]: 9 [3.5-20]). Twelve players (18.5%) suffered an adductor re-injury at a mean latency of 509.5 +/- 503.9 days. Adductor injuries did not result in significant changes in any major statistical category (points, assists, rebounds, steals, blocks, turnovers, field goal percentage), player efficiency rating (PER), minutes/game, games/season, or a number of all-star selections (all P > 0.05) following RTP. Additionally, when compared to

matched controls, no difference was found in pre- to post-injury change of PER, games/season, or minutes/game (all P > 0.05). Career longevity was not significantly different between groups (P = 0.44).Conclusion: Following adductor injury, NBA players returned to gameplay after missing an average of 16 to 17 days, or 7 to 8 games. Adductor injury did not affect player performance, nor game availability or career longevity.

Orthopedics/Bone and Joint
Weber AE, Alluri RK, **Makhni EC**, Bolia IK, Mayer EN, Harris JD, and Nho SJ. Anatomic Evaluation of the Interportal Capsulotomy Made with the Modified Anterior Portal versus Standard Anterior Portal: Comparable Utility with Decreased Capsule Morbidity. *Hip Pelvis* 2020; 32(1):42-49. PMID: 32158728. Full Text

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Purpose: To identify potential differences in interportal capsulotomy size and cross-sectional area (CSA) using the anterolateral portal (ALP) and either the: (i) standard anterior portal (SAP) or (ii) modified anterior portal (MAP). Materials and Methods: Ten cadaveric hemi pelvis specimens were included. A standard arthroscopic ALP was created. Hips were randomized to SAP (n=5) or MAP (n=5) groups. The spinal needle was placed at the center of the anterior triangle or directly adjacent to the ALP in the SAP and MAP groups, respectively. A capsulotomy was created by inserting the knife through the SAP or MAP. The length and width of each capsulotomy was measured using digital calipers under direct visualization. The CSA and length of the capsulotomy as a percentage of total iliofemoral ligament (IFL) side-to-side width were calculated. Results: There were no differences in mean cadaveric age, weight or IFL dimensions between the groups. Capsulotomy CSA was significantly larger in the SAP group compared with the MAP group (SAP 2.16+/-0.64 cm(2) vs. MAP 0.65+/-0.17 cm(2), P=0.008). Capsulotomy length as a percentage of total IFL width was significantly longer in the SAP group compared with the MAP group (SAP 74.2+/-14.1% vs. MAP 32.4+/-3.7%, P=0.008). Conclusion: The CSA of the capsulotomy and the percentage of the total IFL width disrupted are significantly smaller when the interportal capsulotomy is performed between the ALP and MAP portals, compared to the one created between the ALP and SAP. Surgeons should be aware of this fact when performing hip arthroscopy.

Otolaryngology
Iwata AJ, **Chang SS**, **Ghanem TA**, and **Singer MC**. In Response to Regarding Surgical Impact of a Dedicated Endocrine Surgeon on an Academic Otolaryngology Department. *Laryngoscope* 2020. Epub ahead of print. PMID: 32216099. Full Text

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Pathology
Gestrich C, **Cowden D**, and Harbhajanka A. Cytomorphology of glioblastoma metastic to a cervical lymph node diagnosed by fine needle aspiration (FNA): A case report and review of literature. *Diagn Cytopathol* 2020. PMID: 32160396. Full Text

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Glioblastoma is an aggressive primary central nervous system tumor with a dismal prognosis. However, extracranial metastases are extremely rare. Very few cases have been reported in the literature. We present a case of a 64-year-old male with glioblastoma metastatic to a cervical lymph node in which the diagnosis was made on fine needle aspiration cytology (FNAC). The cytomorphologic features of glioblastoma are distinct, with pleomorphic cells in loosely cohesive clusters with prominent nucleoli, coarsely clumped chromatin and cellular processes. We suggest that FNAC, along with clinical history, is a cost effective, safe, and diagnostically accurate method of diagnosing glioblastoma metastases. Cell block is also helpful in establishing the diagnosis.

Pathology
Jebastin Thangaiah J, Vickery J, Selwanes W, Al-Haddad E, **Perry KD**, **Palanisamy N**, Poulik JM, **Williamson SR**, **Chitale DA**, and Shehata BM. A Novel COL1A1-CAMTA1 Rearrangement in Cranial Fasciitis. *Int J Surg Pathol* 2020. Epub ahead of print. PMID: 32192385. Full Text

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Cranial fasciitis is an uncommon benign fibroblastic tumor, generally histologically identical to nodular fasciitis. It develops almost exclusively in children. Cranial fasciitis manifests clinically as a painless rapidly growing solitary nodule in the head and neck area, frequently eroding the underlying bone. Thus, this entity is often confused with aggressive lesions such as sarcomas, both clinically and radiologically. Histopathologic examination is essential to differentiate between cranial fasciitis and fibrohistiocytic or even sarcomatous lesions observed in children. In this article, we present a case of cranial fasciitis with intracranial extension in a 2-year-old boy. Although USP6 rearrangement has recently been recognized as a recurring alteration in nodular fasciitis, we present a novel COL1A1-CAMTA1 fusion in this lesion.

Pharmacy
Alosaimy S, Jorgensen SCJ, Lagnf AM, Melvin S, Mynatt RP, Carlson TJ, Garey KW, Allen D, Venugopalan V, Veve M, Athans V, Saw S, Yost CN, **Davis SL**, and Rybak MJ. Real-world Multicenter Analysis of Clinical Outcomes and Safety of Meropenem-Vaborbactam in Patients Treated for Serious Gram-Negative Bacterial Infections. *Open Forum Infect Dis* 2020; 7(3): 051. PMID: 32161775. Request Article

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Fourty patients were treated with meropenem-vaborbactam (MEV) for serious Gram-negative bacterial (GNB) infections. Carbapenem-resistant Enterobacteriaceae (CRE) comprised 80.0% of all GNB infections. Clinical success occurred in 70.0% of patients. Mortality and recurrence at 30 days were 7.5% and 12.5%, respectively. One patient experienced a probable rash due to MEV.

Pharmacy
Wagner JL, Carreno JJ, **Kenney RM**, **Kilgore PE**, and **Davis SL**. Antimicrobial Stewardship Metrics that Matter. *Infectious Diseases in Clinical Practice* 2020; 28(2):89-93. Full Text

J.L. Wagner, Department of Pharmacy Practice, School of Pharmacy, University of Mississippi, 2500 N State St, Jackson, MS, United States

Background Guidelines for antimicrobial stewardship programs (ASPs) highlight the need for measuring quality metrics as surrogate markers for outcome. The objective of this study was to determine the relationship between ASP quality metrics and patient outcomes at an institution with an established ASP. Methods Retrospective cohort study including 442 patients receiving intravenous antibiotics for 72 hours or more in 1 of 3 designated inpatient units were assessed for compliance with ASP metrics and associated outcomes. Clinical success was defined as discharged alive, without adverse drug reaction and not readmitted within 30 days of discharge. Results The mean (SD) age was 62 (17) years with 205 males (46%) enrolled. A total of 422 patients (96%) had documented indication for therapy, 365 (83%) had appropriate cultures obtained at baseline, 354 (80%) had appropriate empiric therapy at baseline, and 166 (83%) of 199 had appropriate deescalation performed. All metrics were met in 58% of patients. Sixty-two percent of patients achieved clinical success; while, 14% died, 13% had an adverse drug reaction, and 21% were readmitted within 30 days. Completion of all ASP metrics was not associated with clinical success (odds ratio, 0.862; P = 0.46). Documentation of indication for therapy was a significant indicator for clinical success (97.8% vs 91.7%; P = 0.003); this remained associated after adjusting for infection type and severity. Conclusions Documented indication showed strong association with clinical success, providing support for use of the Centers for Disease Control's Core Elements as a metric for quality of care.

Plastic Surgery
Mundy LR, Rosenberger LH, Rushing CN, **Atisha D**, Pusic AL, Hollenbeck ST, Hyslop T, and Hwang ES. The Evolution of Breast Satisfaction and Well-Being after Breast Cancer: A Propensity-Matched Comparison to the Norm. *Plast Reconstr Surg* 2020; 145(3):595-604. PMID: 32097289. Full Text

Durham, N.C.; Detroit, Mich.; and Boston, Mass. From the Divisions of Plastic and Reconstructive Surgery and Surgical Oncology, Department of Surgery, Duke University Medical Center; the Department of Biostatistics and Bioinformatics, Duke

Cancer Institute, Duke University; the Division of Plastic Surgery, Henry Ford Health System; and the Division of Plastic Surgery, Depart PRS-D-19-00046 ment of Surgery, Brigham and Women's Hospital.

BACKGROUND: Breast cancer survival continues to improve, with women living longer after treatment. It is not well understood how long-term satisfaction and well-being differ following treatment or how types of reconstruction differ when compared to the norm. METHODS: In a propensity-matched sample, the authors compared patient-reported outcomes in breast cancer patients at various time intervals from surgery with normative BREAST-Q data. All data were obtained using the Army of Women, an online community fostering breast cancer research. Breast cancer patients were stratified by surgical treatment and reconstruction type. Regression lines were estimated and differences in slope tested between cancer patients and noncancer controls. RESULTS: The authors compared normative (n = 922) and breast cancer (n = 4343) cohorts in a propensity-matched analysis. Among the breast cancer patients, 49.4 percent underwent lumpectomy, 17.0 percent underwent mastectomy, 21.7 percent underwent implant reconstruction, and 11.9 percent underwent autologous reconstruction. Median time since surgery was 4.7 years, with 21.1 percent more than 10 years after surgery. At the time of survey, breast cancer patients reported higher Satisfaction with Breasts and Psychosocial Well-being scores compared to noncancer controls ($p < 0.01$), with the cohorts undergoing lumpectomy and autologous reconstruction both reporting higher scores than the normative controls. After mastectomy, scores averaged lower than the noncancer controls, but improved over time. However, all breast cancer groups reported significantly lower Physical Well-being scores than the noncancer cohort (all $p < 0.01$). CONCLUSIONS: Breast cancer patients undergoing lumpectomy or autologous reconstruction reported higher psychosocial well-being compared to noncancer controls. These differences were influenced both by time since treatment and by choice of surgical procedure.

Public Health Sciences
Arena SK, Wilson CM, and **Peterson E**. Targeted Population Health Utilizing Direct Referral to Home-Based Older Person Upstreaming Prevention Physical Therapy from a Community-Based Senior Center. *Cardiopulmonary Physical Therapy Journal* 2020; 31(1):11-21. Full Text

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Purpose:An older adult's ability to remain safe and active in the community is multifactorial and includes physical and social determinants. The purpose of this study is to describe outcomes of the Home-Based Older Person Upstreaming Prevention Physical Therapy program targeted toward older adults referred from one community senior center.Methods:Older adults identified as "at risk" for decline or becoming homebound were referred by senior center staff. Home-Based Older Person Upstreaming Prevention Physical Therapy is a 6-month in-home preventative program entailing 6 in-person and 3 telehealth visits administered by a physical therapist (PT). Wellness, cardiovascular health, social integration, and frailty metrics resulted in interventions inclusive of cardiovascular and balance exercises, home safety, and community reintegration.Results:Participants (n = 30) demonstrated significant improvements in: Timed Up and Go (P =.02), Four Stage Balance Test (P =.003), STEADI Fall Risk Level (P =.002), Home FAST Assessment (P =.001), self-reported fear of falling (P =.001), Modified Falls Efficacy Scale (P =.01), and a Health Behavior Questionnaire (physical activity [P =.03], fruit and vegetable consumption [P =.03], and recommended weight [P =.01]).Conclusion:Home-Based Older Person Upstreaming Prevention Physical Therapy provided early access to preventative PT services in the homes of older adults. Positive functional, environmental, fall risk, and wellness outcomes were achieved when leveraging direct referral partnerships between community senior centers and PTs.

Public Health Sciences
Bryson TD, **Pandrangi TS**, **Khan SZ**, **Xu J**, **Pavlov TS**, **Ortiz PA**, **Peterson E**, and **Harding P**. The deleterious role of the prostaglandin E2 EP3 receptor in angiotensin II hypertension. *Am J Physiol Heart Circ Physiol* 2020; 318(4):H867-H882. PMID: 32142358. Full Text

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Angiotensin II (ANG II) plays a key role in regulating blood pressure and inflammation. Prostaglandin E2 (PGE2) signals through four different G protein-coupled receptors, eliciting a variety of effects. We reported that activation of the EP3 receptor reduces cardiac contractility. More recently, we have shown that overexpression of the EP4 receptor is protective in a mouse myocardial infarction model. We hypothesize in this study that the relative abundance of EP3 and EP4 receptors is a major determinant of end-organ damage in the diseased heart. Thus EP3 is detrimental to cardiac function and promotes inflammation, whereas antagonism of the EP3 receptor is protective in an ANG II hypertension (HTN) model. To test our hypothesis, male 10- to 12-wk-old C57BL/6 mice were anesthetized with isoflurane and osmotic minipumps containing ANG II were implanted subcutaneously for 2 wk. We found that antagonism of the EP3 receptor using L798,106 significantly attenuated the increase in blood pressure with ANG II infusion. Moreover, antagonism of the EP3 receptor prevented a decline

in cardiac function after ANG II treatment. We also found that 10- to 12-wk-old EP3-transgenic mice, which overexpress EP3 in the cardiomyocytes, have worsened cardiac function. In conclusion, activation or overexpression of EP3 exacerbates end-organ damage in ANG II HTN. In contrast, antagonism of the EP3 receptor is beneficial and reduces cardiac dysfunction, inflammation, and HTN.NEW & NOTEWORTHY This study is the first to show that systemic treatment with an EP3 receptor antagonist (L798,106) attenuates the angiotensin II-induced increase in blood pressure in mice. The results from this project could complement existing hypertension therapies by combining blockade of the EP3 receptor with antihypertensive drugs.

Public Health Sciences
Davatzikos C, Barnholtz-Sloan JS, Bakas S, Colen R, Mahajan A, Quintero CB, Font JC, Puig J, Jain R, Sloan AE, Badve C, Marcus DS, Choi YS, Lee SK, Chang JH, **Poisson LM**, **Griffith B**, Dicker AP, Flanders AE, Booth TC, Rathore S, Akbari H, Sako C, Bilello M, Shukla G, Kazerooni AF, Brem S, Lustig R, Mohan S, Bagley S, Nasrallah M, and O'Rourke DM. AI-based Prognostic Imaging Biomarkers for Precision Neurooncology: the ReSPOND Consortium. *Neuro Oncol* 2020. Epub ahead of print. PMID: 32152622. Full Text

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Public Health Sciences
Garman L, Pezant N, Pastori A, Savoy KA, Li C, **Levin AM**, Iannuzzi MC, **Rybicki BA**, **Adrianto I**, and Montgomery CG. Genome-Wide Association Study of Ocular Sarcoidosis Confirms HLA Associations and Implicates Barrier Function and Autoimmunity in African Americans. *Ocul Immunol Inflamm* 2020:1-6. PMID: 32141793. Request Article

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Purpose: Identify genes associated with ocular sarcoidosis (OS).Methods: We genotyped 1.1 million genetic variants to identify significant OS associations, defined as those that achieved $p < 5 \times 10(-8)$ in a genome-wide comparison of OS cases to healthy controls in our European- or African-American cohorts (EA, AA). Potential functional roles of all associated variants were assessed.Results: Eight significant non-HLA variants were found in AA OS cases compared to healthy controls and confirmed as at least suggestive when comparing OS to non-OS cases. Seven of these were within MAGI1 and include transcription factor binding sites and expression quantitative trait loci. Our EA cohort, while showing similar effect sizes at variants within MAGI1, had no significant variants. Association analysis of HLA-DRB1 alleles confirmed association to OS in EA to *04:01.Conclusion: Our results support organ-specific genetic risk in OS in a compelling candidate, MAGI1, known to be associated with barrier function and autoimmunity.

Public Health Sciences

Viarasilpa T, **Panyavachiraporn N**, **Marashi SM**, **Van Harn M**, **Kowalski RG**, and **Mayer SA**. Prediction of Symptomatic Venous Thromboembolism in Critically Ill Patients: The ICU-Venous Thromboembolism Score. *Crit Care Med* 2020. Epub ahead of print. PMID: 32187076. Full Text

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OBJECTIVES: To identify risk factors and develop a prediction score for in-hospital symptomatic venous thromboembolism in critically ill patients. DESIGN: Retrospective cohort study. SETTING: Henry Ford Health System, a five-hospital system including 18 ICUs. PATIENTS: We obtained data from the electronic medical record of all adult patients admitted to any ICU (total 264 beds) between January 2015 and March 2018. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: Symptomatic venous thromboembolism was defined as deep vein thrombosis, pulmonary embolism, or both, diagnosed greater than 24 hours after ICU admission and confirmed by ultrasound, CT, or nuclear medicine imaging. A prediction score (the ICU-Venous Thromboembolism score) was derived from independent risk factors identified using multivariable logistic regression. Of 37,050 patients who met the eligibility criteria, 529 patients (1.4%) developed symptomatic venous thromboembolism. The ICU-Venous Thromboembolism score consists of six independent predictors: central venous catheterization (5 points), immobilization greater than or equal to 4 days (4 points), prior history of venous thromboembolism (4 points), mechanical ventilation (2 points), lowest hemoglobin during hospitalization greater than or equal to 9 g/dL (2 points), and platelet count at admission greater than 250,000/muL (1 point). Patients with a score of 0-8 (76% of the sample) had a low (0.3%) risk of venous thromboembolism; those with a score of 9-14 (22%) had an intermediate (3.6%) risk of venous thromboembolism (hazard ratio, 6.7; 95% CI, 5.3-8.4); and those with a score of 15-18 (2%) had a high (17.7%) risk of venous thromboembolism (hazard ratio, 28.1; 95% CI, 21.7-36.5). The overall C-statistic of the model was 0.87 (95% CI, 0.85-0.88). CONCLUSIONS: Clinically diagnosed symptomatic venous thromboembolism occurred in 1.4% of this large population of ICU patients with high adherence to chemoprophylaxis. Central venous catheterization and immobilization are potentially modifiable risk factors for venous thromboembolism. The ICU-Venous Thromboembolism score can identify patients at increased risk for venous thromboembolism.

Public Health Sciences

Wallace K, Zhang S, Thomas L, Stewart EA, Nicholson WK, **Wegienka GR**, Wise LA, Laughlin-Tommaso SK, Diamond MP, Marsh EE, Jacoby VL, Anchan RM, Venable S, Larry GM, Lytle B, Wang T, and Myers ER. Comparative effectiveness of hysterectomy versus myomectomy on one-year health-related quality of life in women with uterine fibroids. *Fertil Steril* 2020; 113(3):618-626. PMID: 32192594. Full Text

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Duke Clinical Research Institute, Duke University Medical Center; and Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, North Carolina.

OBJECTIVE: To compare long-term health-related quality of life (HRQOL) 1 year after hysterectomy or myomectomy for treatment of uterine fibroids (UFs) and to determine whether route of procedure, race, or age affected improvements in HRQOL. DESIGN: Prospective cohort study. SETTING: Eight clinical sites throughout the United States. PATIENT(S): A total of 1,113 premenopausal women with UFs who underwent hysterectomy or myomectomy as part of Comparing Options for

Management: Patient-Centered Results for Uterine Fibroids. INTERVENTION(S): None. MAIN OUTCOME MEASURE (S): Self-reported HRQOL measures including Uterine Fibroid Symptom Quality of Life, the European QOL 5 Dimension Health Questionnaire, and the visual analog scale at baseline and 1-year after hysterectomy or myomectomy. RESULT (S): Hysterectomy patients were older with a longer history of symptomatic UF compared with myomectomy patients. There were no differences in baseline HRQOL. After adjustment for baseline differences between groups, compared with myomectomy, patients' HRQOL (95% confidence interval [CI], 5.4, 17.2) and symptom severity (95% CI, -16.3, -8.8) were significantly improved with hysterectomy. When stratified across race/ethnicity and age, hysterectomy had higher HRQOL scores compared with myomectomy. There was little difference in HRQOL (95% CI, 0.1 [-9.5, 9.6]) or symptom severity (95% CI, -3.4 [-10, 3.2]) between abdominal hysterectomy and abdominal myomectomy. CONCLUSION (S): HRQOL improved in all women 1 year after hysterectomy or myomectomy. Hysterectomy patients reported higher HRQOL summary scores compared with myomectomy patients. When stratified by route, minimally invasive hysterectomy had better HRQOL scores than minimally invasive myomectomy. There was little difference in scores with abdominal approaches.

Pulmonary

Al Feghali KA, **Wu QC**, **Devpura S**, **Liu C**, **Ghanem AI**, **Wen NW**, **Ajlouni M**, **Simoff MJ**, **Movsas B**, and **Chetty IJ**. Correlation of normal lung density changes with dose after stereotactic body radiotherapy (SBRT) for early stage lung cancer. *Clin Transl Radiat Oncol* 2020; 22:1-8. PMID: 32140574. Full Text

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Background and Purpose: To investigate the correlation between normal lung CT density changes with dose accuracy and outcome after stereotactic body radiation therapy (SBRT) for patients with early stage non-small-cell lung cancer (NSCLC). Materials and Methods: Thirty-one patients (with a total of 33 lesions) with non-small cell lung cancer were selected out of 270 patients treated with SBRT at a single institution between 2003 and 2009. Out of these 31 patients, 10 patients had developed radiation pneumonitis (RP). Dose distributions originally planned using a 1-D pencil beam-based dose algorithm were retrospectively recomputed using different algorithms. Prescription dose was 48 Gy in 4 fractions in most patients. Planning CT images were rigidly registered to follow-up CT datasets at 3-9 months after treatment. Corresponding dose distributions were mapped from planning to follow-up CT images. Hounsfield Unit (HU) changes in lung density in individual, 5 Gy, dose bins from 5 to 45 Gy were assessed in the peri-tumoral region. Correlations between HU changes in various normal lung regions, dose indices (V20, MLD, generalized equivalent uniform dose (gEUD)), and RP grade were investigated. Results: Strong positive correlation was found between HU changes in the peri-tumoral region and RP grade (Spearman's $r = 0.760$; $p < 0.001$). Positive correlation was also observed between RP and HU changes in the region covered by V20 for all algorithms (Spearman's $r >/= 0.738$; $p < 0.001$). Additionally, V20, MLD, and gEUD were significantly correlated with RP grade ($p < 0.01$). MLD in the peri-tumoral region computed with model-based algorithms was 5-7% lower than the PB-based methods. Conclusion: Changes of lung density in the peri-tumoral lung and in the region covered by V20 were strongly associated with RP grade. Relative to model-based methods, PB algorithms over-estimated mean peri-tumoral dose and showed displacement of the high-dose region, which correlated with HU changes on follow-up CT scans.

Pulmonary

Duong TB, Ceglar S, **Reaume M**, and Lee C. Imaging Approach to Cavitary Lung Disease. *Ann Am Thorac Soc* 2020; 17(3):367-371. PMID: 32108500. Full Text

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Radiation Oncology

Al Feghali KA, **Wu QC**, **Devpura S**, **Liu C**, **Ghanem AI**, **Wen NW**, **Ajlouni M**, **Simoff MJ**, **Movsas B**, and **Chetty IJ**. Correlation of normal lung density changes with dose after stereotactic body radiotherapy (SBRT) for early stage lung cancer. *Clin Transl Radiat Oncol* 2020; 22:1-8. PMID: 32140574. Full Text

Department of Radiation Oncology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI, USA.
Department of Clinical Oncology, Alexandria University, Alexandria, Egypt.
Department of Internal Medicine, Division of Interventional Pulmonology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI, USA.

Background and Purpose: To investigate the correlation between normal lung CT density changes with dose accuracy and outcome after stereotactic body radiation therapy (SBRT) for patients with early stage non-small-cell lung cancer (NSCLC). Materials and Methods: Thirty-one patients (with a total of 33 lesions) with non-small cell lung cancer were selected out of 270

patients treated with SBRT at a single institution between 2003 and 2009. Out of these 31 patients, 10 patients had developed radiation pneumonitis (RP). Dose distributions originally planned using a 1-D pencil beam-based dose algorithm were retrospectively recomputed using different algorithms. Prescription dose was 48 Gy in 4 fractions in most patients. Planning CT images were rigidly registered to follow-up CT datasets at 3-9 months after treatment. Corresponding dose distributions were mapped from planning to follow-up CT images. Hounsfield Unit (HU) changes in lung density in individual, 5 Gy, dose bins from 5 to 45 Gy were assessed in the peri-tumoral region. Correlations between HU changes in various normal lung regions, dose indices (V20, MLD, generalized equivalent uniform dose (gEUD)), and RP grade were investigated. Results: Strong positive correlation was found between HU changes in the peri-tumoral region and RP grade (Spearman's r = 0.760; p < 0.001). Positive correlation was also observed between RP and HU changes in the region covered by V20 for all algorithms (Spearman's r >/= 0.738; p < 0.001). Additionally, V20, MLD, and gEUD were significantly correlated with RP grade (p < 0.01). MLD in the peri-tumoral region computed with model-based algorithms was 5-7% lower than the PB-based methods. Conclusion: Changes of lung density in the peri-tumoral lung and in the region covered by V20 were strongly associated with RP grade. Relative to model-based methods, PB algorithms over-estimated mean peri-tumoral dose and showed displacement of the high-dose region, which correlated with HU changes on follow-up CT scans.

Radiation Oncology

Dai Z, **Carver E**, **Liu C**, **Lee J**, **Feldman A**, **Zong W**, **Pantelic M**, **Elshaikh M**, and **Wen N**. Segmentation of the Prostatic Gland and the Intraprostatic Lesions on Multiparametic Magnetic Resonance Imaging Using Mask Region-Based Convolutional Neural Networks. *Advances in Radiation Oncology* 2020. Epub ahead of print. Full Text

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Purpose: Accurate delineation of the prostate gland and intraprostatic lesions (ILs) is essential for prostate cancer dose-escalated radiation therapy. The aim of this study was to develop a sophisticated deep neural network approach to magnetic resonance image analysis that will help IL detection and delineation for clinicians. Methods and Materials: We trained and evaluated mask region-based convolutional neural networks to perform the prostate gland and IL segmentation. There were 2 cohorts in this study: 78 public patients (cohort 1) and 42 private patients from our institution (cohort 2). Prostate gland segmentation was performed using T2-weighted images (T2WIs), although IL segmentation was performed using T2WIs and coregistered apparent diffusion coefficient maps with prostate patches cropped out. The IL segmentation model was extended to select 5 highly suspicious volumetric lesions within the entire prostate. Results: The mask region-based convolutional neural networks model was able to segment the prostate with dice similarity coefficient (DSC) of 0.88 ± 0.04, 0.86 ± 0.04, and 0.82 ± 0.05; sensitivity (Sens.) of 0.93, 0.95, and 0.95; and specificity (Spec.) of 0.98, 0.85, and 0.90. However, ILs were segmented with DSC of 0.62 ± 0.17, 0.59 ± 0.14, and 0.38 ± 0.19; Sens. of 0.55 ± 0.30, 0.63 ± 0.28, and 0.22 ± 0.24; and Spec. of 0.974 ± 0.010, 0.964 ± 0.015, and 0.972 ± 0.015 in public validation/public testing/private testing patients when trained with patients from cohort 1 only. When trained with patients from both cohorts, the values were as follows: DSC of 0.64 ± 0.11, 0.56 ± 0.15, and 0.46 ± 0.15; Sens. of 0.57 ± 0.23, 0.50 ± 0.28, and 0.33 ± 0.17; and Spec. of 0.980 ± 0.009, 0.969 ± 0.016, and 0.977 ± 0.013. Conclusions: Our research framework is able to perform as an end-to-end system that automatically segmented the prostate gland and identified and delineated highly suspicious ILs within the entire prostate. Therefore, this system demonstrated the potential for assisting the clinicians in tumor delineation.

Research Administration

Hosseini MP, Tran TX, Pompili D, Elisevich K, and **Soltanian-Zadeh H**. Multimodal data analysis of epileptic EEG and rs-fMRI via deep learning and edge computing. *Artificial Intelligence in Medicine* 2020; 104. Full Text

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Background and objective: Multimodal data analysis and large-scale computational capability is entering medicine in an accelerative fashion and has begun to influence investigational work in a variety of disciplines. It is also informing us of therapeutic interventions that will come about with such development. Epilepsy is a chronic brain disorder in which functional changes may precede structural ones and which may be detectable using existing modalities. Methods: Functional connectivity analysis using electroencephalography (EEG) and resting state-functional magnetic resonance imaging (rs-fMRI) has provided such meaningful input in cases of epilepsy. By leveraging the potential of autonomic edge computing in epilepsy, we develop and deploy both noninvasive and invasive methods for monitoring, evaluation, and regulation of the epileptic brain. First, an autonomic edge computing framework is proposed for the processing of big data as part of a decision support system for surgical candidacy. Second, a multimodal data analysis using independently acquired EEG and rs-fMRI is presented for estimation and prediction of the epileptogenic network. Third, an unsupervised feature extraction model is developed for EEG analysis and seizure prediction based on a Convolutional deep learning (CNN) structure for distinguishing preictal (pre-seizure) state from non-preictal periods by support vector machine (SVM) classifier. Results: Experimental and simulation results from actual patient data validate the effectiveness of the proposed methods. Conclusions: The combination of rs-fMRI and EEG/iEEG can reveal more information about dynamic functional connectivity. However, simultaneous fMRI and EEG data acquisition present challenges. We have proposed system models for leveraging and processing independently acquired fMRI and EEG data.

Sleep Medicine

Kalmbach DA, **Roth T**, **Cheng P**, Ong JC, Rosenbaum E, and **Drake CL**. Mindfulness and nocturnal rumination are independently associated with symptoms of insomnia and depression during pregnancy. *Sleep Health* 2020. Epub ahead of print. PMID: 32146168. Full Text

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BACKGROUND: Insomnia and depression are highly prevalent perinatal complications. Ruminating on stress is etiologically implicated in both disorders, and ruminating while trying to fall asleep has been linked to insomnia and depression during pregnancy. Incompatible with rumination is everyday mindfulness, i.e., living with intentional and nonjudgmental awareness of internal and external experiences in the present moment. Responding to stress mindfully may protect against stress-related perinatal complications such as insomnia and depression. The present study described the association between everyday mindfulness and nocturnal rumination, and examined whether these trait characteristics were independently related to perinatal insomnia and depression. METHODS: Cross-sectional and secondary analysis of existing data from 65 pregnant women recruited from a multisite hospital in Metro Detroit, MI, USA. Subjects completed online surveys including the Insomnia Severity Index, Edinburgh Postnatal Depression Scale, Presleep Arousal Scale, and the revised Cognitive and Affective Mindfulness Scale. RESULTS: Over half (53.8%) of women screened positive for clinical insomnia and 12.3% screened positive for major depression. Women high in mindfulness, relative to those low in mindfulness, reported less nocturnal rumination (Cohen's d=1.16), insomnia symptoms (Cohen's d=1.24), and depressive symptoms (Cohen's d=1.35). Multivariate linear regression revealed that both mindfulness (beta=-.24, p=.03) and rumination (beta=.38, p<.01) were independently associated with insomnia. Similarly, a multivariate model showed that mindfulness (beta=-.41, p<.001) and rumination (beta=.35, p<.01) were independently associated with depression. CONCLUSIONS: Ruminating in bed at night is strongly associated with insomnia and depression during pregnancy, whereas mindfulness may potentially protect against these stress-related perinatal complications.

Sleep Medicine

Roehrs T, **Withrow D**, **Koshorek G**, **Verkler J**, **Bazan L**, and **Roth T**. Sleep and pain in humans with fibromyalgia and comorbid insomnia: double-blind, crossover study of suvorexant 20 mg versus placebo. *J Clin Sleep Med* 2020; 16(3):415-421. PMID: 31992394. Full Text

Henry Ford Health System, Sleep Disorders and Research Center, Detroit, Michigan.
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STUDY OBJECTIVES: The chronic pain disorder, fibromyalgia, is associated with sleep disturbance, typically sleep maintenance. No studies have evaluated the effect of sleep medication on pain sensitivity in this population. Suvorexant, an orexin antagonist approved for treatment of insomnia, was evaluated for effects on both sleep and the pain of fibromyalgia. METHODS: Women age 21 to 65 years with fibromyalgia and comorbid insomnia (n = 10) were treated, double-blind, for 9 nights each with suvorexant, 20 mg and placebo in counterbalanced order. All were in good psychiatric and stable physical health and met American College of Rheumatology 2010 criteria for fibromyalgia and Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition criteria for insomnia. Screening 8-hour polysomnography (PSG) was used to rule out other sleep disorders. On nights 8 and 9 of each treatment 8-hour PSG were collected and on days 1 and 8 pain sensitivity was assessed at 1100 and 1500 hours by measuring finger withdrawal latency (FWL) to a radiant heat stimulus at 5 randomly presented intensity levels. RESULTS: Suvorexant versus placebo increased total sleep time (7.2 versus 6.7 hours, P < .05) and reduced wake after sleep onset (37 versus 67 minutes, P < .04) with no night effects or interaction. Latency to persistent sleep and sleep stage measures were not altered. FWL on both am and pm tests varied as a function of intensity (P < .001). Average FWL (over 5 intensities and both days) was increased relative to placebo on both the am (13.9 versus 13.1 seconds) and pm tests (15.8 versus 14.1 seconds, P < .03) following suvorexant the previous night. CONCLUSIONS: Suvorexant 20 mg in patients with fibromyalgia, improved sleep time and reduced next-day pain sensitivity on assessments of FWL to a radiant heat stimulus. CLINICAL TRIAL REGISTRY: Registry: ClinicalTrials.gov; Name: A double-blind cross-over, study to compare the hypnotic, daytime sleepiness/fatigue, and pain effects of nighttime administration of suvorexant 20 mg versus placebo in patients with fibromyalgia and comorbid insomnia; Identifier: NCT02684136; URL: https://clinicaltrials.gov/ct2/show/NCT02684136.

Sleep Medicine
Svetnik V, Snyder ES, Tao P, **Roth T**, Lines C, and Herring WJ. How well can a large number of polysomnography sleep measures predict subjective sleep quality in insomnia patients? *Sleep Med* 2020; 67:137-146. PMID: 31926466. Full Text

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OBJECTIVE: The determinants of sleep quality (sQUAL) are poorly understood. We evaluated how well a large number of objective polysomnography (PSG) parameters can predict sQUAL in insomnia patients participating in trials of sleep medications or placebo. METHODS: PSG recordings over multiple nights from two clinical drug development programs involving 1158 insomnia patients treated with suvorexant or placebo and 903 insomnia patients treated with gaboxadol or placebo were used post-hoc to analyze univariate and multivariate associations between sQUAL and 98 PSG sleep parameters plus patient's age and gender. Analyses were performed separately for each of the two clinical trial databases. For univariate associations, within-subject correlations were estimated using mixed effect modeling of bi-variate longitudinal data with one variable being a given PSG variable and the other being sQUAL. To evaluate how accurately sQUAL could be predicted by all PSG variables jointly plus patient's age and gender, the Random Forest multivariate technique was used. Random Forest was also used to evaluate the accuracy of sQUAL prediction by subjective sleep measures plus age and gender, and to quantitatively describe the relative importance of each variable for predicting sQUAL. RESULTS: In the univariate analyses, total sleep time (TST) had the largest correlation with sQUAL compared with all other PSG sleep parameters, and the magnitude of the correlation between each PSG sleep architecture parameter and sQUAL generally increased with the strength of their associations with TST. In the multivariate analyses, the overall accuracy of sQUAL prediction, even with the large number of PSG parameters plus patient's age and gender, was moderate (area under the Receiver Operating Characteristic curve (AROC): 71.2-71.8%). Ranking of PSG parameters by their contribution to sQUAL indicated that TST was the most important predictor of sQUAL among all PSG variables. Subjective TST and subjective number of awakenings jointly with patient's age classified sQUAL with higher accuracy (AROC: 78.7-81.7%) than PSG variables plus age and gender. The pattern of findings was consistent across the two clinical trial databases. CONCLUSION: In insomnia patients participating in trials of sleep medications or placebo, PSG variables had a moderate but consistent pattern of association with sQUAL across two separate clinical trial databases. Of the PSG variables evaluated, TST was the best predictor of sQUAL. CLINICAL TRIALS: trial registration at www.clinicaltrials.gov: NCT01097616; NCT01097629; NCT00094627; NCT00094666.

Surgery
Chamogeorgakis T, **Cowger J**, **Apostolou D**, **Tanaka D**, and **Nemeh H**. Right Ventricular Device HeartWare Implant to the Right Atrium with Fixation to the Chest Wall in Patient with Biventricular Support. *Asaio j* 2020. Epub ahead of print. PMID: 32205510. Full Text

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Surgery
Kitajima T, **Nagai S**, **Segal A**, **Magee M**, **Blackburn S**, **Ellithorpe D**, **Yeddula S**, **Qadeer Y**, **Yoshida A**, **Moonka D**, **Brown K**, and **Abouljoud MS**. Posttransplant Complications Predict Alcohol Relapse in Liver Transplant Recipients. *Liver Transpl* 2020; 26(3):379-389. PMID: 31872969. Full Text

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Alcohol relapse after liver transplantation (LT) in patients with alcohol-related liver disease (ALD) is a major challenge. Although its association with pretransplant psychosocial factors was extensively studied, the impacts of posttransplant courses on alcohol relapse have not been well investigated. The aim of this study is to analyze peritransplant factors associated with posttransplant alcohol relapse in patients with ALD. This study evaluated 190 adult LT patients with ALD from 2013 to 2019. Risk factors for alcohol relapse were analyzed, focusing on posttransplant chronic complications, which were classified as Clavien-Dindo classification 3a or higher that lasted over 30 days. The posttransplant alcohol relapse rate was 13.7% (26/190) with a median onset time of 18.6 months after transplant. Multivariate Cox regression analysis revealed that posttransplant chronic complications were an independent risk factor for posttransplant alcohol relapse (hazard ratio [HR], 5.40; P = 0.001), along with psychiatric comorbidity (HR, 3.93; P = 0.001), history of alcohol relapse before LT (HR, 3.00; P = 0.008), and an abstinence period <1.5 years (HR, 12.05; P = 0.001). A risk prediction model was created using 3 pretransplant risk factors (psychiatric comorbidity, alcohol relapse before LT, and abstinence period <1.5 years). This model clearly stratified the risk of

alcohol relapse into high-, moderate-, and low-risk groups (P < 0.001). Of the 26 patients who relapsed, 11 (42.3%) continued drinking, of whom 3 died of severe alcoholic hepatitis, and 13 (50.0%) achieved sobriety (outcomes for 2 patients were unknown). In conclusion, posttransplant chronic complications increased the risk of alcohol relapse. Recognition of posttransplant chronic complications in conjunction with the risk stratification model by pretransplant psychosocial factors would help with the prediction of posttransplant alcohol relapse.

Surgery
Leiting JL, Murphy SJ, Bergquist JR, Hernandez MC, **Ivanics T**, Abdelrahman AM, Yang L, Lynch I, Smadbeck JB, Cleary SP, Nagorney DM, Torbenson MS, Graham RP, Roberts LR, Gores GJ, Smoot RL, and Truty MJ. Biliary tract cancer patient-derived xenografts: Surgeon impact on individualized medicine. *JHEP Rep* 2020; 2(2):100068. PMID: 32181445. Full Text

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Background & Aims: Biliary tract tumors are uncommon but highly aggressive malignancies with poor survival outcomes. Due to their low incidence, research into effective therapeutics has been limited. Novel research platforms for pre-clinical studies are desperately needed. We sought to develop a patient-derived biliary tract cancer xenograft catalog. Methods: With appropriate consent and approval, surplus malignant tissues were obtained from surgical resection or radiographic biopsy and implanted into immunocompromised mice. Mice were monitored for xenograft growth. Established xenografts were verified by a hepatobiliary pathologist. Xenograft characteristics were correlated with original patient/tumor characteristics and oncologic outcomes. A subset of xenografts were then genomically characterized using Mate Pair sequencing (MPseq). Results: Between October 2013 and January 2018, 87 patients with histologically confirmed biliary tract carcinomas were enrolled. Of the 87 patients, 47 validated PDX models were successfully generated. The majority of the PDX models were created from surgical resection specimens (n = 44, 94%), which were more likely to successfully engraft when compared to radiologic biopsies (p = 0.03). Histologic recapitulation of original patient tumor morphology was observed in all xenografts. Successful engraftment was an independent predictor for worse recurrence-free survival. MPseq showed genetically diverse tumors with frequent alterations of CDKN2A, SMAD4, NRG1, TP53. Sequencing also identified worse survival in patients with tumors containing tetraploid genomes. Conclusions: This is the largest series of biliary tract cancer xenografts reported to date. Histologic and genomic analysis of patient-derived xenografts demonstrates accurate recapitulation of original tumor morphology with direct correlations to patient outcomes. Successful development of biliary cancer tumografts is feasible and may be used to direct subsequent therapy in high recurrence risk patients. Lay summary: Patient biliary tract tumors grown in immunocompromised mice are an invaluable resource in the treatment of biliary tract cancers. They can be used to guide individualized cancer treatment in high-risk patients.

Surgery
Nagai S, **Chau LC**, **Kitajima T**, **Yeddula S**, **Collins K**, **Rizzari M**, **Yoshida A**, **Abouljoud MS**, and **Moonka D**. A Share 21 Model in Liver Transplantation: Impact on Waitlist Outcomes. *Am J Transplant* 2020. Epub ahead of print. PMID: 32155314. Full Text

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With the introduction of MELD-Na based allocation, the score at which patients benefit from liver transplantation (LT) has shifted from a score of 15 to 21. This study aimed to evaluate waitlist outcomes in patients with MELD-Na scores <21 and explore the utility of replacing "Share 15" with "Share 21". The study uses data from the OPTN/UNOS registry. All adult patients registered for LT after implementation of the MELD-Na based allocation were evaluated. Waitlist patients with initial and final scores <21 were eligible. Patients with exception scores were excluded. To explore the potential impact of a Share 21 model, patients with an initial MELD-Na score of 6-14 (Group 1) and those with a score of 15-20 (Group 2) were compared for waitlist outcomes. There were 3,686 patients with an initial score of 6-14 (Group 1) and 3,282 with a score of 15-20 (Group 2). Group 2, when compared to Group 1, showed comparable risk of mortality (adjusted hazard ratio [aHR] 1.00, P=0.97), higher transplant probability (aHR 3.25, P<0.001), and lower likelihood of removal from listing because of improvement (aHR 0.74, P=0.011). Share 21 may enhance transplant opportunities and increase parity for patients with higher MELD-Na scores without compromising waitlist outcomes.

Surgery
Nagai S, **Kitajima T**, **Yeddula S**, **Salgia R**, Schilke R, **Abouljoud MS**, and **Moonka D**. Effect of mandatory 6-month waiting period on waitlist and transplant outcomes in patients with hepatocellular carcinoma. *Hepatology* 2020. Epub ahead of print. PMID: 32157711. Full Text

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OPTN/UNOS policy mandates a 6-month waiting period before exception scores are granted to liver transplant candidates with hepatocellular carcinoma (HCC). This study aims to evaluate waitlist and post-transplant outcomes, in HCC patients, before and after implementation of the 6-month waiting rule. We examined two groups from the UNOS registry; Group 1 (pre 6-month rule) comprised patients registered as transplant candidates with HCC from Jan. 1, 2013 to Oct. 7, 2015 (n=4,814). Group 2 (post 6-month rule) comprised patients registered from Oct. 8, 2015 to Jun. 30, 2018 (n=3,287). As expected, the transplant probability was higher in the first six months after listing in Group 1 than Group 2 at 42.0% vs 6.3% (P<0.001). However, the 6-month waitlist mortality/dropout rate was lower in Group 2 at 1.2% than Group 1 at 4.1% (P<0.001). To assess regional parity of transplant, UNOS-regions were categorized into three groups based on MELD score at transplant; lower-score (regions 3,10&11), mid-score (1,2,6,8&9), and higher-score region groups (4,5&7). Outcomes were compared from the time exception points were given which we defined as conditional waitlist outcomes. Conditional waitlist mortality/dropout decreased, and transplant probability increased in all region groups, but the benefits of the policy were more pronounced in the higher and mid-score groups, compared to the lower-score group. The decline in waitlist mortality/dropout was only significant in the high MELD group (P<0.001). No effect was observed on post-transplant mortality or percent of patients within Milan criteria on explant. CONCLUSION: The HCC policy change was associated with decreased waitlist mortality/dropout and increased transplant probability. The policy helped decrease but did not eliminate regional disparities in transplant opportunity without an effect on post-transplant outcomes.

Surgery

Rizzari MD, **Safwan M**, **Sobolic M**, **Kitajima T**, **Collins K**, **Yoshida A**, **Abouljoud M**, and **Nagai S**. The Impact of Portal Vein Thrombosis on Liver Transplant Outcomes: Does Grade or Flow Rate Matter? *Transplantation* 2020. Epub ahead of print. PMID: 32217946. Full Text

Division of Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, MI, USA.

BACKGROUND: Portal vein thrombosis (PVT) makes the technical aspect of liver transplantation challenging and also affects outcomes. Our aim was to study impact of PVT grade and postreperfusion portal flow on posttransplant outcomes. METHODS: Patients who underwent transplantation with PVT between January 2007 and May 2017 were selected (n=126). Data on grade of PVT and portal vein flow were collected. Patients were classified into 2 groups; low grade (Yerdel Grade I, n=73) and high grade (Yerdel Grade II or III, n=53). Using portal flow rate, patients were divided into high flow (>/=1000 ml/min, n=95) and low flow (<1000 ml/min, n=31). Additional analyses of flow by graft weight and complications were performed. RESULTS: Postoperatively, incidence of biliary strictures were significantly greater in high grade PVT compared to low grade (p=0.02). Incidence of postoperative portal vein thrombosis was higher in low flow after reperfusion compared to high flow (p=0.02), as was bile leak (p=0.02). On identifying factors associated with graft loss, moderate to severe ascites preoperatively, high PVT grade and bile leak were associated with worse graft survival. Subanalysis performed combining grade and flow showed that low grade, high flow had the highest graft survival while high grade, low flow had the lowest (p=0.006). High grade PVT with low flow also appeared to be an independent risk factor for biliary complications (p=0.01). CONCLUSION: In conclusion, biliary complications, especially strictures are more common in high grade PVT and graft survival is worse in high grade PVT and low portal flow.

Urology

Bronkema C, **Arora S**, **Sood A**, **Dalela D**, **Keeley J**, **Borchert A**, **Baumgarten L**, **Rogers CG**, **Peabody JO**, **Menon M**, and **Abdollah F**. Rare Histological Variants of Prostate Adenocarcinoma: A National Cancer Database Analysis. *J Urol* 2020. Epub ahead of print. PMID: 32141804. Full Text

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PURPOSE: The American Joint Committee on Cancer recognizes six rare histological variants of prostate adenocarcinoma. Our aim was to describe the contemporary presentation and overall survival of these rare variants. MATERIALS AND METHODS: We examined 1345618 patients who were diagnosed with prostate adenocarcinoma, between 2004 and 2015, within the National Cancer Database. We focused on the following variants: mucinous, ductal, signet ring cell, adenosquamous, sarcomatoid, and neuroendocrine. Characteristics at presentation for each variant were compared with nonvariant prostate adenocarcinoma. Cox regression was used to study the impact of histological variant on overall mortality. RESULTS: Few (0.38%) patients presented with rare-variant prostate adenocarcinoma. All variants had higher clinical tumor stage at presentation than nonvariant (all p<0.001). Metastatic disease was most common with neuroendocrine (62.9%), followed by sarcomatoid (33.3%), adenosquamous (31.1%), signet ring cell (10.3%), and ductal (9.8%), compared to 4.2% in nonvariant (all p<0.001). Metastatic disease in mucinous (3.3%) was similar to nonvariant (p=0.2). Estimated 10-year overall survival was highest in mucinous (78.0%), followed by nonvariant (71.1%), signet ring cell (56.8%), ductal (56.3%),

adenosquamous (20.5%), sarcomatoid (14.6%) and neuroendocrine (9.1%). At multivariable analysis, mortality was higher in ductal (HR: 1.38; p<0.001), signet ring cell (HR: 1.53; p<0.01), neuroendocrine (HR: 5.72; p<0.001), sarcomatoid (HR: 5.81; p<0.001), and adenosquamous (HR: 9.34; p<0.001), as compared to nonvariant. CONCLUSIONS: Neuroendocrine, adenosquamous, sarcomatoid, signet ring cell, and ductal variants more commonly present with metastases. All variants present with higher local stage than nonvariant. Neuroendocrine is associated with the worst, and mucinous with the best overall survival.

Urology
Jebastin Thangaiah J, Vickery J, Selwanes W, Al-Haddad E, **Perry KD**, **Palanisamy N**, Poulik JM, **Williamson SR**, **Chitale DA**, and Shehata BM. A Novel COL1A1-CAMTA1 Rearrangement in Cranial Fasciitis. *Int J Surg Pathol* 2020. Epub ahead of print. PMID: 32192385. Full Text

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Cranial fasciitis is an uncommon benign fibroblastic tumor, generally histologically identical to nodular fasciitis. It develops almost exclusively in children. Cranial fasciitis manifests clinically as a painless rapidly growing solitary nodule in the head and neck area, frequently eroding the underlying bone. Thus, this entity is often confused with aggressive lesions such as sarcomas, both clinically and radiologically. Histopathologic examination is essential to differentiate between cranial fasciitis and fibrohistiocytic or even sarcomatous lesions observed in children. In this article, we present a case of cranial fasciitis with intracranial extension in a 2-year-old boy. Although USP6 rearrangement has recently been recognized as a recurring alteration in nodular fasciitis, we present a novel COL1A1-CAMTA1 fusion in this lesion.

Urology
Kamat AM, Shore N, Hahn N, **Alanee S**, Nishiyama H, Shariat S, Nam K, Kapadia E, Frenkl T, and Steinberg G. KEYNOTE-676: Phase III study of BCG and pembrolizumab for persistent/recurrent high-risk NMIBC. *Future Oncol* 2020; 16(10):507-516. PMID: 32162533. Request Article

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Background: Nonmuscle-invasive bladder cancer (NMIBC) is the most common form of bladder cancer, with high rates of disease recurrence and progression. Current treatment for high-risk NMIBC involves Bacillus Calmette-Guerin (BCG) therapy, but treatment options are limited for patients with recurrent or BCG-unresponsive disease. Aberrant programmed death 1 signaling has been implicated in BCG resistance and bladder cancer recurrence and progression, and pembrolizumab has shown efficacy in patients with BCG-unresponsive high-risk NMIBC. Aim: To describe the rationale and design for the randomized, comparator-controlled Phase III KEYNOTE-676 study, which will evaluate the efficacy and safety of pembrolizumab in combination with BCG in patients with persistent/recurrent high-risk NMIBC after BCG induction therapy. Trial registration number: NCT03711032.

Urology
Nazzani S, Preisser F, Mazzone E, Tian Z, Mistretta FA, Soulieres D, Montanari E, Acquati P, Briganti A, Shariat SF, **Abdollah F**, Carmignani L, and Karakiewicz PI. Nephroureterectomy with or without Bladder Cuff Excision for Localized Urothelial Carcinoma of the Renal Pelvis. *Eur Urol Focus* 2020; 6(2):298-304. PMID: 30266210. Full Text

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Cancer Prognostics and Health Outcomes Unit, Centre Hospitalier de l'Universite de Montreal, Montreal, Canada; Centre Hospitalier de l'Universite de Montreal, Montreal, Canada.

BACKGROUND: Few studies examined the rates of guideline implementation and the survival effect of bladder cuff excision (BCE) at nephroureterectomy (NU). OBJECTIVE: To assess the rates of guideline implementation regarding NU with BCE relative to NU without BCE in patients with upper tract urothelial carcinoma (UTUC) and to test the effect of BCE on cancer-specific (CSM) and other-cause mortality (OCM). DESIGN, SETTING, AND PARTICIPANTS: We relied on Surveillance, Epidemiology, and End Results database (2004-2014) for UTUC of the renal pelvis patients (T1-T3, N0, M0) treated with NU with or without BCE. OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Cumulative incidence plots relying on competing-risks methodology illustrated 5-yr CSM and OCM rates. Multivariable competing-risks regression (MCRR) models tested the effect of BCE versus no BCE at NU. RESULTS AND LIMITATIONS: Of 4266 assessable patients, 2913 (68.3%) underwent NU with BCE. Between 2004 and 2014, rates of BCE at NU increased from 63.0% to 74.5% (European Association for Palliative Care: 2%; p<0.001). At 60 mo, CSM rates were 19.7% versus 23.5% (p=0.005) in NU with BCE versus NU without BCE patients, respectively. In MCRR models, no difference in CSM was recorded according to BCE at NU (hazard ratio [HR]: 0.88, confidence interval [CI]: 0.75-1.03, p=0.1). Finally, OCM was unaffected by BCE at NU (HR: 0.94, CI: 0.77-1.15, p=0.5). This study is retrospective. CONCLUSIONS: According to guideline recommendation, the rates of NU with BCE increased over time. However, BCE status does not appear to affect CSM or OCM. Thus, our study was unable to examine the rates of urothelial cancer recurrence or metastatic progression according to BCE status. PATIENT SUMMARY: Rates of bladder cuff excision (BCE) at nephroureterectomy (NU) are increasing. This observation confirms improved adherence to guidelines over time. However, BCE status does not appear to affect survival after NU for upper tract urothelial carcinoma.

Conference Abstracts

Administration

Bryson T, **Debbs JC**, **She R**, **Gui H**, **Luzum JA**, **Zeld N**, **Brawner CA**, **Keteyian SJ**, **Ehrman JK**, **Williams LK**, and **Lanfear DE**. A single nucleotide polymorphism within the rxra gene predicts a favorable response to exercise in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):1012.

Background Heart failure (HF) is a morbid condition associated with impaired exercise capacity. Exercise training is an effective strategy to improve functional capacity and quality of life. However, response to exercise training is highly variable and whether there are genetic factors that may impact response to exercise is unknown. We sought to identify genetic variants in patients with HF participating in cardiac rehabilitation (CR) that are associated with improvement in exercise capacity. Methods The study was conducted at Henry Ford Hospital in Detroit, MI. Patients enrolled in our genomic HF registry who had participated in CR at any time were selected (n=211). The primary endpoint was the change in metabolic equivalents of task (ΔMET) during CR, from week 1 to the last week of CR. All patients were genotyped using the Axiom biobank genotyping array with imputation using 1000 genomes reference panels (filter at R2 = 0.5 in both European and African ancestry). Genome-wide association testing was performed in linear models of ΔMET adjusted for baseline peak VO2, sex, age, and the first principal component (to control for race/population stratification). p<5×10−8 was considered statistically significant. Results The study cohort consisted of 135 African ancestry and 76 European ancestry patients and 36.5% were women. One SNP, rs11103633, met genome-wide significance (p = 8.86 × 10−12). Each additional allele was associated with 2.4 MET greater improvement (std err. = 0.331, p = 8.859 × 10−12). This SNP, in the retinoid x receptor A gene (RXRA), encodes an orphan nuclear receptor belonging to the steroid super-family and acts in a variety of cellular processes. In cardiac and skeletal muscle, RXRA, is the necessary binding partner of PPARA, a key regulator of mitochondrial proliferation and fatty acid oxidation. Conclusion A genetic variant in the RXRA gene appears to impact the beneficial effect of exercise training in HF patients and could act via influencing cellular energetic capacity. This finding could lead to targeted exercise therapy or to novel pharmacologic methods of improving exercise response in HF patients. External validation and investigation of possible mechanisms are needed.

Administration

Debbs J, **Bryson TD**, **Zeld N**, **Aurora L**, **Gui H**, **Luzum JA**, **Peterson E**, **She R**, **Williams LK**, and **Lanfear DE**. Somalogic st2 and ntprobnp assays predict heart failure mortality as effectively as the elisa assay. *Journal of the American College of Cardiology* 2020; 75(11):1091.

Background Biomarkers are critical for modern heart failure (HF) care. There are several established prognostic markers such as N-terminal pro-b-type natriuretic peptide (NTproBNP) and soluble suppressor of tumorgenicity 2 (ST2). Recent advances in multiplexing/multi-marker platforms offer faster and broader data generation. However, how these newer methods compare to FDA-approved ELISA-based assays remains unclear. The SOMALogic® SOMAscan assay is an aptamer-based technology that quantifies thousands of proteins simultaneously, including NTproBNP and ST2. The purpose of this study is to compare the test results and performance in predicting mortality using ELISA vs. SOMA for each marker. Methods Patients age ≥18 years and meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry Ford Hospital. Only patients with an ejection fraction < 50 % were used for the analysis (N= 687 for ST2 and N= 902 for NTproBNP). We tested the correlation of SOMA vs ELISA for each marker and report spearman correlation coefficient. We then tested each marker in Cox models adjusted for clinical risk score (MAGGIC) and compared the HR and model improvement (using calculated area under the curve [AUC]) for ELISA vs SOMA versions. Results First, we calculated the correlation between SOMA and ELISA values for both ST2 and NTproBNP. The correlation for ST2 was 0.74 (p<0.001) and NTproBNP was 0.88 (p<0.001), respectively. Next, we used a Cox proportional hazards model to predict death for the four variables corrected for the clinical score MAGGIC. Both versions of both markers were significantly associated with survival time. The hazard ratio for ELISA-ST2 was 1.12 (95% CI 1.09-1.16, p < 0.001) and for SOMA ST2 was 1.11 (95% CI 1.08-1.15, p<0.001). The hazard ratios for ELISA NTproBNP and SOMA NTproBNP were identical (1.12 95% CI 1.09-1.15, p<0.001). Uno's area under the ROC curve analysis showed there was no difference between marker versions in mortality prediction for ST2 nor for NTproBNP. Conclusion These results indicate that the SOMAscan assay results for ST2 and NTproBNP are strongly correlated to the standard ELISA versions and have equivalent prognostic information.

Allergy and Immunology

Ali M, Atzenhoefer M, Bodker K, Ajam T, Johnsrud D, **Saleh Z**, Wani A, Galazka P, Bajwa T, and Jan MF. Very late presentation of fulminant myocardial immune-related toxicity in a patient on pembrolizumab. *Journal of the American College of Cardiology* 2020; 75(11):3273.

Background Immune checkpoint inhibitors (ICI) can manifest as toxicity in the form of autoimmune, breakthrough or immune-related adverse events. Case A 59-year-old woman presented with worsening dyspnea on exertion for 1 week. Her medical history was significant for non-small cell lung carcinoma treated with pembrolizumab for 6 months. At presentation, she was hypotensive and hypoxic. Electrocardiogram (EKG) revealed complete heart block. Echocardiogram demonstrated severely reduced left ventricular systolic function (LVEF 18% down from 70%). Emergent coronary angiogram showed normal coronary arteries. Cardiac magnetic resonance (CMR) was suggestive of toxic myocarditis. Patient was immediately started on high-dose IV steroids. Decision-making We report a very late presentation of ICI-associated myocarditis complicated by complete heart block and acute systolic heart failure. CMR showed extensive left ventricular late gadolinium enhancement and edema suggestive of toxic myocarditis (yellow arrows); T2 mapping sequences demonstrated prolonged T2 relaxation time consistent with extensive edema (green and red areas). Despite aggressive therapy, her LVEF did not improve on follow-up echocardiograms and she died 6 months later. Conclusion Myocardial immune toxicity is a rare adverse effect of ICI. Early recognition and treatment of left ventricular dysfunction is imperative in this vulnerable population.

Anesthesiology

Swanson B, **Salgia R**, **El-Bashir J**, and **Parikh S**. Accuracy of agitated saline contrast echocardiography for assessment of intracardiac shunting in preoperative liver transplant patients. *Journal of the American College of Cardiology* 2020; 75(11):1600.

Background Patent Foramen Ovale (PFO) is a common clinical condition that is found in up to 20% of adults. Transthoracic Echocardiography (TTE) with agitated saline contrast imaging (ASCi) has become the screening test of choice for PFO with reported sensitivity of 99% and specificity of 85%. Exclusion of significant atrial level shunt is important prior to liver transplant but patients with end stage liver disease (ESLD) can be difficult to evaluate with ASCi given a high prevalence of intra-pulmonary shunting. We sought to evaluate if ASCi can accurately predict presence of atrial level shunting in patients with ESLD prior to transplant. Methods We performed a retrospective chart review of patients in our health system who underwent liver transplant between January 2016 and March of 2019. We screened for TTE with ASCi that was positive for presence of left sided microbubbles who also had a transesophageal echocardiogram (TEE). TTEs were reviewed and categorized as large if there were more than 20 left sided bubbles and early if they appeared within 5 cardiac cycles following opacification of right atrium. TEEs were then reviewed for presence of a PFO or atrial septal defect. Results Of the initial 317 patients that were screened, 124 had TTEs with ASCi performed of which, 51 (41%) were positive for shunt with rest or provocation. Of those, 25 (49%) had an adequate TEE performed in our system, of which 5 (20%) were found to have a PFO. Early vs. late positivity was not significantly associated with presence of PFO (19%vs 22% [p=0.84]) and of patients with early and large positive studies only 23% (3 of 13) had a PFO. Conclusion Our finding of only 20% of positive ASCi studies being associated with PFO is substantially lower than reported in prior literature. Furthermore, there does not seem to be any significant benefit utilizing early positivity or size of shunt to differentiate between PFO and intra-pulmonary shunting in ESLD patients. High prevalence of concomitant hepatopulmonary syndrome as well as high-flow states renders traditional measures of shunt localization and categorization inaccurate. These findings suggest that ASCi lacks adequate positive predictive value to assess for PFO in patients with ESLD.

Cardiology

Al-Darzi W, and **Gindi R**. Smoldering recurrent pericarditis presenting as a loculated pericardial effusion mimicking pericardial cyst. *Journal of the American College of Cardiology* 2020; 75(11):2648.

Background Pericardial effusion could manifest as a loculated cyst on cardiac imaging. Anakinra (Interleukin-1 receptor antagonist) is showing promising results for treating recurrent resistant pericarditis. Case A 24-year-old male with no medical history presented with pleuritic chest pain after flu-like symptoms. He notes 3-4 similar episodes in past few years. Workup revealed diffuse ST elevations on EKG and a new right middle lobe opacity on chest X-ray. Chest CTA showed a pericardial cyst corresponding to the opacity seen on radiograph. No pericardial cyst or effusion was identified on echocardiogram. Further testing resulted in a positive rhinovirus/enterovirus PCR with unremarkable autoimmune workup. Decision-making Outpatient Cardiac MR to follow on the pericardial cyst was completed 6 weeks after the initial presentation. Interestingly, an interval resolution of the pericardial cyst seen on the prior CT chest noted. Patient endorsed recurrent symptoms with doubling of colchicine dose and resuming non-steroidal agents. He continued to have pericarditis flares, and a short course of prednisone was added. Eventually, patient was started on Anakinra, in addition to colchicine and ibuprofen, with improvement in symptoms. Conclusion Loculated pericardial effusion could mimic a pericardial cyst. Clinical correlation is imperative. Interleukin-1 receptor antagonists could result in symptomatic relieve in patients suffering from recurrent persistent pericarditis.

Cardiology

Aljamal AO, **Alalwan Y**, **Coriasso N**, **Hughes C**, **Abdelrahim E**, **Lee JC**, **Wang DD**, **Pantelic M**, **Song T**, **Eng M**, **Frisoli TM**, **Villablanca P**, and **Wyman JF**. Dynamic conformational changes of the left ventricular outflow tract compared to the aortic annulus and implications on transcatheter aortic valve selection and sizing. *Journal of the American College of Cardiology* 2020; 75(11):1491.

Background ECG-gated computed tomography angiography (CTA) has become the standard for assessing the aortic root prior to transcatheter aortic valve replacement (TAVR). Current techniques rely primarily on systolic annular sizing for the selection and sizing of valve prostheses. We sought to evaluate the dynamic conformational changes of the LVOT compared to the aortic annulus, and determine whether LVOT morphology can have implications on prosthetic valve sizing and selection. Methods Preprocedural ECG-gated CTA data of 339 patients (aged 79 ±8.7 years, 52.6% male) who underwent TAVR were analyzed in this single-center retrospective study. The area of the aortic annulus and LVOT were measured by planimetry at 10% intervals throughout the cardiac cycle. Annular measurements were obtained inferior to the coronary cusps, and 10% of sub-annular calcifications were included in the calculated size. LVOT measurements were recorded 5mm inferior to the aortic annulus in a double oblique plane. Results In systole, the average annular size was 452.19 ± 19.52 mm2 compared to 455.74 ± 23.52 mm2 in the LVOT. In diastole, the average annular size was 420.98 ± 18.71 mm2 compared to 430 ± 25.42 mm2 in the LVOT. On average, the LVOT was 3.5mm2 (0.77%) larger in systole and 10mm2 (2.37%) larger in diastole compared to the annulus. Furthermore, a strong linear correlation was noted between the systolic and diastolic sizes of the annulus and LVOT, with a pooled value correlation coefficient (r) value of 0.72 and 0.73, respectively. Conclusion There is a statistically significant difference between the size of the aortic annulus and the LVOT in both systole and diastole. The difference is more pronounced in diastole. The data also shows a strong linear correlation between both the systolic and diastolic sizes of the annulus and the LVOT. The distal portion of the LVOT is within the TAVR valve landing zone but has frequently been neglected in the selection and sizing of valve prostheses. We have found that LVOT morphology varies throughout the cardiac cycle, especially diastole. Further study is required to identify whether distinct LVOT morphologies can be used to improve TAVR valve sizing and procedural outcomes.

Cardiology

Alrayes H, **Radjef R**, and **Tita C**. Cardiogenic shock: A bittersweet diagnosis. *Journal of the American College of Cardiology* 2020; 75(11):2476.

Background Sweet's syndrome (SS), also known as febrile neutrophilic dermatosis, is a rare reactive phenomenon characterized by a pattern of clinical symptoms with physical and pathologic manifestations. We present a case of SS with cardiac, dermatologic, and neurologic manifestations. Case A 73-year-old female presented with slurred speech for several hours, along with preceding fevers and flu-like symptoms. Initial stroke and infectious workups were negative. A transthoracic echocardiogram (TTE) was unremarkable. Two days later, she became tachypneic with pulmonary edema on chest X-ray. A repeat TTE showed an EF of 30% with global hypokinesis. A left heart catheterization revealed no obstructive coronary artery disease. She was intubated and an Impella CP was placed with Dobutamine for concerns of cardiogenic shock. She remained febrile with altered mentation despite an unremarkable infectious workup. ESR and CRP were elevated to 45mm/hr and 19.2mg/dL, respectively. WBC was elevated to 13,400 with a 92% neutrophil predominance. Several days after admission, pink papules on the patient's lower extremities were discovered, biopsied, and revealed neutrophilic dermatitis with negative infectious stains. Decision-making This patient fulfilled two major criteria required for the diagnosis of SS, including the abrupt onset of painful erythematous nodules, and histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis. She met two of the four minor criteria, including pyrexia and at least three abnormal laboratory values (elevated ESR > 20mm/hr, positive CRP, >8000 leukocytes, >70% neutrophils). Given the fulfillment of her criteria and lack of an alternative etiology behind her shock, the patient was started on 1mg/kg of prednisone daily. She had

rapid improvement in her skin papules, mentation, and cardiogenic shock, with discontinuation of her Impella CP and Dobutamine within 24 hours. Repeat TTE showed an EF of 53%. Conclusion This case highlights SS as a rare cause of cardiogenic shock and encephalitis and illustrates the importance of maintaining a broad differential diagnosis when determining the etiology of cardiogenic shock.

Cardiology
Altibi A, **Jebbawi LA**, and **Patel BD**. LVOT obstruction and severe aortic regurgitation caused by anterolateral muscle bundle of the left ventricle: The embryologic remnant of the bulbo-atrioventricular flange. *Journal of the American College of Cardiology* 2020; 75(11):2972.

Background An anterolateral muscle bundle runs along the wall of the left ventricular outflow tract (LVOT) and may extend up to the level of aortic valve (AV). The muscle bundle may occasionally bulge into the LVOT without causing significant obstruction. Case A 53 year old female patient presented with worsening chest discomfort and exercise intolerance. Initial TTE showed ejection fraction of 56% and AV area (AVA) of 0.66 cm2 indicative of severe stenosis, but with peak gradient of 29 mmHg. However, TEE showed very mild aortic stenosis with 3D aortic valve planimetry measuring 1.8 cm2. TEE showed hypertrophied basal septum (thick membrane connecting mitral leaflet with AV). The thickened septum was causing severe LVOT obstruction (LVOT area was 0.85 cm2) and a tertiary cord was attached to its base. The septum attaches to the right coronary cusp causing restriction and severe regurgitation. Cardiac catheterization showed severe stenosis at the LVOT. Decision-making The findings are indicative for anterolateral muscle bundle causing LVOT obstruction, rather than primary AV pathology. Hence, patient underwent septal myectomy, resection of subaortic membrane, and AV repair successfully. Post-myomectomy TTE showed minimal stenosis with AVA of 1.34 cm2. Conclusion LVOT obstruction can be caused by hypertrophied anterolateral muscle bundle in the absence of primary valvular pathology. Proper diagnosis is crucial since resection of the subaortic membrane and septal myectomy is the treatment of choice.

Cardiology
Aurora L, **Grafton G**, **Nemeh H**, **Chamogeorgakis T**, **Apostolou D**, **Tanaka D**, and **Cowger J**. Indications for LVAD Explant and Predictors of Mortality after Explant in IMACS. *Journal of Heart and Lung Transplantation* 2020; 39(4):S137-S138.

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Purpose: As support durations increase, patients' risk for requiring LVAD device explant (Exp) to address complications also increases. The aims of this analysis were to better understand indications and outcomes associated with LVAD explant. Methods: Patients enrolled into IMACS requiring continuous flow LVAD explant (Exp) for nontransplant indications were identified. Survival in those with and without device Exp and by Exp indication were estimated with Kaplan-Meier methods, and correlates of mortality within the combined Exp dysfunction+other cohort were examined with Cox Regression. Results: Of 16,842 patients on CF-LVAD in IMACS, 1,579 patients underwent LVAD Exp. Indications for Exp included non-urgent (83.1%) and urgent (1.5%) device malfunction; LV recovery (12.0%); elective (0.25%) and urgent (0.32%) pump thrombosis; and "other" (3.1%). Median time to explant for "other" causes was shortest at 1.2 [0.0, 14.5] months compared with 8 [2.6,17] months for device dysfunction-Exp and 10.9 [7.5,16.3] months for recovery-Exp ($p<0.05$). Early survival in patients undergoing Exp for any reason was better than those without a history of Exp (figure), findings likely related to statistical "survivorship bias" and excellent survival in recovery patients. Patients undergoing Exp for device malfunction-Exp (61±1.7%) or other causes (62±8.2%) had clinically similar 3 year survivals, but survivals were worse than those undergoing Exp for recovery (91±4.9%). Age at implant (HR 1.016 [1.008-1.024] per year), centrifugal flow device (HR 1.6 [1.2-2.1]), prior cardiac surgery (HR 1.4 [1.1-1.7]) and Profile 1-2 (HR 1.3 [1.0-1.5]) were correlates for mortality in those undergoing Exp for device dysfunction or other indications. Conclusion: Survival was similar for those with device Exp due to malfunction and other indications in IMACS. Older patients and those with a history of multiple sternotomies do poorly after Exp. In the elderly, shared decision-making and engagement of palliative care should be undertaken prior to Exp.

Cardiology
Aurora L, **Snider J**, **Peterson E**, **Bryson T**, **Gui H**, **McCord J**, and **Lanfear DE**. Suppression of tumorigenicity 2 (st2) turbidimetric immunoassay and enzyme-linked immunosorbent assay: Predicting risk in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):883.

Background Heart failure (HF) is a major public health problem worldwide. Cardiac biomarkers aid in diagnosis, prognosis, risk stratification, and management of HF. Soluble suppression of tumorigenicity 2 (ST2) is a significant prognostic indicator in HF and seems to reflect response to treatment, particularly beta blockers. However, a limitation to its adoption is that it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and costly for laboratories. A turbidimetric immunoassay (TIA) that can run on a common chemistry analyzer could overcome this issue. We studied a novel TIA for ST2, comparing its performance to the validated ST2 (ELISA) in predicting survival in HF patients. Methods Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007-March 2015) at Henry Ford Hospital. Exclusion criteria included chronic supplemental oxygen or dialysis. Only patients with HF with reduced ejection fraction (<50%) and available plasma samples were included (n=727). ST2 measurements were obtained on the same sample using

both TIA and ELISA. Correlation was studied between the measures and association with survival using Cox models. Area under the curve (AUC) improvement in Cox models was studied using method of Uno. Results Study cohort included 66.6% males, 46.2% African Americans with 43 deaths over 1 year. Correlation between TIA and ELISA was initially low with spearman coefficient 0.63. There were four outliers with ELISA value greater than the recommended maximum (200 ng/mL). Exclusion of these samples (n=723) resulted in inter-assay correlation 0.87. In this group with only ST2 as a variable, the TIA and ELISA values were significant associates of survival time with similar effect size (HR 4.8 and 3.7, respectively, p=0.001). In models adjusted for clinical risk factors (MAGGIC score), both versions of ST2 remained a significant predictor of survival and were of similar magnitude; the AUC improvement (from MAGGIC only, AUC=0.756) for TIA AUC=0.777 (p=0.035) and for ELISA AUC=0.785 (p=0.028). Conclusion Novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Cardiology
Bernardo M, Jafri S, and **Ananthasubramaniam K**. Challenges in imaging complex pericardial effusions: Incremental value of multimodality imaging. *Journal of the American College of Cardiology* 2020; 75(11):3395.

Background Pericardial effusion can be a common finding, but loculated fluid collections may be missed and require more of a focused examination with complementary imaging studies. Case A 60 years old female with metastatic lung cancer was sent to the emergency room after chest CT completed by her oncologist showed a large (15 × 9 × 7 cm) ring-enhancing lesion causing mass effect to the heart and left lung. She denied complaints of chest pain, palpitations, dyspnea, or syncope. An echocardiogram was completed to further ascertain anatomic delineation and tissue characterization of this lesion. Decision-making In this case, chest CT provides advantages of better evaluating pericardial thickness, extracardiac anatomy and possible tissue content. On the other hand, echocardiography avoids radiation and contrast exposure, can be completed at bedside in critical patients, and shows dynamic information of intracardiac structures. Together, they helped to confirm diagnosis of a loculated pericardial effusion likely due to malignancy in this patient. Conclusion Multimodality imaging is integral for correct diagnosis and appropriate management of cardiovascular conditions, especially that of pericardial diseases. Initial imaging may fail to provide adequate information on anatomic origin of masses or fluid collection. Therefore, pericardial effusion especially loculated effusions, may be misconstrued as pericardial tumors or cysts, extracardiac complex masses, or loculated pleural effusions.

Cardiology
Birchak J, **Khan A**, **Singh G**, **Schuger C**, and **Maskoun W**. An unusual case of sustained ventricular tachycardia from acute pulmonary embolism. *Journal of the American College of Cardiology* 2020; 75(11):2820.

Background Pulmonary embolism (PE) is a known cause of cardiac arrest, typically through pulseless electrical arrest or asystole. Very rarely, PE is linked to ventricular tachycardia (VT). Case A 64 year old male presented with left lower extremity DVT and acute bilateral PE confirmed on CT scan (1A). Echocardiography showed preserved LV EF, an enlarged right ventricle (RV), and McConnell's sign (1B). Pulmonary angiography showed bilateral filling defects (1C). 36 hours after presentation, he had 2 episodes of sustained monomorphic VT with syncope requiring cardioversion. EKG suggested origin from the RV apex (1D), with follow-up EKG being sinus rhythm with PVC's of similar axis (1E). Decision-making This patient was anticoagulated and bilateral catheter directed thrombolysis (EKOS) catheters were placed. Amiodarone was started and an IVC filter was placed for concern of continued embolization despite anticoagulation causing the VT. He was discharged with a Life Vest and had no events 3 months later. Outpatient myocardial perfusion imaging (MPI) and cardiac MRI were normal. He is planned for an EP study to determine if an implantable cardiac defibrillator is indicated. Conclusion Sustained VT from acute PE is rare, and the best management of these arrhythmias is unclear. Case reports suggest ischemia from RV strain and irritation of valve apparatus from clot-in-transit to be the culprit. Further research is needed to determine the best long term management and role of ICD placement in these patients.

Cardiology
Bryce K, **Hariri IM**, **Nemeh A**, **St. John G**, and **Cowger JA**. Poor Social Support Confers Worse Survival after MCS. *Journal of Heart and Lung Transplantation* 2020; 39(4):S91.

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Purpose: Patient selection for mechanical circulatory support (MCS) therapy remains challenging. Psychosocial factors such as psychiatric disorders and poor social support, have been found to be associated with outcomes post heart transplant. Research exploring the impact of such factors on LVAD outcomes is limited. We explored the relationship between psychosocial factors and outcomes following implantation with MCS. Methods: We completed a retrospective chart review of 87 consecutive patients who completed a social work and psychological evaluation prior to durable MCS. Those not surviving to discharge were excluded. Psychosocial variables were tested for association with overall survival using Cox regression models adjusted for age, MSC type, and device intent. Results: Mean patient age was 57±1.3 years, 37% were African American with median [25th, 75th] support time of 9.5 [4.5,16] months. On univariable analysis, poor social support correlated (Fig 1a) with mortality, with non-significant trends towards those living alone and with non-compliance (Fig 1b) (table). On

multivariable regression, poor social support had a marked influence on mortality, most notable after 6 months of support (Hazard Ratio= 0.08, p=0.029, Fig 1a). Conclusion: Poor social support was independently associated with worse outcome after MCS with a very high hazard for early mortality. Important trends were noted to suggest risk in those living alone and with poor compliance. The presence of a dedicated support person/team to assist with the demands of MCS maintenance and close outpatient coordinator clinic and telephone follow-up may help improve outcomes. Larger sample pending acceptance.

Cardiology

Bryson T, **Debbs JC**, **She R**, **Gui H**, **Luzum JA**, **Zeld N**, **Brawner CA**, **Keteyian SJ**, **Ehrman JK**, **Williams LK**, and **Lanfear DE**. A single nucleotide polymorphism within the rxra gene predicts a favorable response to exercise in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):1012.

Background Heart failure (HF) is a morbid condition associated with impaired exercise capacity. Exercise training is an effective strategy to improve functional capacity and quality of life. However, response to exercise training is highly variable and whether there are genetic factors that may impact response to exercise is unknown. We sought to identify genetic variants in patients with HF participating in cardiac rehabilitation (CR) that are associated with improvement in exercise capacity. Methods The study was conducted at Henry Ford Hospital in Detroit, MI. Patients enrolled in our genomic HF registry who had participated in CR at any time were selected (n=211). The primary endpoint was the change in metabolic equivalents of task (ΔMET) during CR, from week 1 to the last week of CR. All patients were genotyped using the Axiom biobank genotyping array with imputation using 1000 genomes reference panels (filter at R2 = 0.5 in both European and African ancestry). Genome-wide association testing was performed in linear models of ΔMET adjusted for baseline peak VO2, sex, age, and the first principal component (to control for race/population stratification). $p<5\times10-8$ was considered statistically significant. Results The study cohort consisted of 135 African ancestry and 76 European ancestry patients and 36.5% were women. One SNP, rs11103633, met genome-wide significance ($p = 8.86 \times 10-12$). Each additional allele was associated with 2.4 MET greater improvement (std err. = 0.331, $p = 8.859 \times 10-12$). This SNP, in the retinoid x receptor A gene (RXRA), encodes an orphan nuclear receptor belonging to the steroid super-family and acts in a variety of cellular processes. In cardiac and skeletal muscle, RXRA, is the necessary binding partner of PPARA, a key regulator of mitochondrial proliferation and fatty acid oxidation. Conclusion A genetic variant in the RXRA gene appears to impact the beneficial effect of exercise training in HF patients and could act via influencing cellular energetic capacity. This finding could lead to targeted exercise therapy or to novel pharmacologic methods of improving exercise response in HF patients. External validation and investigation of possible mechanisms are needed.

Cardiology

Butera B, **Lemor A**, **Ya'qoub L**, **Arman PD**, **Voeltz M**, **Koenig G**, **Alaswad K**, **O'Neill WW**, and **Basir M**. Utilization of coronary interventions and outcomes in weekend versus weekday admissions for stemi complicated by cardiogenic shock. *Journal of the American College of Cardiology* 2020; 75(11):1541.

Background ST-elevation myocardial infarction (STEMI) complicated by cardiogenic shock (CS) is associated with high mortality. We evaluated if there was a difference in the utilization of coronary interventions in patients who present with STEMI associated with CS. Methods The National Inpatient Sample, a publicly available database intended to represent 20% of all annual United States hospital admissions was searched for consecutive admission in patients >18 years old from 2006 to 2015 who presented with STEMI and CS. A comparison of procedural interventions, use of hemodynamic monitoring, implementation of mechanical support and outcomes for weekday versus weekend admissions was recorded. Results 186,316 admissions for STEMI with CS were identified. There was no significant difference in adjusted mortality (OR 1.01, 95% CI: 0.96-1.06, p=0.72). The utilization of PCI was higher in weekend admissions (OR 1.10, 95% CI: 1.04-1.16, p=0.001) but the use of CABG (OR 0.94, 95% CI: 0.87-1.01, p=0.09), right heart catheterization (OR 0.96, 95% CI: 0.89-1.02, p=0.19), ECMO (OR 0.91, 95% CI: 0.71-1.18, p=0.48), percutaneous ventricular assist device (OR.91, 95% CI: 0.79-1.05, p=0.19) and IABP (OR 1.03, 95% CI 0.98-1.08, p=0.27) was similar in weekend versus weekday admissions. Conclusion There was no observed difference in the utilization of invasive procedures or outcomes in patients who are admitted with STEMI complicated by CS based on weekday and weekend admission.

Cardiology

Butera B, **Modi K**, **Cowger JA**, and **Russell C**. Eosinophilic myocarditis in a patient with biopsy proven systemic sarcoidosis who was referred for bradycardia. *Journal of the American College of Cardiology* 2020; 75(11):3098.

Background Eosinophilic myocarditis (EM) is an understudied and often missed diagnosis whose constellation of symptoms are frequently attributed to other morbidities. Case A 57-year-old woman with mediastinal lymphadenopathy (Figure 1A), uveitis, celiac lymph node biopsy in 2013 demonstrating noncaseating granulomas and a questionable prior diagnosis of hypereosinophilic syndrome presented to establish care for dizziness and bradycardia (Figure 1B). She had a stroke in 2004 with an echocardiographic diagnosis of left ventricular (LV) thrombus (Figure 1C-D) for which she was prescribed coumadin. She exhibited a pruritic maculopapular skin rash on several areas of her body (Figure 1E-F) and laboratory tests showed a history of peripheral eosinophilia. Decision-making There was concern for cardiac sarcoidosis or undiagnosed EM. A cardiac MRI demonstrated thickening of the LV apex (Figure G-H) with corresponding sub endocardial perfusion defect and late

gadolinium enhancement, without LV thrombus. These findings were consistent with late stage myocardial fibrosis from EM. Reliance on the single imaging modality of echocardiogram resulted in past misdiagnosis of thrombus and delayed therapy of myocardial fibrosis in this patient. Conclusion This case highlights the need for awareness of EM and the importance of considering alternative or additional diagnoses in patients with complex past medical histories. An association of sarcoidosis and EM has not yet been reported in the literature.

Cardiology

Butera B, **Modi K**, **Klingler D**, **McCord J**, and **Ananthasubramaniam K**. All that glitters is not gold; due diligence when interpreting pyrophosphate cardiac scans to avoid misdiagnosis of transthyretin cardiac amyloidosis. *Journal of the American College of Cardiology* 2020; 75(11):3132.

Background Technetium-99m pyrophosphate (PYP) nuclear scan is currently considered the noninvasive test of choice for transthyretin cardiac amyloidosis (TTRCA) with a heart to lung ratio greater than 1.5 suggesting TTRCA. Case An 81 year old female presented to cardiology clinic for evaluation of previously diagnosed TTRCA. Her electrocardiogram (Figure 1A) showed bifasicular block and an echocardiogram (Figure 1B-D) demonstrated diffuse left ventricular hypertrophy. As part of the workup a PYP scan (Figure 1E) was performed and interpreted to have a planar ratio of 1.5 with Grade 2 Tc-99m pyrophosphate uptake, consistent with TTRCA. Decision-making While planar images appeared to show some cardiac uptake equal to that of bone in the contralateral thorax, review of the single-photon emission computed tomography (SPECT) images (Figure 1F) and blood pool reconstruction images (Figure 1G) demonstrated only bone uptake of the tracer, on a background of blood pool activity with no myocardial uptake. Subsequent testing revealed elevated free kappa light chains and the patient was referred to a hematologist for further evaluation. Conclusion Light chain amyloidosis should be first ruled out given implications for treatment. Furthermore, errors in diagnosis of TTRCA can occur when only planar images and ratio cutoffs are used. Due diligence to evaluate SPECT data to confirm myocardial Tc-99m PYP uptake is important to confirm the diagnosis of TTRCA.

Cardiology

Cogswell R, Rafei AE, **Cowger J**, Joseph S, Schultz J, Estep J, John R, and Eckman P. Defining LVAD Success: A Nationwide Survey of LVAD Program Team Members. *Journal of Heart and Lung Transplantation* 2020; 39(4):S180-S181.

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Purpose: The purpose of this study was to determine how LVAD success is defined by LVAD team members across the United States. Methods: An online, anonymous survey was shared with 32 LVAD programs across the country. Six case vignettes were provided: 1) young active drug user 2) demanding patient 3) medically complicated patient 4) socially isolated patient 5) patient with financial barriers, and 6) a non-compliant patient. Individual respondents were asked: 1) Would your program implant a patient like this? 2) Would you vote to implant a patient like this? 3) Do you think this LVAD will be successful? Clinical follow-up was provided and respondents were asked: 4) Was this LVAD successful? Results: A total of 88 survey responses were completed including 22 (24%) LVAD advance practice providers, 29 (32%) CHF cardiologists, 28 (31%) LVAD coordinators, 8 (9%) surgeons, and 3 social workers (3%). The respondents had an average of 6.5 years of experience in advanced heart failure. Results are shown in the Table. We found frequent differences between individual opinions and program decisions. Responses were also significantly different when stratified by professional role. In addition, respondents often supported implant, even if they predicted it was unlikely to be successful. Finally, the definition of LVAD success varied by years of experience and professional role. Conclusion: This national survey quantifies the lack of consensus around the definition of LVAD success. Society guidelines regarding patient selection will continue to face challenges due to lack of consensus in the community.

Cardiology

Cowger JA, Estep JD, Rinde-Hoffman DA, Givertz MM, Anderson AS, Jacoby D, Chen L, Brieke A, Mahr C, Hall S, Ewald GA, Baker A, Chuang J, and Pinney SP. Variability in Blood Pressure Assessment in Patients Supported with HeartMate 3. *Journal of Heart and Lung Transplantation* 2020; 39(4):S156-S157.

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Purpose: Targeted blood pressure (BP) control is a goal of LVAD medical management, but the interpretation of values obtained from automated cuffs and Doppler opening pressure (DOP) is challenging. The aim herein is to compare BP values obtained using arterial line (A-Line) and noninvasive measures in patients on HeartMate 3 support. Methods: In the MOMENTUM 3 Continued Access Protocol, paired BP values from A-Line and DOP (354 readings in 277 patients) and A-Line and automated cuff (296 readings in 256 patients) were obtained (>90% ≤7 days postop). Pearson (R) correlations between A-Line and cuff systolic blood pressure (SBP), mean arterial pressure (MAP), and DOP were assessed. A-Line and noninvasive BP measurements in the absence or presence of a palpable radial pulse (>1 in 5 seconds) were also compared. Results: There were moderate correlations between A-Line SBP and DOP (R=0.63) and A-Line MAP and DOP (R=0.53) (Fig. A, B). DOP was 4±10 mmHg higher than A-Line MAP and 8±11 mmHg lower than A-Line SBP. When DOP was ≤90 mmHg, the

mean absolute difference between DOP and A-Line MAP was 6 ± 6 mmHg compared to 10 ± 9 mmHg between DOP and A-Line SBP. At higher pressures, the disparity between DOP and A-Line MAP increased. The presence of a palpable pulse and high pulse pressure reduced DOP accuracy (Fig. C, D). With a palpable pulse, only 64% DOP values were within 10 mmHg of the A-Line MAP. The correlations between cuff SBP to A-line SBP and cuff MAP to A-Line MAP were poor (Fig. E, F, R=0.36-0.45), but the presence of a palpable pulse and high pulse pressure improved cuff accuracy (Fig. G,H). With a palpable pulse, 71% of cuff MAP values were within 10 mmHg of A-Line. Conclusion: On average, DOP is lower than A-Line SBP and higher than A-Line MAP. In patients with DOP ≤90 mmHg or without a radial pulse, it may be reasonable to interpret DOP as the MAP. The presence of a palpable pulse or high pulse pressure reduces DOP accuracy but improves cuff MAP accuracy. When DOP is >90 mmHg, DOP should not be interpreted as MAP; cuff measures may yield greater accuracy.

Cardiology
Dabbagh M, **Singh G**, **Schuger C**, and **Cowger JA**. Recurrent syncope: A late presentation of a genetic cardiac disease. *Journal of the American College of Cardiology* 2020; 75(11):2690.

Background Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare but serious cause of sudden cardiac death (SCD) in young patients. We present an unusual case of late presenting ARVC. Case A 72 year old male with history of frequent syncopal episodes presented with chest pain and lightheadedness. He was found to have sustained monomorphic ventricular tachycardia (VT). Further evaluation showed mild left ventricular dysfunction and nonobstructive coronary disease (image). Cardiac MR showed a dilated right ventricle (RV) and focal area of basal RV dyskinesis. An electrophysiology study demonstrated easily inducible VT. He was started on sotalol therapy and subsequently had a dual chamber implantable cardioverter defibrillator placed for secondary prevention. Decision-making Cardiac MR was suggestive of ARVC (image), however sarcoidosis was a possible alternative diagnosis given his advanced age. CT chest was negative for mediastinal lymphadenopathy. Genetic testing revealed a heterozygous gene mutation in desmoplakin (DSP) gene. His genetic defect is autosomal dominant with latent phenotype or haploinsufficiency phenotype which may explain his late presentation. Conclusion ARVC is an uncommon inherited cardiac disorder that is difficult to identify and is associated with high risk arrhythmia and SCD. A high degree of suspicion is needed to suspect the diagnosis, and early recognition can lead to appropriate lifesaving treatment even in late presenting scenarios.

Cardiology
Dagher C, **Modi S**, **Gandhi N**, **Binz S**, and **Rabbani B**. A rare case of spontaneous asymptomatic ventricular tachycardia due to arrhythmogenic right ventricular dysplasia (arvd). *Journal of the American College of Cardiology* 2020; 75(11):2578.

Background Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy that can lead to heart failure and sudden cardiac death. This challenging diagnosis is based on clinical, electrocardiographic, and radiographic findings, along with suggestive genetic testing. Case A 72 year old man presented with stable ventricular tachycardia. 2D echo demonstrated an EF of 45%, grade I diastolic dysfunction, and LV hypokinesis. Left heart catheterization revealed non-obstructive coronary disease. Cardiac MRI revealed: dilated RV with basal RV wall akinesis; RV end-diastolic volume index 134 mL/m2, global LV hypokinesis, an area of mid-myocardial delayed gadolinium enhancement of the mid-inferoseptal LV myocardium at the RV insertion point, and no associated lymphadenopathy. Subsequent Invitae genetic testing revealed desmoplakin (DSP) gene mutation. The patient was managed with AICD placement and sotolol initiation. Decision-making In this rare case of asymptomatic stable VT, cardiac MRI findings met major criteria for ARVD. The differential diagnosis included cardiac sarcoidosis, however contrast enhanced CT imaging did not reveal hilar lymphadenopathy, and cardiac MRI was unimpressive for sarcoidosis. Furthermore, DSP gene mutation is associated with autosomal dominant ARVD. Conclusion The diagnosis of ARVD can be determined with cardiac imaging and genetic testing. It is important to rule out similar diagnoses by looking for differentiating features, such as hilar lymphadenopathy and myocardial granulomatous disease which is frequently seen in cardiac sarcoidosis, but not in ARVD.

Cardiology
Debbs J, **Bryson TD**, **Zeld N**, **Aurora L**, **Gui H**, **Luzum JA**, **Peterson E**, **She R**, **Williams LK**, and **Lanfear DE**. Somalogic st2 and ntprobnp assays predict heart failure mortality as effectively as the elisa assay. *Journal of the American College of Cardiology* 2020; 75(11):1091.

Background Biomarkers are critical for modern heart failure (HF) care. There are several established prognostic markers such as N-terminal pro-b-type natriuretic peptide (NTproBNP) and soluble suppressor of tumorgenicity 2 (ST2). Recent advances in multiplexing/multi-marker platforms offer faster and broader data generation. However, how these newer methods compare to FDA-approved ELISA-based assays remains unclear. The SOMALogic® SOMAscan assay is an aptamer-based technology that quantifies thousands of proteins simultaneously, including NTproBNP and ST2. The purpose of this study is to compare the test results and performance in predicting mortality using ELISA vs. SOMA for each marker. Methods Patients age ≥18 years and meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry Ford Hospital. Only patients with an ejection fraction < 50 % were used for the analysis (N= 687 for ST2 and N= 902 for NTproBNP). We tested the correlation of SOMA vs ELISA for each marker and report spearman correlation coefficient. We then tested each marker in Cox models adjusted for clinical risk score (MAGGIC) and compared the HR and model

improvement (using calculated area under the curve [AUC]) for ELISA vs SOMA versions. Results First, we calculated the correlation between SOMA and ELISA values for both ST2 and NTproBNP. The correlation for ST2 was 0.74 (p<0.001) and NTproBNP was 0.88 (p<0.001), respectively. Next, we used a Cox proportional hazards model to predict death for the four variables corrected for the clinical score MAGGIC. Both versions of both markers were significantly associated with survival time. The hazard ratio for ELISA-ST2 was 1.12 (95% CI 1.09-1.16, p < 0.001) and for SOMA ST2 was 1.11 (95% CI 1.08-1.15, p<0.001). The hazard ratios for ELISA NTproBNP and SOMA NTproBNP were identical (1.12 95% CI 1.09-1.15, p<0.001). Uno's area under the ROC curve analysis showed there was no difference between marker versions in mortality prediction for ST2 nor for NTproBNP. Conclusion These results indicate that the SOMAscan assay results for ST2 and NTproBNP are strongly correlated to the standard ELISA versions and have equivalent prognostic information.

Cardiology
Do A, **Curran K**, **Hughes C**, **Solomon R**, and **Williams CT**. Predictors of poor outcomes in non-ischemic cardiogenic shock and the use of hospice in this population. *Journal of the American College of Cardiology* 2020; 75(11):822.

Background Non-ischemic cardiomyopathy is under-appreciated in terms of both research and literature when compared to its ischemic counterpart. Not much is known about this vulnerable population. Therefore, we sought to identify clinical characteristics associated with poor outcomes amongst non-ischemic cardiogenic shock (NICS). Methods A retrospective chart review of NICS patients who were admitted to a tertiary transplant center from 6/2013 to 7/2018. T-test for continuous and chi-square tests for categorical data were used. Univariate analysis and multivariate regression models were used to analyze outcomes. Results Among 192 patients, 71.4% male, mean age of 57 ± 15, 47.9% white. Compared to the non-supported group, left ventricular assist device (62.5% vs 22.8%, p < 0.0001), Veno-arterial extracorporeal membrane oxygenation (62.5% vs 22.8%, p = 0.11), Intra- aortic balloon pump (IABP) (58.8% vs 21.1%, p = 0.0006) had significantly prolonged length of stay (LOS) which were defined as ≥ 20 days. Higher risks of hospital death were associated with age (OR 1.033, CI 1.002-1.064, p = 0.034) and IABP (OR 4.4, CI 1.4-14.5, p = 0.011). When combing all data, older mean age (58 years old vs 51 years old, p = 0.045), prior dialysis (100% vs 86.3%, p = 0.026), and inotrope usage (91% vs 80%, p = 0.011) were associated with the composite poor outcomes. Only 42 patients (22%) received hospice consultation during hospitalization. Hospice were consulted more for black patients (black 32.5% vs white 15.2%, p = 0.009). Conclusion In patients presenting with NICS, older age, prior dialysis, usage of inotropes were predictors of overall poor outcome. Mechanical circulatory support did not shorten inpatient LOS. Surprisingly, we did not identify any factors that increased the risk of readmission. Older age and IABP seemed to have higher inpatient mortality rate. Hospice was significantly underused in practice, especially in Caucasians. Future studies such as directly comparing non-ischemic and ischemic cardiomyopathy are needed to further understand NICS.

Cardiology
Do A, **Radjef R**, **Aurora L**, **Singh A**, **Tawney A**, **Kraus D**, **Jacobsen G**, and **McCord J**. Safety of evaluating for acute coronary syndrome in the emergency department using a modified heart score. *Journal of the American College of Cardiology* 2020; 75(11):127.

Background Chest pain is a common complaint in the emergency department (ED). The evaluation of these patients, which commonly involves stress testing, is time-consuming and costly. Prior retrospective studies demonstrated that a modified HEART score (m-HS) which combines the traditional HS and serial high-sensitivity cardiac troponin measurements could be used to identify low risk patients for discharge from the ED without further cardiac testing. The HS combines elements of the history, cardiac risk factors, and ECG. A HS ≤ 3 is considered low risk. In this study, we evaluated the safety of implementing this concept prospectively. Methods A prospective implementation trial conducted at an ED in 2017 included adult patients who were evaluated for possible acute coronary syndrome. Patients needed to have Siemens cardiac troponin I ultra < 40 ng/L (99th%) at 0 and 3 hours in addition to a HS ≤ 3 to be discharged without further testing. Thirty-day major adverse cardiovascular events (MACE) (death, acute myocardial infarction, revascularization procedure and readmission) were recorded. Results Of 422 patients, 33 were lost to follow up, resulting in 389 for analysis. The mean age was 50.6 ± 14.4. There were 161 (41.6%) male, 203 white (52.6%), 135 (35%) black and 48 (12.4%) classified as others. Baseline risk factors: 128 (33%) hypertension, 35 (9.1%) diabetes, 100 (25.8%) hyperlipidemia, 14 (3.6%) coronary artery disease, 98 (25.5%) active smoker, 25 (6.5%) with family history of cardiac disease. Among the 3 MACEs (0.8%) which were all 30-day readmissions, 2 (0.5%) were non-cardiac related while 1 (0.3%) was for atypical chest pain that was determined to be non-cardiac chest pain by cardiology consultation. This patient also had the only positive cardiac test (1.8%) (myocardial perfusion imaging with minimal ischemia) out of the 56 outpatient cardiac stress tests. Conclusion In the ED setting, m-HS is an effective tool to identify low risk patients who are safe for early discharge. At 30 days, no significant MACEs were detected and these low risk patients likely do not require stress testing.

Cardiology
Eng MH, **Kargoli F**, **Frisoli TM**, **Wang DD**, **Lee JC**, **Villablanca P**, **Guerrero M**, **Greenbaum A**, **So CY**, **Kang G**, **Wyman JF**, and **O'Neill WW**. Long-term outcomes of transcatheter mitral valve replacement using a balloon expandable valve. *Journal of the American College of Cardiology* 2020; 75(11):1307.

Background Transcatheter mitral valve replacement (TMVR) using commercially available balloon expandable valves via a percutaneous, transseptal access has previously been reported but only short-term outcomes have been discussed. Long-term outcomes of this percutaneous strategy should be elucidated. Methods From 1/2013-12/2018, retrospective review of all percutaneous TMVR using the Edwards Lifesciences, Sapien family of valves was reviewed. Clinical characteristics, procedure outcomes, and ambulatory clinic interactions were abstracted. Survival according to procedure type (valve-in-valve (ViV), valve-in-ring (ViR) and valve-in-mitral annuluar calcification (ViMAC)) was calculated using the Kaplan-Meier (KM) method. Results A total of 65 TMVR cases were performed between 2013-2018, some as part of the MITRAL trial. Using KM analysis, the 2 year survival approximates 50% and by 5 years, almost all of the patients have died (p=0.2579). Conclusion Despite the relatively lower risk of ViV procedures, this population did exhibit survival advantages compared to ViR and ViMAC. The TMVR population is a sick elderly cohort and this series bears the limitations of retrospective research and observations of the early learning curve of performing a complex procedure. Further investigation is warranted to better select patients.

Cardiology
Gibbs J, **McCord J**, **Moyer M**, **Jacobsen G**, and **Nowak RM**. A machine learning algorithm to predict acute myocardial infarction over 30 minutes. *Journal of the American College of Cardiology* 2020; 75(11):175.

Background Chest pain is a common presentation in the emergency department (ED). Variation in high sensitivity cardiac troponin I (hs-cTnI) by age and gender make diagnosis of AMI more challenging. Machine learning integrates these variables to allow more accurate and rapid evaluation of possible AMI. Methods We applied a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, gender, and hs-cTnI levels at time 0 and 30 minutes in 529 patients evaluated for possible AMI in a single urban ED. MI3 calculates a value from 0-100 reflecting the likelihood of AMI. Diagnosis of AMI was adjudicated by 2 independent physicians in accordance with the universal definition of AMI and required at least 1 hs-cTnI >99th% (Abbott Architect; 26 ng/L). Patients were followed at 30 days for major adverse cardiac events (MACE): death or AMI. Results There were 42 (7.9%) patients that had an AMI. Patients were divided into 3 groups by the MI3 score: low-risk (≤3.13), intermediate-risk (>3.13-51.0), and high-risk (>51.0) (Table). The sensitivity for AMI was 100% with a MI3 value ≤3.13 and 353 (67%) ruled-out for AMI at 30 minutes. At 30 days there were 2 (0.6%) MACEs (0 AMI, 2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 AMIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 AMIs, 2 cardiac deaths). Conclusion The MI3 algorithm had 100% sensitivity for AMI at 30 minutes and identified a low-risk cohort who may be considered for early discharge.

Cardiology
Gorgis S, **Ahluwalia G**, **Hana A**, **Fram G**, **Dabbagh M**, **Dhillon D**, **Murad A**, **Khan A**, **O'Neill WW**, **Kaatz S**, and **Wang DD**. To bleed or to clot: Stroke prevention strategies in patients with atrial fibrillation or flutter after bleeding. *Journal of the American College of Cardiology* 2020; 75(11):472.

Background Patients with atrial fibrillation or atrial flutter (AF) on anticoagulation (AC) for stroke prevention are at an increased risk of bleeding events. A common dilemma is deciding when to safely restart AC after bleeding. Studies have shown better outcomes with reinitiation of AC 7 days after stabilization of gastrointestinal bleeds and 4 weeks after intracranial hemorrhage. Our aim was to assess stroke prevention strategies upon discharge in patients with AF hospitalized with a bleeding event. Methods We retrospectively identified patients with AF on AC who were admitted with a bleeding event. The type of AC, form of bleeding, and CHADS2VASC were collected. Stroke prevention strategies on discharge were noted. Results Between January 2016 and August 2019, 174 patient with AF were hospitalized with a bleeding event. Nearly 10% of patients died, emphasizing the severity of this clinical situation. AC was restarted in 40% of patients upon discharge, 8.6% of patients were referred for LAA closure, and the remaining 40% were discharged without a stroke prevention strategy. CHADS2VASC did not differ among the groups. Of patients discharged on AC, 16% had a repeat bleeding episode requiring hospitalization within 30 days. Conclusion A significant portion of patients with AF hospitalized with a bleed were discharged with no definitive stroke prevention strategy. Barriers to restarting oral anticoagulation should lead to consideration of LAA closure as an alternative.

Cardiology
Gorgis S, **Dhillon D**, **Mishra K**, **Saleh A**, **Basir M**, and **Fuller B**. Aggressive acute coronary thrombosis in ulcerative colitis flare. *Journal of the American College of Cardiology* 2020; 75(11):3302.

Background Thromboembolic disease is a well-recognized complication of Ulcerative Colitis (UC), but coronary involvement is rare. Chest pain in UC flare should raise suspicion for acute coronary thrombosis. Case A 46 year old male with UC was admitted after 3 weeks of bloody diarrhea despite treatment with prednisone. He also reported severe refractory chest pain. ECG showed ST-segment elevation myocardial infarction in inferior/lateral leads. Emergent left heart catheterization (LHC) revealed a large thrombus in mid left anterior descending (LAD) artery with distal embolization. Aspiration thrombectomy was unsuccessful. A drug eluting stent (DES) was placed in mid-LAD. Intracoronary vasodilators improved distal coronary flow. The patient was continued on DAPT. Five days later, his chest pain recurred. Decision-making LHC showed acute in-stent thrombosis. Two DES were placed in overlapping fashion to proximal-mid LAD with PTCA on the diagonal. Persistent thrombus was treated with balloon inflations. The patient continued to be symptomatic, so an intra-aortic balloon bump (IABP)

was placed. He was continued on DAPT. Hemodynamics and chest pain improved in next 2 days, and IABP was removed. Conclusion Acute coronary thrombosis in pro-inflammatory states are challenging to treat, since both the underlying condition and treatment of UC are pro-thrombotic. Close monitoring and consideration of mechanical support devices may improve coronary perfusion while controlling the underlying flare.

Cardiology
Gupta RC, **Singh-Gupta V**, and **Sabbah HN**. Dysregulation of H11 Kinase in the Failing Human Left Ventricular Myocardium. *Journal of Heart and Lung Transplantation* 2020; 39(4):S357.

H.N. Sabbah, Medicine, Henry Ford Health System, Detroit, MI, United States

Purpose: Mitochondrial dysfunction and ongoing cardiomyocyte loss from apoptosis contribute to the progressive LV dysfunction characteristic of the heart failure (HF) state. H11 kinase (H11K) is a 22-kD serine/threonine kinase protein abundantly expressed in the heart. Dysregulation of H11K occurs in HF but its potential contribution to the progression of HF is not fully understood. Cardiac deletion of H11K in mice with LV pressure overload has been shown to result in LV dilation, reduced hypertrophy, impaired contractile function, increased interstitial fibrosis and faster transition to HF. In this study, we examined the expression of H11K in LV myocardium and separately in cytosolic and mitochondrial fractions of explanted failing human hearts. Methods: Sodium-dodecyl sulfate (SDS) extracts were prepared from LV tissue of 7 explanted failed human hearts due to idiopathic dilated cardiomyopathy (IDC), 7 due to ischemic cardiomyopathy (ICM) and of 7 non-failing human donor hearts (DNR). Western blotting and specific antibodies were used to assess protein levels of H11K normalized to the internal control GAPDH in homogenate and cytosolic fractions and protein levels of H11K normalized to the internal control porin in mitochondrial fractions. Results: There were no differences in GAPDH and porin among the 3 groups. H11K protein levels were significantly increased in LV homogenate and cytosolic fractions but significantly decreased in mitochondrial fractions of both IDC and ICM failed human hearts compared to DNR hearts (Table). Conclusion: The failing human LV manifests increased H11K protein levels independent of HF etiology. The reduced H11K protein level in mitochondria and its increase in the cytosolic compartment of failing cardiomyocytes represents an adverse maladaptation capable of reducing ATP synthesis by mitochondria and activation of cardiomyocyte pro-apoptotic cell death pathways in the cytosol respectively thus likely contributing to the progression of HF.

Cardiology
Hana A, **McCord J**, **Hudson MP**, **Cook B**, **Mueller C**, **Miller J**, **Moyer M**, **Akoegbe G**, **Jacobsen G**, and **Nowak RM**. Evaluation of acute myocardial infarction using a change in high-sensitivity cardiac troponin i over 1 hour. *Journal of the American College of Cardiology* 2020; 75(11):19.

Background The use of a high sensitivity cardiac troponin (hs-cTn) 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has been widely studied outside the United States (US). The algorithm divides patients into a rule-out, observation, or rule-in zone. This study evaluated the 0/1-hour algorithm using hs-cTnI in a US cohort. Methods Patients (N=552) at a single US urban emergency department (ED) were enrolled if they had symptoms suggestive of AMI which led the clinician to order cardiac markers. Patients with an ECG that led to immediate reperfusion therapy or required resuscitation were excluded. Baseline and 1-hour blood samples for hs-cTnI (Beckman Coulter) were obtained. AMI diagnosis was independently adjudicated by 2 physicians using the universal definition of AMI and measurement of hs-cTnT (Roche Diagnostics) at 0,1 and 3 hours. Results In total, 45(8.2%) had AMI during the index hospitalization while at 30 days events occurred in 14(2.5%) of patients (3 cardiac deaths, 2 non-cardiac deaths, 8 additional MIs, and 4 revascularizations). Hs-cTnI (0/1-hour) algorithm rule-out zone had high negative predictive value for AMI (99.6%), while the rule-in zone had moderate positive predictive value for AMI (56.6%). Conclusion We demonstrated that the rule-out zone of the 0/1-hour algorithm using a hs-cTnI assay has high negative predictive value for AMI and identifies patients with a good 30-day prognosis. These patients may be considered for early discharge from the ED.

Cardiology
Hariri IM, **Hannawi B**, **Grafton G**, **Nemeh HW**, **Chamogeorgakis T**, **Lanfear DE**, **Apostolou D**, **Selektor Y**, **Williams CT**, **Tita C**, **Tanaka D**, Myers SL, Kirklin JK, Pagani FD, and **Cowger JA**. Ventricular Assist Device Patient Phenotypes: What Attributes Describe Long Term Survival? *Journal of Heart and Lung Transplantation* 2020; 39(4):S181-S182.

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Purpose: Presently, 50% of patients on LVAD support are alive on therapy at 5 years. While preoperative (preop) variables can predict short term (ST) survival, correlates of long term (LT) survival remain poorly characterized. Using Intermacs-STS, we aim to identify preop and postoperative correlates of LT survival. Methods: Patients (n=16474) undergoing LVAD implant (2012-18) in Intermacs-STS were categorized as ST (survival ≤1 year postoperative, n=7483), mid-term (MT, 1-3 years, n=5976) and LT (>3 years, n=3015) survivors. Pre-implant characteristics and events during support were compared between the three groups to identify mortality correlates. Results: Compared with patients dying in the ST, LT survivors were more likely to be younger, not listed for transplant, with higher BSA and VAS scores and several lower risk preop characteristics but

differences between MT and LT survivors were not clinically significant (table). On multi-variable analysis, patients suffering post-LVAD stroke (HR 1.42, image), any major infection (HR 1.13), pump related infection (HR 1.19), and/or device malfunction (HR=1.22) (all p<0.001) were less likely to live >1 year, as were patients with a history of pulmonary disease (HR 1.19, 0.01), cancer (HR 1.26, p=0.01), CABG (HR 1.24, p<0.001), hepatitis (HR 1.54, p=0.002) and active smoking (1.44, p <0.001). Conclusion: The preop clinical features of ST and LT survivors vary significantly. Preop characteristics mainly select out early deaths, failing to accurately characterize survival after 1 year. LT survival is heavily influenced by device complications and pre-existing medical co-morbidities.

Cardiology
Nayak A, Hu Y, Ko Y, Mehta A, Liu C, Xie R, **Cowger JA**, Kirklin JK, Kormos RL, Simon MA, and Morris AA. Gender Differences in Early Mortality after LVAD: An IMACS Analysis. *Journal of Heart and Lung Transplantation* 2020; 39(4):S108.

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Purpose: Prior studies have observed higher mortality in women after LVAD; however a paucity of data exists on mediators of observed disparities. We used the International Registry for Mechanically Assisted Circulatory Support (IMACS) database to examine what clinical factors might mediate observed gender differences in mortality after LVAD. Methods: We analyzed 15,498 adults (>18 years) who received a CF LVAD from Jan 2013 - Sep 2017 (age: 56.0 ± 13.2 yrs, 20.8% female, 35.9% centrifugal pumps, median follow-up:13.4 [IQR 5.6, 25.9] months). Inverse probability weighted Cox proportional hazards model was used to estimate the association of female gender with all-cause mortality. Covariates included age, BSA, pump type, sodium, BUN, bilirubin, INR, hemoglobin, eGFR, MELD score, modified HeartMate II Risk Score (without center volume), INTERMACS profile, PADP and CI. Restricted cubic spline regression analysis was used to examine hazard ratio (HR) variation with time. Causal mediation analysis was performed to test plausible pre-implant mediators that were significantly different between genders (p<0.05). Results: Women were younger, less likely to have ischemic HF, and more likely to have a centrifugal pump (all p<0.001). Women had higher mortality after LVAD (adjusted HR: 1.38, 95% CI: 1.20 - 1.57, p<0.001). Gender*time interaction was significant (p<0.001), with women experiencing increased mortality during the first 3 months after implant (adj HR: 1.76, 95% CI: 1.42 - 2.19, p<0.001), but not after (adj HR: 1.17, 95% CI: 0.98-1.39, p=0.08). Increased tricuspid regurgitation (TR), and smaller LV end-diastolic diameter (LVEDD) at baseline mediated ~20.6% of the increased early hazard of death in females; however most of the mechanisms underlying the increased hazard remained unexplained. Conclusion: Women have higher post-LVAD mortality during the first 3 months after implant, that is partly mediated by increased TR and smaller LVEDD at baseline. Further studies are needed to explore additional underlying mechanisms.

Cardiology
Patel A, **Grafton G**, **Tita C**, Hannawi B, **Selektor Y**, **Chamogeorgakis T**, **Apostolou D**, **Lanfear DE**, **Williams CT**, **Nemeh HW**, and **Cowger JA**. Survival and Predictors of Mortality in Patients Undergoing RVAD Explant in IMACS. *Journal of Heart and Lung Transplantation* 2020; 39(4):S25-S26.

A. Patel, Cardiology, Beaumont Hospital, Dearborn, MI, United States

Purpose: Survival in patients requiring RVAD support is known to be poor. However, outcomes in those undergoing subsequent RVAD explant and predictors of mortality remain unknown. Methods: Of 16482 patients in IMACS, 723 patients had an isolated RVAD (n=29) or BiVAD (n=694) in place. Using Kaplan Meier methods, survival was estimated for the LVAD-only cohort and within the subgroup of RVAD/BiVAD patients with and without RVAD explant. Correlates of mortality in the RVAD explant group were identified with Cox multivariable regression. Results: Within the BiVAD group, 240 patients (33%) had an RVAD explant. Of these, 221 (92%) were performed for RV recovery, 17 (7.1%) for device malfunction and 2 (0.8%) were for other reasons. Survival at 1Y was 53±2.0% in the BiVAD group vs. 82±0.3% in LVAD-only patients (p<0.0001). Within the BiVAD group, patients undergoing RVAD explant had equivalent survival (1Y=54±2.5%) to those with ongoing BiVAD support (1Y=52±3.4%, p=0.54). BiVAD patients who died after RVAD explant were older, more likely to be BTT, and had higher preimplant creatinine (table). On multivariable analysis, older age, higher preimplant pulmonary systolic pressure, explant for RVAD dysfunction, and BTT indication predicted death after RVAD explant (table). Within the subgroup of BTT BiVAD (n=51) patients undergoing RVAD explant, survival was only 62% at 3 months. Conclusion: Patients undergoing RVAD explant, even for RV-recovery, have very poor survival. Patients who are transplant eligible with signs of RVAD dysfunction should be given urgent listing status. Rather than RVAD explant, BTT patients with signs of RV recovery may be better served with transplant.

Cardiology
Swanson B, **Salgia R**, **El-Bashir J**, and **Parikh S**. Accuracy of agitated saline contrast echocardiography for assessment of intracardiac shunting in preoperative liver transplant patients. *Journal of the American College of Cardiology* 2020; 75(11):1600.

Background Patent Foramen Ovale (PFO) is a common clinical condition that is found in up to 20% of adults. Transthoracic Echocardiography (TTE) with agitated saline contrast imaging (ASCi) has become the screening test of choice for PFO with

reported sensitivity of 99% and specificity of 85%. Exclusion of significant atrial level shunt is important prior to liver transplant but patients with end stage liver disease (ESLD) can be difficult to evaluate with ASCi given a high prevalence of intra-pulmonary shunting. We sought to evaluate if ASCi can accurately predict presence of atrial level shunting in patients with ESLD prior to transplant. Methods We performed a retrospective chart review of patients in our health system who underwent liver transplant between January 2016 and March of 2019. We screened for TTE with ASCi that was positive for presence of left sided microbubbles who also had a transesophageal echocardiogram (TEE). TTEs were reviewed and categorized as large if there were more than 20 left sided bubbles and early if they appeared within 5 cardiac cycles following opacification of right atrium. TEEs were then reviewed for presence of a PFO or atrial septal defect. Results Of the initial 317 patients that were screened, 124 had TTEs with ASCi performed of which, 51 (41%) were positive for shunt with rest or provocation. Of those, 25 (49%) had an adequate TEE performed in our system, of which 5 (20%) were found to have a PFO. Early vs. late positivity was not significantly associated with presence of PFO (19%vs 22% [p=0.84]) and of patients with early and large positive studies only 23% (3 of 13) had a PFO. Conclusion Our finding of only 20% of positive ASCi studies being associated with PFO is substantially lower than reported in prior literature. Furthermore, there does not seem to be any significant benefit utilizing early positivity or size of shunt to differentiate between PFO and intra-pulmonary shunting in ESLD patients. High prevalence of concomitant hepatopulmonary syndrome as well as high-flow states renders traditional measures of shunt localization and categorization inaccurate. These findings suggest that ASCi lacks adequate positive predictive value to assess for PFO in patients with ESLD.

Cardiology

Teuteberg J, Hiesinger W, **Cowger JA**, Rich J, Najjar SS, Jacoski M, Markham D, and Rogers J. More Frequent Hospitalizations and Worse Quality of Life with Late Right Heart Failure Compared to Early Right Heart Failure after Left Ventricular Assist as Destination Therapy. *Journal of Heart and Lung Transplantation* 2020; 39(4):S91-S92.

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Purpose: Right heart failure (RHF) is a common adverse event (AE) after left ventricular assist device (LVAD) implantation in destination therapy (DT) patients. However, the timing of RHF may have differential impact on outcomes, AEs and functionality in this population. Methods: All HVAD patients enrolled in the ENDURANCE and ENDURANCE Supplemental trials (n=604) were assessed for RHF as defined by Intermacs (IM) and separated into two groups: (1) early RHF (ERHF) - RHF prior to discharge, but not afterwards or (2) late RHF (LRHF) - RHF only after discharge. Patients were followed for 2 years. Results: Overall, patients with ERHF (n=176) and LRHF (n=33) had similar pre-implant characteristics: Mean Age 62.7 years, Male 75.6%, White 68.9%, Ischemic 52.2%, IM 1: 4.8%, and IM 2-3: 73.9%. Baseline hemodynamics were also similar: RA 11.6 mmHg, PA s/d/m 49.6/23.5 (32.6) mmHg, and PVR 3.0. There was no difference in 2-year survival in ERHF v. LRHF (64.2% v. 63.6%, p=0.96), despite more non-device infections in the ERHF group (Figure 1a), and significantly higher all-cause rehospitalizations in the LRHF group (4.1 vs 26.0 eppy, p<0.0001). Although baseline quality of life (QoL) and 6-minute walk (6MW) were similar, both were significantly worse at 3 and 12 months in LRHF (Figure 1b). Conclusion: Baseline characteristics, including hemodynamics, QOL and functional capacity were similar between ERHF and LRHF. LRHF is associated with more frequent all-cause hospitalizations, worse quality of life and functionality post-discharge despite a similar 2-year survival.

Center for Individualized and Genomic Medicine Research

Aurora L, **Snider J**, **Peterson E**, **Bryson T**, **Gui H**, **McCord J**, and **Lanfear DE**. Suppression of tumorigenicity 2 (st2) turbidimetric immunoassay and enzyme-linked immunosorbent assay: Predicting risk in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):883.

Background Heart failure (HF) is a major public health problem worldwide. Cardiac biomarkers aid in diagnosis, prognosis, risk stratification, and management of HF. Soluble suppression of tumorigenicity 2 (ST2) is a significant prognostic indicator in HF and seems to reflect response to treatment, particularly beta blockers. However, a limitation to its adoption is that it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and costly for laboratories. A turbidimetric immunoassay (TIA) that can run on a common chemistry analyzer could overcome this issue. We studied a novel TIA for ST2, comparing its performance to the validated ST2 (ELISA) in predicting survival in HF patients. Methods Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007-March 2015) at Henry Ford Hospital. Exclusion criteria included chronic supplemental oxygen or dialysis. Only patients with HF with reduced ejection fraction (<50%) and available plasma samples were included (n=727). ST2 measurements were obtained on the same sample using both TIA and ELISA. Correlation was studied between the measures and association with survival using Cox models. Area under the curve (AUC) improvement in Cox models was studied using method of Uno. Results Study cohort included 66.6% males, 46.2% African Americans with 43 deaths over 1 year. Correlation between TIA and ELISA was initially low with spearman coefficient 0.63. There were four outliers with ELISA value greater than the recommended maximum (200 ng/mL). Exclusion of these samples (n=723) resulted in inter-assay correlation 0.87. In this group with only ST2 as a variable, the TIA and ELISA values were significant associates of survival time with similar effect size (HR 4.8 and 3.7, respectively, p=0.001). In models adjusted for clinical risk factors (MAGGIC score), both versions of ST2 remained a significant predictor of survival and were of similar magnitude; the AUC improvement (from MAGGIC only, AUC=0.756) for TIA AUC=0.777 (p=0.035) and for

ELISA AUC=0.785 (p=0.028). Conclusion Novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Center for Individualized and Genomic Medicine Research
Bryson T, **Debbs JC**, **She R**, **Gui H**, **Luzum JA**, **Zeld N**, **Brawner CA**, **Keteyian SJ**, **Ehrman JK**, **Williams LK**, and **Lanfear DE**. A single nucleotide polymorphism within the rxra gene predicts a favorable response to exercise in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):1012.

Background Heart failure (HF) is a morbid condition associated with impaired exercise capacity. Exercise training is an effective strategy to improve functional capacity and quality of life. However, response to exercise training is highly variable and whether there are genetic factors that may impact response to exercise is unknown. We sought to identify genetic variants in patients with HF participating in cardiac rehabilitation (CR) that are associated with improvement in exercise capacity. Methods The study was conducted at Henry Ford Hospital in Detroit, MI. Patients enrolled in our genomic HF registry who had participated in CR at any time were selected (n=211). The primary endpoint was the change in metabolic equivalents of task (ΔMET) during CR, from week 1 to the last week of CR. All patients were genotyped using the Axiom biobank genotyping array with imputation using 1000 genomes reference panels (filter at R2 = 0.5 in both European and African ancestry). Genome-wide association testing was performed in linear models of ΔMET adjusted for baseline peak VO2, sex, age, and the first principal component (to control for race/population stratification). $p<5\times10-8$ was considered statistically significant. Results The study cohort consisted of 135 African ancestry and 76 European ancestry patients and 36.5% were women. One SNP, rs11103633, met genome-wide significance ($p = 8.86 \times 10-12$). Each additional allele was associated with 2.4 MET greater improvement (std err. = 0.331, $p = 8.859 \times 10-12$). This SNP, in the retinoid x receptor A gene (RXRA), encodes an orphan nuclear receptor belonging to the steroid super-family and acts in a variety of cellular processes. In cardiac and skeletal muscle, RXRA, is the necessary binding partner of PPARA, a key regulator of mitochondrial proliferation and fatty acid oxidation. Conclusion A genetic variant in the RXRA gene appears to impact the beneficial effect of exercise training in HF patients and could act via influencing cellular energetic capacity. This finding could lead to targeted exercise therapy or to novel pharmacologic methods of improving exercise response in HF patients. External validation and investigation of possible mechanisms are needed.

Center for Individualized and Genomic Medicine Research
Debbs J, **Bryson TD**, **Zeld N**, **Aurora L**, **Gui H**, **Luzum JA**, **Peterson E**, **She R**, **Williams LK**, and **Lanfear DE**. Somalogic st2 and ntprobnp assays predict heart failure mortality as effectively as the elisa assay. *Journal of the American College of Cardiology* 2020; 75(11):1091.

Background Biomarkers are critical for modern heart failure (HF) care. There are several established prognostic markers such as N-terminal pro-b-type natriuretic peptide (NTproBNP) and soluble suppressor of tumorgenicity 2 (ST2). Recent advances in multiplexing/multi-marker platforms offer faster and broader data generation. However, how these newer methods compare to FDA-approved ELISA-based assays remains unclear. The SOMALogic® SOMAscan assay is an aptamer-based technology that quantifies thousands of proteins simultaneously, including NTproBNP and ST2. The purpose of this study is to compare the test results and performance in predicting mortality using ELISA vs. SOMA for each marker. Methods Patients age ≥18 years and meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry Ford Hospital. Only patients with an ejection fraction < 50 % were used for the analysis (N= 687 for ST2 and N= 902 for NTproBNP). We tested the correlation of SOMA vs ELISA for each marker and report spearman correlation coefficient. We then tested each marker in Cox models adjusted for clinical risk score (MAGGIC) and compared the HR and model improvement (using calculated area under the curve [AUC]) for ELISA vs SOMA versions. Results First, we calculated the correlation between SOMA and ELISA values for both ST2 and NTproBNP. The correlation for ST2 was 0.74 ($p<0.001$) and NTproBNP was 0.88 ($p<0.001$), respectively. Next, we used a Cox proportional hazards model to predict death for the four variables corrected for the clinical score MAGGIC. Both versions of both markers were significantly associated with survival time. The hazard ratio for ELISA-ST2 was 1.12 (95% CI 1.09-1.16, $p < 0.001$) and for SOMA ST2 was 1.11 (95% CI 1.08-1.15, $p<0.001$). The hazard ratios for ELISA NTproBNP and SOMA NTproBNP were identical (1.12 95% CI 1.09-1.15, $p<0.001$). Uno's area under the ROC curve analysis showed there was no difference between marker versions in mortality prediction for ST2 nor for NTproBNP. Conclusion These results indicate that the SOMAscan assay results for ST2 and NTproBNP are strongly correlated to the standard ELISA versions and have equivalent prognostic information.

Emergency Medicine
Akarakian R, **White N**, **Nayak M**, **Jaskulka B**, and **Guyer C**. Interrater reliability among primary care sports medicine fellowship application reviewers. *Clinical Journal of Sport Medicine* 2020; 30(2):162.

R. Akarakian, Henry Ford Hospital, Detroit, MI, United States

Purpose: This study seeks to determine whether reviewers of fellowship applications agree upon differing elements in the evaluation process. To our knowledge, no published data currently exists for interrater reliability in assessment of Primary Care Sports Medicine fellowship applications. Methods: All fellowship candidate applications from a single cycle were

reviewed by 4 Primary Care Sports Medicine faculty at a large, urban hospital accepting 3 Primary Care Sports Medicine fellows. Each reviewer scored all applications independently using a scoring manual developed by the group. No formal training had been completed by the raters. Scoring was completed for 14 unique domains. Results: During a single application cycle (1 year), 53 unique applications underwent review. Reviewers achieve excellent interrater reliability when scoring USMLE step 1, 2, and 3 scores including weighted scores; event and team coverage; medical school performance during the first 2 years; letters of recommendation; and sports medicine rotation. Raters reach fair/good agreement in evaluating leadership experience; research experience; event and team coverage weighted scores; medical school clerkship performance; Medical Student Performance Evaluation; and sports medicine rotation weighted scores. Evaluators have poor agreement on scoring special skills; personal statement; and gestalt. Conclusions: Excellent and fair interrater reliability has been achieved for most of the application elements. Weighted scores have not proven consistently reliable among different reviewers. Future research could investigate why certain application domains yield less than excellent interrater reliability and if greater interrater reliability could be achieved with training raters on use of an application scoring guide. Significance: Fellowship directors would benefit from efficient and reliable methods to review applications. Developing application review tools that have high interrater reliability allows multiple stakeholders to participate in the application review process.

Emergency Medicine

Aurora L, **Snider J**, **Peterson E**, **Bryson T**, **Gui H**, **McCord J**, and **Lanfear DE**. Suppression of tumorigenicity 2 (st2) turbidimetric immunoassay and enzyme-linked immunosorbent assay: Predicting risk in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):883.

Background Heart failure (HF) is a major public health problem worldwide. Cardiac biomarkers aid in diagnosis, prognosis, risk stratification, and management of HF. Soluble suppression of tumorigenicity 2 (ST2) is a significant prognostic indicator in HF and seems to reflect response to treatment, particularly beta blockers. However, a limitation to its adoption is that it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and costly for laboratories. A turbidimetric immunoassay (TIA) that can run on a common chemistry analyzer could overcome this issue. We studied a novel TIA for ST2, comparing its performance to the validated ST2 (ELISA) in predicting survival in HF patients. Methods Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007-March 2015) at Henry Ford Hospital. Exclusion criteria included chronic supplemental oxygen or dialysis. Only patients with HF with reduced ejection fraction (<50%) and available plasma samples were included (n=727). ST2 measurements were obtained on the same sample using both TIA and ELISA. Correlation was studied between the measures and association with survival using Cox models. Area under the curve (AUC) improvement in Cox models was studied using method of Uno. Results Study cohort included 66.6% males, 46.2% African Americans with 43 deaths over 1 year. Correlation between TIA and ELISA was initially low with spearman coefficient 0.63. There were four outliers with ELISA value greater than the recommended maximum (200 ng/mL). Exclusion of these samples (n=723) resulted in inter-assay correlation 0.87. In this group with only ST2 as a variable, the TIA and ELISA values were significant associates of survival time with similar effect size (HR 4.8 and 3.7, respectively, p=0.001). In models adjusted for clinical risk factors (MAGGIC score), both versions of ST2 remained a significant predictor of survival and were of similar magnitude; the AUC improvement (from MAGGIC only, AUC=0.756) for TIA AUC=0.777 (p=0.035) and for ELISA AUC=0.785 (p=0.028). Conclusion Novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Emergency Medicine

Dagher C, **Modi S**, **Gandhi N**, **Binz S**, and **Rabbani B**. A rare case of spontaneous asymptomatic ventricular tachycardia due to arrhythmogenic right ventricular dysplasia (arvd). *Journal of the American College of Cardiology* 2020; 75(11):2578.

Background Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy that can lead to heart failure and sudden cardiac death. This challenging diagnosis is based on clinical, electrocardiographic, and radiographic findings, along with suggestive genetic testing. Case A 72 year old man presented with stable ventricular tachycardia. 2D echo demonstrated an EF of 45%, grade I diastolic dysfunction, and LV hypokinesis. Left heart catheterization revealed non-obstructive coronary disease. Cardiac MRI revealed: dilated RV with basal RV wall akinesis; RV end-diastolic volume index 134 mL/m2, global LV hypokinesis, an area of mid-myocardial delayed gadolinium enhancement of the mid-inferoseptal LV myocardium at the RV insertion point, and no associated lymphadenopathy. Subsequent Invitae genetic testing revealed desmoplakin (DSP) gene mutation. The patient was managed with AICD placement and sotolol initiation. Decision-making In this rare case of asymptomatic stable VT, cardiac MRI findings met major criteria for ARVD. The differential diagnosis included cardiac sarcoidosis, however contrast enhanced CT imaging did not reveal hilar lymphadenopathy, and cardiac MRI was unimpressive for sarcoidosis. Furthermore, DSP gene mutation is associated with autosomal dominant ARVD. Conclusion The diagnosis of ARVD can be determined with cardiac imaging and genetic testing. It is important to rule out similar diagnoses by looking for differentiating features, such as hilar lymphadenopathy and myocardial granulomatous disease which is frequently seen in cardiac sarcoidosis, but not in ARVD.

Emergency Medicine

Do A, **Radjef R**, **Aurora L**, **Singh A**, **Tawney A**, **Kraus D**, **Jacobsen G**, and **McCord J**. Safety of evaluating for acute coronary syndrome in the emergency department using a modified heart score. *Journal of the American College of Cardiology* 2020; 75(11):127.

Background Chest pain is a common complaint in the emergency department (ED). The evaluation of these patients, which commonly involves stress testing, is time-consuming and costly. Prior retrospective studies demonstrated that a modified HEART score (m-HS) which combines the traditional HS and serial high-sensitivity cardiac troponin measurements could be used to identify low risk patients for discharge from the ED without further cardiac testing. The HS combines elements of the history, cardiac risk factors, and ECG. A HS ≤ 3 is considered low risk. In this study, we evaluated the safety of implementing this concept prospectively. Methods A prospective implementation trial conducted at an ED in 2017 included adult patients who were evaluated for possible acute coronary syndrome. Patients needed to have Siemens cardiac troponin I ultra < 40 ng/L (99th%) at 0 and 3 hours in addition to a HS ≤ 3 to be discharged without further testing. Thirty-day major adverse cardiovascular events (MACE) (death, acute myocardial infarction, revascularization procedure and readmission) were recorded. Results Of 422 patients, 33 were lost to follow up, resulting in 389 for analysis. The mean age was 50.6 ± 14.4. There were 161 (41.6%) male, 203 white (52.6%), 135 (35%) black and 48 (12.4%) classified as others. Baseline risk factors: 128 (33%) hypertension, 35 (9.1%) diabetes, 100 (25.8%) hyperlipidemia, 14 (3.6%) coronary artery disease, 98 (25.5%) active smoker, 25 (6.5%) with family history of cardiac disease. Among the 3 MACEs (0.8%) which were all 30-day readmissions, 2 (0.5%) were non-cardiac related while 1 (0.3%) was for atypical chest pain that was determined to be non-cardiac chest pain by cardiology consultation. This patient also had the only positive cardiac test (1.8%) (myocardial perfusion imaging with minimal ischemia) out of the 56 outpatient cardiac stress tests. Conclusion In the ED setting, m-HS is an effective tool to identify low risk patients who are safe for early discharge. At 30 days, no significant MACEs were detected and these low risk patients likely do not require stress testing.

Emergency Medicine

Gibbs J, **McCord J**, **Moyer M**, **Jacobsen G**, and **Nowak RM**. A machine learning algorithm to predict acute myocardial infarction over 30 minutes. *Journal of the American College of Cardiology* 2020; 75(11):175.

Background Chest pain is a common presentation in the emergency department (ED). Variation in high sensitivity cardiac troponin I (hs-cTnI) by age and gender make diagnosis of AMI more challenging. Machine learning integrates these variables to allow more accurate and rapid evaluation of possible AMI. Methods We applied a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, gender, and hs-cTnI levels at time 0 and 30 minutes in 529 patients evaluated for possible AMI in a single urban ED. MI3 calculates a value from 0-100 reflecting the likelihood of AMI. Diagnosis of AMI was adjudicated by 2 independent physicians in accordance with the universal definition of AMI and required at least 1 hs-cTnI >99th% (Abbott Architect; 26 ng/L). Patients were followed at 30 days for major adverse cardiac events (MACE): death or AMI. Results There were 42 (7.9%) patients that had an AMI. Patients were divided into 3 groups by the MI3 score: low-risk (≤3.13), intermediate-risk (>3.13-51.0), and high-risk (>51.0) (Table). The sensitivity for AMI was 100% with a MI3 value ≤3.13 and 353 (67%) ruled-out for AMI at 30 minutes. At 30 days there were 2 (0.6%) MACEs (0 AMI, 2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 AMIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 AMIs, 2 cardiac deaths). Conclusion The MI3 algorithm had 100% sensitivity for AMI at 30 minutes and identified a low-risk cohort who may be considered for early discharge.

Emergency Medicine

Hana A, **McCord J**, **Hudson MP**, **Cook B**, **Mueller C**, **Miller J**, **Moyer M**, **Akoegbe G**, **Jacobsen G**, and **Nowak RM**. Evaluation of acute myocardial infarction using a change in high-sensitivity cardiac troponin i over 1 hour. *Journal of the American College of Cardiology* 2020; 75(11):19.

Background The use of a high sensitivity cardiac troponin (hs-cTn) 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has been widely studied outside the United States (US). The algorithm divides patients into a rule-out, observation, or rule-in zone. This study evaluated the 0/1-hour algorithm using hs-cTnI in a US cohort. Methods Patients (N=552) at a single US urban emergency department (ED) were enrolled if they had symptoms suggestive of AMI which led the clinician to order cardiac markers. Patients with an ECG that led to immediate reperfusion therapy or required resuscitation were excluded. Baseline and 1-hour blood samples for hs-cTnI (Beckman Coulter) were obtained. AMI diagnosis was independently adjudicated by 2 physicians using the universal definition of AMI and measurement of hs-cTnT (Roche Diagnostics) at 0,1 and 3 hours. Results In total, 45(8.2%) had AMI during the index hospitalization while at 30 days events occurred in 14(2.5%) of patients (3 cardiac deaths, 2 non-cardiac deaths, 8 additional MIs, and 4 revascularizations). Hs-cTnI (0/1-hour) algorithm rule-out zone had high negative predictive value for AMI (99.6%), while the rule-in zone had moderate positive predictive value for AMI (56.6%). Conclusion We demonstrated that the rule-out zone of the 0/1-hour algorithm using a hs-cTnI assay has high negative predictive value for AMI and identifies patients with a good 30-day prognosis. These patients may be considered for early discharge from the ED.

Endocrinology and Metabolism

Gal R, Cohen N, **Kruger D**, Beck R, Bergenstal R, Calhoun P, **Cushman T**, Hoffmann A, Hood K, Johnson M, McArthur T, Olson B, Weinstock R, and Aleppo G. A study to assess initiation of CGM outside of a clinic. *Diabetes Technology and Therapeutics* 2020; 22:A-40.

R. Gal, Jaeb Center for Health Research, Remote Cgm, Tampa, United States

Background and Aims: Our study assessed the feasibility of remotely initiating continuous glucose monitoring (CGM) at home outside of the clinic, as a means to expand CGM access. Methods: 35 adults 19-80 years old (mean HbA1c 8.5%) with T1D (N = 28) or T2D (N = 7) using basal-bolus insulin (7 pump, 28 MDI) with no CGM use within 24 months of enrollment were assigned a certified diabetes educator to provide remote CGM training via videoconference and/or phone. Participants selected either the Dexcom G6 or Abbott Free Style Libre and were followed for 12 weeks to assess adherence to CGM use and glycemic control. Results: One participant withdrew immediately after CGM initiation training. The remaining 34 were using CGM at 12 weeks; median CGM usage in the final 4 weeks was 7.0 days/ week (interquartile range 6.7 to 7.0). One additional participant did not have an HbA1c at 12 weeks. Mean HbA1c reduction from baseline to 12 weeks was 1.1% (P < 0.001). Mean time in range (70-180mg/dL) was 59% over the 12 weeks compared with baseline time in range estimated from HbA1c of 48%. Over 12 weeks, median time <70mg/dL was 1.4% and <54mg/dL was 0.2%. Surveys indicated substantial benefit of CGM with reduced diabetes distress, increased satisfaction with glucose monitoring and fewer perceived technology barriers to management. Conclusions: Remote CGM initiation and training was successful in achieving sustained CGM use and improved glycemic control after 12 weeks. If widely implemented, this approach could substantially increase the adoption of CGM by people with diabetes using insulin.

Gastroenterology

Swanson B, **Salgia R**, **El-Bashir J**, and **Parikh S**. Accuracy of agitated saline contrast echocardiography for assessment of intracardiac shunting in preoperative liver transplant patients. *Journal of the American College of Cardiology* 2020; 75(11):1600.

Background Patent Foramen Ovale (PFO) is a common clinical condition that is found in up to 20% of adults. Transthoracic Echocardiography (TTE) with agitated saline contrast imaging (ASCi) has become the screening test of choice for PFO with reported sensitivity of 99% and specificity of 85%. Exclusion of significant atrial level shunt is important prior to liver transplant but patients with end stage liver disease (ESLD) can be difficult to evaluate with ASCi given a high prevalence of intra-pulmonary shunting. We sought to evaluate if ASCi can accurately predict presence of atrial level shunting in patients with ESLD prior to transplant. Methods We performed a retrospective chart review of patients in our health system who underwent liver transplant between January 2016 and March of 2019. We screened for TTE with ASCi that was positive for presence of left sided microbubbles who also had a transesophageal echocardiogram (TEE). TTEs were reviewed and categorized as large if there were more than 20 left sided bubbles and early if they appeared within 5 cardiac cycles following opacification of right atrium. TEEs were then reviewed for presence of a PFO or atrial septal defect. Results Of the initial 317 patients that were screened, 124 had TTEs with ASCi performed of which, 51 (41%) were positive for shunt with rest or provocation. Of those, 25 (49%) had an adequate TEE performed in our system, of which 5 (20%) were found to have a PFO. Early vs. late positivity was not significantly associated with presence of PFO (19%vs 22% [p=0.84]) and of patients with early and large positive studies only 23% (3 of 13) had a PFO. Conclusion Our finding of only 20% of positive ASCi studies being associated with PFO is substantially lower than reported in prior literature. Furthermore, there does not seem to be any significant benefit utilizing early positivity or size of shunt to differentiate between PFO and intra-pulmonary shunting in ESLD patients. High prevalence of concomitant hepatopulmonary syndrome as well as high-flow states renders traditional measures of shunt localization and categorization inaccurate. These findings suggest that ASCi lacks adequate positive predictive value to assess for PFO in patients with ESLD.

Hematology-Oncology

Ghanem AI, **Schymick MA**, **Bachiri S**, **Khalil R**, **Burmeister C**, **Sheqwara J**, **Chang S**, **Ghanem T**, and **Siddiqui F**. Does Age Impact Outcomes of Oropharyngeal squamous cell carcinoma? *International Journal of Radiation Oncology Biology Physics* 2020; 106(5):1141.

Purpose/Objective(s): It is well-established that human papilloma virus (HPV) positive (+ve) oropharyngeal (OP) squamous cell carcinoma (SCC) carries a better overall prognosis than HPV negative (-ve) tumors. We sought to investigate the impact of age upon survival endpoints for HPV +ve and -ve OP SCC as well as the differences in acute radiotherapy (RT) toxicity. Materials/Methods: We included all OP SCC cases treated definitively between 2010-2017. All cases underwent either surgery ± adjuvant RT; or definitive RT; ± chemotherapy according to the multidisciplinary tumor board decision. After determining p16 status we dichotomized each HPV group by age at diagnosis into old (> or = 65 years) and young (<65 years) sub-groups. Patients' demographics, clinico-pathological data and treatment modalities were compared across age groups for both HPV sub-types. Log-rank test and Kaplan-Meier curves were utilized to measure effect of age on overall (OS), local recurrence free (LRFS) and distant metastases free (DMFS) survival for HPV +ve and -ve. For patients receiving RT we compared weight loss, feeding tube insertion, treatment breaks and hospitalization during RT as parameters for acute toxicity across age

groups. Results: We identified 217 OP SCC who fit our inclusion criteria. Seventy percent were HPV+ve, males were 82%, mean age at diagnosis was 61 years, 75% were white, 67% were ever smokers and 54% were frequent/heavy alcohol drinkers. According to AJCC 7th edition, Stages III and IVA formed 87%; however, these were regrouped as stage I (51%) and stage IVA (62%) as prevalent stages for HPV+ve and -ve respectively as per AJCC 8th version. Definitive CRT was utilized in 58% and surgery ± adjuvant therapy in 31% of the study cohort. For HPV+ve sub-group, 31% were old (n=47); whereas they constituted 40% (n=27) of HPV-ve cases. Clinicopathological and treatment characteristics were generally equivalent among age groups except that HPV +ve younger patients had more adequate surgical margins (≥5mm) (78% vs 36%; p=0.03) than old; and HPV-ve old cases had a trend towards more utilization of concomitant cetuximab (30% vs 13%; p=0.09) than younger ones. All endpoints were not significantly different between old vs young HPV+ve cases with 2-year OS and LRFS of (64% vs 59%; p=0.41 and 88% vs 87%; p=0.98 for both respectively). Similar outcomes were observed between study age groups for HPV-ve cases (p>0.05 for all endpoints). Hospitalization during RT was more frequent in old patients (44% vs 28%; p=0.03). Median weight loss during RT was 9.5% (0-22%) vs 9.3% (0-17%) for old vs young (p=0.35) and RT breaks were also non-significant (39% vs 27%, p=0.8). Feeding tubes were inserted after RT initiation in 41% of old and 36% in young (p=0.5). Conclusion: Older patients with OP SCC have equivalent outcomes compared to younger ones irrespective of HPV status. Optimal treatments must be offered following standard of care as determined by a multi-disciplinary group of providers.

Hematology-Oncology

Graff JN, Antonarakis ES, Hoimes CJ, Tagawa ST, **Hwang C**, Kilari D, Ten Tije AJ, Omlin AG, McDermott RS, Vaishampayan UN, Elliott A, Wu H, Kim J, Schloss C, and De Bono JS. Pembrolizumab (pembro) plus enzalutamide (enza) for enza-resistant metastatic castration-resistant prostate cancer (mCRPC): KEYNOTE-199 cohorts 4-5. *Journal of Clinical Oncology* 2020; 38(6).

J.N. Graff

Background: KEYNOTE-199 (NCT02787005) is a multicohort phase 2 study. Cohort (C)4 (RECIST-measurable disease) and C5 (bone-predominant disease) consist of chemotherapy-naive patients (pts) with mCRPC treated with enza + pembro after progression with enza. Results for C4 and C5 presented. Methods: Pts with or without prior abiraterone had clinically meaningful response/benefit to enza followed by disease progression. Pts received pembro 200 mg Q3W with continuation of enza for up to 35 cycles or until progression/intolerable toxicity. Primary end point: ORR, blinded independent central review (C4). Secondary end points: DCR, PSA response rate (>50% reduction), rPFS, OS, and safety (C4, C5); DOR (C4). Results: Of 126 pts (C4, 81 ; C5, 45), 107 discontinued, primarily due to progression. Median follow-up: 13.7 mo (C4, 11.8; C5, 18.6). ORR (95% CI) for pts with measurable disease was 12% (6-22) in C4; DCR for all pts: 51% (39-62) in C4 and 51 % (36-66) in C5 (Table). Any grade/grade 3-5 treatment-related AEs occurred in 75%/26% pts in C4 and 69%/24% in C5. Two pts in C4 died of immune-related AEs (Miller Fisher syndrome and myasthenia gravis). Incidence of any grade/grade 3-4 rash (regardless of treatment relatedness) was higher than previously reported for individual agents (33%/6%). All except one pt (grade 3 treated with IV steroids) were treated with oral/topical steroids or had no intervention. Conclusions: Addition of pembro to enza following enza resistance showed modest antitumor activity in pts with RECIST-measurable and bone-predominant mCRPC. Combination had manageable safety and is being evaluated in a phase 3 trial.

Hematology-Oncology

Sak M, Duric N, Pfeiffer R, Sherman M, Littrup P, Simon M, Gorski D, Albrecht T, **Ali H**, Brem R, Fan S, and Gierach G. Tissue sound speed is more strongly associated with breast cancer risk than mammographic percent density: A comparative case-control study. *Cancer Research* 2020; 80(4).

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PURPOSE. Increased mammographic percent density (MPD) is a strong independent risk factor for developing breast cancer. Previous studies have shown that tissue sound speed, derived from ultrasound tomography, is a surrogate biomarker of MPD. We examined associations of sound speed and MPD with breast cancer risk in a casecontrol study. METHOD AND MATERIALS. We evaluated breast cancer risk associated with sound speed and MPD in a casecontrol study involving 59 participants with recent breast cancer diagnoses (cases, aged 30-70 years) and 150 participants with no history of breast cancer (controls), who were matched to cases on age, race, and menopausal status. The cases and controls were imaged with both ultrasound tomography (UST) and mammography. In cases, breast density was measured pre-treatment in the contralateral breast to avoid potential influences of tumor-related changes on MPD or sound speed. In controls, a randomly selected breast was imaged. The ultrasound tomography images were used to estimate the volume averaged sound speed of the breast, and the Cumulus software package was applied to mammograms to determine MPD. Odds Ratios (ORs) and 95% Confidence Intervals (CIs), adjusted for matching factors, were calculated for the relation of quartiles of MPD and sound speed with breast cancer risk. OR differences were tested using a bootstrap approach. RESULTS. MPD was associated with elevated breast cancer risk compared to controls, consistent with previous studies, although the trend did not reach statistical significance (OR per quartile=1.28, 95%CI: 0.95, 1.73; ptrend =0.10). In contrast, elevated sound speed was significantly associated with increased breast cancer risk in a dose-response fashion (OR per quartile=1.79, 95%CI: 1.30, 2.48; ptrend =0.0004). The OR-trend for sound speed was statistically significantly different from that observed for MPD (p=0.01).

DISCUSSION. Our case-control study showed that increasing quartiles of whole breast sound speed were consistently and more strongly associated with increasing breast cancer risk than quartiles of MPD. These results show promise for UST's role in breast cancer risk stratification. CONCLUSION. Elevated breast density strongly increases breast cancer risk. UST has the potential to provide a more accurate, non-ionizing method for assessing breast density and its associated breast cancer risk.

Internal Medicine
Alrayes H, **Radjef R**, and **Tita C**. Cardiogenic shock: A bittersweet diagnosis. *Journal of the American College of Cardiology* 2020; 75(11):2476.

Background Sweet's syndrome (SS), also known as febrile neutrophilic dermatosis, is a rare reactive phenomenon characterized by a pattern of clinical symptoms with physical and pathologic manifestations. We present a case of SS with cardiac, dermatologic, and neurologic manifestations. Case A 73-year-old female presented with slurred speech for several hours, along with preceding fevers and flu-like symptoms. Initial stroke and infectious workups were negative. A transthoracic echocardiogram (TTE) was unremarkable. Two days later, she became tachypneic with pulmonary edema on chest X-ray. A repeat TTE showed an EF of 30% with global hypokinesis. A left heart catheterization revealed no obstructive coronary artery disease. She was intubated and an Impella CP was placed with Dobutamine for concerns of cardiogenic shock. She remained febrile with altered mentation despite an unremarkable infectious workup. ESR and CRP were elevated to 45mm/hr and 19.2mg/dL, respectively. WBC was elevated to 13,400 with a 92% neutrophil predominance. Several days after admission, pink papules on the patient's lower extremities were discovered, biopsied, and revealed neutrophilic dermatitis with negative infectious stains. Decision-making This patient fulfilled two major criteria required for the diagnosis of SS, including the abrupt onset of painful erythematous nodules, and histopathologic evidence of dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis. She met two of the four minor criteria, including pyrexia and at least three abnormal laboratory values (elevated ESR > 20mm/hr, positive CRP, >8000 leukocytes, >70% neutrophils). Given the fulfillment of her criteria and lack of an alternative etiology behind her shock, the patient was started on 1mg/kg of prednisone daily. She had rapid improvement in her skin papules, mentation, and cardiogenic shock, with discontinuation of her Impella CP and Dobutamine within 24 hours. Repeat TTE showed an EF of 53%. Conclusion This case highlights SS as a rare cause of cardiogenic shock and encephalitis and illustrates the importance of maintaining a broad differential diagnosis when determining the etiology of cardiogenic shock.

Internal Medicine
Altibi A, **Al Jebbawi L**, **Patel BD**, **Vuong HG**, and **Masri AM**. Clinicopathological implications of prkar1a mutation in patients with cardiac myxoma: Pooled data analysis from 101 myxoma cases. *Journal of the American College of Cardiology* 2020; 75(11):1195.

Background PRKAR1A is a novel genetic mutation traditionally linked to Carney Complex (CNC) and cardiac myxoma. We hypothesized that presence of PRKAR1A mutation (Mut+) identifies a subset of cardiac myxoma patients with distinct clinicopathologic features from those without the mutation (Mut-). Methods We searched PubMed, Web of Science, and Scopus from inception to September 2019 to identify individual patient data of cardiac myxoma cases. Cases were included if the mutational status of PRKAR1A gene was reported. Extracted data included: mutational status, age at diagnosis, gender, location of myxoma, multifocality, recurrence, and concomitant extra-cardiac myxomas. Results Twenty-six articles reporting on 101 individual myxoma cases with known PRKAR1A mutational status were identified. Mean age at diagnosis was 36.6 ± 16.1 years. Two-third of the cases were females (n=62), 82% of cases were Mut+ (n=83), and 93.9% (n=78) met criteria for CNC. Mean age at diagnosis for the Mut+ group and Mut- group were 35.2 and 43.3 years, retrospectively (p-value = 0.058). Overall, left atrium was the most common location for myxomas (58%). While all myxoma cases in the Mut- group were localized to the left atrium, multi-chamber myxomas occurred exclusively in patients with the mutation (p-value= 0.003). Similarly, 96% of all cases of multiple cardiac myxomas occurred in the Mut+ group. The risk of developing multiple myxomas was significantly higher in the Mut+ compared to Mut- group (RR= 4.1, p-value= 0.03). Myxoma recurrence after resection occurred in 20.8% (n=21) of all cases, 20 of them were in the Mut+ group. Time duration from surgical resection to recurrence had a mean of 7.3 ± 5.7 years. Similarly, Mut+ carried a significantly higher risk of developing extra-cardiac myxomas compared to Mut- (p-value= 0.009), as 90.6% of extra-cardiac myxomas occurred in individuals harboring the mutation. Conclusion PRKAR1A mutation identifies a subset of cardiac myxoma patients with dismal clinicopathologic features, including higher risk for multifocality, recurrence, and developing extra-cardiac myxomas. Screening for PRKAR1A mutation might need to be considered routinely at the time of diagnosis.

Internal Medicine
Altibi A, **Asghar S**, **Al Jebbawi LN**, **Battisha A**, and **Kak V**. Cryptococcus neoformans automated implantable cardioverter-defibrillator (aicd) endocarditis: A challenging case of a rare fungal endocarditis. *Journal of the American College of Cardiology* 2020; 75(11):2973.

Background Fungal endocarditis is a rare form of endocarditis accounting for less than 2% of all cases. Common offending pathogens include: Candida and Aspergillus. Cryptococcal endocarditis is extremely rare with only ten prior cases reported. To our knowledge, only one prior case of AICD-associated cryptococcal endocarditis was described in the literature. Case A 57-

year-old female patient presented to the emergency department with headache, fatigue, and a near-syncope event. Her past medical history includes ischemic cardiomyopathy with AICD implantation and vasculitis (on prednisone and cyclophosphamide). Examination was unremarkable. CT scan of the head was negative for acute intracranial process. In lieu of persistent headache, lumbar puncture (LP) was performed revealing lymphocytic pleocytosis. Transthoracic and transesophageal echocardiography revealed vegetations on the ventricular lead of the defibrillator measuring 2.0 × 0.67 cm. Decision-making Patient was initially started on IV vancomycin before adding flucanzole empirically to the regimen given her immunosuppressed status and lymphocytic pleocytosis on LP. On the 4th day of admission, two sets of blood cultures grew Cryptococcal Neoformans. Hence, patient was switched into amphotericin B and flucytosine for 2 weeks before resuming fluconazole. Concomitantly, a decision was made to remove the AICD device along with leads to achieve source control. Despite lack of data on proper duration of treatment, high-dose fluconazole was continued for a total of 4 weeks (one year is typically recommended in cryptococcal meningitis). Patient improved gradually before achieving complete recovery, without relapse. Conclusion Cryptococcal endocarditis is an extremely rare event with no prior standardized treatment protocol established. Hence, treatment duration with antifungals need to be individualized. Following an initial inductive phase, prolonged suppressive therapy with Fluconazole might be warranted to prevent recurrence, especially in immunocompromised patients. AICD-related infections mandate device removal. Surgical intervention has no clear indication but should be considered.

Internal Medicine

Altibi A, **Jebbawi LA**, and **Patel BD**. LVOT obstruction and severe aortic regurgitation caused by anterolateral muscle bundle of the left ventricle: The embryologic remnant of the bulbo-atrioventricular flange. *Journal of the American College of Cardiology* 2020; 75(11):2972.

Background An anterolateral muscle bundle runs along the wall of the left ventricular outflow tract (LVOT) and may extend up to the level of aortic valve (AV). The muscle bundle may occasionally bulge into the LVOT without causing significant obstruction. Case A 53 year old female patient presented with worsening chest discomfort and exercise intolerance. Initial TTE showed ejection fraction of 56% and AV area (AVA) of 0.66 cm2 indicative of severe stenosis, but with peak gradient of 29 mmHg. However, TEE showed very mild aortic stenosis with 3D aortic valve planimetry measuring 1.8 cm2. TEE showed hypertrophied basal septum (thick membrane connecting mitral leaflet with AV). The thickened septum was causing severe LVOT obstruction (LVOT area was 0.85 cm2) and a tertiary cord was attached to its base. The septum attaches to the right coronary cusp causing restriction and severe regurgitation. Cardiac catheterization showed severe stenosis at the LVOT. Decision-making The findings are indicative for anterolateral muscle bundle causing LVOT obstruction, rather than primary AV pathology. Hence, patient underwent septal myectomy, resection of subaortic membrane, and AV repair successfully. Post-myomectomy TTE showed minimal stenosis with AVA of 1.34 cm2. Conclusion LVOT obstruction can be caused by hypertrophied anterolateral muscle bundle in the absence of primary valvular pathology. Proper diagnosis is crucial since resection of the subaortic membrane and septal myectomy is the treatment of choice.

Internal Medicine

Butera B, **Modi K**, **Cowger JA**, and **Russell C**. Eosinophilic myocarditis in a patient with biopsy proven systemic sarcoidosis who was referred for bradycardia. *Journal of the American College of Cardiology* 2020; 75(11):3098.

Background Eosinophilic myocarditis (EM) is an understudied and often missed diagnosis whose constellation of symptoms are frequently attributed to other morbidities. Case A 57-year-old woman with mediastinal lymphadenopathy (Figure 1A), uveitis, celiac lymph node biopsy in 2013 demonstrating noncaseating granulomas and a questionable prior diagnosis of hypereosinophilic syndrome presented to establish care for dizziness and bradycardia (Figure 1B). She had a stroke in 2004 with an echocardiographic diagnosis of left ventricular (LV) thrombus (Figure 1C-D) for which she was prescribed coumadin. She exhibited a pruritic maculopapular skin rash on several areas of her body (Figure 1E-F) and laboratory tests showed a history of peripheral eosinophilia. Decision-making There was concern for cardiac sarcoidosis or undiagnosed EM. A cardiac MRI demonstrated thickening of the LV apex (Figure G-H) with corresponding sub endocardial perfusion defect and late gadolinium enhancement, without LV thrombus. These findings were consistent with late stage myocardial fibrosis from EM. Reliance on the single imaging modality of echocardiogram resulted in past misdiagnosis of thrombus and delayed therapy of myocardial fibrosis in this patient. Conclusion This case highlights the need for awareness of EM and the importance of considering alternative or additional diagnoses in patients with complex past medical histories. An association of sarcoidosis and EM has not yet been reported in the literature.

Internal Medicine

Butera B, **Modi K**, **Klingler D**, **McCord J**, and **Ananthasubramaniam K**. All that glitters is not gold; due diligence when interpreting pyrophosphate cardiac scans to avoid misdiagnosis of transthyretin cardiac amyloidosis. *Journal of the American College of Cardiology* 2020; 75(11):3132.

Background Technetium-99m pyrophosphate (PYP) nuclear scan is currently considered the noninvasive test of choice for transthyretin cardiac amyloidosis (TTRCA) with a heart to lung ratio greater than 1.5 suggesting TTRCA. Case An 81 year old female presented to cardiology clinic for evaluation of previously diagnosed TTRCA. Her electrocardiogram (Figure 1A)

showed bifasicular block and an echocardiogram (Figure 1B-D) demonstrated diffuse left ventricular hypertrophy. As part of the workup a PYP scan (Figure 1E) was performed and interpreted to have a planar ratio of 1.5 with Grade 2 Tc-99m pyrophosphate uptake, consistent with TTRCA. Decision-making While planar images appeared to show some cardiac uptake equal to that of bone in the contralateral thorax, review of the single-photon emission computed tomography (SPECT) images (Figure 1F) and blood pool reconstruction images (Figure 1G) demonstrated only bone uptake of the tracer, on a background of blood pool activity with no myocardial uptake. Subsequent testing revealed elevated free kappa light chains and the patient was referred to a hematologist for further evaluation. Conclusion Light chain amyloidosis should be first ruled out given implications for treatment. Furthermore, errors in diagnosis of TTRCA can occur when only planar images and ratio cutoffs are used. Due diligence to evaluate SPECT data to confirm myocardial Tc-99m PYP uptake is important to confirm the diagnosis of TTRCA.

Internal Medicine
Dagher C, **Modi S**, **Gandhi N**, **Binz S**, and **Rabbani B**. A rare case of spontaneous asymptomatic ventricular tachycardia due to arrhythmogenic right ventricular dysplasia (arvd). *Journal of the American College of Cardiology* 2020; 75(11):2578.

Background Arrhythmogenic right ventricular dysplasia (ARVD) is an inherited cardiomyopathy that can lead to heart failure and sudden cardiac death. This challenging diagnosis is based on clinical, electrocardiographic, and radiographic findings, along with suggestive genetic testing. Case A 72 year old man presented with stable ventricular tachycardia. 2D echo demonstrated an EF of 45%, grade I diastolic dysfunction, and LV hypokinesis. Left heart catheterization revealed non-obstructive coronary disease. Cardiac MRI revealed: dilated RV with basal RV wall akinesis; RV end-diastolic volume index 134 mL/m2, global LV hypokinesis, an area of mid-myocardial delayed gadolinium enhancement of the mid-inferoseptal LV myocardium at the RV insertion point, and no associated lymphadenopathy. Subsequent Invitae genetic testing revealed desmoplakin (DSP) gene mutation. The patient was managed with AICD placement and sotolol initiation. Decision-making In this rare case of asymptomatic stable VT, cardiac MRI findings met major criteria for ARVD. The differential diagnosis included cardiac sarcoidosis, however contrast enhanced CT imaging did not reveal hilar lymphadenopathy, and cardiac MRI was unimpressive for sarcoidosis. Furthermore, DSP gene mutation is associated with autosomal dominant ARVD. Conclusion The diagnosis of ARVD can be determined with cardiac imaging and genetic testing. It is important to rule out similar diagnoses by looking for differentiating features, such as hilar lymphadenopathy and myocardial granulomatous disease which is frequently seen in cardiac sarcoidosis, but not in ARVD.

Internal Medicine
Do A, **Curran K**, **Hughes C**, **Solomon R**, and **Williams CT**. Predictors of poor outcomes in non-ischemic cardiogenic shock and the use of hospice in this population. *Journal of the American College of Cardiology* 2020; 75(11):822.

Background Non-ischemic cardiomyopathy is under-appreciated in terms of both research and literature when compared to its ischemic counterpart. Not much is known about this vulnerable population. Therefore, we sought to identify clinical characteristics associated with poor outcomes amongst non-ischemic cardiogenic shock (NICS). Methods A retrospective chart review of NICS patients who were admitted to a tertiary transplant center from 6/2013 to 7/2018. T-test for continuous and chi-square tests for categorical data were used. Univariate analysis and multivariate regression models were used to analyze outcomes. Results Among 192 patients, 71.4% male, mean age of 57 ± 15, 47.9% white. Compared to the non-supported group, left ventricular assist device (62.5% vs 22.8%, $p < 0.0001$), Veno-arterial extracorporeal membrane oxygenation (62.5% vs 22.8%, $p = 0.11$), Intra- aortic balloon pump (IABP) (58.8% vs 21.1%, $p = 0.0006$) had significantly prolonged length of stay (LOS) which were defined as ≥ 20 days. Higher risks of hospital death were associated with age (OR 1.033, CI 1.002-1.064, $p = 0.034$) and IABP (OR 4.4, CI 1.4-14.5, $p = 0.011$). When combing all data, older mean age (58 years old vs 51 years old, $p = 0.045$), prior dialysis (100% vs 86.3%, $p = 0.026$), and inotrope usage (91% vs 80%, $p = 0.011$) were associated with the composite poor outcomes. Only 42 patients (22%) received hospice consultation during hospitalization. Hospice were consulted more for black patients (black 32.5% vs white 15.2%, $p = 0.009$). Conclusion In patients presenting with NICS, older age, prior dialysis, usage of inotropes were predictors of overall poor outcome. Mechanical circulatory support did not shorten inpatient LOS. Surprisingly, we did not identify any factors that increased the risk of readmission. Older age and IABP seemed to have higher inpatient mortality rate. Hospice was significantly underused in practice, especially in Caucasians. Future studies such as directly comparing non-ischemic and ischemic cardiomyopathy are needed to further understand NICS.

Internal Medicine
Do A, **Radjef R**, **Aurora L**, **Singh A**, **Tawney A**, **Kraus D**, **Jacobsen G**, and **McCord J**. Safety of evaluating for acute coronary syndrome in the emergency department using a modified heart score. *Journal of the American College of Cardiology* 2020; 75(11):127.

Background Chest pain is a common complaint in the emergency department (ED). The evaluation of these patients, which commonly involves stress testing, is time-consuming and costly. Prior retrospective studies demonstrated that a modified HEART score (m-HS) which combines the traditional HS and serial high-sensitivity cardiac troponin measurements could be used to identify low risk patients for discharge from the ED without further cardiac testing. The HS combines elements of the

history, cardiac risk factors, and ECG. A HS ≤ 3 is considered low risk. In this study, we evaluated the safety of implementing this concept prospectively. Methods A prospective implementation trial conducted at an ED in 2017 included adult patients who were evaluated for possible acute coronary syndrome. Patients needed to have Siemens cardiac troponin I ultra < 40 ng/L (99th%) at 0 and 3 hours in addition to a HS ≤ 3 to be discharged without further testing. Thirty-day major adverse cardiovascular events (MACE) (death, acute myocardial infarction, revascularization procedure and readmission) were recorded. Results Of 422 patients, 33 were lost to follow up, resulting in 389 for analysis. The mean age was 50.6 ± 14.4. There were 161 (41.6%) male, 203 white (52.6%), 135 (35%) black and 48 (12.4%) classified as others. Baseline risk factors: 128 (33%) hypertension, 35 (9.1%) diabetes, 100 (25.8%) hyperlipidemia, 14 (3.6%) coronary artery disease, 98 (25.5%) active smoker, 25 (6.5%) with family history of cardiac disease. Among the 3 MACEs (0.8%) which were all 30-day readmissions, 2 (0.5%) were non-cardiac related while 1 (0.3%) was for atypical chest pain that was determined to be non-cardiac chest pain by cardiology consultation. This patient also had the only positive cardiac test (1.8%) (myocardial perfusion imaging with minimal ischemia) out of the 56 outpatient cardiac stress tests. Conclusion In the ED setting, m-HS is an effective tool to identify low risk patients who are safe for early discharge. At 30 days, no significant MACEs were detected and these low risk patients likely do not require stress testing.

Internal Medicine
Gorgis S, **Ahluwalia G**, **Hana A**, **Fram G**, **Dabbagh M**, **Dhillon D**, **Murad A**, **Khan A**, **O'Neill WW**, **Kaatz S**, and **Wang DD**. To bleed or to clot: Stroke prevention strategies in patients with atrial fibrillation or flutter after bleeding. *Journal of the American College of Cardiology* 2020; 75(11):472.

Background Patients with atrial fibrillation or atrial flutter (AF) on anticoagulation (AC) for stroke prevention are at an increased risk of bleeding events. A common dilemma is deciding when to safely restart AC after bleeding. Studies have shown better outcomes with reinitiation of AC 7 days after stabilization of gastrointestinal bleeds and 4 weeks after intracranial hemorrhage. Our aim was to assess stroke prevention strategies upon discharge in patients with AF hospitalized with a bleeding event. Methods We retrospectively identified patients with AF on AC who were admitted with a bleeding event. The type of AC, form of bleeding, and CHADS2VASC were collected. Stroke prevention strategies on discharge were noted. Results Between January 2016 and August 2019, 174 patient with AF were hospitalized with a bleeding event. Nearly 10% of patients died, emphasizing the severity of this clinical situation. AC was restarted in 40% of patients upon discharge, 8.6% of patients were referred for LAA closure, and the remaining 40% were discharged without a stroke prevention strategy. CHADS2VASC did not differ among the groups. Of patients discharged on AC, 16% had a repeat bleeding episode requiring hospitalization within 30 days. Conclusion A significant portion of patients with AF hospitalized with a bleed were discharged with no definitive stroke prevention strategy. Barriers to restarting oral anticoagulation should lead to consideration of LAA closure as an alternative.

Internal Medicine
Gorgis S, **Dhillon D**, **Mishra K**, **Saleh A**, **Basir M**, and **Fuller B**. Aggressive acute coronary thrombosis in ulcerative colitis flare. *Journal of the American College of Cardiology* 2020; 75(11):3302.

Background Thromboembolic disease is a well-recognized complication of Ulcerative Colitis (UC), but coronary involvement is rare. Chest pain in UC flare should raise suspicion for acute coronary thrombosis. Case A 46 year old male with UC was admitted after 3 weeks of bloody diarrhea despite treatment with prednisone. He also reported severe refractory chest pain. ECG showed ST-segment elevation myocardial infarction in inferior/lateral leads. Emergent left heart catheterization (LHC) revealed a large thrombus in mid left anterior descending (LAD) artery with distal embolization. Aspiration thrombectomy was unsuccessful. A drug eluting stent (DES) was placed in mid-LAD. Intracoronary vasodilators improved distal coronary flow. The patient was continued on DAPT. Five days later, his chest pain recurred. Decision-making LHC showed acute in-stent thrombosis. Two DES were placed in overlapping fashion to proximal-mid LAD with PTCA on the diagonal. Persistent thrombus was treated with balloon inflations. The patient continued to be symptomatic, so an intra-aortic balloon bump (IABP) was placed. He was continued on DAPT. Hemodynamics and chest pain improved in next 2 days, and IABP was removed. Conclusion Acute coronary thrombosis in pro-inflammatory states are challenging to treat, since both the underlying condition and treatment of UC are pro-thrombotic. Close monitoring and consideration of mechanical support devices may improve coronary perfusion while controlling the underlying flare.

Internal Medicine
Hana A, **McCord J**, **Hudson MP**, **Cook B**, **Mueller C**, **Miller J**, **Moyer M**, **Akoegbe G**, **Jacobsen G**, and **Nowak RM**. Evaluation of acute myocardial infarction using a change in high-sensitivity cardiac troponin i over 1 hour. *Journal of the American College of Cardiology* 2020; 75(11):19.

Background The use of a high sensitivity cardiac troponin (hs-cTn) 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has been widely studied outside the United States (US). The algorithm divides patients into a rule-out, observation, or rule-in zone. This study evaluated the 0/1-hour algorithm using hs-cTnI in a US cohort. Methods Patients (N=552) at a single US urban emergency department (ED) were enrolled if they had symptoms suggestive of AMI which led the clinician to order cardiac markers. Patients with an ECG that led to immediate reperfusion therapy or required resuscitation were excluded. Baseline and 1-hour blood samples for hs-cTnI (Beckman Coulter) were obtained. AMI diagnosis was

independently adjudicated by 2 physicians using the universal definition of AMI and measurement of hs-cTnT (Roche Diagnostics) at 0,1 and 3 hours. Results In total, 45(8.2%) had AMI during the index hospitalization while at 30 days events occurred in 14(2.5%) of patients (3 cardiac deaths, 2 non-cardiac deaths, 8 additional MIs, and 4 revascularizations). Hs-cTnI (0/1-hour) algorithm rule-out zone had high negative predictive value for AMI (99.6%), while the rule-in zone had moderate positive predictive value for AMI (56.6%). Conclusion We demonstrated that the rule-out zone of the 0/1-hour algorithm using a hs-cTnI assay has high negative predictive value for AMI and identifies patients with a good 30-day prognosis. These patients may be considered for early discharge from the ED.

Neurosurgery
Asmaro K, **Rock J**, and **Craig J**. Vertical vector surgical knot in endoscopic endonasal surgery and repair: An exonasal knot for endonasal application. *Journal of Neurological Surgery, Part B Skull Base* 2020; 81.

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Developing innovative surgical approaches through narrow anatomic corridors requires continual adaptation surgical techniques and maneuvers. Regarding skull base surgery, endoscopic endonasal approaches have become extremely popular, resulting in lower patient morbidity, without sacrificing clinical outcomes. Although surgical approaches have changed dramatically over the last few decades, suturing and knot tying in these narrow corridors have not been developed at the same pace. Endoscopic repair of skull base defects after endoscopic endonasal surgery is often achieved with 90-95% success through multilayered reconstruction with a variety of grafts or flaps, sealants, and possibly sinonasal packing to avoid postoperative cerebrospinal fluid leaks. These high success rates are achieved without any direct suturing of the grafts/flaps to adjacent tissues. In some situations, perhaps suturing could limit the risk of graft/flap migration, and increase the chance of graft/flap water-tight closure and integration. The utility of endonasal suturing of grafts/flaps is largely unknown because intranasal geometry restricts the hand and instrument movements needed to achieve traditional surgeons' or square knots. The current study demonstrates a suturing technique resulting in a facile surgical knot through vertical vector motions, making it an ideal candidate when operating through narrow corridors. The advantages of this technique are its cost-effectiveness, the ability to use any type of needle or suture for tissue approximation, and the elimination of horizontal vectors and maneuvers which are limited in endonasal. This facile knot can be employed during endoscopic endonasal surgery potentially to facilitate watertight closure in scenarios where it is felt necessary or when repairing vascular structures.

Nursing
Alanee SR, Roumayah Z, Deebajah M, **Peabody JO**, Mora R, **Guevara J**, Francisco B, and Patterson BK. Adaptive genetic algorithms combined with high sensitivity single cell-based technology derived urine-based score to differentiate between high-grade and low-grade transitional cell carcinoma of the bladder. *Journal of Clinical Oncology* 2020; 38(6).

S.R. Alanee

Background: We previously showed that adaptive genetic algorithms (AGA), in combination with single-cell flow cytometry technology, can be used to develop a noninvasive urine-based score to detect bladder cancer with high accuracy. Our aim in this analysis was to investigate if that same score can differentiate between high grade (HG) and low grade (LG) transitional cell carcinoma of the bladder (BC). Methods: We collected urine samples from cystoscopy confirmed HG and LG superficial bladder cancer patients and healthy donors in an optimized urine collection media. We then examined these samples using an assay developed from AGA in combination with single-cell flow cytometry technology. Results: We examined 50 BC and 15 healthy donor urine samples. Patients were majorly White (59.2%), males (61.2%), and had HG BC (66.7%). AGA derived score of 1.1 differentiated between BCa and healthy patients with high precision (AUC 0.92). The median score was 2.8 for LG BC and 6 for LG BC. Mann-Whitney Rank Sum Test indicated that the difference between the median score of HG and LG BC was significant at P value = 0.003. The score performed well independent of patients' sex or smoking history. Conclusions: Using single-cell technology and machine learning, we developed a new urine-based score that can potentially differentiate between HG and LG bladder cancer. Future studies are planned to validate this score.

Nursing
Hana A, **McCord J**, **Hudson MP**, **Cook B**, **Mueller C**, **Miller J**, **Moyer M**, **Akoegbe G**, **Jacobsen G**, and **Nowak RM**. Evaluation of acute myocardial infarction using a change in high-sensitivity cardiac troponin i over 1 hour. *Journal of the American College of Cardiology* 2020; 75(11):19.

Background The use of a high sensitivity cardiac troponin (hs-cTn) 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has been widely studied outside the United States (US). The algorithm divides patients into a rule-out, observation, or rule-in zone. This study evaluated the 0/1-hour algorithm using hs-cTnI in a US cohort. Methods Patients (N=552) at a single US urban emergency department (ED) were enrolled if they had symptoms suggestive of AMI which led the clinician to order cardiac markers. Patients with an ECG that led to immediate reperfusion therapy or required resuscitation were excluded. Baseline and 1-hour blood samples for hs-cTnI (Beckman Coulter) were obtained. AMI diagnosis was independently adjudicated by 2 physicians using the universal definition of AMI and measurement of hs-cTnT (Roche

Diagnostics) at 0,1 and 3 hours. Results In total, 45(8.2%) had AMI during the index hospitalization while at 30 days events occurred in 14(2.5%) of patients (3 cardiac deaths, 2 non-cardiac deaths, 8 additional MIs, and 4 revascularizations). Hs-cTnI (0/1-hour) algorithm rule-out zone had high negative predictive value for AMI (99.6%), while the rule-in zone had moderate positive predictive value for AMI (56.6%). Conclusion We demonstrated that the rule-out zone of the 0/1-hour algorithm using a hs-cTnI assay has high negative predictive value for AMI and identifies patients with a good 30-day prognosis. These patients may be considered for early discharge from the ED.

Orthopedics/Bone and Joint
Akarakian R, **White N**, **Nayak M**, **Jaskulka B**, and **Guyer C**. Interrater reliability among primary care sports medicine fellowship application reviewers. *Clinical Journal of Sport Medicine* 2020; 30(2):162.

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Purpose: This study seeks to determine whether reviewers of fellowship applications agree upon differing elements in the evaluation process. To our knowledge, no published data currently exists for interrater reliability in assessment of Primary Care Sports Medicine fellowship applications. Methods: All fellowship candidate applications from a single cycle were reviewed by 4 Primary Care Sports Medicine faculty at a large, urban hospital accepting 3 Primary Care Sports Medicine fellows. Each reviewer scored all applications independently using a scoring manual developed by the group. No formal training had been completed by the raters. Scoring was completed for 14 unique domains. Results: During a single application cycle (1 year), 53 unique applications underwent review. Reviewers achieve excellent interrater reliability when scoring USMLE step 1, 2, and 3 scores including weighted scores; event and team coverage; medical school performance during the first 2 years; letters of recommendation; and sports medicine rotation. Raters reach fair/good agreement in evaluating leadership experience; research experience; event and team coverage weighted scores; medical school clerkship performance; Medical Student Performance Evaluation; and sports medicine rotation weighted scores. Evaluators have poor agreement on scoring special skills; personal statement; and gestalt. Conclusions: Excellent and fair interrater reliability has been achieved for most of the application elements. Weighted scores have not proven consistently reliable among different reviewers. Future research could investigate why certain application domains yield less than excellent interrater reliability and if greater interrater reliability could be achieved with training raters on use of an application scoring guide. Significance: Fellowship directors would benefit from efficient and reliable methods to review applications. Developing application review tools that have high interrater reliability allows multiple stakeholders to participate in the application review process.

Orthopedics/Bone and Joint
Kuhlmann NA, **Taylor KA**, **Franovic S**, Zuckerman JD, Roche CP, Schoch BS, Wright TW, Flurin PH, Carofino BC, and **Muh SJ**. Acute Reverse Total Shoulder Arthroplasty Treatment for Proximal Humerus Fracture Displays Equal or Superior Outcomes to Delayed Treatment. *Journal of Shoulder and Elbow Surgery* 2020; 29(4):e161.

Background: Treatment of proximal humerus fractures (PHFs) via reverse total shoulder arthroplasty (RTSA) has shown early promise when compared to historical treatment modalities. Ideal surgical timing remains unclear. The purpose of this study was to compare the outcomes of early versus delayed RTSA for PHF. We hypothesized that acute RTSA would display superior outcomes compared to those receiving delayed surgical intervention. Methods: This multicenter study retrospectively analyzed 142 patients who underwent RTSA for fracture. Patients treated within 4 weeks of injury were placed in the acute group (n=102), and patients treated longer than 4 weeks after injury were placed in the chronic group (n=38). A comprehensive panel of patient reported outcome measures, VAS pain scores, range of motion, and patient satisfaction were evaluated. Results: The acute group had significantly better final follow-up SPADI scores (20.8 ± 23.9 vs. 30.7 ± 31.7) ($p<0.05$). The acute group demonstrated higher passive external rotation compared to the chronic group (47.8 ± 16.5 vs. 40.4 ± 16.1) ($p<0.05$). No further differences were detected in other postoperative range of motion measurements, subjective outcomes, or VAS scores. The acute group displayed significantly greater overall improvements (pre vs post) in all range of motion measurements as well as patient-reported outcome and VAS scores. Average follow-up was 51.4 months. Conclusion: Our results suggest that patients treated acutely display similar mid-term outcomes to those who receive delayed treatment. Surgeons may first give consideration to a period of nonoperative treatment.

Otolarnygology
Asmaro K, **Rock J**, and **Craig J**. Vertical vector surgical knot in endoscopic endonasal surgery and repair: An exonasal knot for endonasal application. *Journal of Neurological Surgery, Part B Skull Base* 2020; 81.

K. Asmaro, Henry Ford Health System, Detroit, MI, United States

Developing innovative surgical approaches through narrow anatomic corridors requires continual adaptation surgical techniques and maneuvers. Regarding skull base surgery, endoscopic endonasal approaches have become extremely popular, resulting in lower patient morbidity, without sacrificing clinical outcomes. Although surgical approaches have changed dramatically over the last few decades, suturing and knot tying in these narrow corridors have not been developed at the same pace. Endoscopic repair of skull base defects after endoscopic endonasal surgery is often achieved with 90-95% success

through multilayered reconstruction with a variety of grafts or flaps, sealants, and possibly sinonasal packing to avoid postoperative cerebrospinal fluid leaks. These high success rates are achieved without any direct suturing of the grafts/flaps to adjacent tissues. In some situations, perhaps suturing could limit the risk of graft/flap migration, and increase the chance of graft/flap water-tight closure and integration. The utility of endonasal suturing of grafts/flaps is largely unknown because intranasal geometry restricts the hand and instrument movements needed to achieve traditional surgeons' or square knots. The current study demonstrates a suturing technique resulting in a facile surgical knot through vertical vector motions, making it an ideal candidate when operating through narrow corridors. The advantages of this technique are its cost-effectiveness, the ability to use any type of needle or suture for tissue approximation, and the elimination of horizontal vectors and maneuvers which are limited in endonasal. This facile knot can be employed during endoscopic endonasal surgery potentially to facilitate watertight closure in scenarios where it is felt necessary or when repairing vascular structures.

Otolarnygology

Ghanem AI, **Schymick MA**, **Bachiri S**, **Khalil R**, **Burmeister C**, **Sheqwara J**, **Chang S**, **Ghanem T**, and **Siddiqui F**. Does Age Impact Outcomes of Oropharyngeal squamous cell carcinoma? *International Journal of Radiation Oncology Biology Physics* 2020; 106(5):1141.

Purpose/Objective(s): It is well-established that human papilloma virus (HPV) positive (+ve) oropharyngeal (OP) squamous cell carcinoma (SCC) carries a better overall prognosis than HPV negative (-ve) tumors. We sought to investigate the impact of age upon survival endpoints for HPV +ve and -ve OP SCC as well as the differences in acute radiotherapy (RT) toxicity. Materials/Methods: We included all OP SCC cases treated definitively between 2010-2017. All cases underwent either surgery ± adjuvant RT; or definitive RT; ± chemotherapy according to the multidisciplinary tumor board decision. After determining p16 status we dichotomized each HPV group by age at diagnosis into old (> or = 65 years) and young (<65 years) sub-groups. Patients' demographics, clinico-pathological data and treatment modalities were compared across age groups for both HPV sub-types. Log-rank test and Kaplan-Meier curves were utilized to measure effect of age on overall (OS), local recurrence free (LRFS) and distant metastases free (DMFS) survival for HPV +ve and -ve. For patients receiving RT we compared weight loss, feeding tube insertion, treatment breaks and hospitalization during RT as parameters for acute toxicity across age groups. Results: We identified 217 OP SCC who fit our inclusion criteria. Seventy percent were HPV+ve, males were 82%, mean age at diagnosis was 61 years, 75% were white, 67% were ever smokers and 54% were frequent/heavy alcohol drinkers. According to AJCC 7th edition, Stages III and IVA formed 87%; however, these were regrouped as stage I (51%) and stage IVA (62%) as prevalent stages for HPV+ve and -ve respectively as per AJCC 8th version. Definitive CRT was utilized in 58% and surgery ± adjuvant therapy in 31% of the study cohort. For HPV+ve sub-group, 31% were old (n=47); whereas they constituted 40% (n=27) of HPV-ve cases. Clinicopathological and treatment characteristics were generally equivalent among age groups except that HPV +ve younger patients had more adequate surgical margins (≥5mm) (78% vs 36%; p=0.03) than old; and HPV-ve old cases had a trend towards more utilization of concomitant cetuximab (30% vs 13%; p=0.09) than younger ones. All endpoints were not significantly different between old vs young HPV+ve cases with 2-year OS and LRFS of (64% vs 59%; p=0.41 and 88% vs 87%; p=0.98 for both respectively). Similar outcomes were observed between study age groups for HPV-ve cases (p>0.05 for all endpoints). Hospitalization during RT was more frequent in old patients (44% vs 28%; p=0.03). Median weight loss during RT was 9.5% (0-22%) vs 9.3% (0-17%) for old vs young (p=0.35) and RT breaks were also non-significant (39% vs 27%, p=0.8). Feeding tubes were inserted after RT initiation in 41% of old and 36% in young (p=0.5). Conclusion: Older patients with OP SCC have equivalent outcomes compared to younger ones irrespective of HPV status. Optimal treatments must be offered following standard of care as determined by a multi-disciplinary group of providers.

Pathology

Hana A, **McCord J**, **Hudson MP**, **Cook B**, **Mueller C**, **Miller J**, **Moyer M**, **Akoegbe G**, **Jacobsen G**, and **Nowak RM**. Evaluation of acute myocardial infarction using a change in high-sensitivity cardiac troponin i over 1 hour. *Journal of the American College of Cardiology* 2020; 75(11):19.

Background The use of a high sensitivity cardiac troponin (hs-cTn) 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has been widely studied outside the United States (US). The algorithm divides patients into a rule-out, observation, or rule-in zone. This study evaluated the 0/1-hour algorithm using hs-cTnI in a US cohort. Methods Patients (N=552) at a single US urban emergency department (ED) were enrolled if they had symptoms suggestive of AMI which led the clinician to order cardiac markers. Patients with an ECG that led to immediate reperfusion therapy or required resuscitation were excluded. Baseline and 1-hour blood samples for hs-cTnI (Beckman Coulter) were obtained. AMI diagnosis was independently adjudicated by 2 physicians using the universal definition of AMI and measurement of hs-cTnT (Roche Diagnostics) at 0,1 and 3 hours. Results In total, 45(8.2%) had AMI during the index hospitalization while at 30 days events occurred in 14(2.5%) of patients (3 cardiac deaths, 2 non-cardiac deaths, 8 additional MIs, and 4 revascularizations). Hs-cTnI (0/1-hour) algorithm rule-out zone had high negative predictive value for AMI (99.6%), while the rule-in zone had moderate positive predictive value for AMI (56.6%). Conclusion We demonstrated that the rule-out zone of the 0/1-hour algorithm using a hs-cTnI assay has high negative predictive value for AMI and identifies patients with a good 30-day prognosis. These patients may be considered for early discharge from the ED.

Public Health Sciences

Aurora L, **Snider J**, **Peterson E**, **Bryson T**, **Gui H**, **McCord J**, and **Lanfear DE**. Suppression of tumorigenicity 2 (st2) turbidimetric immunoassay and enzyme-linked immunosorbent assay: Predicting risk in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):883.

Background Heart failure (HF) is a major public health problem worldwide. Cardiac biomarkers aid in diagnosis, prognosis, risk stratification, and management of HF. Soluble suppression of tumorigenicity 2 (ST2) is a significant prognostic indicator in HF and seems to reflect response to treatment, particularly beta blockers. However, a limitation to its adoption is that it is an enzyme-linked immunosorbent assay (ELISA) which may be cumbersome and costly for laboratories. A turbidimetric immunoassay (TIA) that can run on a common chemistry analyzer could overcome this issue. We studied a novel TIA for ST2, comparing its performance to the validated ST2 (ELISA) in predicting survival in HF patients. Methods Patients age ≥18 years meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007-March 2015) at Henry Ford Hospital. Exclusion criteria included chronic supplemental oxygen or dialysis. Only patients with HF with reduced ejection fraction (<50%) and available plasma samples were included (n=727). ST2 measurements were obtained on the same sample using both TIA and ELISA. Correlation was studied between the measures and association with survival using Cox models. Area under the curve (AUC) improvement in Cox models was studied using method of Uno. Results Study cohort included 66.6% males, 46.2% African Americans with 43 deaths over 1 year. Correlation between TIA and ELISA was initially low with spearman coefficient 0.63. There were four outliers with ELISA value greater than the recommended maximum (200 ng/mL). Exclusion of these samples (n=723) resulted in inter-assay correlation 0.87. In this group with only ST2 as a variable, the TIA and ELISA values were significant associates of survival time with similar effect size (HR 4.8 and 3.7, respectively, p=0.001). In models adjusted for clinical risk factors (MAGGIC score), both versions of ST2 remained a significant predictor of survival and were of similar magnitude; the AUC improvement (from MAGGIC only, AUC=0.756) for TIA AUC=0.777 (p=0.035) and for ELISA AUC=0.785 (p=0.028). Conclusion Novel TIA method for ST2 quantification correlates highly with ELISA and offers similarly powerful risk-stratification.

Public Health Sciences

Bryson T, **Debbs JC**, **She R**, **Gui H**, **Luzum JA**, **Zeld N**, **Brawner CA**, **Keteyian SJ**, **Ehrman JK**, **Williams LK**, and **Lanfear DE**. A single nucleotide polymorphism within the rxra gene predicts a favorable response to exercise in heart failure. *Journal of the American College of Cardiology* 2020; 75(11):1012.

Background Heart failure (HF) is a morbid condition associated with impaired exercise capacity. Exercise training is an effective strategy to improve functional capacity and quality of life. However, response to exercise training is highly variable and whether there are genetic factors that may impact response to exercise is unknown. We sought to identify genetic variants in patients with HF participating in cardiac rehabilitation (CR) that are associated with improvement in exercise capacity. Methods The study was conducted at Henry Ford Hospital in Detroit, MI. Patients enrolled in our genomic HF registry who had participated in CR at any time were selected (n=211). The primary endpoint was the change in metabolic equivalents of task (ΔMET) during CR, from week 1 to the last week of CR. All patients were genotyped using the Axiom biobank genotyping array with imputation using 1000 genomes reference panels (filter at R2 = 0.5 in both European and African ancestry). Genome-wide association testing was performed in linear models of ΔMET adjusted for baseline peak VO2, sex, age, and the first principal component (to control for race/population stratification). $p<5\times10-8$ was considered statistically significant. Results The study cohort consisted of 135 African ancestry and 76 European ancestry patients and 36.5% were women. One SNP, rs11103633, met genome-wide significance ($p = 8.86 \times 10-12$). Each additional allele was associated with 2.4 MET greater improvement (std err. = 0.331, $p = 8.859 \times 10-12$). This SNP, in the retinoid x receptor A gene (RXRA), encodes an orphan nuclear receptor belonging to the steroid super-family and acts in a variety of cellular processes. In cardiac and skeletal muscle, RXRA, is the necessary binding partner of PPARA, a key regulator of mitochondrial proliferation and fatty acid oxidation. Conclusion A genetic variant in the RXRA gene appears to impact the beneficial effect of exercise training in HF patients and could act via influencing cellular energetic capacity. This finding could lead to targeted exercise therapy or to novel pharmacologic methods of improving exercise response in HF patients. External validation and investigation of possible mechanisms are needed.

Public Health Sciences

Debbs J, **Bryson TD**, **Zeld N**, **Aurora L**, **Gui H**, **Luzum JA**, **Peterson E**, **She R**, **Williams LK**, and **Lanfear DE**. Somalogic st2 and ntprobnp assays predict heart failure mortality as effectively as the elisa assay. *Journal of the American College of Cardiology* 2020; 75(11):1091.

Background Biomarkers are critical for modern heart failure (HF) care. There are several established prognostic markers such as N-terminal pro-b-type natriuretic peptide (NTproBNP) and soluble suppressor of tumorgenicity 2 (ST2). Recent advances in multiplexing/multi-marker platforms offer faster and broader data generation. However, how these newer methods compare to FDA-approved ELISA-based assays remains unclear. The SOMALogic® SOMAscan assay is an aptamer-based technology that quantifies thousands of proteins simultaneously, including NTproBNP and ST2. The purpose of this study is to compare the test results and performance in predicting mortality using ELISA vs. SOMA for each marker. Methods Patients age ≥18 years and meeting Framingham definition for HF were enrolled in a prospective registry (Oct 2007 - March 2015) at Henry

Ford Hospital. Only patients with an ejection fraction < 50 % were used for the analysis (N= 687 for ST2 and N= 902 for NTproBNP). We tested the correlation of SOMA vs ELISA for each marker and report spearman correlation coefficient. We then tested each marker in Cox models adjusted for clinical risk score (MAGGIC) and compared the HR and model improvement (using calculated area under the curve [AUC]) for ELISA vs SOMA versions. Results First, we calculated the correlation between SOMA and ELISA values for both ST2 and NTproBNP. The correlation for ST2 was 0.74 (p<0.001) and NTproBNP was 0.88 (p<0.001), respectively. Next, we used a Cox proportional hazards model to predict death for the four variables corrected for the clinical score MAGGIC. Both versions of both markers were significantly associated with survival time. The hazard ratio for ELISA-ST2 was 1.12 (95% CI 1.09-1.16, p < 0.001) and for SOMA ST2 was 1.11 (95% CI 1.08-1.15, p<0.001). The hazard ratios for ELISA NTproBNP and SOMA NTproBNP were identical (1.12 95% CI 1.09-1.15, p<0.001). Uno's area under the ROC curve analysis showed there was no difference between marker versions in mortality prediction for ST2 nor for NTproBNP. Conclusion These results indicate that the SOMAscan assay results for ST2 and NTproBNP are strongly correlated to the standard ELISA versions and have equivalent prognostic information.

Public Health Sciences

Do A, **Radjef R**, **Aurora L**, **Singh A**, **Tawney A**, **Kraus D**, **Jacobsen G**, and **McCord J**. Safety of evaluating for acute coronary syndrome in the emergency department using a modified heart score. *Journal of the American College of Cardiology* 2020; 75(11):127.

Background Chest pain is a common complaint in the emergency department (ED). The evaluation of these patients, which commonly involves stress testing, is time-consuming and costly. Prior retrospective studies demonstrated that a modified HEART score (m-HS) which combines the traditional HS and serial high-sensitivity cardiac troponin measurements could be used to identify low risk patients for discharge from the ED without further cardiac testing. The HS combines elements of the history, cardiac risk factors, and ECG. A HS ≤ 3 is considered low risk. In this study, we evaluated the safety of implementing this concept prospectively. Methods A prospective implementation trial conducted at an ED in 2017 included adult patients who were evaluated for possible acute coronary syndrome. Patients needed to have Siemens cardiac troponin I ultra < 40 ng/L (99th%) at 0 and 3 hours in addition to a HS ≤ 3 to be discharged without further testing. Thirty-day major adverse cardiovascular events (MACE) (death, acute myocardial infarction, revascularization procedure and readmission) were recorded. Results Of 422 patients, 33 were lost to follow up, resulting in 389 for analysis. The mean age was 50.6 ± 14.4. There were 161 (41.6%) male, 203 white (52.6%), 135 (35%) black and 48 (12.4%) classified as others. Baseline risk factors: 128 (33%) hypertension, 35 (9.1%) diabetes, 100 (25.8%) hyperlipidemia, 14 (3.6%) coronary artery disease, 98 (25.5%) active smoker, 25 (6.5%) with family history of cardiac disease. Among the 3 MACEs (0.8%) which were all 30-day readmissions, 2 (0.5%) were non-cardiac related while 1 (0.3%) was for atypical chest pain that was determined to be non-cardiac chest pain by cardiology consultation. This patient also had the only positive cardiac test (1.8%) (myocardial perfusion imaging with minimal ischemia) out of the 56 outpatient cardiac stress tests. Conclusion In the ED setting, m-HS is an effective tool to identify low risk patients who are safe for early discharge. At 30 days, no significant MACEs were detected and these low risk patients likely do not require stress testing.

Public Health Sciences

Ghanem AI, **Schymick MA**, **Bachiri S**, **Khalil R**, **Burmeister C**, **Sheqwara J**, **Chang S**, **Ghanem T**, and **Siddiqui F**. Does Age Impact Outcomes of Oropharyngeal squamous cell carcinoma? *International Journal of Radiation Oncology Biology Physics* 2020; 106(5):1141.

Purpose/Objective(s): It is well-established that human papilloma virus (HPV) positive (+ve) oropharyngeal (OP) squamous cell carcinoma (SCC) carries a better overall prognosis than HPV negative (-ve) tumors. We sought to investigate the impact of age upon survival endpoints for HPV +ve and -ve OP SCC as well as the differences in acute radiotherapy (RT) toxicity. Materials/Methods: We included all OP SCC cases treated definitively between 2010-2017. All cases underwent either surgery ± adjuvant RT; or definitive RT; ± chemotherapy according to the multidisciplinary tumor board decision. After determining p16 status we dichotomized each HPV group by age at diagnosis into old (> or = 65 years) and young (<65 years) sub-groups. Patients' demographics, clinico-pathological data and treatment modalities were compared across age groups for both HPV sub-types. Log-rank test and Kaplan-Meier curves were utilized to measure effect of age on overall (OS), local recurrence free (LRFS) and distant metastases free (DMFS) survival for HPV +ve and -ve. For patients receiving RT we compared weight loss, feeding tube insertion, treatment breaks and hospitalization during RT as parameters for acute toxicity across age groups. Results: We identified 217 OP SCC who fit our inclusion criteria. Seventy percent were HPV+ve, males were 82%, mean age at diagnosis was 61 years, 75% were white, 67% were ever smokers and 54% were frequent/heavy alcohol drinkers. According to AJCC 7th edition, Stages III and IVA formed 87%; however, these were regrouped as stage I (51%) and stage IVA (62%) as prevalent stages for HPV+ve and -ve respectively as per AJCC 8th version. Definitive CRT was utilized in 58% and surgery ± adjuvant therapy in 31% of the study cohort. For HPV+ve sub-group, 31% were old (n=47); whereas they constituted 40% (n=27) of HPV-ve cases. Clinicopathological and treatment characteristics were generally equivalent among age groups except that HPV +ve younger patients had more adequate surgical margins (≥5mm) (78% vs 36%; p=0.03) than old; and HPV-ve old cases had a trend towards more utilization of concomitant cetuximab (30% vs 13%; p=0.09) than younger ones. All endpoints were not significantly different between old vs young HPV+ve cases with 2-year OS and LRFS of (64% vs 59%; p=0.41 and 88% vs 87%; p=0.98 for both respectively). Similar outcomes were observed between study age groups for

HPV-ve cases (p>0.05 for all endpoints). Hospitalization during RT was more frequent in old patients (44% vs 28%; p=0.03). Median weight loss during RT was 9.5% (0-22%) vs 9.3% (0-17%) for old vs young (p=0.35) and RT breaks were also non-significant (39% vs 27%, p=0.8). Feeding tubes were inserted after RT initiation in 41% of old and 36% in young (p=0.5). Conclusion: Older patients with OP SCC have equivalent outcomes compared to younger ones irrespective of HPV status. Optimal treatments must be offered following standard of care as determined by a multi-disciplinary group of providers.

Public Health Sciences

Gibbs J, **McCord J**, **Moyer M**, **Jacobsen G**, and **Nowak RM**. A machine learning algorithm to predict acute myocardial infarction over 30 minutes. *Journal of the American College of Cardiology* 2020; 75(11):175.

Background Chest pain is a common presentation in the emergency department (ED). Variation in high sensitivity cardiac troponin I (hs-cTnI) by age and gender make diagnosis of AMI more challenging. Machine learning integrates these variables to allow more accurate and rapid evaluation of possible AMI. Methods We applied a machine learning algorithm (myocardial-ischemic-injury-index [MI3]) that incorporates age, gender, and hs-cTnI levels at time 0 and 30 minutes in 529 patients evaluated for possible AMI in a single urban ED. MI3 calculates a value from 0-100 reflecting the likelihood of AMI. Diagnosis of AMI was adjudicated by 2 independent physicians in accordance with the universal definition of AMI and required at least 1 hs-cTnI >99th% (Abbott Architect; 26 ng/L). Patients were followed at 30 days for major adverse cardiac events (MACE): death or AMI. Results There were 42 (7.9%) patients that had an AMI. Patients were divided into 3 groups by the MI3 score: low-risk (≤3.13), intermediate-risk (>3.13-51.0), and high-risk (>51.0) (Table). The sensitivity for AMI was 100% with a MI3 value ≤3.13 and 353 (67%) ruled-out for AMI at 30 minutes. At 30 days there were 2 (0.6%) MACEs (0 AMI, 2 non-cardiac deaths) in the low-risk group, in the intermediate-risk group 4 (3.0%) MACEs (3 AMIs, 1 cardiac death), and in the high-risk group 4 (9.1%) MACEs (4 AMIs, 2 cardiac deaths). Conclusion The MI3 algorithm had 100% sensitivity for AMI at 30 minutes and identified a low-risk cohort who may be considered for early discharge.

Public Health Sciences

Hana A, **McCord J**, **Hudson MP**, **Cook B**, **Mueller C**, **Miller J**, **Moyer M**, **Akoegbe G**, **Jacobsen G**, and **Nowak RM**. Evaluation of acute myocardial infarction using a change in high-sensitivity cardiac troponin i over 1 hour. *Journal of the American College of Cardiology* 2020; 75(11):19.

Background The use of a high sensitivity cardiac troponin (hs-cTn) 0/1-hour algorithm to evaluate for acute myocardial infarction (AMI) has been widely studied outside the United States (US). The algorithm divides patients into a rule-out, observation, or rule-in zone. This study evaluated the 0/1-hour algorithm using hs-cTnI in a US cohort. Methods Patients (N=552) at a single US urban emergency department (ED) were enrolled if they had symptoms suggestive of AMI which led the clinician to order cardiac markers. Patients with an ECG that led to immediate reperfusion therapy or required resuscitation were excluded. Baseline and 1-hour blood samples for hs-cTnI (Beckman Coulter) were obtained. AMI diagnosis was independently adjudicated by 2 physicians using the universal definition of AMI and measurement of hs-cTnT (Roche Diagnostics) at 0,1 and 3 hours. Results In total, 45(8.2%) had AMI during the index hospitalization while at 30 days events occurred in 14(2.5%) of patients (3 cardiac deaths, 2 non-cardiac deaths, 8 additional MIs, and 4 revascularizations). Hs-cTnI (0/1-hour) algorithm rule-out zone had high negative predictive value for AMI (99.6%), while the rule-in zone had moderate positive predictive value for AMI (56.6%). Conclusion We demonstrated that the rule-out zone of the 0/1-hour algorithm using a hs-cTnI assay has high negative predictive value for AMI and identifies patients with a good 30-day prognosis. These patients may be considered for early discharge from the ED.

Radiation Oncology

Ghanem AI, **Schymick MA**, **Bachiri S**, **Khalil R**, **Burmeister C**, **Sheqwara J**, **Chang S**, **Ghanem T**, and **Siddiqui F**. Does Age Impact Outcomes of Oropharyngeal squamous cell carcinoma? *International Journal of Radiation Oncology Biology Physics* 2020; 106(5):1141.

Purpose/Objective(s): It is well-established that human papilloma virus (HPV) positive (+ve) oropharyngeal (OP) squamous cell carcinoma (SCC) carries a better overall prognosis than HPV negative (-ve) tumors. We sought to investigate the impact of age upon survival endpoints for HPV +ve and -ve OP SCC as well as the differences in acute radiotherapy (RT) toxicity. Materials/Methods: We included all OP SCC cases treated definitively between 2010-2017. All cases underwent either surgery ± adjuvant RT; or definitive RT; ± chemotherapy according to the multidisciplinary tumor board decision. After determining p16 status we dichotomized each HPV group by age at diagnosis into old (> or = 65 years) and young (<65 years) sub-groups. Patients' demographics, clinico-pathological data and treatment modalities were compared across age groups for both HPV sub-types. Log-rank test and Kaplan-Meier curves were utilized to measure effect of age on overall (OS), local recurrence free (LRFS) and distant metastases free (DMFS) survival for HPV +ve and -ve. For patients receiving RT we compared weight loss, feeding tube insertion, treatment breaks and hospitalization during RT as parameters for acute toxicity across age groups. Results: We identified 217 OP SCC who fit our inclusion criteria. Seventy percent were HPV+ve, males were 82%, mean age at diagnosis was 61 years, 75% were white, 67% were ever smokers and 54% were frequent/heavy alcohol drinkers. According to AJCC 7th edition, Stages III and IVA formed 87%; however, these were regrouped as stage I (51%) and stage IVA (62%) as prevalent stages for HPV+ve and -ve respectively as per AJCC 8th version. Definitive CRT was utilized in

58% and surgery ± adjuvant therapy in 31% of the study cohort. For HPV+ve sub-group, 31% were old (n=47); whereas they constituted 40% (n=27) of HPV-ve cases. Clinicopathological and treatment characteristics were generally equivalent among age groups except that HPV +ve younger patients had more adequate surgical margins (≥5mm) (78% vs 36%; p=0.03) than old; and HPV-ve old cases had a trend towards more utilization of concomitant cetuximab (30% vs 13%; p=0.09) than younger ones. All endpoints were not significantly different between old vs young HPV+ve cases with 2-year OS and LRFS of (64% vs 59%; p=0.41 and 88% vs 87%; p=0.98 for both respectively). Similar outcomes were observed between study age groups for HPV-ve cases (p>0.05 for all endpoints). Hospitalization during RT was more frequent in old patients (44% vs 28%; p=0.03). Median weight loss during RT was 9.5% (0-22%) vs 9.3% (0-17%) for old vs young (p=0.35) and RT breaks were also non-significant (39% vs 27%, p=0.8). Feeding tubes were inserted after RT initiation in 41% of old and 36% in young (p=0.5). Conclusion: Older patients with OP SCC have equivalent outcomes compared to younger ones irrespective of HPV status. Optimal treatments must be offered following standard of care as determined by a multi-disciplinary group of providers.

Radiation Oncology

Kennedy WR, Srivastava A, Chundury A, Cosper P, Contreras J, Gay HA, **Parikh PJ**, Wang X, Gondim D, Chernock R, and Thorstad WL. HPV-Positive EBV-Negative Nasopharyngeal Cancer: Prevalence and Impact on Outcomes in a Non-Endemic Population. *International Journal of Radiation Oncology Biology Physics* 2020; 106(5):1170.

Purpose/Objective(s): To determine the prevalence of high-risk human papillomavirus (HPV) in non-endemic nasopharyngeal cancer (NPC), its association with p16 status, and potential influence on clinical outcomes in a cohort treated with definitive chemoradiotherapy (CRT). Materials/Methods: We identified 24 patients from a prospectively-maintained database treated with CRT for NPC from 1997 to 2014. All patients had paraffin-embedded tumor specimens on which Epstein-Barr virus-encoded small RNAs (EBER) in-situ hybridization and p16 immunohistochemistry (IHC) were performed. All specimens were then reviewed by an experienced head and neck pathologist who isolated and reverse transcribed total RNA from tumor regions, then performed quantitative PCR for E6 and E7 of 13 different high-risk HPV types. Log-rank tests and Cox proportional hazard models were performed to evaluate the impact of clinical factors on patient outcomes. Survival estimates were derived via the Kaplan Meier method. Results: Of the 24 tumors, 7 were HPV-positive/EBV-negative (29%), 15 were HPV-negative/EBV-positive (63%), and 2 were negative for both HPV and EBV (8%). All tumors positive for HPV mRNA expression were also positive for p16 IHC, and all tumors negative for HPV were also negative for p16, resulting in a 100% sensitivity and 100% specificity of p16 as a surrogate for high-risk HPV expression. Median age of diagnosis was 48 (19 – 68). All but 1 HPV-positive tumor was WHO II and no patients with HPV-positive tumors were WHO III. All patients received concurrent chemotherapy, with 3 patients also receiving neoadjuvant and 16 receiving adjuvant chemotherapy. Median doses to the primary and neck were 70 Gy (69.96 – 72) and 56 Gy (50.4 – 64.6), respectively. Median follow-up was 5.9 years (0.9 – 18.0) and was not different when stratified by HPV status. Local-regional control at 5 years was 100% for HPV-positive versus 81.9% for HPV-negative patients (p=0.171). Distant control at 5 years was 83.3% for HPV-positive versus 70.1% for HPV-negative patients (p=0.414). Overall survival at 5 years was 100% for HPV-positive versus 74.5% for HPV-negative patients (p=0.044). Multivariable analysis revealed that older age (HR 1.15, 95% CI 1.01-1.28) and advanced nodal stage (HR 33, 95% CI 1.19-91.44) remained as independent predictors of OS. Conclusion: We revealed that in a group of patients diagnosed with NPC in the midwest United States, HPV-driven NPC comprised a significant proportion of NPC cases, and was mutually exclusive from EBV positivity. Importantly, we discovered that p16 IHC is a strong surrogate marker for HPV-positivity in NPC. Patients with HPV-positive NPC had significantly improved overall survival in our cohort.

Sleep Medicine

Drake C, Yardley J, Pinner K, Perdomo C, and Moline M. Subject-reported perception of long-term effectiveness of lemborexant versus placebo in nonelderly and elderly subgroups. *American Journal of Geriatric Psychiatry* 2020; 28(4):S133-S134.

Introduction: Demonstrating improvement from the patient's perspective is an important objective for an insomnia treatment regimen to be regarded as successful. Clinical trials for insomnia therapies generally include outpatient data using daily sleep diaries to assess the magnitude of change in sleep onset and, in some cases, sleep maintenance outcomes. Instruments that assess patient perception of disease severity and symptom improvement can provide additional information on treatment effectiveness. Change in severity of insomnia symptoms is often assessed using the Insomnia Severity Index. The Patient Global Impression – Insomnia version (PGI-I) is another self-report questionnaire that evaluates subjects' perception of the effects of a study medication on their sleep. The PGI-I does not have a baseline; therefore, the outcome is the global impression of the study medication's effects during or at the end of treatment relative to their sleep prior to study enrollment. The PGI-I contains 3 items related to study medication effects (helped/worsened sleep; decreased/increased time to fall asleep; and increased/decreased total sleep), rated on a 3-point scale (1=positive, 2=neutral, 3=negative), and 1 item related to perceived appropriateness of study medication strength, rated on a different 3-point scale (1=too strong, 2=just right, 3=too weak). SUNRISE-2 (NCT02952820; E2006-G000-303) examined the efficacy and safety of lemborexant (LEM), a dual orexin receptor antagonist under development for the treatment of insomnia, vs placebo (PBO) in adult subjects with insomnia disorder. Here we present the results of the PGI-I at the end of 6 months of treatment based on age of subjects (<65y [nonelderly] and ≥65y [elderly]). Methods: SUNRISE-2 was a Phase 3, 12-month, double-blind, global study in female and male adults aged ≥18y with insomnia disorder that included a 6-month PBO-controlled treatment period (after a PBO run-in)

followed by a 6-month active-only treatment period. Subjects received PBO, LEM 5mg (LEM5) or LEM 10mg (LEM10) for the first 6 months. Titration to higher or lower doses was not possible. The PGI-I was administered at Months 1, 3, 6, 9, and 12; results from the end of PBO-controlled treatment are reported. Chi-square tests were used to compare the percentage of "positive" (or "just right") responses with the combined "neutral" and "negative" (or combined "too strong" and "too weak") response categories for LEM vs PBO subjects. Results: The full analysis set of SUNRISE-2 included 949 subjects. The subgroup of subjects <65y included 687 (72.4%) subjects, with n=229 in each treatment group. The subgroup of subjects age ≥65y included 262 (27.6%) subjects, with 89, 87, and 86 subjects in the PBO, LEM5 and LEM10 groups, respectively. In the <65y subgroup, significantly more subjects who received LEM5 or LEM10 versus subjects who received PBO reported that their study medication "helped" sleep (PBO, 49.4%; LEM5, 68.6% [P<0.001]; LEM10, 70.7% [P<0.0001]) and reduced time to fall asleep (PBO, 48.9%; LEM5, 71.9% [P<0.0001]; LEM10, 72.5% [P<0.0001]) at Month 6. Similarly, in the ≥65y subgroup, significantly more subjects who received LEM5 or LEM10, vs subjects who received PBO, reported that their study medication "helped" sleep (PBO, 35.0%; LEM5, 63.9% [P<0.001]; LEM10, 64.2% [P<0.001]) and reduced time to fall asleep (PBO, 40.0%; LEM5, 75.0% [P<0.0001]; LEM10, 74.6% [P<0.0001]) at Month 6. For both subgroups, significantly more LEM subjects reported an increase in total sleep time vs PBO subjects at Month 6 (<65y subgroup: PBO, 43.3%, LEM5, 57.3% [P<0.01], LEM10, 61.7% [P<0.001]; ≥65y subgroup: PBO, 32.5%, LEM5, 59.7%, LEM10, 62.7% [P<0.001, both comparisons]). Additionally, in the <65y subgroup, a significantly greater percentage of subjects in the LEM5 and LEM10 groups selected that the treatment strength was "just right" vs PBO at Month 6 (PBO, 37.6%; LEM5, 53.0% [P<0.01]; LEM10, 53.3% [P<0.01]). Similarly, in the ≥65y subgroup, a significantly g eater percentage of subjects in the LEM5 and LEM10 groups selected that the treatment strength was "just right" vs PBO at Month 6 (PBO, 32.5%; LEM5, 62.5% [P<0.001]; LEM10, 53.7% [P<0.01]). LEM was well tolerated in both subgroups. The majority of treatment-emergent adverse events were mild or moderate. Conclusions: Overall, in both the <65y and ≥65y subgroups, a greater number of LEM vs PBO subjects reported positive effects of their study treatment with regards to helping them sleep, reducing time to fall asleep, and total sleep time at Month 6. Thus, the positive subject perception of LEM effectiveness was consistent across age subgroups. The results of the PGI-I are also consistent with the benefits of LEM observed on sleep onset and maintenance outcomes as assessed by sleep diary data in SUNRISE-2. This research was funded by: Eisai, Inc.

Surgery

Aljamal AO, **Alalwan Y**, **Coriasso N**, **Hughes C**, **Abdelrahim E**, **Lee JC**, **Wang DD**, **Pantelic M**, **Song T**, **Eng M**, **Frisoli TM**, **Villablanca P**, and **Wyman JF**. Dynamic conformational changes of the left ventricular outflow tract compared to the aortic annulus and implications on transcatheter aortic valve selection and sizing. *Journal of the American College of Cardiology* 2020; 75(11):1491.

Background ECG-gated computed tomography angiography (CTA) has become the standard for assessing the aortic root prior to transcatheter aortic valve replacement (TAVR). Current techniques rely primarily on systolic annular sizing for the selection and sizing of valve prostheses. We sought to evaluate the dynamic conformational changes of the LVOT compared to the aortic annulus, and determine whether LVOT morphology can have implications on prosthetic valve sizing and selection. Methods Preprocedural ECG-gated CTA data of 339 patients (aged 79 ±8.7 years, 52.6% male) who underwent TAVR were analyzed in this single-center retrospective study. The area of the aortic annulus and LVOT were measured by planimetry at 10% intervals throughout the cardiac cycle. Annular measurements were obtained inferior to the coronary cusps, and 10% of sub-annular calcifications were included in the calculated size. LVOT measurements were recorded 5mm inferior to the aortic annulus in a double oblique plane. Results In systole, the average annular size was 452.19 ± 19.52 mm2 compared to 455.74 ± 23.52 mm2 in the LVOT. In diastole, the average annular size was 420.98 ± 18.71 mm2 compared to 430 ± 25.42 mm2 in the LVOT. On average, the LVOT was 3.5mm2 (0.77%) larger in systole and 10mm2 (2.37%) larger in diastole compared to the annulus. Furthermore, a strong linear correlation was noted between the systolic and diastolic sizes of the annulus and LVOT, with a pooled value correlation coefficient (r) value of 0.72 and 0.73, respectively. Conclusion There is a statistically significant difference between the size of the aortic annulus and the LVOT in both systole and diastole. The difference is more pronounced in diastole. The data also shows a strong linear correlation between both the systolic and diastolic sizes of the annulus and the LVOT. The distal portion of the LVOT is within the TAVR valve landing zone but has frequently been neglected in the selection and sizing of valve prostheses. We have found that LVOT morphology varies throughout the cardiac cycle, especially diastole. Further study is required to identify whether distinct LVOT morphologies can be used to improve TAVR valve sizing and procedural outcomes.

Surgery

Aurora L, **Grafton G**, **Nemeh H**, **Chamogeorgakis T**, **Apostolou D**, **Tanaka D**, and **Cowger J**. Indications for LVAD Explant and Predictors of Mortality after Explant in IMACS. *Journal of Heart and Lung Transplantation* 2020; 39(4):S137-S138.

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Purpose: As support durations increase, patients' risk for requiring LVAD device explant (Exp) to address complications also increases. The aims of this analysis were to better understand indications and outcomes associated with LVAD explant. Methods: Patients enrolled into IMACS requiring continuous flow LVAD explant (Exp) for nontransplant indications were identified. Survival in those with and without device Exp and by Exp indication were estimated with Kaplan-Meier methods, and

correlates of mortality within the combined Exp dysfunction+other cohort were examined with Cox Regression. Results: Of 16,842 patients on CF-LVAD in IMACS, 1,579 patients underwent LVAD Exp. Indications for Exp included non-urgent (83.1%) and urgent (1.5%) device malfunction; LV recovery (12.0%); elective (0.25%) and urgent (0.32%) pump thrombosis; and "other" (3.1%). Median time to explant for "other" causes was shortest at 1.2 [0.0, 14.5] months compared with 8 [2.6,17] months for device dysfunction-Exp and 10.9 [7.5,16.3] months for recovery-Exp ($p<0.05$). Early survival in patients undergoing Exp for any reason was better than those without a history of Exp (figure), findings likely related to statistical "survivorship bias" and excellent survival in recovery patients. Patients undergoing Exp for device malfunction-Exp (61±1.7%) or other causes (62±8.2%) had clinically similar 3 year survivals, but survivals were worse than those undergoing Exp for recovery (91±4.9%). Age at implant (HR 1.016 [1.008-1.024] per year), centrifugal flow device (HR 1.6 [1.2-2.1]), prior cardiac surgery (HR 1.4 [1.1-1.7]) and Profile 1-2 (HR 1.3 [1.0-1.5]) were correlates for mortality in those undergoing Exp for device dysfunction or other indications. Conclusion: Survival was similar for those with device Exp due to malfunction and other indications in IMACS. Older patients and those with a history of multiple sternotomies do poorly after Exp. In the elderly, shared decision-making and engagement of palliative care should be undertaken prior to Exp.

Surgery

Bryce K, **Hariri IM**, **Nemeh A**, **St. John G**, and **Cowger JA**. Poor Social Support Confers Worse Survival after MCS. *Journal of Heart and Lung Transplantation* 2020; 39(4):S91.

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Purpose: Patient selection for mechanical circulatory support (MCS) therapy remains challenging. Psychosocial factors such as psychiatric disorders and poor social support, have been found to be associated with outcomes post heart transplant. Research exploring the impact of such factors on LVAD outcomes is limited. We explored the relationship between psychosocial factors and outcomes following implantation with MCS. Methods: We completed a retrospective chart review of 87 consecutive patients who completed a social work and psychological evaluation prior to durable MCS. Those not surviving to discharge were excluded. Psychosocial variables were tested for association with overall survival using Cox regression models adjusted for age, MSC type, and device intent. Results: Mean patient age was 57±1.3 years, 37% were African American with median [25th, 75th] support time of 9.5 [4.5,16] months. On univariable analysis, poor social support correlated (Fig 1a) with mortality, with non-significant trends towards those living alone and with non-compliance (Fig 1b) (table). On multivariable regression, poor social support had a marked influence on mortality, most notable after 6 months of support (Hazard Ratio= 0.08, p=0.029, Fig 1a). Conclusion: Poor social support was independently associated with worse outcome after MCS with a very high hazard for early mortality. Important trends were noted to suggest risk in those living alone and with poor compliance. The presence of a dedicated support person/team to assist with the demands of MCS maintenance and close outpatient coordinator clinic and telephone follow-up may help improve outcomes. Larger sample pending acceptance.

Surgery

Hariri IM, **Hannawi B**, **Grafton G**, **Nemeh HW**, **Chamogeorgakis T**, **Lanfear DE**, **Apostolou D**, **Selektor Y**, **Williams CT**, **Tita C**, **Tanaka D**, Myers SL, Kirklin JK, Pagani FD, and **Cowger JA**. Ventricular Assist Device Patient Phenotypes: What Attributes Describe Long Term Survival? *Journal of Heart and Lung Transplantation* 2020; 39(4):S181-S182.

I.M. Hariri, Henry Ford Hospital, Detroit, MI, United States

Purpose: Presently, 50% of patients on LVAD support are alive on therapy at 5 years. While preoperative (preop) variables can predict short term (ST) survival, correlates of long term (LT) survival remain poorly characterized. Using Intermacs-STS, we aim to identify preop and postoperative correlates of LT survival. Methods: Patients (n=16474) undergoing LVAD implant (2012-18) in Intermacs-STS were categorized as ST (survival ≤1 year postoperative, n=7483), mid-term (MT, 1-3 years, n=5976) and LT (>3 years, n=3015) survivors. Pre-implant characteristics and events during support were compared between the three groups to identify mortality correlates. Results: Compared with patients dying in the ST, LT survivors were more likely to be younger, not listed for transplant, with higher BSA and VAS scores and several lower risk preop characteristics but differences between MT and LT survivors were not clinically significant (table). On multi-variable analysis, patients suffering post-LVAD stroke (HR 1.42, image), any major infection (HR 1.13), pump related infection (HR 1.19), and/or device malfunction (HR=1.22) (all $p<0.001$) were less likely to live >1 year, as were patients with a history of pulmonary disease (HR 1.19, 0.01), cancer (HR 1.26, p=0.01), CABG (HR 1.24, $p<0.001$), hepatitis (HR 1.54, p=0.002) and active smoking (1.44, $p<0.001$). Conclusion: The preop clinical features of ST and LT survivors vary significantly. Preop characteristics mainly select out early deaths, failing to accurately characterize survival after 1 year. LT survival is heavily influenced by device complications and pre-existing medical co-morbidities.

Surgery

Patel A, **Grafton G**, **Tita C**, Hannawi B, **Selektor Y**, **Chamogeorgakis T**, **Apostolou D**, **Lanfear DE**, **Williams CT**, **Nemeh HW**, and **Cowger JA**. Survival and Predictors of Mortality in Patients Undergoing RVAD Explant in IMACS. *Journal of Heart and Lung Transplantation* 2020; 39(4):S25-S26.

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Purpose: Survival in patients requiring RVAD support is known to be poor. However, outcomes in those undergoing subsequent RVAD explant and predictors of mortality remain unknown. Methods: Of 16482 patients in IMACS, 723 patients had an isolated RVAD (n=29) or BiVAD (n=694) in place. Using Kaplan Meier methods, survival was estimated for the LVAD-only cohort and within the subgroup of RVAD/BiVAD patients with and without RVAD explant. Correlates of mortality in the RVAD explant group were identified with Cox multivariable regression. Results: Within the BiVAD group, 240 patients (33%) had an RVAD explant. Of these, 221 (92%) were performed for RV recovery, 17 (7.1%) for device malfunction and 2 (0.8%) were for other reasons. Survival at 1Y was 53±2.0% in the BiVAD group vs. 82±0.3% in LVAD-only patients (p<0.0001). Within the BiVAD group, patients undergoing RVAD explant had equivalent survival (1Y=54±2.5%) to those with ongoing BiVAD support (1Y=52±3.4%, p=0.54). BiVAD patients who died after RVAD explant were older, more likely to be BTT, and had higher preimplant creatinine (table). On multivariable analysis, older age, higher preimplant pulmonary systolic pressure, explant for RVAD dysfunction, and BTT indication predicted death after RVAD explant (table). Within the subgroup of BTT BiVAD (n=51) patients undergoing RVAD explant, survival was only 62% at 3 months. Conclusion: Patients undergoing RVAD explant, even for RV-recovery, have very poor survival. Patients who are transplant eligible with signs of RVAD dysfunction should be given urgent listing status. Rather than RVAD explant, BTT patients with signs of RV recovery may be better served with transplant.

Surgery

Sanchez PG, Cantu E, Hartwig M, D'Ovidio F, Machuca T, Whitson B, Daneshmand M, Bermudez C, Mulligan M, D'Cunha J, Weyant M, Lynch W, Garcia J, Caldeira C, **Nemeh H**, Song T, Kreisel D, Jessen M, Camp P, Ramzy D, Griffith B, and Davis D. The NOVEL Study. A Multi-Center Clinical Trial Studying the Safety of Ex Vivo Lung Perfusion. *Journal of Heart and Lung Transplantation* 2020; 39(4):S110.

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Purpose: lung transplantation continues to be a life saving therapy for patients with end stage lung disease. In a donor restrictive environment and with only 22% of donor lungs currently being transplanted ex vivo lung perfusion can increase donor use and transplantation preserving safety and good outcomes Methods: the NOVEL study is a prospective, multi-center, controlled clinical trial. Seventeen US lung transplant centers evaluated the safety of screening donors initially considered unacceptable for transplant with normothermic ex vivo lung perfusion (EVLP). Results: from 2011 to 2017 seventeen lung transplant centers evaluated 216 donors with EVLP. 110 were transplanted for a 50.9% conversion rate. Early and long-term outcomes were compared to 116 control patients that underwent transplantation using standard criteria lungs. The primary endpoints for this study were Primary Graft Dysfunction (PGD) grade 3 at 72 hours and 1-year survival. The rate of PGD grade 3 at 72 hrs. was non-inferior between the ELVP and Control group (8.9% vs 9.5%, p 0.12). The 1-year survival for the EVLP group was 93.2% vs. 96.5% for the Control group, p 0.84. Secondary endpoints such as ICU length of stay, 9.9 vs 9.8 days, hospital length of stay, 23.9 vs 28.5 days, duration of mechanical ventilation, 7.0 vs 5.7 days, were also not significantly different between the EVLP and Control groups. Median FEV 1 was also no different between the EVLP and Control groups 12 months post transplant 65 vs 70 %. Conclusion: data from this multi-center, controlled clinical trial demonstrates that the use of ex vivo lung perfusion to screen for viable grafts within the unused donor pool is safe and provides equal short and long therm outcomes to standard criteria donor lungs.

Urology

Alanee SR, Deebajah M, Roumayah Z, **Dabaja A**, **Peabody JO**, and **Menon M**. Detection of significant prostate cancer through magnetic resonance imaging targeted biopsy of PI-RADS3 lesions in African American patients based on prostate specific antigen density threshold of 0.15 ng/ml2: Analysis of patient population from the Vattikuti Urology Institute. *Journal of Clinical Oncology* 2020; 38(6).

S.R. Alanee

Background: A prostate specific antigen density (PSAD) threshold of 0.15 ng/ml2 have been suggested for significant cancer detection in PI-RADS 3 lesions to avoid unnecessary magnetic resonance imaging targeted biopsy (MRI-TB) of these lesions. However, the performance of this threshold in African American (AA) patients is not well characterized. Methods: We analyzed our institutional data base of MRI-TB to identify the rate of significant prostate cancer (Pca) detection in PI-RADS3 lesions in AA patients stratified by PSAD threshold of < 0.15 vs. >0.15 ng/ml2 and lesion size of < 1 cm vs > 1 cm. Significant prostate cancer was defined as Gleason grade group 2 or higher on MRI-TB of the PI-RADS 3 lesion. Results: Of 768 patients included in the database, 211 (27.5%) patients identified themselves as AAs. Mean age of AA patients was 63 years and mean PSAD was 0.21. Sixty nine (32.7%) AA patients were found to have PI-RADS 3 lesions. Mean PSAD of AA patients with PI-RADS 3 lesions was 0.21 ng/ml2 as well. Fifty percent of AA patients with PI-RADS 3 lesions had PSAD >0.15 ng/ml2. Significant Pca detection rate for AA patients with PI-RADS 3 lesions was 9% for PSAD of > 0.15 vs. 0.03% percent for AA patients with PSAD < 0.15 ng/ml2 (OR 7.056, CI 1.017-167.9, P=0.04). Stratification by lesion size (< 1 cm vs. > 1 cm) resulted in missing 0% percentage of significant Pca when only AA patients with PSAD ∗ 0.15 ng/ml2 and lesion size > 1 cm received MRI-TB.

Conclusions: We report on the performance of a reported PSAD density threshold in detecting significant Pca in one of the largest series of AA patients receiving MRI-TB of the prostate. Our results have direct clinical implications when counseling AA patients with PI-RADS 3 lesion on whether they should undergo MRI-TB of such lesions.

Urology

Alanee SR, Roumayah Z, Deebajah M, **Peabody JO**, Mora R, **Guevara J**, Francisco B, and Patterson BK. Adaptive genetic algorithms combined with high sensitivity single cell-based technology derived urine-based score to differentiate between high-grade and low-grade transitional cell carcinoma of the bladder. *Journal of Clinical Oncology* 2020; 38(6).

S.R. Alanee

Background: We previously showed that adaptive genetic algorithms (AGA), in combination with single-cell flow cytometry technology, can be used to develop a noninvasive urine-based score to detect bladder cancer with high accuracy. Our aim in this analysis was to investigate if that same score can differentiate between high grade (HG) and low grade (LG) transitional cell carcinoma of the bladder (BC). Methods: We collected urine samples from cystoscopy confirmed HG and LG superficial bladder cancer patients and healthy donors in an optimized urine collection media. We then examined these samples using an assay developed from AGA in combination with single-cell flow cytometry technology. Results: We examined 50 BC and 15 healthy donor urine samples. Patients were majorly White (59.2%), males (61.2%), and had HG BC (66.7%). AGA derived score of 1.1 differentiated between BCa and healthy patients with high precision (AUC 0.92). The median score was 2.8 for LG BC and 6 for LG BC. Mann-Whitney Rank Sum Test indicated that the difference between the median score of HG and LG BC was significant at P value = 0.003. The score performed well independent of patients' sex or smoking history. Conclusions: Using single-cell technology and machine learning, we developed a new urine-based score that can potentially differentiate between HG and LG bladder cancer. Future studies are planned to validate this score.