

Henry Ford Health System Publication List – March 2021

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 Web of Science during the month, and then imported into EndNote for formatting. There are **98 unique citations** listed this month, with **15 articles** and **1 conference abstract on COVID-19**. Articles are listed first, followed by [conference abstracts](#), books and book chapters, and a [bibliography of publications on COVID-19](#). 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

Anesthesiology

Aiyer R, Noori S, Schirripa F, Schirripa M, Aboud T, Jain S, Gulati A, Puttanniah V, Gungor S, and Hunter C. Treatment of knee osteoarthritic pain with platelet-rich plasma: a systematic review of clinical studies. *Pain Manag* 2021; Epub ahead of print. PMID: 33764185. [Request Article](#)

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Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA.

Pain Centers of America, White Hall, AK, USA.

Department of Anesthesia & Critical Care, Memorial Sloan Kettering Cancer Center, Weill Cornell Medicine, NY, USA.

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Ainsworth Institute of Pain Management & Department of Rehabilitation & Human Performance, Mount Sinai Health System, NY, USA.

Introduction: Knee osteoarthritis is a degenerative joint disease that is secondary to degradation of articular cartilage, reformation of subchondral bone through degradation and proliferation as well as presence of synovitis. Materials & methods: This systematic review was conducted and reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Results: A total of 30 of the 48 comparators showed statistically significant superiority with platelet-rich plasma (PRP) compared with a control, while the other 16 comparators showed no significant difference between PRP and the comparator. Conclusion: We can only recommend PRP for patients with early-stage osteoarthritis (I or II) and who are aged below 65, based on our findings. Based on the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) recommendations, while studies reviewed were

randomized controlled studies, and therefore, high grade, due to variance in imprecision, risk of bias and inconsistency among the 37 studies, it would be reasonable to rate this paper as subjectively moderate.

Anesthesiology

Hamadnalla H, Sessler DI, Troianos CA, Fang J, Rivas E, Ma C, Mascha EJ, and Turan A. Optimal interval and duration of CAM-ICU assessments for delirium detection after cardiac surgery. *J Clin Anesth* 2021; 71:110233. PMID: 33706033. [Full Text](#)

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STUDY OBJECTIVE: Our goal was to determine when postoperative delirium first occurs, and to assess evaluation strategies that reliably detect delirium with lowest frequency of testing'. **DESIGN:** This was a retrospective study that used a database from a five-center randomized trial. **SETTING:** Postoperative cardiothoracic ICU and surgical wards. **PARTICIPANT:** Adults scheduled for elective coronary artery bypass and/or valve surgery. **INTERVENTION AND MEASUREMENTS:** Postoperative delirium was assessed using CAM-ICU questionnaires twice daily for 5 days or until hospital discharge. Data were analyzed using frequency tables and Kaplan-Meier time-to-event estimators, the latter being used to summarize time to first positive CAM-ICU over POD1-5 for all patients for various evaluation strategies, including all assessments, only morning assessment, and only afternoon assessments. Sensitivity for various strategies were compared using McNemar's test for paired proportions. **MAIN RESULTS:** A total of 95 of 788 patients (12% [95% CI, 10% to 15%]) had at least 1 episode of delirium within the first 5 postoperative days. Among all patients with delirium, 65% were identified by the end of the first postoperative day. Delirium was detected more often in the mornings (10% of patients) than evenings (7% of patients). Compared to delirium assessments twice daily for five days, we found that twice daily assessments for 4 days detected an estimated 97% (95% CI 91%, 99%) of delirium. Measurements twice daily for three days detected 90% (82%, 95%) of delirium. **CONCLUSIONS:** Postoperative delirium is common, and CAM-ICU assessments twice daily for 4 days, versus 5 days, detects nearly all delirium with 20% fewer assessments. Four days of assessment may usually be sufficient for clinical and research purposes.

Behavioral Health Services/Psychiatry

Lamparyk K, **Williams AM**, Robiner WN, Bruschein HM, and Ward WL. Interprofessional Education: Current State in Psychology Training. *J Clin Psychol Med Settings* 2021; Epub ahead of print. PMID: 33689102. [Full Text](#)

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Healthcare reform has led to the consideration of interprofessional team-based, collaborative care as a way to provide comprehensive, high-quality care to patients and families. Interprofessional education is the mechanism by which the next generation health professional workforce is preparing for the future of health care-team-based, collaborative care. This literature review explored the extent and content of

published studies documenting Interprofessional Education (IPE) activities with psychology trainees across learner level. A systematic review following PRISMA guidelines was conducted of studies describing IPE involving psychology learners. Electronic databases (MEDLINE, CINAHL, PsychINFO, and EMBASE) were searched for the following terms: inter/multi-professional education/practice, inter/multidisciplinary education/practice, and psychology/psychologists. Thirty-seven articles were identified that included psychology in clinical outcome studies or other reviews of interprofessional education initiatives. The review addresses the nature of current IPE learning activities, the impact of IPE activities on participating trainees, opportunities for, and challenges of, involving psychology trainees in IPE, and future directions for research. This review illuminates the relative paucity of the literature about IPE in psychology training. Given the trend toward increasing team-based collaborative care, the limited inclusion of psychology in the IPE literature is concerning. The next generation of health professional trainees is learning about, from, and with each other with the objective of building collaboration and teamwork. Given the few articles documenting psychology trainees' involvement in IPE, future health professionals quite possibly will have limited understanding of, and contact with, psychologists. Our findings are a call to action for greater psychology involvement in IPE.

Cardiology/Cardiovascular Research

Al-Kindi SG, Xie R, Kirklin JK, **Cowger J**, Oliveira GH, Krabatsch T, Nakatani T, Schueler S, Leet A, Golstein D, and Elamm CA. Outcomes of Durable Mechanical Circulatory Support in Myocarditis: Analysis of the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support Registry. *Asaio j* 2021; Epub ahead of print. PMID: 33769352. [Full Text](#)

From the Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, Ohio Department of Surgery, The University of Alabama at Birmingham, Birmingham, Alabama Department of Cardiology, Advanced Heart Failure and Transplant Cardiology, Henry Ford Health System, Detroit, Michigan Division of Cardiovascular Sciences, University of South Florida, Tampa, Florida Deutsches Herzzentrum Berlin, Berlin, Germany Department of Transplantation, National Cerebral and Cardiovascular Center, Osaka, Japan Department of Cardiothoracic & Vascular Surgery, Newcastle/Freeman Hospital, UK, Newcastle, United Kingdom Alfred Heart Center, Melbourne, Victoria, Australia Department of Cardiovascular Surgery, Montefiore Medical Center, Bronx, New York.

Myocarditis can be refractory to medical therapy and require durable mechanical circulatory support (MCS). The characteristics and outcomes of these patients are not known. We identified all patients with clinically-diagnosed or pathology-proven myocarditis who underwent mechanical circulatory support in the International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support registry (2013-2016). The characteristics and outcomes of these patients were compared to those of patients with nonischemic cardiomyopathy (NICM). Out of 14,062 patients in the registry, 180 (1.2%) had myocarditis and 6,602 (46.9%) had NICM. Among patients with myocarditis, duration of heart failure was <1 month in 22%, 1-12 months in 22.6%, and >1 year in 55.4%. Compared with NICM, patients with myocarditis were younger (45 vs. 52 years, $P < 0.001$) and were more often implanted with Interagency Registry for Mechanically Assisted Circulatory Support profile 1 (30% vs. 15%, $P < 0.001$). Biventricular mechanical support (biventricular ventricular assist device [BIVAD] or total artificial heart) was implanted more frequently in myocarditis (18% vs. 6.7%, $P < 0.001$). Overall postimplant survival was not different between myocarditis and NICM (left ventricular assist device: $P = 0.27$, BIVAD: $P = 0.50$). The proportion of myocarditis patients that have recovered by 12 months postimplant was significantly higher in myocarditis compared to that of NICM (5% vs. 1.7%, $P = 0.0003$). Adverse events (bleeding, infection, and neurologic dysfunction) were all lower in the myocarditis than NICM. In conclusion, although myocarditis patients who receive durable MCS are sicker preoperatively with higher needs for biventricular MCS, their overall MCS survival is noninferior to NICM. Patients who received MCS for myocarditis are more likely than NICM to have MCS explanted due to recovery, however, the absolute rates of recovery were low.

Cardiology/Cardiovascular Research

Ananthasubramaniam K, Kitt TM, Saxena A, Feng Q, Nimke D, Spalding JR, and Xu Y. Healthcare resource utilization among patients receiving non-invasive testing for coronary artery disease in an outpatient setting: A cohort study reflecting daily practice trends. *J Nucl Cardiol* 2021; Epub ahead of print. PMID: 33660216. [Full Text](#)

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BACKGROUND: Accurate, early diagnosis and the initiation of appropriate treatment is central to reducing the clinical burden of coronary artery disease (CAD); however, real-world evidence characterizing healthcare resource utilization (HCRU) associated with testing for CAD is lacking. **METHODS AND RESULTS:** Using a non-interventional, retrospective, secondary database analysis, patients aged ≥ 18 years who underwent outpatient non-invasive cardiac diagnostic testing were identified. The primary objective was to gain an understanding of pre- and post-assessment care pathways and the associated interventions for patients who underwent non-invasive testing for CAD in either an outpatient or emergency department setting. Overall, chest pain was the primary reason for the index visit (54.8%), followed by shortness of breath (23.7%), myocardial infarction (MI), coronary artery disease (CAD) or congestive heart failure (CHF) (3.8%), and other (46.8%); 3.0% of patients had no apparent reason for testing in the last 45 days. Single-photon emission computed tomography (SPECT) was the dominant diagnostic testing modality (40.3%). During the 90-day follow-up, 7.3% ($n = 22,083$) of patients were diagnosed with CAD; among these patients, 19.4% had repeat diagnostic testing, 26.0% of patients had a revascularization procedure, and 65.6% underwent cardiac catheterization. These rates varied by testing modality. **CONCLUSIONS:** In this study of a large real-world data sample, variability in the use of non-invasive tests and HCRU were evident. These results may assist efforts to optimize system-wide care/diagnostic pathways and value-based treatment decisions for patients.

Cardiology/Cardiovascular Research

Basir MB, Pinto DS, Ziaean B, **Khandelwal A**, **Cowger J**, Suh W, and Althouse A. Mechanical circulatory support in acute myocardial infarction and cardiogenic shock: Challenges and importance of randomized control trials. *Catheter Cardiovasc Interv* 2021; Epub ahead of print. PMID: 33682260. [Full Text](#)

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BACKGROUND: Acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) is associated with significant morbidity and mortality. **METHODS:** We provide an overview of previously conducted studies on the use of mechanical circulatory support (MCS) devices in the treatment of AMI-CS and difficulties which may be encountered in conducting such trials in the United States. **RESULTS:** Well powered randomized control trials are difficult to conduct in a critically ill patient population due to physician preferences, perceived lack of equipoise and challenges obtaining informed consent. **CONCLUSIONS:** With growth in utilization of MCS devices in patients with AMI-CS, efforts to perform well-powered, randomized control trials must be undertaken.

Cardiology/Cardiovascular Research

Brener MI, Burkhoff D, **Basir MB**, and **Alqarqaz M**. Pressure-Volume Analysis Illustrating the Mechanisms of Short-Term Hemodynamic Effects Produced by Premature Ventricular Contractions. *Circ Heart Fail* 2021; 14(3):e007766. PMID: 33691463. [Full Text](#)

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Cardiology/Cardiovascular Research

Eng MH, and Fang HK. Transcarotid: A sign from above? *Catheter Cardiovasc Interv* 2021; 97(4):734-735. PMID: 33721408. [Full Text](#)

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Cardiology/Cardiovascular Research

Kerrigan DJ, **Brawner CA**, **Ehrman JK**, and **Keteyian S**. Cardiorespiratory Fitness Attenuates the Impact of Risk Factors Associated With COVID-19 Hospitalization. *Mayo Clin Proc* 2021; 96(3):822-823. PMID: 33673935. [Full Text](#)

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Cardiology/Cardiovascular Research

Megaly M, Brilakis ES, Sedhom R, Tawadros M, Elbadawi A, Mentias A, **Alaswad K**, Kirtane AJ, Garcia S, and Pershad A. Outcomes with Orbital and Rotational Atherectomy for Inpatient Percutaneous Coronary Intervention. *Cardiol Ther* 2021; Epub ahead of print. PMID: 33710602. [Full Text](#)

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INTRODUCTION: Our objective was to describe the contemporary outcomes of orbital atherectomy (OA) vs. rotational atherectomy (RA) use for inpatient percutaneous coronary intervention (PCI) in the United States. Data on the use of OA vs. RA in contemporary inpatient PCI are limited. **METHODS:** We queried the Nationwide Readmission Database (NRD) from January to November for the years 2016-2017 to identify hospitalizations of patients who underwent PCI with atherectomy. We conducted a multivariate regression analysis to identify variables associated with in-hospital mortality. **RESULTS:** We included 77,040 records of patients who underwent inpatient PCI with atherectomy. Of those, 71,610 (93%) had RA, and 5430 (7%) had OA. There was no significant change in the trend of using OA or RA over 2016 and 2017. OA was less utilized in patients presenting with ST-segment elevation myocardial infarction (STEMI) (4.3% vs. 46.8%, $p < 0.001$). In our cohort, OA was associated with lower in-hospital mortality (3.1% vs. 5%, $p < 0.001$) and 30-day urgent readmission ($< 0.01\%$ vs. 0.2%, $p = 0.009$), but a higher risk of coronary perforation (1.7% vs. 0.6%, $p < 0.001$) and cardiac tamponade (1% vs. 0.3%, $p < 0.001$) and a higher cost of index hospitalization (\$28,199 vs. \$23,188, $p < 0.001$) compared with RA. **CONCLUSION:** RA remains the predominant atherectomy modality for inpatient PCI in the United States (93%). There was no change in the trend of use for either modality over the years 2016 and 2017. OA was noted to have a lower incidence of in-hospital death, but a higher risk of coronary perforation and a higher cost of index hospitalization for the overall unmatched cohorts.

Cardiology/Cardiovascular Research

Megaly M, Sedhom R, Zordok M, Burke MN, **Basir M**, Rinfret S, Nicholson W, Karpaliotis D, **Alaswad K**, and Brilakis ES. Complications and failure modes of Stingray LP balloon: Insights from the MAUDE Database. *Cardiovasc Revasc Med* 2021; Epub ahead of print. PMID: 33722540. [Full Text](#)

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Cardiology/Cardiovascular Research

Nayak A, Hu Y, Ko YA, Steinberg R, Das S, Mehta A, Liu C, Pennington J, Xie R, Kirklin JK, Kormos RL, **Cowger J**, Simon MA, and Morris AA. Creation and Validation of a Novel Sex-Specific Mortality Risk Score in LVAD Recipients. *J Am Heart Assoc* 2021; Epub ahead of print.:e020019. PMID: 33764158. [Full Text](#)

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Background Prior studies have shown that women have worse 3-month survival after receiving a left ventricular assist device compared with men. Currently used prognostic scores, including the Heartmate II Risk Score, do not account for the increased residual risk in women. We used the IMACS (International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support) registry to create and validate a sex-specific risk score for early mortality in left ventricular assist device recipients. **Methods and Results** Adult patients with a continuous-flow LVAD from the IMACS registry were randomly divided into a derivation cohort (DC; n=9113; 21% female) and a validation cohort (VC; n=6074; 21% female). The IMACS Risk Score was developed in the DC to predict 3-month mortality, from preoperative candidate predictors selected using the Akaike information criterion, or significant sex x variable interaction. In the DC, age, cardiogenic shock at implantation, body mass index, blood urea nitrogen, bilirubin, hemoglobin, albumin, platelet count, left ventricular end-diastolic diameter, tricuspid regurgitation, dialysis, and major infection before implantation were retained as significant predictors of 3-month mortality. There was significant ischemic heart failure x sex and platelet count x sex interaction. For each quartile increase in IMACS risk score, men (odds ratio [OR], 1.86; 95% CI, 1.74-2.00; P<0.0001), and women (OR, 1.93; 95% CI, 1.47-2.59; P<0.0001) had higher odds of 3-month mortality. The IMACS risk score represented a significant improvement over Heartmate II Risk Score (IMACS risk score area under the receiver operating characteristic curve: men: DC, 0.71; 95% CI, 0.69-0.73; VC, 0.69; 95% CI, 0.66-0.72; women: DC, 0.73; 95% CI, 0.70-0.77; VC, 0.71 [95% CI, 0.66-0.76; P<0.01 for improvement in receiver operating characteristic) and provided excellent risk calibration in both sexes. Removal of sex-specific interaction terms resulted in significant loss of model fit. **Conclusions** A sex-specific risk score provides excellent risk prediction in LVAD recipients.

Cardiology/Cardiovascular Research

Ooms JF, **Wang DD**, Rajani R, Redwood S, Little SH, Chuang ML, Popma JJ, Dahle G, Pfeiffer M, Kanda B, Minet M, Hirsch A, Budde RP, De Jaegere PP, Prendergast B, **O'Neill W**, and Van Mieghem NM. Computed Tomography-Derived 3D Modeling to Guide Sizing and Planning of Transcatheter Mitral Valve Interventions. *JACC Cardiovasc Imaging* 2021; Epub ahead of print. PMID: 33744155. [Full Text](#)

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A plethora of catheter-based strategies have been developed to treat mitral valve disease. Evolving 3-dimensional (3D) multidetector computed tomography (MDCT) technology can accurately reconstruct the mitral valve by means of 3-dimensional computational modeling (3DCM) to allow virtual implantation of catheter-based devices. 3D printing complements computational modeling and offers implanting physician teams the opportunity to evaluate devices in life-size replicas of patient-specific cardiac anatomy. MDCT-derived 3D computational and 3D-printed modeling provides unprecedented insights to facilitate hands-on procedural planning, device training, and retrospective procedural evaluation. This overview summarizes current concepts and provides insight into the application of MDCT-derived 3DCM and 3D printing for the planning of transcatheter mitral valve replacement and closure of paravalvular leaks. Additionally, future directions in the development of 3DCM will be discussed.

Cardiology/Cardiovascular Research

Qintar M, Asala EA, Frisoli T, O'Neill B, Alaswad K, Lee J, Wang DD, Eng MH, O'Neill WW, and Villablanca PA. Utility of cerebral embolic protection in non-TAVR transcatheter procedures. *Cardiovasc Revasc Med* 2021; Epub ahead of print. PMID: 33771481. [Full Text](#)

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BACKGROUND: Cerebrovascular events that occur during structural and interventional procedures are a well known risk which is associated with increased mortality. The FDA has approved the use of the Sentinel device in TAVR. Hereby we report on our experience on the safety and efficacy of using Sentinel in a patient population undergoing non-TAVR transcatheter procedures. **METHODS:** Retrospective analysis of a single center experience with using the Sentinel device for non-TAVR transcatheter procedures. **RESULTS:** We identified 33 patients (average age was 73.8 years, 36.7% females, and 30% with history of a prior stroke) felt to be at high risk for cerebroembolic events that underwent Sentinel device placement. Sentinel placement was successful in all patients. Examples of high risk features

included high atheroma burden in the aortic arch, left sided valve vegetations, intra-cardiac thrombi and severe left sided valve calcifications/thrombi. No patients developed periprocedural stroke or vascular complications. CONCLUSION: Overall, the use of Sentinel for non-TAVR indications appears feasible and safe. The use of cerebral protection devices should be studied further in non-TAVR patients to establish its role and its benefits, especially with expanding the number of non-TAVR transcatheter interventions.

Cardiology/Cardiovascular Research

Schuger C, Daubert JP, Zareba W, Rosero S, Yong P, McNitt S, and Kutiyifa V. Reassessing the role of antitachycardia pacing in fast ventricular arrhythmias in primary prevention implantable cardioverter-defibrillator recipients: Results from MADIT-RIT. *Heart Rhythm* 2021; 18(3):399-403. PMID: 33232811.

[Full Text](#)

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BACKGROUND: In Multicenter Automatic Defibrillator Implantation Trial - Reduce Inappropriate Therapy (MADIT-RIT), high-rate cutoff (arm B) and delayed therapy (arm C) reduced the risk of inappropriate implantable cardioverter-defibrillator (ICD) interventions when compared with conventional programming (arm A); however, appropriate but unnecessary therapies were not evaluated. **OBJECTIVE:** The purpose of this study was to assess the value of antitachycardia pacing (ATP) for fast ventricular arrhythmias (VAs) ≥ 200 beats/min in patients with primary prevention ICD. **METHODS:** We compared ATP only, ATP and shock, and shock only rates in patients in MADIT-RIT treated for VAs ≥ 200 beats/min. The only difference between these randomized groups was the time delay between ventricular tachycardia detection and therapy (3.4 seconds vs 4.9 seconds vs 14.4 seconds). **RESULTS:** In arm A, 11.5% patients had events, the initial therapy was ATP in 10.5% and shock in 1%, and the final therapy was ATP in 8% and shock in 3.5%. In arm B, 6.6% had events, 4.2% were initially treated with ATP and 2.4% with shock, and the final therapy was ATP in 2.8% and shock in 3.8%. In arm C, 4.7% had events, 2.5% were initially treated with ATP and 2.3% with shock, and the final therapy was ATP in 1.4% and shock in 3.3%. The final shock rate was similar in arm A vs arm B (3.5% vs 3.8%; $P = .800$) and in arm A vs arm C (3.5% vs 3.3%; $P = .855$) despite the marked discrepancy in initial ATP therapy utilization. **CONCLUSION:** In MADIT-RIT, there was a significant reduction in ATP interventions with therapy delays due to spontaneous termination, with no difference in shock therapies, suggesting that earlier interventions for VAs ≥ 200 beats/min are likely unnecessary, leading to an overestimation of the value of ATP in primary prevention ICD recipients.

Cardiology/Cardiovascular Research

Shah K, **Patel S**, Hanson I, Williamson B, Kutinsky I, Dixon S, Haines D, and Mehta N. Navigating Inferior Vena Cava Filters in Invasive Cardiology Procedures: A Systematic Review. *J Cardiovasc Electrophysiol* 2021; Epub ahead of print. PMID: 33772931. [Full Text](#)

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BACKGROUND: Transfemoral venous access (TFV) is the cornerstone of minimally invasive cardiac procedures. Although the presence of inferior vena cava filters (IVCF) was considered a relative contraindication to TFV procedures, small experiences have suggested safety. We conducted a systematic review of the available literature on cardiac procedural success of TFV with IVCF in-situ. **METHODS:** Two independent reviewers searched PubMed, EMBASE, SCOPUS and Google Scholar from inception to October 2020 for studies that reported outcomes in patients with IVCFs undergoing TFV for invasive cardiac procedures. We investigated a primary outcome of acute procedural success and reviewed the pooled data for patient demographics, procedural complications, types of IVCF, IVCF dwell

time and procedural specifics. RESULTS: Of the 120 studies initially screened, 8 studies were used in the final analysis with a total of 100 patients who underwent 110 procedures. The most common IVCF was the Greenfield Filter (36%), 60% of patients were males and the mean age was 67.8 years. The overall pooled incidence of acute procedural success was 95.45% (95% confidence interval 89.54. - 98.1) with no heterogeneity ($I^2 = 0\%$, $p = 1$) and there were no reported filter related complications. CONCLUSION: This systematic review is the largest study of its kind to demonstrate the safety and feasibility of TFV access in a variety of cardiac procedures in the presence of IVCF. This article is protected by copyright. All rights reserved.

Cardiology/Cardiovascular Research

Siddiqi TJ, Usman MS, Shahid I, Ahmed J, Khan SU, **Ya'qoub L**, Rihal CS, and Alkhouli M. Utility of the CHA2DS2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2021; Epub ahead of print. PMID: 33693717.

[Full Text](#)

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AIMS: Anticoagulants are the mainstay treatment for stroke prevention in patients with non-valvular atrial fibrillation (NVAF), and the CHA2DS2-VASc score is widely used to guide anticoagulation therapy in this cohort. However, utility of CHA2DS2-VASc in NVAF patients is debated, primarily because it is a vascular scoring system, which does not incorporate atrial fibrillation related parameters. Therefore, we conducted a meta-analysis to estimate the discrimination ability of CHA2DS2-VASc in predicting ischaemic stroke overall, and in subgroups of patients with or without NVAF. METHODS AND RESULTS: PubMed and Embase databases were searched till June 2020 for published articles that assessed the discrimination ability of CHA2DS2-VASc, as measured by C-statistics, during mid-term (2-5 years) and long-term (>5 years) follow-up. Summary estimates were reported as random effects C-statistics with 95% confidence intervals (CIs). Seventeen articles were included in the analysis. Nine studies ($n = 453\ 747$ patients) reported the discrimination ability of CHA2DS2-VASc in NVAF patients, and 10 studies ($n = 138\ 262$ patients) in patients without NVAF. During mid-term follow-up, CHA2DS2-VASc predicted stroke with modest discrimination in the overall cohort [0.67 (0.65-0.69)], with similar discrimination ability in patients with NVAF [0.65 (0.63-0.68)] and in those without NVAF [0.69 (0.68-0.71)] (P-interaction = 0.08). Similarly, at long-term follow-up, CHA2DS2-VASc had modest discrimination [0.66 (0.63-0.69)], which was consistent among patients with NVAF [0.63 (0.54-0.71)] and those without NVAF [0.67 (0.64-0.70)] (P-interaction = 0.39). CONCLUSION: This meta-analysis suggests that the discrimination power of the CHA2DS2-VASc score in predicting ischaemic stroke is modest, and is similar in the presence or absence of NVAF. More accurate stroke prediction models are thus needed for the NVAF population.

Cardiology/Cardiovascular Research

Spertus JA, Birmingham MC, Butler J, Lingvay I, **Lanfeard DE**, Abbate A, Kosiborod ML, Fawcett C, Burton P, Damaraju CV, Januzzi JL, and Whang J. Novel Trial Design: CHIEF-HF. *Circ Heart Fail* 2021; 14(3):e007767. PMID: 33724883. [Full Text](#)

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BACKGROUND: The expense of clinical trials mandates new strategies to efficiently generate evidence and test novel therapies. In this context, we designed a decentralized, patient-centered randomized clinical trial leveraging mobile technologies, rather than in-person site visits, to test the efficacy of 12 weeks of canagliflozin for the treatment of heart failure, regardless of ejection fraction or diabetes status, on the reduction of heart failure symptoms. **METHODS:** One thousand nine hundred patients will be enrolled with a medical record-confirmed diagnosis of heart failure, stratified by reduced ($\leq 40\%$) or preserved ($>40\%$) ejection fraction and randomized 1:1 to 100 mg daily of canagliflozin or matching placebo. The primary outcome will be the 12-week change in the total symptom score of the Kansas City Cardiomyopathy Questionnaire. Secondary outcomes will be daily step count and other scales of the Kansas City Cardiomyopathy Questionnaire. **RESULTS:** The trial is currently enrolling, even in the era of the coronavirus disease 2019 (COVID-19) pandemic. **CONCLUSIONS:** CHIEF-HF (Canagliflozin: Impact on Health Status, Quality of Life and Functional Status in Heart Failure) is deploying a novel model of conducting a decentralized, patient-centered, randomized clinical trial for a new indication for canagliflozin to improve the symptoms of patients with heart failure. It can model a new method for more cost-effectively testing the efficacy of treatments using mobile technologies with patient-reported outcomes as the primary clinical end point of the trial. Registration: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT04252287.

Cardiology/Cardiovascular Research

Ya'qoub L, **Lemor A, Dabbagh M, O'Neill W, Khandelwal A**, Martinez SC, Ibrahim NE, Grines C, Voeltz M, and **Basir MB**. Racial, Ethnic, and Sex Disparities in Patients With STEMI and Cardiogenic Shock. *JACC Cardiovasc Interv* 2021; 14(6):653-660. PMID: 33736772. [Full Text](#)

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OBJECTIVES: The aim of this study was to evaluate the combined impact of race, ethnicity, and sex on in-hospital outcomes using data from the National Inpatient Sample. **BACKGROUND:** Cardiogenic shock (CS) is a major cause of mortality following ST-segment elevation myocardial infarction (STEMI). Early revascularization reduces mortality in such patients. Mechanical circulatory support (MCS) devices are increasingly used to hemodynamically support patients during revascularization. Little is known about racial, ethnic, and sex disparities in patients with STEMI and CS. **METHODS:** The National Inpatient Sample was queried from January 2006 to September 2015 for hospitalizations with STEMI and CS. The associations between sex, race, ethnicity, and outcomes were examined using complex-samples multivariate logistic or generalized linear model regressions. **RESULTS:** Of 159,339 patients with STEMI and CS, 57,839 (36.3%) were women. In-hospital mortality was higher for all women (range 40% to 45.4%) compared with men (range 30.4% to 34.7%). Women (adjusted odds ratio [aOR]: 1.11; 95% confidence interval [CI]: 1.06 to 1.16; $p < 0.001$) as well as Black (aOR: 1.18; 95% CI: 1.04 to 1.34; $p = 0.011$) and Hispanic (aOR: 1.19; 95% CI: 1.06 to 1.33; $p = 0.003$) men had higher odds of in-hospital mortality compared with White men, with Hispanic women having the highest odds of in-hospital mortality (aOR: 1.46; 95% CI: 1.26 to 1.70; $p < 0.001$). Women were older (age: 69.8 years vs. 63.2 years), had more comorbidities, and underwent fewer invasive cardiac procedures, including revascularization, right heart catheterization, and MCS. **CONCLUSIONS:** There are significant racial, ethnic, and sex differences in procedural utilization and clinical outcomes in patients with STEMI and CS. Women are less likely to undergo invasive cardiac procedures, including revascularization and MCS. Women as well as Black and Hispanic patients have a higher likelihood of death compared with White men.

Center for Health Policy and Health Services Research

Graff M, Justice AE, Young KL, **Levin AM, Neslund-Dudas C, Padhukasahasram B, Rybicki BA**, et al. Discovery and fine-mapping of height loci via high-density imputation of GWASs in individuals of African ancestry. *Am J Hum Genet* 2021; Epub ahead of print. PMID: 33713608. [Request Article](#)

Although many loci have been associated with height in European ancestry populations, very few have been identified in African ancestry individuals. Furthermore, many of the known loci have yet to be generalized to and fine-mapped within a large-scale African ancestry sample. We performed sex-combined and sex-stratified meta-analyses in up to 52,764 individuals with height and genome-wide genotyping data from the African Ancestry Anthropometry Genetics Consortium (AAAGC). We additionally combined our African ancestry meta-analysis results with published European genome-wide association study (GWAS) data. In the African ancestry analyses, we identified three novel loci (SLC4A3, NCOA2, ECD/FAM149B1) in sex-combined results and two loci (CRB1, KLF6) in women only. In the African plus European sex-combined GWAS, we identified an additional three novel loci (RCCD1, G6PC3, CEP95) which were equally driven by AAAGC and European results. Among 39 genome-wide significant signals at known loci, conditioning index SNPs from European studies identified 20 secondary signals. Two of the 20 new secondary signals and none of the 8 novel loci had minor allele frequencies (MAF) < 5%. Of 802 known European height signals, 643 displayed directionally consistent associations with height, of which 205 were nominally significant ($p < 0.05$) in the African ancestry sex-combined sample. Furthermore, 148 of 241 loci contained ≤ 20 variants in the credible sets that jointly account for 99% of the posterior probability of driving the associations. In summary, trans-ethnic meta-analyses revealed novel signals and further improved fine-mapping of putative causal variants in loci shared between African and European ancestry populations.

Center for Health Policy and Health Services Research

Li J, Gordon SC, Zhou Y, Boscarino JA, Schmidt MA, Daida YG, Rupp LB, Trudeau S, and Lu M. Sex Differences in Extrahepatic Outcomes After Antiviral Treatment for Hepatitis C. *Am J Gastroenterol* 2021; 116(3):576-583. PMID: 33399360. [Full Text](#)

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INTRODUCTION: Despite recognized differences in the rates of cardiovascular and renal disease between men and women in the general population, studies of the downstream effects of antiviral treatment for hepatitis C (HCV) have not investigated differences in outcomes based on sex. We analyzed sex differences in risk of acute coronary syndrome (ACS), end-stage renal disease (ESRD), and ischemic stroke by treatment and response in a large US-based multisite cohort of HCV patients. **METHODS:** Observation started at the HCV diagnosis date (untreated) or last antiviral treatment start (treated). Treatment selection bias was addressed using an inverse probability-weighting approach. We estimated the effect of treatment on the cumulative incidence of outcomes using the Fine-Gray method (subdistribution hazard ratios [sHR] and 95% confidence intervals [95% CI]). Death was a competing risk. **RESULTS:** Roughly 40% of 15,295 HCV patients were women. After controlling for other risk factors, sustained virological response (SVR) (interferon-based [IFN] or direct-acting antiviral [DAA]) significantly reduced risk of all outcomes, particularly among female patients. Female patients who achieved SVR after IFN-based treatment had significantly lower risk of ACS compared with male patients with SVR from either treatment type (sHR 0.45 [95% CI 0.35-0.59] vs 0.81 [95% CI 0.69-0.96, for DAA SVR] and sHR 0.72 [95% CI 0.62, 0.85, for IFN SVR]). Successful treatment seemed to be most protective against ESRD; female patients who achieved SVR were at 66%-68% lower risk than untreated patients (sHR 0.32 [95% CI 0.17-0.60 for DAA SVR] and 0.34 [95% CI 0.20-0.58 for IFN SVR]), whereas men were at 38%-42% lower risk (sHR 0.62 [95% CI 0.46-0.85 for DAA SVR] and 0.58 [95% CI 0.43-0.76 for IFN SVR]). IFN treatment failure significantly increased risk of all outcomes by 50%-100% among female patients. Compared with no treatment, female patients who experienced IFN treatment failure were at 63% increased risk of ACS (sHR 1.63 [95% CI 1.35-1.96]), almost twice the risk of ESRD (sHR 1.95 [95% CI 1.43-2.66]) and 51% increased risk of stroke (sHR 1.49 [95% CI 1.11-2.00]). **DISCUSSION:** SVR reduced

the risk of extrahepatic complications, particularly in females. The significantly increased risk associated with IFN TF in women—a subset who represented roughly 10% of that group—underscores the importance of prioritizing these patients for DAA treatment irrespective of the fibrosis stage.

Center for Health Policy and Health Services Research

Lu M, Li J, Zhou Y, Rupp LB, Moorman AC, Spradling PR, Teshale EH, Boscarino JA, Daida YG, Schmidt MA, **Trudeau S**, and **Gordon SC**. Trends in Cirrhosis and Mortality by Age, Sex, Race, and Antiviral Treatment Status Among US Chronic Hepatitis B Patients (2006-2016). *J Clin Gastroenterol* 2021; Epub ahead of print. PMID: 33780209. [Full Text](#)

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BACKGROUND: Changing US demographics and evolving chronic hepatitis B (CHB) treatments may affect longitudinal trends in CHB-related complications. We studied trends in the prevalence of cirrhosis (past or present) and incidence of all-cause mortality, stratified by patient age, sex, race, and antiviral treatment status, in a sample from US health care systems. **METHODS:** Joinpoint and Poisson regression (univariate and multivariable) were used to estimate the annual percent change in each outcome from 2006 to 2016. **RESULTS:** Among 5528 CHB patients, cirrhosis prevalence (including decompensated cirrhosis) rose from 6.7% in 2006 to 13.7% in 2016; overall mortality was unchanged. Overall rates of cirrhosis and mortality were higher among treated patients, but adjusted annual percent changes (aAPC) were significantly lower among treated than untreated patients (cirrhosis: aAPC +2.4% vs. +6.2%, mortality: aAPC -3.9% vs. +4.0%). Likewise, among treated patients, the aAPC for mortality declined -3.9% per year whereas among untreated patients, mortality increased +4.0% per year. **CONCLUSIONS:** From 2006 to 2016, the prevalence of cirrhosis among CHB patients doubled. Notably, all-cause mortality increased among untreated patients but decreased among treated patients. These results suggest that antiviral treatment attenuates the progression of cirrhosis and the risk of death among patients with CHB.

Center for Health Policy and Health Services Research

Simon GE, Matarazzo BB, Walsh CG, Smoller JW, Boudreaux ED, Yarborough BJH, Shortreed SM, Coley RY, **Ahmedani BK**, Doshi RP, Harris LI, and Schoenbaum M. Reconciling Statistical and Clinicians' Predictions of Suicide Risk. *Psychiatr Serv* 2021; Epub ahead of print. PMID: 33691491. [Full Text](#)

Kaiser Permanente Washington Health Research Institute, Seattle (Simon, Shortreed, Coley); Department of Veterans Affairs Rocky Mountain Mental Illness Research, Education and Clinical Center, and Department of Psychiatry, University of Colorado School of Medicine, Aurora (Matarazzo); Department of Medicine and Department of Biomedical Informatics, Vanderbilt University, Nashville, Tennessee (Walsh); Department of Psychiatry, Massachusetts General Hospital, Boston (Smoller); Department of Emergency Medicine and Department of Psychiatry, University of Massachusetts Medical School, Worcester (Boudreaux); Kaiser Permanente Northwest Center for Health Research, Portland, Oregon (Yarborough); Department of Biostatistics, University of Washington, Seattle (Shortreed, Coley); Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit (Ahmedani); Department of Community Medicine and Healthcare, University of Connecticut, Farmington (Doshi); Shifa Consulting, Arlington, Virginia (Harris); Division of Services and Intervention Research, National Institute of Mental Health, Bethesda, Maryland (Schoenbaum).

Statistical models, including those based on electronic health records, can accurately identify patients at high risk for a suicide attempt or death, leading to implementation of risk prediction models for population-based suicide prevention in health systems. However, some have questioned whether statistical predictions can really inform clinical decisions. Appropriately reconciling statistical algorithms with

traditional clinician assessment depends on whether predictions from these two methods are competing, complementary, or merely duplicative. In June 2019, the National Institute of Mental Health convened a meeting, "Identifying Research Priorities for Risk Algorithms Applications in Healthcare Settings to Improve Suicide Prevention." Here, participants of this meeting summarize key issues regarding the potential clinical application of suicide prediction models. The authors attempt to clarify the key conceptual and technical differences between traditional risk prediction by clinicians and predictions from statistical models, review the limited evidence regarding both the accuracy of and the concordance between these alternative methods of prediction, present a conceptual framework for understanding agreement and disagreement between statistical and clinician predictions, identify priorities for improving data regarding suicide risk, and propose priority questions for future research. Future suicide risk assessment will likely combine statistical prediction with traditional clinician assessment, but research is needed to determine the optimal combination of these two methods.

Center for Health Policy and Health Services Research

Spradling PR, Zhong Y, Moorman AC, **Rupp LB, Lu M, Gordon SC**, Teshale EH, Schmidt MA, Daida YG, and Boscarino JA. Psychosocial Obstacles to Hepatitis C Treatment Initiation Among Patients in Care: A Hitch in the Cascade of Cure. *Hepatol Commun* 2021; 5(3):400-411. PMID: 33681675. [Full Text](#)

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There are limited data examining the relationship between psychosocial factors and receipt of direct-acting antiviral (DAA) treatment among patients with hepatitis C in large health care organizations in the United States. We therefore sought to determine whether such factors were associated with DAA initiation. We analyzed data from an extensive psychological, behavioral, and social survey (that incorporated several health-related quality of life assessments) coupled with clinical data from electronic health records of patients with hepatitis C enrolled at four health care organizations during 2017-2018. Of 2,681 patients invited, 1,051 (39.2%) responded to the survey; of 894 respondents eligible for analysis, 690 (77.2%) initiated DAAs. Mean follow-up among respondents was 9.2 years. Compared with DAA recipients, nonrecipients had significantly poorer standardized scores for depression, anxiety, and life-related stressors as well as poorer scores related to physical and mental function. Lower odds of DAA initiation in multivariable analysis (adjusted by age, race, sex, study site, payment provider, cirrhosis status, comorbidity status, and duration of follow-up) included Black race (adjusted odds ratio [aOR], 0.59 vs. White race), perceived difficulty getting medical care in the preceding year (aOR, 0.48 vs. no difficulty), recent injection drug use (aOR, 0.11 vs. none), alcohol use disorder (aOR, 0.58 vs. no alcohol use disorder), severe depression (aOR, 0.42 vs. no depression), recent homelessness (aOR, 0.36 vs. no homelessness), and recent incarceration (aOR, 0.34 vs. no incarceration). Conclusion: In addition to racial differences, compared with respondents who initiated DAAs, those who did not were more likely to have several psychological, behavioral, and social impairments. Psychosocial barriers to DAA initiation among patients in care should also be addressed to reduce hepatitis C-related morbidity and mortality.

Dermatology

Bissonnette R, **Gold LS**, Rubenstein DS, Tallman AM, and Armstrong A. Folliculitis with tapinarof, when it occurs, is generally mild, self-limiting, and rarely interferes with therapy. *J Am Acad Dermatol* 2021; Epub ahead of print. PMID: 33676999. [Full Text](#)

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Dermatology

Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Desai SR, Fassett M, French LE, **Lim HW**, Hruza GJ, and Fox LP. Cold and COVID: Recurrent Pernio during the COVID-19 Pandemic. *Br J Dermatol* 2021; Epub ahead of print. PMID: 33657646. [Full Text](#)

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Pernio is a commonly reported cutaneous manifestation of SARS-CoV-2 infection.(1) Our international registry of COVID-19 dermatologic manifestations has collected 1,176 total cases of COVID-19 skin manifestations, including 619 cases of pernio in suspected or confirmed COVID-19 patients.(1) Most patients with new-onset pernio were entered into the registry after the first pandemic wave (79% in March-May 2020). Starting in September 2020, the registry received reports of a subset of these patients who developed recurrent pernio in the following months.

Dermatology

Jones LR, Levin AM, Dai X, Datta I, Li J, Yin C, and Mi QS. MicroRNA Profile Differentiates Head and Neck Keloid and Adjacent Normal Skin Tissue. *Facial Plast Surg Aesthet Med* 2021; Epub ahead of print. PMID: 33710934. [Full Text](#)

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Dermatology

Mohammad TF, and Lim HW. The Important Role of Dermatologists in Public Education on Sunscreens. *JAMA Dermatol* 2021; Epub ahead of print. PMID: 33760054. [Full Text](#)

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Dermatology

Passeron T, **Lim HW**, Goh CL, Kang HY, Ly F, Morita A, Ocampo Candiani J, Puig S, Schalka S, Wei L, Dréno B, and Krutmann J. Photoprotection according to skin phototype and dermatoses: Practical recommendations from an expert panel. *J Eur Acad Dermatol Venereol* 2021; Epub ahead of print. PMID: 33764577. [Full Text](#)

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Increasing evidence on the impact of the different wavelengths of sunlight on the skin demonstrates the need for tailored recommendations of sunscreen according to skin phototype and dermatoses, which is now possible due to advances in the filters and formulations of sunscreens. A selective literature search was performed by an international expert panel, focusing on the type of sunscreen to recommend for photoaging, skin cancers, photodermatoses, pigmentary disorders and skin inflammatory disorders. Protection against ultraviolet (UV)B is especially important for light skin as there is a high risk of sunburn, DNA damage and skin cancers. Darker skin may be naturally better protected against UVB but is more prone to hyperpigmentation induced by visible light (VL) and UVA. Protection against UVA, VL and infrared A can be helpful for all skin phototypes as they penetrate deeply and cause photoaging. Long wave UVA1 plays a critical role in pigmentation, photoaging, skin cancer, DNA damage and photodermatoses. Adapting the formulation and texture of the sunscreen to the type of skin and dermatoses is also essential. Practical recommendations on the type of sunscreen to prescribe are provided to support the clinician in daily practice.

Dermatology

Van Voorhees AS, **Stein Gold L**, Lebwohl M, Strober B, Sofen H, Papp K, Bagel J, Zhang Z, Paris M, and Wang Y. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: results up to 32 weeks from a randomised, phase 3 study. *Br J Dermatol* 2021; Epub ahead of print. PMID: 33763874. [Full Text](#)

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Scalp psoriasis is common and is often severe enough to negatively impact quality of life (QOL).(1,2) In STYLE (NCT03123471), oral apremilast 30 mg twice daily (BID) demonstrated significantly greater improvements in moderate to severe plaque psoriasis of the scalp, scalp itch, whole body itch, and QOL versus placebo(3) during the 16-week, placebo-controlled phase; safety and tolerability were consistent with the known safety profile of apremilast.(3,4) We report the efficacy and safety of apremilast during the apremilast extension phase of STYLE (Weeks 16 to 32). During the extension phase, patients initially randomised to placebo were switched to apremilast (placebo/apremilast group; with titration during Week 16) and patients initially randomised to apremilast continued active treatment (apremilast/apremilast group; with dummy titration during Week 16) through Week 32. We also present efficacy of apremilast at Week 16 in patient subgroups based on baseline demographics and treatment characteristics.

Diagnostic Radiology

Pfeifer CM, Reddy N, Burton KR, **Griffith B**, Bazylewicz MP, Pakkal MV, and Milburn JM. The Evolving Status of Fellowships and Mini-Fellowships in Diagnostic Radiology: A Survey of Program Directors and Chief Residents. *Acad Radiol* 2021; Epub ahead of print. PMID: 33775517. [Full Text](#)

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RATIONALE AND OBJECTIVES: Recent changes in radiology fellowships include musculoskeletal radiology adopting a match system, interventional radiology transitioning away from diagnostic radiology to offer direct-entry programs, and a common fellowship application timeline created by the Society for Chairs of Academic Radiology Departments (SCARD). The concept of mini-fellowships has also emerged with the elimination of the oral American Board of Radiology examinations that had been administered in the final year of residency training prior to 2014. This paper seeks to assess the opinions of fellowship program directors, residency program directors, and chief residents regarding these recent changes.

MATERIALS AND METHODS: This is a cross-sectional study using a web-based survey posed to fellowship program directors, residency program directors, and chief residents in 2020. Questions sought to explore current attitudes toward the following topics: (1) a common fellowship application timeline; (2) a common fellowship match; and (3) the status of mini-fellowships in diagnostic radiology. In addition, the number of fellowship positions for each subspecialty was estimated using subspecialty society directories, Accreditation Council for Graduate Medical Education (ACGME) data, and individual program websites.

RESULTS: Deidentified responses were collected electronically and aggregated. The three respondent groups preferred a common fellowship application timeline at rates of 67% among fellowship program directors, 80% residency program directors, and 74% residents. A common match system across all subspecialties was preferred at rates of 50% fellowship program directors, 74% residency program directors, and 26% chief residents. There was widespread reported compliance with the SCARD fellowship timeline policy. Subspecialty programs using the match system reported interviewing greater numbers of applicants per position. Fellowship directors and chief residents reported that the most common duration of mini-fellowship experiences was 2 to 3 months. **CONCLUSION:** There is a division between chief residents and program directors regarding the preference for a common radiology match. Adopting a radiology-wide fellowship match would increase the number of interviews required. The SCARD fellowship timeline policy has been successful, and there is support across stakeholders regarding the common timeline. Mini-fellowships are highly variable in length and structure.

Diagnostic Radiology

Rozenstein A, **Griffith BD**, and Ruchman RB. Residency Match During the COVID-19 Pandemic: The Clear and Present Danger of the Remote Interview. *J Am Coll Radiol* 2021; 18(3 Pt A):438-441. PMID: 33129766. [Full Text](#)

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Emergency Medicine

Illg Z, Muller G, Mueller M, Nippert J, and Allen B. Analysis of absolute lymphocyte count in patients with COVID-19. *Am J Emerg Med* 2021; 46:16-19. PMID: 33706251. [Full Text](#)

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INTRODUCTION: Symptoms of COVID-19 vary in severity and presentation. When admitting patients to the hospital, it is desirable to isolate patients with COVID-19 from those without the disease. However, reliably identifying patients with COVID-19 in the emergency department before hospital admission is often limited by the speed and availability of testing. Previous studies determined a low lymphocyte count is commonly found in patients with COVID-19. We sought to explore the sensitivity of absolute lymphocyte count in patients presenting to the emergency department requiring subsequent hospitalization who were found to have COVID-19. **METHODS:** A retrospective chart review was performed on 312 patients with laboratory-confirmed COVID-19 who were admitted to the hospital from the emergency department. The absolute lymphocyte count for these patients was used to calculate sensitivities at various cut-off values. The relationships between absolute lymphocyte count and variables, including age, sex, need for intubation, and mortality, were also explored. **RESULTS:** Cut-off values for absolute lymphocyte count ranged from 1.1 K/uL to 2.0 K/uL, with sensitivities of 72% and 94%, respectively. Additionally, lower mean absolute lymphocyte counts were identified in males, patients who required intubation, and patients who died. **CONCLUSION:** Knowing the sensitivity of absolute lymphocyte count in patients with COVID-19 may help identify patients who are unlikely to have the disease. Additionally, absolute lymphocyte count can be used as a marker of disease severity in patients with COVID-19.

Emergency Medicine

Robinson TG, Minhas JS, and **Miller J.** Review of major trials of acute blood pressure management in stroke. *J Cereb Blood Flow Metab* 2021; Epub ahead of print. PMID: 33761781. [Full Text](#)

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Over the last two decades, there have been a number of major landmark clinical trials, classified as "major" as they sought to address clear clinical practice driven questions, in a pragmatic yet robust trial design, using a large powered sample size ($n > 1000$), in order to help improve patient outcome through informing guidelines. A commonality across all stroke sub-types included in these trials is the tendency to acute hypertensive crises within the acute stroke period. This phenomenon is associated with greater stroke complications and worsened overall prognosis. Multiple trials have attempted to address the issue of acute blood pressure management during the acute stroke period, with consideration for timing, magnitude of lowering, agent and relationship to other interventions. This review will consider the major clinical trials performed in ischaemic and haemorrhagic stroke that test the hypothesis that acute BP reduction improves clinical outcomes.

Endocrinology and Metabolism

Shakaroun D, Bhan A, and Ishani D. A rare case of lingual thyroid in a man. *Applied Radiology* 2021; 50(2):42-43. PMID: Not assigned. [Request Article](#)

Gastroenterology

Barton KN, Siddiqui F, Pompa R, Freytag SO, Khan G, Dobrosotskaya I, Ajlouni M, Zhang Y, Cheng J, Movsas B, and Kwon D. Phase I trial of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for the treatment of metastatic pancreatic cancer. *Mol Ther Oncolytics* 2021; 20:94-104. PMID: 33575474. [Full Text](#)

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The safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL 12) gene therapy was evaluated in metastatic pancreatic cancer patients. In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTK(SR39) rep-hIL-12) expressing yCD/mutTK(SR39) (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL 12) was injected into tumors of 12 subjects with metastatic pancreatic cancer (T2N0M1-T4N1M1) at escalating doses (1×10^{11}), 3×10^{11} , or 1×10^{12} viral particles). Subjects received 5-fluorocytosine (5-FC) therapy for 7 days followed by chemotherapy (FOLFIRINOX or gemcitabine/albumin-bound paclitaxel) starting 21 days after adenovirus injection. The study endpoint was toxicity through day 21. Experimental endpoints included measurements of serum IL 12, interferon gamma (IFNG), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells and proliferation markers were analyzed by flow cytometry. Twelve patients received Ad5-yCD/mutTK(SR39) rep-hIL-12 and oral 5-FC. Approximately 94% of the 121 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTK(SR39) rep-hIL-12 DNA was detected in the blood of two patients. Elevated serum IL 12, IFNG, and CXCL10 levels were detected in 42%, 75%, and 92% of subjects, respectively. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTK(SR39) rep-hIL-12 administration. The median survival of patients in the third cohort is 18.1 (range, 3.5-20.0) months. The study maximum tolerated dose (MTD) was not reached.

Gastroenterology

Li J, Gordon SC, Zhou Y, Boscarino JA, Schmidt MA, Daida YG, Rupp LB, Trudeau S, and Lu M. Sex Differences in Extrahepatic Outcomes After Antiviral Treatment for Hepatitis C. *Am J Gastroenterol* 2021; 116(3):576-583. PMID: 33399360. [Full Text](#)

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INTRODUCTION: Despite recognized differences in the rates of cardiovascular and renal disease between men and women in the general population, studies of the downstream effects of antiviral treatment for hepatitis C (HCV) have not investigated differences in outcomes based on sex. We analyzed sex differences in risk of acute coronary syndrome (ACS), end-stage renal disease (ESRD), and ischemic stroke by treatment and response in a large US-based multisite cohort of HCV patients.

METHODS: Observation started at the HCV diagnosis date (untreated) or last antiviral treatment start (treated). Treatment selection bias was addressed using an inverse probability-weighting approach. We estimated the effect of treatment on the cumulative incidence of outcomes using the Fine-Gray method (subdistribution hazard ratios [sHR] and 95% confidence intervals [95% CI]). Death was a competing risk.

RESULTS: Roughly 40% of 15,295 HCV patients were women. After controlling for other risk factors, sustained virological response (SVR) (interferon-based [IFN] or direct-acting antiviral [DAA]) significantly reduced risk of all outcomes, particularly among female patients. Female patients who achieved SVR after IFN-based treatment had significantly lower risk of ACS compared with male patients with SVR from either treatment type (sHR 0.45 [95% CI 0.35-0.59] vs 0.81 [95% CI 0.69-0.96, for DAA SVR] and sHR 0.72 [95% CI 0.62, 0.85, for IFN SVR]). Successful treatment seemed to be most protective against ESRD;

female patients who achieved SVR were at 66%-68% lower risk than untreated patients (sHR 0.32 [95% CI 0.17-0.60 for DAA SVR] and 0.34 [95% CI 0.20-0.58 for IFN SVR]), whereas men were at 38%-42% lower risk (sHR 0.62 [95% CI 0.46-0.85 for DAA SVR] and 0.58 [95% CI 0.43-0.76 for IFN SVR]). IFN treatment failure significantly increased risk of all outcomes by 50%-100% among female patients. Compared with no treatment, female patients who experienced IFN treatment failure were at 63% increased risk of ACS (sHR 1.63 [95% CI 1.35-1.96]), almost twice the risk of ESRD (sHR 1.95 [95% CI 1.43-2.66]) and 51% increased risk of stroke (sHR 1.49 [95% CI 1.11-2.00]). DISCUSSION: SVR reduced the risk of extrahepatic complications, particularly in females. The significantly increased risk associated with IFN TF in women—a subset who represented roughly 10% of that group—underscores the importance of prioritizing these patients for DAA treatment irrespective of the fibrosis stage.

Gastroenterology

Lu M, Li J, Zhou Y, Rupp LB, Moorman AC, Spradling PR, Teshale EH, Boscarino JA, Daida YG, Schmidt MA, Trudeau S, and Gordon SC. Trends in Cirrhosis and Mortality by Age, Sex, Race, and Antiviral Treatment Status Among US Chronic Hepatitis B Patients (2006-2016). *J Clin Gastroenterol* 2021; Epub ahead of print. PMID: 33780209. [Full Text](#)

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BACKGROUND: Changing US demographics and evolving chronic hepatitis B (CHB) treatments may affect longitudinal trends in CHB-related complications. We studied trends in the prevalence of cirrhosis (past or present) and incidence of all-cause mortality, stratified by patient age, sex, race, and antiviral treatment status, in a sample from US health care systems. METHODS: Joinpoint and Poisson regression (univariate and multivariable) were used to estimate the annual percent change in each outcome from 2006 to 2016. RESULTS: Among 5528 CHB patients, cirrhosis prevalence (including decompensated cirrhosis) rose from 6.7% in 2006 to 13.7% in 2016; overall mortality was unchanged. Overall rates of cirrhosis and mortality were higher among treated patients, but adjusted annual percent changes (aAPC) were significantly lower among treated than untreated patients (cirrhosis: aAPC +2.4% vs. +6.2%, mortality: aAPC -3.9% vs. +4.0%). Likewise, among treated patients, the aAPC for mortality declined -3.9% per year whereas among untreated patients, mortality increased +4.0% per year. CONCLUSIONS: From 2006 to 2016, the prevalence of cirrhosis among CHB patients doubled. Notably, all-cause mortality increased among untreated patients but decreased among treated patients. These results suggest that antiviral treatment attenuates the progression of cirrhosis and the risk of death among patients with CHB.

Gastroenterology

Spradling PR, Zhong Y, Moorman AC, **Rupp LB, Lu M, Gordon SC**, Teshale EH, Schmidt MA, Daida YG, and Boscarino JA. Psychosocial Obstacles to Hepatitis C Treatment Initiation Among Patients in Care: A Hitch in the Cascade of Cure. *Hepatol Commun* 2021; 5(3):400-411. PMID: 33681675. [Full Text](#)

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There are limited data examining the relationship between psychosocial factors and receipt of direct-acting antiviral (DAA) treatment among patients with hepatitis C in large health care organizations in the United States. We therefore sought to determine whether such factors were associated with DAA initiation. We analyzed data from an extensive psychological, behavioral, and social survey (that

incorporated several health-related quality of life assessments) coupled with clinical data from electronic health records of patients with hepatitis C enrolled at four health care organizations during 2017-2018. Of 2,681 patients invited, 1,051 (39.2%) responded to the survey; of 894 respondents eligible for analysis, 690 (77.2%) initiated DAAs. Mean follow-up among respondents was 9.2 years. Compared with DAA recipients, nonrecipients had significantly poorer standardized scores for depression, anxiety, and life-related stressors as well as poorer scores related to physical and mental function. Lower odds of DAA initiation in multivariable analysis (adjusted by age, race, sex, study site, payment provider, cirrhosis status, comorbidity status, and duration of follow-up) included Black race (adjusted odds ratio [aOR], 0.59 vs. White race), perceived difficulty getting medical care in the preceding year (aOR, 0.48 vs. no difficulty), recent injection drug use (aOR, 0.11 vs. none), alcohol use disorder (aOR, 0.58 vs. no alcohol use disorder), severe depression (aOR, 0.42 vs. no depression), recent homelessness (aOR, 0.36 vs. no homelessness), and recent incarceration (aOR, 0.34 vs. no incarceration). Conclusion: In addition to racial differences, compared with respondents who initiated DAAs, those who did not were more likely to have several psychological, behavioral, and social impairments. Psychosocial barriers to DAA initiation among patients in care should also be addressed to reduce hepatitis C-related morbidity and mortality.

Gastroenterology

Suresh S, Siddiqui M, Abu Ghanimeh M, Jou J, Simmer S, Mendiratta V, Russell S, Al-Shammari M, Chatfield A, Alsheik E, Dang D, Genaw J, and Zuchelli T. Association of obesity with illness severity in hospitalized patients with COVID-19: A retrospective cohort study. *Obes Res Clin Pract* 2021; 15(2):172-176. PMID: 33653666. [Full Text](#)

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BACKGROUND: Although recent studies have shown an association between obesity and adverse coronavirus disease 2019 (COVID-19) patient outcomes, there is a paucity in large studies focusing on hospitalized patients. We aimed to analyze outcomes associated with obesity in a large cohort of hospitalized COVID-19 patients. **METHODS:** We performed a retrospective study at a tertiary care health system of adult patients with COVID-19 who were admitted between March 1 and April 30, 2020. Patients were stratified by body mass index (BMI) into obese (BMI \geq 30 kg/m²) and non-obese (BMI < 30 kg/m²) cohorts. Primary outcomes were mortality, intensive care unit (ICU) admission, intubation, and 30-day readmission. **RESULTS:** A total of 1983 patients were included of whom 1031 (51.9%) had obesity and 952 (48.9%) did not have obesity. Patients with obesity were younger ($P < 0.001$), more likely to be female ($P < 0.001$) and African American ($P < 0.001$) compared to patients without obesity. Multivariable logistic models adjusting for differences in age, sex, race, medical comorbidities, and treatment modalities revealed no difference in 60-day mortality and 30-day readmission between obese and non-obese groups. In these models, patients with obesity had increased odds of ICU admission (adjusted OR, 1.37; 95% CI, 1.07-1.76; $P = 0.012$) and intubation (adjusted OR, 1.37; 95% CI, 1.04-1.80; $P = 0.026$). **CONCLUSIONS:** Obesity in patients with COVID-19 is independently associated with increased risk for ICU admission and intubation. Recognizing that obesity impacts morbidity in this manner is crucial for appropriate management of COVID-19 patients.

Health Alliance Plan

Watson PY. Value of Discharging Heart Failure Patients Home. *JAMA Cardiol* 2021; Epub ahead of print. PMID: 33759992. [Full Text](#)

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Hematology-Oncology

Barton KN, Siddiqui F, Pompa R, Freytag SO, Khan G, Dobrosotskaya I, Ajlouni M, Zhang Y, Cheng J, Movsas B, and Kwon D. Phase I trial of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for the treatment of metastatic pancreatic cancer. *Mol Ther Oncolytics* 2021; 20:94-104. PMID: 33575474. [Full Text](#)

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The safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL 12) gene therapy was evaluated in metastatic pancreatic cancer patients. In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTK(SR39) rep-hIL-12) expressing yCD/mutTK(SR39) (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL 12) was injected into tumors of 12 subjects with metastatic pancreatic cancer (T2N0M1-T4N1M1) at escalating doses (1×10^{11}), 3×10^{11} , or 1×10^{12} viral particles). Subjects received 5-fluorocytosine (5-FC) therapy for 7 days followed by chemotherapy (FOLFIRINOX or gemcitabine/albumin-bound paclitaxel) starting 21 days after adenovirus injection. The study endpoint was toxicity through day 21. Experimental endpoints included measurements of serum IL 12, interferon gamma (IFNG), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells and proliferation markers were analyzed by flow cytometry. Twelve patients received Ad5-yCD/mutTK(SR39) rep-hIL-12 and oral 5-FC. Approximately 94% of the 121 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTK(SR39) rep-hIL-12 DNA was detected in the blood of two patients. Elevated serum IL 12, IFNG, and CXCL10 levels were detected in 42%, 75%, and 92% of subjects, respectively. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTK(SR39) rep-hIL-12 administration. The median survival of patients in the third cohort is 18.1 (range, 3.5-20.0) months. The study maximum tolerated dose (MTD) was not reached.

Hematology-Oncology

Dinh TT, Mitin T, Bagshaw HP, Hoffman KE, **Hwang C**, Jeffrey Karnes R, Kishan AU, Liauw SL, Lloyd S, Potters L, Showalter TN, Taira AV, Vapiwala N, Zaorsky NG, D'Amico AV, Nguyen PL, and Davis BJ. Executive Summary of the American Radium Society Appropriate Use Criteria for Radiation Treatment of Node-Negative Muscle Invasive Bladder Cancer. *Int J Radiat Oncol Biol Phys* 2021; 109(4):953-963. PMID: 33127490. [Full Text](#)

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PURPOSE: Definitive radiation therapy (RT), with or without concurrent chemotherapy, is an alternative to radical cystectomy for patients with localized, muscle-invasive bladder cancer (MIBC) who are either not surgical candidates or prefer organ preservation. We aim to synthesize an evidence-based guideline regarding the appropriate use of RT. **METHODS AND MATERIALS:** We performed a Preferred Reporting Items for Systematic Reviews and Meta-analyses literature review using the PubMed and Embase databases. Based on the literature review, critical management topics were identified and reformulated into consensus questions. An expert panel was assembled to address key areas of both consensus and controversy using the modified Delphi framework. **RESULTS:** A total of 761 articles were screened, of which 61 were published between 1975 and 2019 and included for full review. There were 7 well-designed studies, 20 good quality studies, 28 quality studies with design limitations, and 6 references not suited as primary evidence. Adjuvant radiation therapy after cystectomy was not included owing to lack of high-quality data or clinical use. An expert panel consisting of 14 radiation oncologists, 1 medical oncologist, and 1 urologist was assembled. We identified 4 clinical variants of MIBC: surgically fit patients who wish to pursue organ preservation, patients surgically unfit for cystectomy, patients medically unfit for cisplatin-based chemotherapy, and borderline cystectomy candidates based on age with unilateral hydronephrosis and normal renal function. We identified key areas of controversy, including use of definitive radiation therapy for patients with negative prognostic factors, appropriate radiation therapy dose, fractionation, fields and technique when used, and chemotherapy sequencing and choice of agent. **CONCLUSIONS:** There is limited level-one evidence to guide appropriate treatment of MIBC. Studies vary significantly with regards to patient selection, chemotherapy use, and radiation therapy technique. A consensus guideline on the appropriateness of RT for MIBC may aid practicing oncologists in bridging the gap between data and clinical practice.

Hematology-Oncology

Gandara D, Reck M, Moro-Sibilot D, Mazieres J, **Gadgeel S**, Morris S, Cardona A, Mendus D, Ballinger M, Rittmeyer A, and Peters S. Fast progression in non-small cell lung cancer: results from the randomized phase III OAK study evaluating second-line atezolizumab versus docetaxel. *J Immunother Cancer* 2021; 9(3). PMID: 33737340. [Full Text](#)

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BACKGROUND: Treatment-induced accelerated tumor growth is a progression pattern reported with immune checkpoint inhibitors that has never been evaluated in randomized phase III studies because it requires two pretreatment scans. This study aimed to develop clinically relevant and applicable criteria for fast progression (FP), incorporating tumor growth kinetics and early death from disease progression to analyze data from the randomized phase III OAK study. **METHODS:** The OAK study evaluated the efficacy and safety of atezolizumab versus docetaxel as second-line or third-line treatment for stage

IIIb/IV non-small cell lung cancer. FP rates and associated baseline factors were analyzed. FP was defined as either a $\geq 50\%$ increase in the sum of largest diameters (SLDs) within 6 weeks of treatment initiation or death due to cancer progression within 12 weeks (absent post-baseline scan). RESULTS: Forty-two of 421 patients (10%) receiving atezolizumab and 37 of 402 (9%) receiving docetaxel had FP. Twenty patients with FP (48%) receiving atezolizumab versus 12 (30%) receiving docetaxel had a $\geq 50\%$ SLD increase within 6 weeks. FP was significantly associated with an ECOG (Eastern Cooperative Oncology Group) performance status of 1 (vs 0), ≥ 3 metastatic sites at baseline, and failure of preceding first-line treatment within 6 months, but not with epidermal growth factor receptor mutation, programmed cell death 1 ligand 1 or tumor mutational burden. Overall survival in patients with FP and a $\geq 50\%$ SLD increase at week 6 was similar with atezolizumab and docetaxel (unstratified HR 0.89 (95% CI 0.41 to 1.92)). CONCLUSIONS: FP rates were similar with atezolizumab and docetaxel in the OAK study, suggesting that FP may not be unique to checkpoint inhibitors, although the underlying mechanisms may differ from those of chemotherapy. Applying the FP criteria to other phase III checkpoint inhibitor trials may further elucidate the risk factors for FP. TRIAL REGISTRATION NUMBER: NCT02008227.

Hematology-Oncology

Grivas P, Khaki AR, Wise-Draper TM, **Gadgeel SM, Hwang C, Singh SRK**, et al. Association of Clinical Factors and Recent Anti-Cancer Therapy with COVID-19 Severity among Patients with Cancer: A Report from the COVID-19 and Cancer Consortium. *Ann Oncol* 2021; Epub ahead of print. PMID: 33746047. [Full Text](#)

BACKGROUND: Patients with cancer may be at high risk of adverse outcomes from SARS-CoV-2 infection. We analyzed a cohort of patients with cancer and COVID-19 reported to the COVID-19 and Cancer Consortium (CCC19) to identify prognostic clinical factors, including laboratory measurements and anti-cancer therapies. PATIENTS AND METHODS: Patients with active or historical cancer and a laboratory-confirmed SARS-CoV-2 diagnosis recorded between March 17-November 18, 2020 were included. The primary outcome was COVID-19 severity measured on an ordinal scale (uncomplicated, hospitalized, admitted to intensive care unit, mechanically ventilated, died within 30 days). Multivariable regression models included demographics, cancer status, anti-cancer therapy and timing, COVID-19-directed therapies, and laboratory measurements (among hospitalized patients). RESULTS: 4,966 patients were included (median age 66 years, 51% female, 50% non-Hispanic white); 2,872 (58%) were hospitalized and 695 (14%) died; 61% had cancer that was present, diagnosed, or treated within the year prior to COVID-19 diagnosis. Older age, male sex, obesity, cardiovascular and pulmonary comorbidities, renal disease, diabetes mellitus, non-Hispanic Black race, Hispanic ethnicity, worse ECOG performance status, recent cytotoxic chemotherapy, and hematologic malignancy were associated with higher COVID-19 severity. Among hospitalized patients, low or high absolute lymphocyte count, high absolute neutrophil count, low platelet count, abnormal creatinine, troponin, LDH, and CRP were associated with higher COVID-19 severity. Patients diagnosed early in the COVID-19 pandemic (January-April 2020) had worse outcomes than those diagnosed later. Specific anti-cancer therapies (e.g. R-CHOP, platinum combined with etoposide, and DNA methyltransferase inhibitors) were associated with high 30-day all-cause mortality. CONCLUSIONS: Clinical factors (e.g. older age, hematological malignancy, recent chemotherapy) and laboratory measurements were associated with poor outcomes among patients with cancer and COVID-19. Although further studies are needed, caution may be required in utilizing particular anti-cancer therapies.

Hematology-Oncology

Malapati S, **Singh SRK**, Kumar R, and Hadid T. Outcomes of in-hospital cardiopulmonary resuscitation for cardiac arrest in adult patients with metastatic solid cancers: A Nationwide Inpatient Sample database analysis from 2012 to 2014. *Cancer* 2021; Epub ahead of print. PMID: 33687740. [Full Text](#)

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BACKGROUND: Cardiopulmonary arrest is known to have a poor prognosis, further worsened by preexisting comorbidities. With improved treatment, the prevalence of metastatic cancers is rapidly increasing; however, the outcomes of in-hospital cardiopulmonary resuscitation (ICPR) remain to be well described. This study examines the epidemiology, associations, and outcomes of ICPR in these patients. **METHODS:** This is a retrospective cohort analysis of the Nationwide Inpatient Sample database (2012-2014) including patients aged ≥ 18 years with metastatic cancers. Primary outcome was inpatient mortality following ICPR. Factors associated with the primary outcome were analyzed using univariate/multivariate logistic regression analysis. **RESULTS:** Among all admissions with metastatic cancers ($n = 5,500,684$), 0.47% ($n = 26,070$) received ICPR. Inpatient mortality was 81.77% ($n = 8905$) versus 68.90% among those without metastatic solid cancers and receiving ICPR. Inpatient palliative care encounter was documented in 18.95% of patients with metastatic cancer who received ICPR. On multivariate logistic regression, some of the notable factors associated with higher mortality included being of African American or Hispanic race and hospital admission over the weekend. Factors associated with lower mortality included female sex, elective admission, and head and neck as the primary site. Admissions with ICPR were associated with higher mean total charge of hospitalization (by \$48,670) compared with admissions without ICPR. Of those who survived ICPR, 43.82% were transferred to another facility after discharge. **CONCLUSIONS:** Among adult patients with metastatic solid cancers having ICPR, 81.8% died within the same hospital admission. Race and admission type predicted mortality. Despite known poor prognosis, only a minority had palliative care. **LAY SUMMARY:** Cardiopulmonary resuscitation during hospitalization for patients who have metastatic cancer has a very poor outcome with a mortality rate of 81.77%. Inpatient cardiopulmonary resuscitation in these patients is also associated with a significantly higher cost of care, longer length of stay, and high rate of transfer to a different health care facility upon discharge. Knowledge of these outcomes is helpful in discussing the pros and cons of pursuing aggressive resuscitative interventions with patients and families.

Hematology-Oncology

Merriman KW, Broome RG, De Las Pozas G, **Landvogt LD**, Qi Y, and Keating J. Evolution of the Cancer Registrar in the Era of Informatics. *JCO Clin Cancer Inform* 2021; 5:272-278. PMID: 33739855. [Full Text](#)

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The cancer registrar reports accurate, complete, and timely abstracted cancer data to various healthcare agencies. The data are used for understanding the incidence of cancer, evaluating the effectiveness of public health efforts in the prevention of new cases and improving patient care outcomes and survival. There are increasing demands placed on registrars for additional data points with real-time submission to reporting agencies. To that end, registrars are increasing the use of informatics to meet the demand. The purpose of this article is the role of the registrar in the collection and reporting of critical cancer data and how registrars are currently using informatics to enhance their work. This article describes how informatics can be leveraged in the future and how registrars play a vital role in meeting the increasing demands placed on them to provide timely, meaningful, and accurate data for the cancer community.

Hematology-Oncology

Singh SRK, Malapati SJ, Kumar R, **Willner C**, and **Wang D**. NCDB analysis of melanoma 2004–2015: Epidemiology and outcomes by subtype, sociodemographic factors impacting clinical presentation, and real-world survival benefit of immunotherapy approval. *Cancers* 2021; 13(6):1-16. PMID: Not assigned. [Full Text](#)

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Background: The incidence of invasive melanoma is rising, and approval for the first immune checkpoint inhibitor (ICI) to treat metastatic melanoma occurred in 2011. We aim to describe the epidemiology and outcomes in recent years, sociodemographic factors associated with the presence of metastasis at

diagnosis, and the real-world impact of ICI approval on survival based on melanoma subtype and race. Methods: This is a retrospective analysis of the National Cancer Database (NCDB) from the years 2004–2015. The primary outcome was the overall survival of meta-static melanoma by subtype. Secondary outcomes included sociodemographic factors associated with the presence of metastasis at diagnosis and the impact of treatment facility type and ICI approval on the survival of metastatic melanoma. Results: Of the 419,773 invasive melanoma cases, 93.80% were cutaneous, and 4.92% were metastatic at presentation. The odds of presenting with metastatic disease were higher in African Americans (AA) compared to Caucasians (OR 2.37; 95% CI 2.11–2.66, $p < 0.001$). Treatment of metastatic melanoma at an academic/research facility was associated with lower mortality versus community cancer programs (OR 0.75, 95 % CI 0.69–0.81, p - value <0.001). Improvement in survival of metastatic melanoma was noted for Caucasians after the introduction of ICI (adjusted HR 0.80, 95% CI 0.78–0.83, $p < 0.001$); however, this was not statistically significant for AA (adjusted HR 0.80, 95% CI 0.62–1.02, p -value = 0.073) or ocular cases (HR 1.03, 95% CI 0.81–1.31, p -value 0.797). Conclusion: Real-world data suggest a 20% improvement in survival of metastatic melanoma since the introduction of ICI. The disproportionately high odds of metastatic disease at presentation in AA patients with melanoma suggest the need for a better understanding of the disease and improvement in care delivery.

Hospital Medicine

Kaatz S. Leadership & Professional Development: Lessons Learned From the Other Side of the Stethoscope (and Endotracheal Tube). *J Hosp Med* 2021; 16(3):164. PMID: 33656980. [Full Text](#)

Division of Hospital Medicine, Henry Ford Hospital, Detroit, Michigan.

Hospital Medicine

Watson PY. Value of Discharging Heart Failure Patients Home. *JAMA Cardiol* 2021; Epub ahead of print. PMID: 33759992. [Full Text](#)

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Hypertension and Vascular Research

Romero C, Mathew S, Wasinski B, Reed B, Brody A, Dawood R, Twiner MJ, McNaughton CD, Fridman R, Flack JM, **Carretero OA,** and Levy PD. Angiotensin-converting enzyme inhibitors increase anti-fibrotic biomarkers in African Americans with left ventricular hypertrophy. *J Clin Hypertens (Greenwich)* 2021; Epub ahead of print. PMID: 33694311. [Full Text](#)

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Angiotensin-converting enzyme inhibitors (ACEi) are part of the indicated treatment in hypertensive African Americans. ACEi have blood pressure-independent effects that may make them preferred for certain patients. We aimed to evaluate the impact of ACEi on anti-fibrotic biomarkers in African American hypertensive patients with left ventricular hypertrophy (LVH). We conducted a post hoc analysis of a randomized controlled trial in which hypertensive African American patients with LVH and vitamin D deficiency were randomized to receive intensive antihypertensive therapy plus vitamin D supplementation or placebo. We selected patients who had detectable lisinopril (lisinopril group) in plasma using liquid-chromatography/mass spectrometry analysis and compared them to subjects who did not (comparison group) at the one-year follow-up. The pro-fibrotic marker type 1 procollagen C-terminal propeptide (PICP) and the anti-fibrotic markers matrix metalloproteinase-1 (MMP-1), tissue inhibitor of metalloproteinases 1

(TIMP-1), telopeptide of collagen type I (CITP), and N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) peptide were measured. Sixty-six patients were included, and the mean age was 46.2 ± 8 years. No difference was observed in the number and intensity of antihypertensive medications prescribed in each group. Patients with detectable lisinopril had lower blood pressure than those in the comparison group. The anti-fibrotic markers Ac-SDKP, MMP-1, and MMP-1/TIMP-1 ratio were higher in patients with detectable ACEi (all $p < .05$). In a model adjusted for systolic blood pressure, MMP-1/TIMP-1 ($p = .02$) and Ac-SDKP ($p < .001$) levels were associated with lisinopril. We conclude that ACEi increase anti-fibrotic biomarkers in hypertensive African Americans with LVH, suggesting that they may offer added benefit over other agents in such patients.

Infectious Diseases

Altibi AM, Pallavi B, Liaqat H, Slota AA, Sheth R, Al Jebbawi L, George ME, LeDuc A, Abdallah E, Russell LR, Jain S, Shirvanian N, Masri A, and Kak V. Characteristics and comparative clinical outcomes of prisoner versus non-prisoner populations hospitalized with COVID-19. *Sci Rep* 2021; 11(1):6488. PMID: 33753786. [Full Text](#)

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Prisons in the United States have become a hotbed for spreading COVID-19 among incarcerated individuals. COVID-19 cases among prisoners are on the rise, with more than 143,000 confirmed cases to date. However, there is paucity of data addressing clinical outcomes and mortality in prisoners hospitalized with COVID-19. An observational study of all patients hospitalized with COVID-19 between March 10 and May 10, 2020 at two Henry Ford Health System hospitals in Michigan. Clinical outcomes were compared amongst hospitalized prisoners and non-prisoner patients. The primary outcomes were intubation rates, in-hospital mortality, and 30-day mortality. Multivariable logistic regression and Cox-regression models were used to investigate primary outcomes. Of the 706 hospitalized COVID-19 patients (mean age 66.7 ± 16.1 years, 57% males, and 44% black), 108 were prisoners and 598 were non-prisoners. Compared to non-prisoners, prisoners were more likely to present with fever, tachypnea, hypoxemia, and markedly elevated inflammatory markers. Prisoners were more commonly admitted to the intensive care unit (ICU) (26.9% vs. 18.7%), required vasopressors (24.1% vs. 9.9%), and intubated (25.0% vs. 15.2%). Prisoners had higher unadjusted inpatient mortality (29.6% vs. 20.1%) and 30-day mortality (34.3% vs. 24.6%). In the adjusted models, prisoner status was associated with higher in-hospital death (odds ratio, 2.32; 95% confidence interval (CI), 1.33 to 4.05) and 30-day mortality (hazard ratio, 2.00; 95% CI, 1.33 to 3.00). In this cohort of hospitalized COVID-19 patients, prisoner status was associated with more severe clinical presentation, higher rates of ICU admissions, vasopressors requirement, intubation, in-hospital mortality, and 30-day mortality.

Infectious Diseases

Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, Fadel R, Morrison A, Kenney RM, Alangaden G, Ramesh M, and Mor G. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics* 2021; Epub ahead of print. PMID: 33693506. [Full Text](#)

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MOTIVATION: COVID-19 has several distinct clinical phases: a viral replication phase, an inflammatory phase, and in some patients, a hyper-inflammatory phase. High mortality is associated with patients developing cytokine storm syndrome. Treatment of hyper-inflammation in these patients using existing, approved therapies with proven safety profiles could address the immediate need to reduce mortality. **RESULTS:** We analyzed the changes in the gene expression, pathways and putative mechanisms induced by SARS-CoV2 in NHBE, and A549 cells, as well as COVID-19 lung vs. their respective controls. We used these changes to identify FDA approved drugs that could be repurposed to help COVID-19 patients with severe symptoms related to hyper-inflammation. We identified methylprednisolone (MP) as a potential leading therapy. The results were then confirmed in five independent validation data sets including Vero E6 cells, lung and intestinal organoids, as well as additional patient lung sample vs. their respective controls. Finally, the efficacy of MP was validated in an independent clinical study. Thirty-day all-cause mortality occurred at a significantly lower rate in the MP-treated group compared to control group (29.6% vs. 16.6%, $p = 0.027$). Clinical results confirmed the in silico prediction that MP could improve outcomes in severe cases of COVID-19. A low number needed to treat (NNT = 5) suggests MP may be more efficacious than dexamethasone or hydrocortisone. **AVAILABILITY:** iPathwayGuide is available at <https://ipathwayguide.advaitabio.com/>. **SUPPLEMENTARY INFORMATION:** Supplementary data are available at Bioinformatics online.

Internal Medicine

Altibi AM, Pallavi B, Liaqat H, Slota AA, Sheth R, Al Jebbawi L, George ME, LeDuc A, Abdallah E, Russell LR, Jain S, Shirvanian N, Masri A, and Kak V. Characteristics and comparative clinical outcomes of prisoner versus non-prisoner populations hospitalized with COVID-19. *Sci Rep* 2021; 11(1):6488. PMID: 33753786. [Full Text](#)

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Prisons in the United States have become a hotbed for spreading COVID-19 among incarcerated individuals. COVID-19 cases among prisoners are on the rise, with more than 143,000 confirmed cases to date. However, there is paucity of data addressing clinical outcomes and mortality in prisoners hospitalized with COVID-19. An observational study of all patients hospitalized with COVID-19 between March 10 and May 10, 2020 at two Henry Ford Health System hospitals in Michigan. Clinical outcomes were compared amongst hospitalized prisoners and non-prisoner patients. The primary outcomes were intubation rates, in-hospital mortality, and 30-day mortality. Multivariable logistic regression and Cox-regression models were used to investigate primary outcomes. Of the 706 hospitalized COVID-19 patients (mean age 66.7 ± 16.1 years, 57% males, and 44% black), 108 were prisoners and 598 were non-prisoners. Compared to non-prisoners, prisoners were more likely to present with fever, tachypnea, hypoxemia, and markedly elevated inflammatory markers. Prisoners were more commonly admitted to the intensive care unit (ICU) (26.9% vs. 18.7%), required vasopressors (24.1% vs. 9.9%), and intubated (25.0% vs. 15.2%). Prisoners had higher unadjusted inpatient mortality (29.6% vs. 20.1%) and 30-day mortality (34.3% vs. 24.6%). In the adjusted models, prisoner status was associated with higher in-hospital death (odds ratio, 2.32; 95% confidence interval (CI), 1.33 to 4.05) and 30-day mortality (hazard ratio, 2.00; 95% CI, 1.33 to 3.00). In this cohort of hospitalized COVID-19 patients, prisoner status was

associated with more severe clinical presentation, higher rates of ICU admissions, vasopressors requirement, intubation, in-hospital mortality, and 30-day mortality.

Internal Medicine

Coleman CM, Bossick AS, Zhou Y, Hopkins-Johnson L, Otto MG, Nair AS, Willens DE, and Wegienka GR. Introduction of a community health worker diabetes coach improved glycemic control in an urban primary care clinic. *Prev Med Rep* 2021; 21:101267. PMID: 33364150. [Full Text](#)

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The burden of diabetes is higher in urban areas and among racial and ethnic minorities. The purpose of this research was to evaluate the effectiveness of extending a diabetes intervention program (DIP) by engaging a team, including a community health worker (CHW), to provide care for patients to meet glycemic control, specifically in a predominantly urban, minority patient population. The DIP enrolled diabetic patients from an internal medicine clinic. A CHW facilitated the collection of glucose meter readings. The CHW coached patients on glycemic control while the CHW's registered nurse partner titrated the patient's recommended insulin dose. Subsequent HbA1c values for participants were compared to those seen at the same clinic who were not enrolled. The DIP was deployed for nine months. One hundred forty-four patients were enrolled in the DIP and 348 patients constituted the comparator group. Ninety-three DIP participants had pre- and post-intervention HbA1c values and were compared to 348 non-DIP participants. Propensity score weighted adjusted analyses suggest that participants were more likely to reduce their HbA1c values by at least 1.0% and have HbA1c values of less than 8.0% (64 mmol/mol) than non-participants (adjusted odds ratio = aOR = 1.47, 95% CI 1.26-1.71, and aOR = 1.23, 95% CI 1.06-1.43, respectively). CHW coaches as part of a team in a clinical setting improved glycemic control in a predominantly urban, minority patient population.

Internal Medicine

Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, Fadel R, Morrison A, Kenney RM, Alangaden G, Ramesh M, and Mor G. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics* 2021; Epub ahead of print. PMID: 33693506. [Full Text](#)

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Division of Infectious Diseases, Henry Ford Health System, USA.

MOTIVATION: COVID-19 has several distinct clinical phases: a viral replication phase, an inflammatory phase, and in some patients, a hyper-inflammatory phase. High mortality is associated with patients developing cytokine storm syndrome. Treatment of hyper-inflammation in these patients using existing, approved therapies with proven safety profiles could address the immediate need to reduce mortality. **RESULTS:** We analyzed the changes in the gene expression, pathways and putative mechanisms induced by SARS-CoV2 in NHBE, and A549 cells, as well as COVID-19 lung vs. their respective controls. We used these changes to identify FDA approved drugs that could be repurposed to help COVID-19 patients with severe symptoms related to hyper-inflammation. We identified methylprednisolone (MP) as a potential leading therapy. The results were then confirmed in five independent validation data sets including Vero E6 cells, lung and intestinal organoids, as well as additional patient lung sample vs. their respective controls. Finally, the efficacy of MP was validated in an independent clinical study. Thirty-day all-cause mortality occurred at a significantly lower rate in the MP-treated group compared to control group (29.6% vs. 16.6%, $p = 0.027$). Clinical results confirmed the in silico prediction that MP could improve outcomes in severe cases of COVID-19. A low number needed to treat (NNT = 5) suggests MP may be more efficacious than dexamethasone or hydrocortisone. **AVAILABILITY:** iPathwayGuide is

available at <https://ipathwayguide.adva.bio.com/>. SUPPLEMENTARY INFORMATION: Supplementary data are available at Bioinformatics online.

Internal Medicine

Jiwani RA, and **Rehana RW**. Cough to Dyspnea to Acute Respiratory Distress Syndrome. *Am J Med Sci* 2021; 361(3):396-397. PMID: 33097195. [Full Text](#)

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Internal Medicine

Vosoughi K, **Ichkhanian Y**, Benias P, Miller L, Aadam AA, Triggs JR, Law R, Hasler W, Bowers N, Chaves D, Ponte-Neto AM, Draganov P, Yang D, El Halabi M, Sanaei O, Brewer Gutierrez OI, Bulat RS, Pandolfino J, and Khashab M. Gastric per-oral endoscopic myotomy (G-POEM) for refractory gastroparesis: results from an international prospective trial. *Gut* 2021; Epub ahead of print. PMID: 33741641. [Full Text](#)

Division of Gastroenterology and Hepatology, Johns Hopkins Medicine, Baltimore, Maryland, USA.

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OBJECTIVE: Although gastric per-oral endoscopic myotomy (G-POEM) is considered a promising technique for the management of refractory gastroparesis, high-quality evidence is limited. We prospectively investigated the efficacy and safety of G-POEM in unselected patients with refractory gastroparesis. **DESIGN:** In five tertiary centres, patients with symptomatic gastroparesis refractory to standard medical therapy and confirmed by impaired gastric emptying were included. The primary endpoint was clinical success, defined as at least one score decrease in Gastroparesis Cardinal Symptom Index (GCSI) with $\geq 25\%$ decrease in two subscales, at 12 months. GCSI Score and subscales, adverse events (AEs) and 36-Item Short Form questionnaire of quality of life were evaluated at baseline and 1, 3, 6 and 12 months after G-POEM. Gastric emptying study was performed before and 3 months after the procedure. **RESULTS:** Of 80 enrolled patients, 75 patients (94%) completed 12-month follow-up. Clinical success at 12 months was 56% (95% CI, 44.8 to 66.7). GCSI Score (including subscales) improved moderately after G-POEM ($p < 0.05$). In a regression model, a baseline GCSI Score > 2.6 (OR=3.23, $p = 0.04$) and baseline gastric retention $> 20\%$ at 4 hours (OR=3.65, $p = 0.03$) were independent predictors of clinical success at 12 months, as was early response to G-POEM at 1 month after therapy (OR 8.75, $p < 0.001$). Mild procedure-related AEs occurred in 5 (6%) patients. **CONCLUSION:** G-POEM is a safe procedure, but showed only modest overall effectiveness in the treatment of refractory gastroparesis. Further studies are required to identify the best candidates for G-POEM; unselective use of this procedure should be discouraged. **TRIAL REGISTRATION NUMBER:** ClinicalTrials.gov Registry NCT02732821.

Nephrology

Garcia de Mattos Barbosa M, Liu H, Huynh D, Shelley G, Keller ET, Emmer BT, Sherman EJ, Ginsburg D, Kennedy AA, Tai AW, Wobus CE, Mirabelli C, Lanigan TM, **Samaniego M**, Meng W, Rosenfeld AM, Luning Prak ET, Platt JL, and Cascalho M. IgV somatic mutation of human anti-SARS-CoV-2 monoclonal antibodies governs neutralization and breadth of reactivity. *JCI Insight* 2021; Epub ahead of print. PMID: 33769311. [Full Text](#)

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Antibodies that neutralize SARS-CoV-2, are thought to provide the most immediate and effective treatment for those severely afflicted by this virus. Because coronavirus potentially diversifies by mutation, broadly neutralizing antibodies are especially sought. Here we report a novel approach to rapid generation of potent broadly neutralizing human anti-SARS-CoV-2 antibodies. We isolated SARS-CoV-2 Spike protein-specific memory B cells by panning from the blood of convalescent human subjects after infection with SARS-CoV-2, sequenced and expressed Ig genes from individual B cells as human monoclonal antibodies (mAbs). All of 43 human mAbs generated in this way neutralized SARS-CoV-2. Eighteen of the 43 human mAbs exhibited half-maximal inhibitory concentration (IC50s) of 6.7×10^{-12} M to 6.7×10^{-15} M for spike pseudotyped virus. Seven of the human mAbs also neutralized with $IC_{50} < 6.7 \times 10^{-12}$ M viruses pseudotyped with mutant spike proteins (including receptor binding domain mutants and the S1 C-terminal D614G mutant). Neutralization of the Wuhan Hu-1 founder strain and of some variants decreased when coding sequences were reverted to germline, suggesting that potency of neutralization was acquired by somatic hypermutation and selection of B cells. The results indicate that infection with SARS-CoV-2 evokes high affinity B cell responses, some products of which are broadly neutralizing and others highly strain-specific. We also identify variants that would potentially resist immunity evoked by infection with the Wuhan Hu-1 founder strain or by vaccines developed with products of that strain, suggesting evolutionary courses SARS-CoV-2 could take.

Nephrology

Roehm B, Yau A, **Sohaney R**, and Seethapathy H. Cultivating the Pipeline of Clinician Investigators in Nephrology: A Perspective From the 2019-2020 AJKD Editorial Interns. *Am J Kidney Dis* 2021; Epub ahead of print. PMID: 33785368. [Full Text](#)

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Neurology

Aboul Nour H, Affan M, Mohamed G, Mohamud A, Schultz L, Latack K, Brady M, Scozzari D, Haddad Y, Katramados A, Bou Chebl A, and Ramadan AR. Impact of the COVID-19 Pandemic on Acute Stroke Care, Time Metrics, Outcomes, and Racial Disparities in a Southeast Michigan Health System. *J Stroke Cerebrovasc Dis* 2021; 30(6):105746. PMID: 33780695. [Full Text](#)

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BACKGROUND: COVID-19 has impacted acute stroke care with several reports showing worldwide drops in stroke caseload during the pandemic. We studied the impact of COVID-19 on acute stroke care in our health system serving Southeast Michigan as we rolled out a policy to limit admissions and transfers. **METHODS:** in this retrospective study conducted at two stroke centers, we included consecutive patients presenting to the ED for whom a stroke alert was activated during the period extending from 3/20/20 to 5/20/20 and a similar period in 2019. We compared demographics, time metrics, and discharge outcomes between the two groups. **RESULTS:** of 385 patients presented to the ED during the two time periods, 58% were African American. There was a significant decrease in the number of stroke patients presenting to the ED and admitted to the hospital between the two periods ($p < 0.001$). In 2020, patients had higher presenting NIHSS (median: 2 vs 5, $p = 0.012$), discharge NIHSS (median: 2 vs 3, $p = 0.004$), and longer times from LKW to ED arrival (4.8 vs 9.4 h, $p = 0.031$) and stroke team activation (median: 10 vs 15 min, $p = 0.006$). In 2020, stroke mimics rates were lower among African Americans. There were fewer hospitalizations ($p < 0.001$), and transfers from outside facilities ($p = 0.015$). **CONCLUSION:** a trend toward faster stroke care in the ED was observed during the pandemic along with dramatically reduced numbers of ED visits, hospitalizations and stroke mimics. Delayed ED presentations and higher stroke severity characterized the African American population, highlighting deepening of racial disparities during the pandemic.

Neurology

Danoun OA, Zillgitt A, Hill C, Zutshi D, Harris D, Osman G, Marawar R, Rath S, Syed MJ, Affan M, **Schultz L**, and **Wasade VS**. Outcomes of seizures, status epilepticus, and EEG findings in critically ill patient with COVID-19. *Epilepsy Behav* 2021; 118:107923. PMID: 33770609. [Full Text](#)

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OBJECTIVE: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a myriad of neurological manifestations and its effects on the nervous system are increasingly recognized. Seizures and status epilepticus (SE) are reported in the novel coronavirus disease (COVID-19), both new onset and worsening of existing epilepsy; however, the exact prevalence is still unknown. The primary aim of this study was to correlate the presence of seizures, status epilepticus, and specific critical care EEG patterns with patient functional outcomes in those with COVID-19. **METHODS:** This is a retrospective, multicenter cohort of COVID-19-positive patients in Southeast Michigan who underwent electroencephalography (EEG) from March 12th through May 15th, 2020. All patients had confirmed nasopharyngeal PCR for COVID-19. EEG patterns were characterized per 2012 ACNS critical care EEG terminology. Clinical and demographic variables were collected by medical chart review. Outcomes were divided into recovered, recovered with disability, or deceased. **RESULTS:** Out of the total of 4100 patients hospitalized with COVID-19, 110 patients (2.68%) had EEG during their hospitalization; 64% were male, 67% were African American with mean age of 63 years (range 20-87). The majority (70%) had severe COVID-19, were intubated, or had multi-organ failure. The median length of hospitalization was 26.5 days (IQR = 15 to 44 days). During hospitalization, of the patients who had EEG, 21.8% had new-onset seizure including 7% with status epilepticus, majority (87.5%) with no prior epilepsy. Forty-nine (45%) patients died in the hospital, 46 (42%) recovered but maintained a disability and 15 (14%) recovered without a disability. The EEG findings associated with outcomes were background slowing/attenuation (recovered 60% vs recovered/disabled 96% vs died 96%, $p < 0.001$) and normal (recovered 27% vs recovered/disabled 0% vs died 1%, $p < 0.001$). However, these findings were no longer significant after adjusting for severity of COVID-19. **CONCLUSION:** In this large multicenter study from Southeast Michigan, one of the early COVID-19 epicenters in the US, none of the EEG findings were significantly correlated with outcomes in critically ill COVID-19 patients. Although seizures and status epilepticus could be encountered in COVID-19, the occurrence did not correlate with the patients' functional outcome.

Neurology

Fan B, Chopp M, Zhang ZG, and Liu XS. Treatment of diabetic peripheral neuropathy with engineered mesenchymal stromal cell-derived exosomes enriched with microRNA-146a provide amplified therapeutic efficacy. *Exp Neurol* 2021; 341:113694. PMID: 33727097. [Full Text](#)

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Diabetic peripheral neuropathy (DPN) is one of the most prevalent chronic complications of diabetes mellitus with no effective treatment. We recently demonstrated that mesenchymal stromal cell (MSC)-derived exosomes (exo-naïve) alleviate neurovascular dysfunction and improve functional recovery. MicroRNA (miRNA), one of the exosomal cargos, downregulates inflammation-related genes, resulting in suppression of pro-inflammatory gene activation. In the present study, we developed engineered MSC-exosomes loaded with miR-146a (exo-146a) and compared the therapeutic effects of exo-146a with exo-naïve in diabetic (db/db) mice with DPN. Exo-146a possesses a high loading capacity, robust ability to accumulate in peripheral nerve tissues upon systemic administration, and evokes substantially enhanced therapeutic efficacy on neurological recovery compared with exo-naïve. Treatment of DPN in diabetic mice with exo-146a for two weeks significantly increased and decreased nerve conduction velocity, and thermal and mechanical stimuli threshold, respectively, whereas it took four weeks of exo-naïve treatment to achieve these improvements. Compared with exo-naïve, exo-146a significantly suppressed the peripheral blood inflammatory monocytes and the activation of endothelial cells via inhibiting Toll-like receptor (TLR)-4/NF- κ B signaling pathway. These data provide a proof-of-concept about both the

feasibility and efficacy of the exosome-based gene therapy for DPN. The translation of this approach to the clinic has the potential to improve the prospects for people who suffer from DPN.

Neurology

Ge W, Jing J, An S, Herlopian A, Ng M, Struck AF, Appavu B, Johnson EL, **Osman G**, Haider HA, Karakis I, Kim JA, Halford JJ, Dhakar MB, Sarkis RA, Swisher CB, Schmitt S, Lee JW, Tabaeizadeh M, Rodriguez A, Gaspard N, Gilmore E, Herman ST, Kaplan PW, Pathmanathan J, Hong S, Rosenthal ES, Zafar S, Sun J, and Westover MB. Deep active learning for Interictal Ictal Injury Continuum EEG patterns. *J Neurosci Methods* 2021; 351:108966. PMID: 33131680. [Request Article](#)

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OBJECTIVES: Seizures and seizure-like electroencephalography (EEG) patterns, collectively referred to as "ictal interictal injury continuum" (IIIC) patterns, are commonly encountered in critically ill patients. Automated detection is important for patient care and to enable research. However, training accurate detectors requires a large labeled dataset. Active Learning (AL) may help select informative examples to label, but the optimal AL approach remains unclear. **METHODS:** We assembled >200,000 h of EEG from 1,454 hospitalized patients. From these, we collected 9,808 labeled and 120,000 unlabeled 10-second EEG segments. Labels included 6 IIIC patterns. In each AL iteration, a Dense-Net Convolutional Neural Network (CNN) learned vector representations for EEG segments using available labels, which were used to create a 2D embedding map. Nearest-neighbor label spreading within the embedding map was used to create additional pseudo-labeled data. A second Dense-Net was trained using real- and pseudo-labels. We evaluated several strategies for selecting candidate points for experts to label next. Finally, we compared two methods for class balancing within queries: standard balanced-based querying (SBBQ), and high confidence spread-based balanced querying (HCSBBQ). **RESULTS:** Our results show: 1) Label spreading increased convergence speed for AL. 2) All query criteria produced similar results to random sampling. 3) HCSBBQ query balancing performed best. Using label spreading and HCSBBQ query balancing, we were able to train models approaching expert-level performance across all pattern

categories after obtaining ~7000 expert labels. CONCLUSION: Our results provide guidance regarding the use of AL to efficiently label large EEG datasets in critically ill patients.

Neurology

Go V, Sarikaya D, Zhou Y, Bowley BGE, Pessina MA, Rosene DL, **Zhang ZG**, **Chopp M**, Finklestein SP, Medalla M, **Buller B**, and Moore TL. Extracellular vesicles derived from bone marrow mesenchymal stem cells enhance myelin maintenance after cortical injury in aged rhesus monkeys. *Exp Neurol* 2021; 337:113540. PMID: 33264634. [Full Text](#)

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Cortical injury, such as stroke, causes neurotoxic cascades that lead to rapid death and/or damage to neurons and glia. Axonal and myelin damage in particular, are critical factors that lead to neuronal dysfunction and impair recovery of function after injury. These factors can be exacerbated in the aged brain where white matter damage is prevalent. Therapies that can ameliorate myelin damage and promote repair by targeting oligodendroglia, the cells that produce and maintain myelin, may facilitate recovery after injury, especially in the aged brain where these processes are already compromised. We previously reported that a novel therapeutic, Mesenchymal Stem Cell derived extracellular vesicles (MSC-EVs), administered intravenously at both 24 h and 14 days after cortical injury, reduced microgliosis (Go et al. 2019), reduced neuronal pathology (Medalla et al. 2020), and improved motor recovery (Moore et al. 2019) in aged female rhesus monkeys. Here, we evaluated the effect of MSC-EV treatment on changes in oligodendrocyte maturation and associated myelin markers in the sublesional white matter using immunohistochemistry, confocal microscopy, stereology, qRT-PCR, and ELISA. Compared to vehicle control monkeys, EV-treated monkeys showed a reduction in the density of damaged oligodendrocytes. Further, EV-treatment was associated with enhanced myelin maintenance, evidenced by upregulation of myelin-related genes and increases in actively myelinating oligodendrocytes in sublesional white matter. These changes in myelination correlate with the rate of motor recovery, suggesting that improved myelin maintenance facilitates this recovery. Overall, our results suggest that EVs act on oligodendrocytes to support myelination and improves functional recovery after injury in the aged brain. SIGNIFICANCE: We previously reported that EVs facilitate recovery of function after cortical injury in the aged monkey brain, while also reducing neuronal pathology (Medalla et al. 2020) and microgliosis (Go et al. 2019). However, the effect of injury and EVs on oligodendrocytes and myelination has not been characterized in the primate brain (Dewar et al. 1999; Sozmen et al. 2012; Zhang et al. 2013). In the present study, we assessed changes in myelination after cortical injury in aged monkeys. Our results show, for the first time, that MSC-EVs support recovery of function after cortical injury by enhancing myelin maintenance in the aged primate brain.

Neurology

Nguyen TN, Haussen DC, Qureshi MM, **Chebl A**, et al. Decline in subarachnoid haemorrhage volumes associated with the first wave of the COVID-19 pandemic. *Stroke Vasc Neurol* 2021; Epub ahead of print. PMID: 33771936. [Full Text](#)

BACKGROUND: During the COVID-19 pandemic, decreased volumes of stroke admissions and mechanical thrombectomy were reported. The study's objective was to examine whether subarachnoid

haemorrhage (SAH) hospitalisations and ruptured aneurysm coiling interventions demonstrated similar declines. **METHODS:** We conducted a cross-sectional, retrospective, observational study across 6 continents, 37 countries and 140 comprehensive stroke centres. Patients with the diagnosis of SAH, aneurysmal SAH, ruptured aneurysm coiling interventions and COVID-19 were identified by prospective aneurysm databases or by International Classification of Diseases, 10th Revision, codes. The 3-month cumulative volume, monthly volumes for SAH hospitalisations and ruptured aneurysm coiling procedures were compared for the period before (1 year and immediately before) and during the pandemic, defined as 1 March-31 May 2020. The prior 1-year control period (1 March-31 May 2019) was obtained to account for seasonal variation. **FINDINGS:** There was a significant decline in SAH hospitalisations, with 2044 admissions in the 3 months immediately before and 1585 admissions during the pandemic, representing a relative decline of 22.5% (95% CI -24.3% to -20.7%, $p < 0.0001$). Embolisation of ruptured aneurysms declined with 1170-1035 procedures, respectively, representing an 11.5% (95%CI -13.5% to -9.8%, $p = 0.002$) relative drop. Subgroup analysis was noted for aneurysmal SAH hospitalisation decline from 834 to 626 hospitalisations, a 24.9% relative decline (95% CI -28.0% to -22.1%, $p < 0.0001$). A relative increase in ruptured aneurysm coiling was noted in low coiling volume hospitals of 41.1% (95% CI 32.3% to 50.6%, $p = 0.008$) despite a decrease in SAH admissions in this tertile. **INTERPRETATION:** There was a relative decrease in the volume of SAH hospitalisations, aneurysmal SAH hospitalisations and ruptured aneurysm embolisations during the COVID-19 pandemic. These findings in SAH are consistent with a decrease in other emergencies, such as stroke and myocardial infarction.

Neurology

Parasar P, Guru N, and Nayak NR. Contribution of macrophages to fetomaternal immunological tolerance. *Hum Immunol* 2021; Epub ahead of print. PMID: 33715911. [Full Text](#)

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The semi-allogeneic fetus develops in a uniquely immune tolerant environment within the uterus. For successful pregnancy, both the innate and adaptive immune systems must favor acceptance of the fetal allograft. Macrophages are the second most abundant immune cells after natural killer (NK) cells in the decidua. In coordination with decidual NK cells and dendritic cells, macrophages aid in implantation, vascular remodeling, placental development, immune tolerance to placental cells, and maintenance of tissue homeostasis at the maternal-fetal interface. Decidual macrophages show the classical activated (M1) and alternatively activated (M2) phenotypes under the influence of the local milieu of growth factors and cytokines, and appropriate temporal regulation of the M1/M2 switch is vital for successful pregnancy. Disturbances in the mechanisms that control the M1/M2 balance and associated functions during pregnancy can trigger a spectrum of pregnancy complications ranging from preeclampsia and fetal growth restriction to preterm delivery. This review addresses various mechanisms of tolerance, focusing on the basic biology of macrophages, their plasticity and polarization, and their protective roles at the immune-privileged maternal-fetal interface, including direct and indirect roles in promoting fetomaternal immune tolerance.

Neurology

Teng H, Li C, Zhang Y, Lu M, Chopp M, Zhang ZG, Melcher-Mourgas M, and Fleckenstein B. Therapeutic effect of Cerebrolysin on reducing impaired cerebral endothelial cell permeability. *Neuroreport* 2021; 32(5):359-366. PMID: 33661804. [Full Text](#)

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Cerebrolysin has been shown to promote neurovascular protection and repair in preclinical models of stroke and neural injury and is demonstrating promise for stroke and neural injury therapeutic application in the clinic. The effect of Cerebrolysin on the human cerebral endothelial cell function has not been investigated. Using an in-vitro cerebral endothelial cell permeability assay and western blot analyses of tight junction and proinflammatory and procoagulant proteins, the present study showed that tissue plasminogen activator (tPA) and fibrin substantially impaired human cerebral endothelial cell barrier function and increased permeability, which persisted for at least 24 h. western blot analysis revealed that tPA and fibrin significantly increased proinflammatory and procoagulation proteins of intercellular adhesion molecule 1, high mobility group box 1, tumor necrosis factor α and phosphorylated nuclear factor kappa B-p65, and significantly reduced tight junction proteins zonular 1, occludin and claudin. However, Cerebrolysin significantly diminished and reversed tPA- and fibrin-impaired endothelial cell permeability, which was associated with significant reductions of tPA- and fibrin-augmented proinflammatory and procoagulation proteins and significant elevations of tPA- and fibrin-decreased tight junction proteins. The beneficial effect of Cerebrolysin appears specific because cerebroprotein hydrolysate, with a distinct peptide composition, failed to show the reduction of tPA- and fibrin-impaired permeability. These data indicate that cererbrolysin has a therapeutic effect on tPA- and fibrin-impaired cerebral endothelial cell permeability by reducing proinflammatory and procoagulation proteins and by elevating tight junction proteins.

Neurology

Zhang Y, Li C, Qin Y, Cepparulo P, Millman M, Chopp M, Kemper A, Szalad A, Lu X, Wang L, and Zhang ZG. Small extracellular vesicles ameliorate peripheral neuropathy and enhance chemotherapy of oxaliplatin on ovarian cancer. *J Extracell Vesicles* 2021; 10(5):e12073. PMID: 33728031. [Full Text](#)

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There are no effective treatments for chemotherapy induced peripheral neuropathy (CIPN). Small extracellular vesicles (sEVs) facilitate intercellular communication and mediate nerve function and tumour progression. We found that the treatment of mice bearing ovarian tumour with sEVs derived from cerebral endothelial cells (CEC-sEVs) in combination with a chemo-drug, oxaliplatin, robustly reduced oxaliplatin-induced CIPN by decreasing oxaliplatin-damaged myelination and nerve fibres of the sciatic nerve and significantly amplified chemotherapy of oxaliplatin by reducing tumour size. The combination therapy substantially increased a set of sEV cargo-enriched miRNAs, but significantly reduced oxaliplatin-increased proteins in the sciatic nerve and tumour tissues. Bioinformatics analysis revealed the altered miRNAs and proteins formed two distinct networks that regulate neuropathy and tumour growth, respectively. Intravenously administered CEC-sEVs were internalized by axons of the sciatic nerve and cancer cells. Reduction of CEC-sEV cargo miRNAs abolished the effects of CEC-sEVs on oxaliplatin-inhibited axonal growth and on amplification of the anti-cancer effect in ovarian cancer cells, suggesting that alterations in the networks of miRNAs and proteins in recipient cells contribute to the therapeutic effect of CEC-sEVs on CIPN. Together, the present study demonstrates that CEC-sEVs suppressed CIPN and enhanced chemotherapy of oxaliplatin in the mouse bearing ovarian tumour.

Neurosurgery

Air EL, Orrico KO, Benzil DL, Scarrow AM, Bean JR, Mazzola CA, Liau LM, Rutka JT, and Muraszko KM. Developing a Professionalism and Harassment Policy for Organized Neurosurgery. *Neurosurgery* 2021; Epub ahead of print. PMID: 33755153. [Full Text](#)

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Annual conferences, educational courses, and other meetings draw a diverse community of individuals, yet also create a unique environment without the traditional guard rails. Unlike events held at one's home institution, clear rules and jurisdiction have not been universally established. To promote the open exchange of ideas, as well as an environment conducive to professional growth of all participants, the leading neurosurgical professional organizations joined forces to delineate the expectations for anyone who participates in sponsored events. The One Neurosurgery Summit Taskforce on Professionalism and Harassment developed a foundational policy that establishes common expectations for behavior and a unified roadmap for the prompt response to untoward events. We hope that publishing this policy will inspire other medical organizations to establish their own meeting and conference policies. More importantly, we wish to bring greater attention to everyone's responsibility for ensuring a safe and respectful space for education, scientific debate, and networking during organized events.

Neurosurgery

Claus CF, Tong D, Lytle E, Bahoura M, Garmo L, Li C, Park P, Carr DA, Easton R, **Abdulhak M, Chang V**, Houseman C, Bono P, Richards B, and Soo TM. Age as a Predictor for Complications and Patient-reported Outcomes in Multilevel Transforaminal Lumbar Interbody Fusions: Analyses From the Michigan Spine Surgery Improvement Collaborative (MSSIC). *Spine (Phila Pa 1976)* 2021; 46(6):356-365. PMID: 33620179. [Full Text](#)

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STUDY DESIGN: Retrospective review of a multi-institutional data registry. OBJECTIVE: The authors sought to determine the association between age and complications & patient-reported outcomes (PRO) in patients undergoing multilevel transforaminal interbody lumbar fusion (MTLIF). SUMMARY OF BACKGROUND DATA: Elderly patients undergoing MTLIF are considered high risk. However, data on complications and PRO are lacking. Additionally, safety of multilevel lumbar fusion in the elderly remains uncertain. METHODS: Patients ≥ 50 -year-old who underwent MTLIF for degenerative lumbar spine conditions were analyzed. Ninety-day complications and PROs (baseline, 90-d, 1-y, 2-y) were queried using the MSSIC database. PROs were measured by back & leg visual analog scale (VAS), Patient-reported Outcomes Measurement Information System (PROMIS), EuroQol-5D (EQ-5D), and North American Spine Society (NASS) Patient Satisfaction Index. Univariate analyses were used to compare among elderly and complication cohorts. Generalized estimating equation (GEE) was used to identify predictors of complications and PROs. RESULTS: A total of 3120 patients analyzed with 961 (31%) ≥ 70 -y-o and 2159 (69%) between 50-69. A higher proportion of elderly experienced postoperative complications ($P=.003$) including urinary retention ($P<.001$) and urinary tract infection ($P=.002$). Multivariate analysis demonstrated that age was not independently associated with complications. Number of operative levels was associated with any ($P=.001$) and minor ($P=.002$) complication. Incurring a complication was independently associated with worse leg VAS and PROMIS scores ($P<.001$). Preoperative independent ambulation was independently associated with improved PROMIS, and EQ5D ($P<.001$). Within the elderly, preoperative independent ambulation and lower BMI were associated with improved PROMIS ($P<.001$). Complications had no significant effect on PROs in the elderly.

CONCLUSIONS: Age was not associated with complications nor predictive of functional outcomes in patients who underwent MTLIF. Age alone, therefore, may not be an appropriate surrogate for risk. Furthermore, baseline preoperative independent ambulation was associated with better clinical outcomes and should be considered during preoperative surgical counseling. Level of Evidence: 3.

Neurosurgery

Harbaugh RE, Devin C, Leavy MB, Ghogawala Z, Archer KR, Bydon M, Goertz C, Dinstein D, **Nerenz DR**, Eakin GS, Lavelle W, Shaffer WO, Arnold PM, Washabaugh CH, and Gliklich RE. Harmonized outcome measures for use in degenerative lumbar spondylolisthesis patient registries and clinical practice. *J Neurosurg Spine* 2021; Epub ahead of print.:1-9. PMID: 33740766. [Full Text](#)

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OBJECTIVE: The development of new treatment approaches for degenerative lumbar spondylolisthesis (DLS) has introduced many questions about comparative effectiveness and long-term outcomes. Patient registries collect robust, longitudinal data that could be combined or aggregated to form a national and potentially international research data infrastructure to address these and other research questions. However, linking data across registries is challenging because registries typically define and capture different outcome measures. Variation in outcome measures occurs in clinical practice and other types of research studies as well, limiting the utility of existing data sources for addressing new research questions. The purpose of this project was to develop a minimum set of patient- and clinician-relevant standardized outcome measures that are feasible for collection in DLS registries and clinical practice. **METHODS:** Nineteen DLS registries, observational studies, and quality improvement efforts were invited to participate and submit outcome measures. A stakeholder panel was organized that included representatives from medical specialty societies, health systems, government agencies, payers, industries, health information technology organizations, and patient advocacy groups. The panel categorized the measures using the Agency for Healthcare Research and Quality's Outcome Measures Framework (OMF), identified a minimum set of outcome measures, and developed standardized definitions through a consensus-based process. **RESULTS:** The panel identified and harmonized 57 outcome measures into a minimum set of 10 core outcome measure areas and 6 supplemental outcome measure areas. The measures are organized into the OMF categories of survival, clinical response, events of interest, patient-reported outcomes, and resource utilization. **CONCLUSIONS:** This effort identified a minimum set of standardized measures that are relevant to patients and clinicians and appropriate for use in DLS registries, other research efforts, and clinical practice. Collection of these measures across registries and clinical practice is an important step for building research data infrastructure, creating learning healthcare systems, and improving patient management and outcomes in DLS.

Neurosurgery

Maragkos GA, Schüpfer AJ, Lakomkin N, Sideras P, Price G, Baron R, **Hamilton T**, **Haider S**, **Lee IY**, Hadjipanayis CG, and **Robin AM**. Fluorescence-Guided High-Grade Glioma Surgery More Than Four Hours After 5-Aminolevulinic Acid Administration. *Front Neurol* 2021; 12:644804. PMID: 33767664. [Full Text](#)

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Background: Fluorescence-guided surgery (FGS) using 5-aminolevulinic acid (5-ALA) is a widely used strategy for delineating tumor tissue from surrounding brain intraoperatively during high-grade glioma (HGG) resection. 5-ALA reaches peak plasma levels ~4 h after oral administration and is currently approved by the FDA for use 2-4 h prior to induction to anesthesia. **Objective:** To demonstrate that there is adequate intraoperative fluorescence in cases undergoing surgery more than 4 h after 5-ALA administration and compare survival and radiological recurrence to previous data. **Methods:** Retrospective analysis of HGG patients undergoing FGS more than 4 h after 5-ALA administration was performed at two institutions. Clinical, operative, and radiographic pre- and post-operative characteristics are presented. **Results:** Sixteen patients were identified, 6 of them female (37.5%), with mean (SD) age of 59.3 ± 11.5 years. Preoperative mean modified Rankin score (mRS) was 2 ± 1 . All patients were dosed with 20 mg/kg 5-ALA the morning of surgery. Mean time to anesthesia induction was 425 ± 334 min. All cases had adequate intraoperative fluorescence. Eloquent cortex was involved in 12 cases (75%), and 13 cases (81.3%) had residual contrast enhancement on postoperative MRI. Mean progression-free survival was 5 ± 3 months. In the study period, 6 patients died (37.5%), mean mRS was 2.3 ± 1.3 , Karnofsky score 71.9 ± 22.1 , and NIHSS 3.9 ± 2.4 . **Conclusion:** Here we demonstrate that 5-ALA-guided HGG resection can be performed safely more than 4 h after administration, with clinical results largely similar to previous reports. Relaxation of timing restrictions could improve procedure workflow in busy neurosurgical centers, without additional risk to patients.

Neurosurgery

Mummaneni PV, Hussain I, Shaffrey CI, Eastlack RK, Mundis GM, Uribe JS, Fessler RG, Park P, Robinson L, Rivera J, Chou D, Kanter AS, Okonkwo DO, Nunley PD, Wang MY, **La Marca F**, Than KD, and Fu KM. The minimally invasive interbody selection algorithm for spinal deformity. *J Neurosurg Spine* 2021; Epub ahead of print. PMID: 33711811. [Full Text](#)

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OBJECTIVE: Minimally invasive surgery (MIS) for spinal deformity uses interbody techniques for correction, indirect decompression, and arthrodesis. Selection criteria for choosing a particular interbody

approach are lacking. The authors created the minimally invasive interbody selection algorithm (MIISA) to provide a framework for rational decision-making in MIS for deformity. METHODS: A retrospective data set of circumferential MIS (cMIS) for adult spinal deformity (ASD) collected over a 5-year period was analyzed by level in the lumbar spine to identify surgeon preferences and evaluate segmental lordosis outcomes. These data were used to inform a Delphi session of minimally invasive deformity surgeons from which the algorithm was created. The algorithm leads to 1 of 4 interbody approaches: anterior lumbar interbody fusion (ALIF), anterior column release (ACR), lateral lumbar interbody fusion (LLIF), and transforaminal lumbar interbody fusion (TLIF). Preoperative and 2-year postoperative radiographic parameters and clinical outcomes were compared. RESULTS: Eleven surgeons completed 100 cMISs for ASD with 338 interbody devices, with a minimum 2-year follow-up. The type of interbody approach used at each level from L1 to S1 was recorded. The MIISA was then created with substantial agreement. The surgeons generally preferred LLIF for L1-2 (91.7%), L2-3 (85.2%), and L3-4 (80.7%). ACR was most commonly performed at L3-4 (8.4%) and L2-3 (6.2%). At L4-5, LLIF (69.5%), TLIF (15.9%), and ALIF (9.8%) were most commonly utilized. TLIF and ALIF were the most selected approaches at L5-S1 (61.4% and 38.6%, respectively). Segmental lordosis at each level varied based on the approach, with greater increases reported using ALIF, especially at L4-5 (9.2°) and L5-S1 (5.3°). A substantial increase in lordosis was achieved with ACR at L2-3 (10.9°) and L3-4 (10.4°). Lateral interbody arthrodesis without the use of an ACR did not generally result in significant lordosis restoration. There were statistically significant improvements in lumbar lordosis (LL), pelvic incidence-LL mismatch, coronal Cobb angle, and Oswestry Disability Index at the 2-year follow-up. CONCLUSIONS: The use of the MIISA provides consistent guidance for surgeons who plan to perform MIS for deformity. For L1-4, the surgeons preferred lateral approaches to TLIF and reserved ACR for patients who needed the greatest increase in segmental lordosis. For L4-5, the surgeons' order of preference was LLIF, TLIF, and ALIF, but TLIF failed to demonstrate any significant lordosis restoration. At L5-S1, the surgical team typically preferred an ALIF when segmental lordosis was desired and preferred a TLIF if preoperative segmental lordosis was adequate.

Neurosurgery

Schucht P, **Rock J**, Park KB, Kato Y, Andrews RJ, Germano IM, and Servadei F. Letter: A Neurosurgical Community Under Attack. *World Neurosurg* 2021; Epub ahead of print. PMID: 33716153. [Full Text](#)

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Neurosurgery

Turfe Z, Saleh N, **George C**, **Rock J**, and **Craig JR**. Cavernous Sinus Syndrome After Barotraumatic Sneeze. *J Neuroophthalmol* 2021; Epub ahead of print. PMID: 33734154. [Full Text](#)

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Neurosurgery

Wong QH, Li KK, Wang WW, **Malta TM**, **Noushmehr H**, Grabovska Y, Jones C, Chan AK, Kwan JS, Huang QJ, Wong GC, Li WC, Liu XZ, Chen H, Chan DT, Mao Y, Zhang ZY, Shi ZF, and Ng HK.

Molecular landscape of IDH-mutant primary astrocytoma Grade IV/glioblastomas. *Mod Pathol* 2021; Epub ahead of print. PMID: 33692446. [Full Text](#)

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WHO 2016 classified glioblastomas into IDH-mutant and IDH-wildtype with the former having a better prognosis but there was no study on IDH-mutant primary glioblastomas only, as previous series included secondary glioblastomas. We recruited a series of 67 IDH-mutant primary glioblastomas/astrocytoma IV without a prior low-grade astrocytoma and examined them using DNA-methylation profiling, targeted sequencing, RNA sequencing and TERT promoter sequencing, and correlated the molecular findings with clinical parameters. The median OS of 39.4 months of 64 cases and PFS of 25.9 months of 57 cases were better than the survival data of IDH-wildtype glioblastomas and IDH-mutant secondary glioblastomas retrieved from datasets. The molecular features often seen in glioblastomas, such as EGFR amplification, combined +7/-10, and TERT promoter mutations were only observed in 6/53 (11.3%), 4/53 (7.5%), and 2/67 (3.0%) cases, respectively, and gene fusions were found only in two cases. The main mechanism for telomere maintenance appeared to be alternative lengthening of telomeres as ATRX mutation was found in 34/53 (64.2%) cases. In t-SNE analyses of DNA-methylation profiles, with an exception of one case, a majority of our cases clustered to IDH-mutant high-grade astrocytoma subclass (40/53; 75.5%) and the rest to IDH-mutant astrocytoma subclass (12/53; 22.6%). The latter was also enriched with G-CIMP high cases (12/12; 100%). G-CIMP-high status and MGMT promoter methylation were independent good prognosticators for OS ($p = 0.022$ and $p = 0.002$, respectively) and TP53 mutation was an independent poor prognosticator ($p = 0.013$) when correlated with other clinical parameters. Homozygous deletion of CDKN2A/B was not correlated with OS ($p = 0.197$) and PFS ($p = 0.278$). PDGFRA amplification or mutation was found in 16/59 (27.1%) of cases and was correlated with G-CIMP-low status ($p = 0.010$). Aside from the three well-known pathways of pathogenesis in glioblastomas, chromatin modifying and mismatch repair pathways were common aberrations (88.7% and 20.8%, respectively), the former due to high frequency of ATRX involvement. We conclude that IDH-mutant primary glioblastomas have better prognosis than secondary glioblastomas and have major molecular differences from other commoner glioblastomas. G-CIMP subgroups, MGMT promoter methylation, and TP53 mutation are useful prognostic adjuncts.

Obstetrics, Gynecology, and Women's Health Services

Hathout L, Wang Y, Wang Q, Vergalasova I, **Elshaikh MA**, **Dimitrova I**, Damast S, Li JY, Fields EC, Beriwal S, Keller A, Kidd EA, Uoz M, Jolly S, Jaworski E, Leung EW, Donovan E, Taunk NK, Chino J, Natesan D, Russo AL, Lea JS, Albuquerque KV, and Lee LJ. A Multi-Institutional Analysis of Adjuvant Chemotherapy and Radiation Sequence in Women with Stage IIIC Endometrial Cancer. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 33677053. [Full Text](#)

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PURPOSE/OBJECTIVES: To evaluate the impact of sequence and type of adjuvant therapy for patients with stage IIIC endometrial carcinoma (EC) on outcomes. **MATERIALS/METHODS:** In a multi-institutional retrospective cohort study, patients with stage IIIC EC who had surgical staging and received both adjuvant chemotherapy and radiation treatment (RT) were included. Adjuvant treatment regimens were classified as: adjuvant chemotherapy followed by sequential RT (upfront chemo) which was predominant sequence, RT with concurrent chemotherapy followed by chemotherapy (concurrent), systemic chemotherapy before and after RT (sandwich), adjuvant RT followed by chemotherapy (upfront RT) or chemotherapy concurrent with vaginal cuff brachytherapy alone (chemo-brachy). Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by Kaplan-Meier method. **RESULTS:** A total of 686 eligible patients were included with a median follow-up of 45.3 months. The estimated 5-year OS and RFS rates were 74% and 66%, respectively. The sequence and type of adjuvant therapy was not correlated with OS or RFS (adjusted $p=0.68$ and 0.84 , respectively). On multivariate analysis, black race, non-endometrioid histology, grade 3 tumor, stage IIIC2, presence of adnexal and cervical involvement were associated with worse OS and RFS (all $p<0.05$). Regardless of the sequence of treatment, the most common site of first recurrence was distant metastasis (20.1%). Vaginal only, pelvic only and para-aortic lymph node (PALN) recurrences occurred in 11 (1.6%), 15 (2.2%) and 43 (6.3%) patients, respectively. Brachytherapy alone was associated with a higher rate of PALN recurrence (15%) compared to External Beam Radiotherapy (EBRT) (5%) $p<0.0001$. **CONCLUSIONS:** The sequence and type of combined adjuvant therapy did not impact OS or RFS rates. Brachytherapy alone was associated with a higher rate of PALN recurrence emphasizing the role of nodal radiation for stage IIIC EC. The vast proportion of recurrences were distant despite systemic chemotherapy, highlighting the need for novel regimens.

Obstetrics, Gynecology, and Women's Health Services

Lehrberg A, Davis MB, Baidoun F, Petersen L, Susick L, Jenkins B, Chen Y, Ivanics T, Rakitin I, Bensenhaver J, Proctor E, Nathanson SD, and Newman LA. Outcome of African-American compared to White-American patients with early-stage breast cancer, stratified by phenotype. *Breast J* 2021; Epub ahead of print. PMID: 33738890. [Full Text](#)

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BACKGROUND: Breast cancer mortality rates are 39% higher in the African-American (AA) women compared to White-American (WA) women despite the advances in overall breast cancer screening and treatments. Several studies have undertaken to identify the factors leading to this disparity in United States with possible effects of lower socioeconomic status and underlying aggressive biology.

METHODS: A retrospective analysis was done using a prospectively maintained database of a metropolitan health system. Patients were selected based on diagnosis of early-stage breast cancer between 10/1998 and 02/2017, and included women over age of 18 with clinically node-negative disease. Patients were then stratified by phenotype confirmed by pathology and patient-identified race. **RESULTS:** A total of 2,298 women were identified in the cohort with 39% AA and 61% WA women. The overall mean

age at the time of diagnosis for AA women was slightly younger at 60 years compared to 62 years for WA women ($p = 0.003$). Follow-up time was longer for the WA women at 95 months vs. 86 months in AA women. The overall 5-year survival was analyzed for the entire cohort, with the lowest survival occurring in patients with triple-negative breast cancer (TNBC). Phenotype distribution revealed a higher incidence of TNBC in AA women compared to WA women (AA 16% vs. WA 10%; $p < 0.0001$). AA women also had higher incidence of HER2 positive cancers (AA 16.8% vs. WA 15.3%; $p < 0.0001$). WA women had a significantly higher distribution of Non-TNBC/HER2-negative phenotype (AA 55% vs. WA 65%; $p < 0.0001$). Furthermore, a subgroup analysis was done for a sentinel lymph node (SLN) negative cohort that showed higher rates of grade 3 tumors in AA (AA 35% vs. WA 23%; $p < 0.0001$); and higher rates of grade 1 and grade 2 tumors in WA (30% vs. 21% and 44% vs. 40%). Despite higher grade tumors in AA women, five-year overall survival outcomes in SLN-negative cohort did not differ between AA and WA women when stratifying based on tumor subtype. **CONCLUSION:** Breast cancer survival disparities in AA and WA women with SLN-negative breast cancer are diminished when evaluated at early-stage cancers defined by SLN-negative tumors. Our evaluation suggests that when diagnosed early, phenotype does not contribute to racial survival outcomes. The lower survival rate in AA women with breast cancer may be attributed to later stage biology between the two races, or underlying socioeconomic disparities.

Ophthalmology and Eye Care Services

Turfe Z, Saleh N, George C, Rock J, and Craig JR. Cavernous Sinus Syndrome After Barotraumatic Sneeze. *J Neuroophthalmol* 2021; Epub ahead of print. PMID: 33734154. [Full Text](#)

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Orthopedics/Bone and Joint Center

Battista EB, Yedulla NR, Koolmees DS, Montgomery ZA, Ravi K, and Day CS. Manufacturing Workers Have a Higher Incidence of Carpal Tunnel Syndrome. *J Occup Environ Med* 2021; 63(3):e120-e126. PMID: 33394876. [Full Text](#)

Henry Ford Health System, Detroit, Michigan (Dr Day); Wayne State University School of Medicine, Ann Arbor, MI (Mr Battista, Mr Yedulla, Mr Koolmees, Mr Montgomery, Dr Day); University of Michigan (Mr Ravi), Detroit, Michigan.

OBJECTIVE: It is unclear whether clerical or labor-type work is more associated with risk for developing work-related carpal tunnel syndrome (WrCTS). **METHODS:** National employment, demographic, and injury data were examined from the Bureau of Labor Statistics databases for the years 2003 to 2018. Injuries for clerical and labor industries were compared using linear regression, two-group t test, and one-way analysis of variance (ANOVA) analysis. **RESULTS:** WrCTS injuries are decreasing over time ($B = -1002.62$, $P < 0.001$). The labor industry demonstrated a significantly higher incidence of WrCTS when compared with the clerical industries ($P < 0.001$). Within labor industries, the manufacturing industry had the highest incidence of WrCTS over time ($P < 0.001$). **CONCLUSIONS:** Our study showed WrCTS injuries have declined over time. Additionally, our findings may suggest that the labor industry has a stronger association with WrCTS than the clerical industry.

Orthopedics/Bone and Joint Center

Jildeh TR, Okoroha KR, Kuhlmann N, Cross A, Abbas MJ, and Moutzouros V. Multimodal Nonopioid Pain Protocol Provides Equivalent Pain Versus Opioid Control Following Meniscus Surgery: A Prospective Randomized Controlled Trial. *Arthroscopy* 2021; Epub ahead of print. PMID: 33713756. [Full Text](#)

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PURPOSE: To assess the effectiveness of a nonopioid pain regimen in controlling postoperative pain as compared to a traditional opioid pain control following primary meniscectomy or meniscal repair. **STUDY DESIGN:** Level of Evidence: Level I, Prospective Randomized Controlled Trial **METHODS:** Ninety-nine patients undergoing primary meniscectomy or meniscal repair were assessed for participation. A prospective randomized control trial was performed in accordance with the Consolidated Standards of Reporting Trials 2010 (CONSORT) statement. The two arms of the study included a multimodal non-opioid analgesic protocol and a standard opioid regimen with a primary outcome of postoperative pain level (visual analog scale) for the first 10 days post-operatively. Secondary outcomes included patient reported outcomes, complications and patient satisfaction. Randomization was achieved using a random number generator. Patients were not blinded. Data collection was done by a blinded observer. **RESULTS:** Eleven patients did not meet the inclusion criteria, and 27 declined participation. A total of 61 patients were analyzed with 30 randomized to the opioid regimen, and 31 randomized to the non-opioid regimen. Patients receiving the nonopioid regimen demonstrated non-inferior VAS scores compared to patients who received opioid pain medication ($p > 0.05$) No significant differences were found in preoperative (opioid: 58.9 ± 7.0 ; nonopioid: 58.2 ± 5.5 , $p = 0.724$) nor postoperative (opioid: 59.8 ± 6.5 ; nonopioid: 54.9 ± 7.1 , $p = 0.064$) PROMIS-Pain Interference Short Form scores. No difference was found in recorded side effects between both groups at any given time point: constipation, nausea, diarrhea, upset stomach, and drowsiness ($p > 0.05$). **CONCLUSION:** This study found that multimodal nonopioid pain protocol provided equivalent pain control and patient outcomes following primary meniscus surgery while having an equivalent side effect profile. All patients reported satisfaction with their pain management without requiring emergency opioid analgesia.

Orthopedics/Bone and Joint Center

Lawrence RL, Zauel R, and Bey MJ. Measuring 3D In-vivo Shoulder Kinematics using Biplanar Videoradiography. *J Vis Exp* 2021; Epub ahead of print.(169). PMID: 33779606. [Full Text](#)

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The shoulder is one of the human body's most complex joint systems, with motion occurring through the coordinated actions of four individual joints, multiple ligaments, and approximately 20 muscles. Unfortunately, shoulder pathologies (e.g., rotator cuff tears, joint dislocations, arthritis) are common, resulting in substantial pain, disability, and decreased quality of life. The specific etiology for many of these pathologic conditions is not fully understood, but it is generally accepted that shoulder pathology is often associated with altered joint motion. Unfortunately, measuring shoulder motion with the necessary level of accuracy to investigate motion-based hypotheses is not trivial. However, radiographic-based motion measurement techniques have provided the advancement necessary to investigate motion-based hypotheses and provide a mechanistic understanding of shoulder function. Thus, the purpose of this article is to describe the approaches for measuring shoulder motion using a custom biplanar videoradiography system. The specific objectives of this article are to describe the protocols to acquire biplanar videoradiographic images of the shoulder complex, acquire CT scans, develop 3D bone models, locate anatomical landmarks, track the position and orientation of the humerus, scapula, and torso from the biplanar radiographic images, and calculate the kinematic outcome measures. In addition, the article will describe special considerations unique to the shoulder when measuring joint kinematics using this approach.

Orthopedics/Bone and Joint Center

Nwachukwu B, Rasio J, Sullivan S, **Okoroha K**, Mather RC, and Nho SJ. Surgical Treatment of Labral Tears: Debridement, Repair, and Reconstruction. *Sports Med Arthrosc Rev* 2021; 29(1):e1-e8. PMID: 33395227. [Full Text](#)

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Advances in hip preservation surgery have to lead to increased utilization of hip arthroscopy. With this, there has also been a growth in the understanding of various hip conditions, therefore, leading to an increase in hip conditions amenable to arthroscopic intervention. The acetabular hip labrum has been at the forefront of arthroscopic advances in the hip. The labrum is important for hip stability, provision of the suction seal, and joint proprioception. Given the labrum's central role in hip biomechanics, there is increasing emphasis on labral preservation in the form of debridement and repair. In revision settings, advanced techniques such as labral augmentation and reconstruction may play a role in the management of labral pathology. Appropriate management of the hip labrum at the time of surgery can be an important mediator of the outcome. As such, an understanding of the evolving evidence base and surgical indications and techniques are integral to the treatment and management of labral pathology.

Orthopedics/Bone and Joint Center

Potla P, **Ali SA**, and Kapoor M. A bioinformatics approach to microRNA-sequencing analysis. *Osteoarthr Cartil Open* 2021; 3(1). PMID: Not assigned. [Full Text](#)

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The rapid expansion of Next Generation Sequencing (NGS) data availability has made exploration of appropriate bioinformatics analysis pipelines a timely issue. Since there are multiple tools and combinations thereof to analyze any dataset, there can be uncertainty in how to best perform an analysis in a robust and reproducible manner. This is especially true for newer omics applications, such as miRNomics, or microRNA-sequencing (miRNA-sequencing). As compared to transcriptomics, there have been far fewer miRNA-sequencing studies performed to date, and those that are reported seldom provide detailed description of the bioinformatics analysis, including aspects such as Unique Molecular Identifiers (UMIs). In this article, we attempt to fill the gap and help researchers understand their miRNA-sequencing data and its analysis. This article will specifically discuss a customizable miRNA bioinformatics pipeline that was developed using miRNA-sequencing datasets generated from human osteoarthritis plasma samples. We describe quality assessment of raw sequencing data files, reference-based alignment, counts generation for miRNA expression levels, and novel miRNA discovery. This report is expected to improve clarity and reproducibility of the bioinformatics portion of miRNA-sequencing analysis, applicable across any sample type, to promote sharing of detailed protocols in the NGS field.

Orthopedics/Bone and Joint Center

Tramer JS, Khalil LS, Buckley P, Ziedas A, Kolowich PA, and Okoroha KR. Effect of Achilles Tendon Rupture on Player Performance and Longevity in Women's National Basketball Association Players. *Orthop J Sports Med* 2021; 9(3):6. PMID: Not assigned. [Full Text](#)

[Tramer, Joseph S.; Khalil, Lafi S.; Buckley, Patrick; Ziedas, Alexander; Kolowich, Patricia A.; Okoroha, Kelechi R.] Henry Ford Hlth Syst, Detroit, MI USA. [Tramer, Joseph S.; Khalil, Lafi S.; Kolowich, Patricia A.; Okoroha, Kelechi R.] Henry Ford Hosp, Dept Orthopaed Surg, 2799 W Grand Blvd, Detroit, MI 48202 USA. [Buckley, Patrick; Ziedas, Alexander] Wayne State Univ, Sch Med, Detroit, MI USA.
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Background: Women's National Basketball Association (WNBA) players have a greater incidence of lower extremity injury compared with male players, yet no data exist on functional outcomes after Achilles tendon rupture (ATR). Purpose: To evaluate the effect of Achilles tendon repair on game utilization,

player performance, and career longevity in WNBA athletes. Study Design: Cohort study; Level of evidence, 3. Methods: WNBA players from 1997 to 2019 with a history of ATR (n = 12) were matched 1:2 to a healthy control group. Player characteristics, game utilization, and in-game performance data were collected for each athlete, from which the player efficiency rating (PER) was calculated. Statistical analysis was performed comparing postinjury data to preinjury baseline as well as cumulative career data. Changes at each time point relative to the preinjury baseline were also compared between groups. Results: Of the 12 players with ATR, 10 (83.3%) returned to play at the WNBA level at a mean (+/- SD) of 12.5 +/- 3.3 months. Four players participated in only 1 WNBA season after injury. There were no differences in characteristics between the 10 players who returned to play after injury and the control group. After return to play, the WNBA players demonstrated a significant decrease in game utilization compared with preinjury, playing in 6.0 +/- 6.9 fewer games, starting in 12.7 +/- 15.4 fewer games, and playing 10.2 +/- 9.1 fewer minutes per game (P < .05 for all). After the index date of injury, the players with Achilles repair played 2.1 +/- 1.2 more years in the WNBA, while control players played 5.35 +/- 3.2 years (P < .01). Additionally, the players with Achilles repair had a significant decrease in PER in the year after injury compared with preinjury (7.1 +/- 5.3 vs 11.0 +/- 4.4; P = .02). The reduction in game utilization and decrease in PER in these players was maintained when compared with the matched controls (P < .05 for both). Conclusion: The majority of WNBA players who sustained ATR were able to return to sport after their injury; however, their career longevity was shorter than that of healthy controls. There was a significant decrease in game utilization and performance in the year after return to play compared with healthy controls.

Otolaryngology – Head and Neck Surgery

Jones LR, Levin AM, Dai X, Datta I, Li J, Yin C, and Mi QS. MicroRNA Profile Differentiates Head and Neck Keloid and Adjacent Normal Skin Tissue. *Facial Plast Surg Aesthet Med* 2021; Epub ahead of print. PMID: 33710934. [Full Text](#)

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Otolaryngology – Head and Neck Surgery

Lamparyk K, **Williams AM**, Robiner WN, Bruschnwein HM, and Ward WL. Interprofessional Education: Current State in Psychology Training. *J Clin Psychol Med Settings* 2021; Epub ahead of print. PMID: 33689102. [Full Text](#)

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Healthcare reform has led to the consideration of interprofessional team-based, collaborative care as a way to provide comprehensive, high-quality care to patients and families. Interprofessional education is the mechanism by which the next generation health professional workforce is preparing for the future of health care-team-based, collaborative care. This literature review explored the extent and content of published studies documenting Interprofessional Education (IPE) activities with psychology trainees across learner level. A systematic review following PRISMA guidelines was conducted of studies describing IPE involving psychology learners. Electronic databases (MEDLINE, CINAHL, PsychINFO, and EMBASE) were searched for the following terms: inter/multi-professional education/practice, inter/multidisciplinary education/practice, and psychology/psychologists. Thirty-seven articles were identified that included psychology in clinical outcome studies or other reviews of interprofessional education initiatives. The review addresses the nature of current IPE learning activities, the impact of IPE activities on participating trainees, opportunities for, and challenges of, involving psychology trainees in IPE, and future directions for research. This review illuminates the relative paucity of the literature about

IPE in psychology training. Given the trend toward increasing team-based collaborative care, the limited inclusion of psychology in the IPE literature is concerning. The next generation of health professional trainees is learning about, from, and with each other with the objective of building collaboration and teamwork. Given the few articles documenting psychology trainees' involvement in IPE, future health professionals quite possibly will have limited understanding of, and contact with, psychologists. Our findings are a call to action for greater psychology involvement in IPE.

Otolaryngology – Head and Neck Surgery

Turfe Z, Saleh N, George C, Rock J, and Craig JR. Cavernous Sinus Syndrome After Barotraumatic Sneeze. *J Neuroophthalmol* 2021; Epub ahead of print. PMID: 33734154. [Full Text](#)

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Pathology and Laboratory Medicine

Rybicki BA, Sadasivan SM, Chen Y, Kravtsov O, Palangmonthip W, Arora K, Gupta NS, Williamson S, Bobbitt K, Chitale DA, Tang D, Rundle AG, and Iczkowski KA. Growth and differentiation factor 15 and NF- κ B expression in benign prostatic biopsies and risk of subsequent prostate cancer detection. *Cancer Med* 2021; Epub ahead of print. PMID: 33784024. [Full Text](#)

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Growth and differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine 1 (MIC-1), may act as both a tumor suppressor and promotor and, by regulating NF- κ B and macrophage signaling, promote early prostate carcinogenesis. To determine whether expression of these two inflammation-related proteins affect prostate cancer susceptibility, dual immunostaining of benign prostate biopsies for GDF-15 and NF- κ B was done in a study of 503 case-control pairs matched on date, age, and race, nested within a historical cohort of 10,478 men. GDF-15 and NF- κ B expression levels were positively correlated ($r = 0.39$; $p < 0.0001$), and both were significantly lower in African American (AA) compared with White men. In adjusted models that included both markers, the odds ratio (OR) for NF- κ B expression was statistically significant, OR =0.87; $p = 0.03$; 95% confidence interval (CI) =0.77-0.99, while GDF-15 expression was associated with a nominally increased risk, OR =1.06; $p = 0.27$; 95% CI =0.96-1.17. When modeling expression levels by quartiles, the highest quartile of NF- κ B expression was associated with almost a fifty percent reduction in prostate cancer risk (OR =0.51; $p = 0.03$; 95% CI =0.29-0.92). In stratified models, NF- κ B had the strongest negative association with prostate cancer in non-aggressive cases ($p = 0.03$), older men ($p = 0.03$), and in case-control pairs with longer follow-up ($p = 0.02$). Risk associated with GDF-15 expression was best fit using nonlinear regression modeling where both first ($p = 0.02$) and second ($p = 0.03$) order GDF-15 risk terms were associated with significantly increased risk. This modeling approach also revealed significantly increased risk associated with GDF-15 expression for subsamples defined by AA race, aggressive disease, younger age, and in case-control pairs with longer follow-up. Therefore, although positively correlated in benign prostatic biopsies, NF- κ B and GDF-15 expression appear to exert opposite effects on risk of prostate tumor development.

Pathology and Laboratory Medicine

Zhang Y, Li C, Qin Y, Cepparulo P, Millman M, Chopp M, Kemper A, Szalad A, Lu X, Wang L, and Zhang ZG. Small extracellular vesicles ameliorate peripheral neuropathy and enhance chemotherapy of oxaliplatin on ovarian cancer. *J Extracell Vesicles* 2021; 10(5):e12073. PMID: 33728031. [Full Text](#)

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There are no effective treatments for chemotherapy induced peripheral neuropathy (CIPN). Small extracellular vesicles (sEVs) facilitate intercellular communication and mediate nerve function and tumour progression. We found that the treatment of mice bearing ovarian tumour with sEVs derived from cerebral endothelial cells (CEC-sEVs) in combination with a chemo-drug, oxaliplatin, robustly reduced oxaliplatin-induced CIPN by decreasing oxaliplatin-damaged myelination and nerve fibres of the sciatic nerve and significantly amplified chemotherapy of oxaliplatin by reducing tumour size. The combination therapy substantially increased a set of sEV cargo-enriched miRNAs, but significantly reduced oxaliplatin-increased proteins in the sciatic nerve and tumour tissues. Bioinformatics analysis revealed the altered miRNAs and proteins formed two distinct networks that regulate neuropathy and tumour growth, respectively. Intravenously administered CEC-sEVs were internalized by axons of the sciatic nerve and cancer cells. Reduction of CEC-sEV cargo miRNAs abolished the effects of CEC-sEVs on oxaliplatin-inhibited axonal growth and on amplification of the anti-cancer effect in ovarian cancer cells, suggesting that alterations in the networks of miRNAs and proteins in recipient cells contribute to the therapeutic effect of CEC-sEVs on CIPN. Together, the present study demonstrates that CEC-sEVs suppressed CIPN and enhanced chemotherapy of oxaliplatin in the mouse bearing ovarian tumour.

Pharmacy

Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, **Fadel R**, **Morrison A**, **Kenney RM**, **Alangaden G**, **Ramesh M**, and Mor G. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics* 2021; Epub ahead of print. PMID: 33693506. [Full Text](#)

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MOTIVATION: COVID-19 has several distinct clinical phases: a viral replication phase, an inflammatory phase, and in some patients, a hyper-inflammatory phase. High mortality is associated with patients developing cytokine storm syndrome. Treatment of hyper-inflammation in these patients using existing, approved therapies with proven safety profiles could address the immediate need to reduce mortality. **RESULTS:** We analyzed the changes in the gene expression, pathways and putative mechanisms induced by SARS-CoV2 in NHBE, and A549 cells, as well as COVID-19 lung vs. their respective controls. We used these changes to identify FDA approved drugs that could be repurposed to help COVID-19 patients with severe symptoms related to hyper-inflammation. We identified methylprednisolone (MP) as a potential leading therapy. The results were then confirmed in five independent validation data sets including Vero E6 cells, lung and intestinal organoids, as well as additional patient lung sample vs. their respective controls. Finally, the efficacy of MP was validated in an independent clinical study. Thirty-day all-cause mortality occurred at a significantly lower rate in the MP-treated group compared to control group (29.6% vs. 16.6%, $p = 0.027$). Clinical results confirmed the in silico prediction that MP could improve outcomes in severe cases of COVID-19. A low number needed to treat (NNT = 5) suggests MP may be more efficacious than dexamethasone or hydrocortisone. **AVAILABILITY:** iPathwayGuide is available at <https://ipathwayguide.advaitabio.com/>. **SUPPLEMENTARY INFORMATION:** Supplementary data are available at Bioinformatics online.

Public Health Sciences

Aboul Nour H, Affan M, Mohamed G, Mohamud A, Schultz L, Latack K, Brady M, Scozzari D, Haddad Y, Katramados A, Bou Chebl A, and Ramadan AR. Impact of the COVID-19 Pandemic on Acute Stroke Care, Time Metrics, Outcomes, and Racial Disparities in a Southeast Michigan Health System. *J Stroke Cerebrovasc Dis* 2021; 30(6):105746. PMID: 33780695. [Full Text](#)

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BACKGROUND: COVID-19 has impacted acute stroke care with several reports showing worldwide drops in stroke caseload during the pandemic. We studied the impact of COVID-19 on acute stroke care in our health system serving Southeast Michigan as we rolled out a policy to limit admissions and transfers. **METHODS:** in this retrospective study conducted at two stroke centers, we included consecutive patients presenting to the ED for whom a stroke alert was activated during the period extending from 3/20/20 to 5/20/20 and a similar period in 2019. We compared demographics, time metrics, and discharge outcomes between the two groups. **RESULTS:** of 385 patients presented to the ED during the two time periods, 58% were African American. There was a significant decrease in the number of stroke patients presenting to the ED and admitted to the hospital between the two periods ($p < 0.001$). In 2020, patients had higher presenting NIHSS (median: 2 vs 5, $p = 0.012$), discharge NIHSS (median: 2 vs 3, $p = 0.004$), and longer times from LKW to ED arrival (4.8 vs 9.4 h, $p = 0.031$) and stroke team activation (median: 10 vs 15 min, $p = 0.006$). In 2020, stroke mimics rates were lower among African Americans. There were fewer hospitalizations ($p < 0.001$), and transfers from outside facilities ($p = 0.015$). **CONCLUSION:** a trend toward faster stroke care in the ED was observed during the pandemic along with dramatically reduced numbers of ED visits, hospitalizations and stroke mimics. Delayed ED presentations and higher stroke severity characterized the African American population, highlighting deepening of racial disparities during the pandemic.

Public Health Sciences

Altibi AM, Pallavi B, Liaqat H, Slota AA, Sheth R, Al Jebbawi L, George ME, LeDuc A, Abdallah E, Russell LR, Jain S, Shirvanian N, Masri A, and Kak V. Characteristics and comparative clinical outcomes of prisoner versus non-prisoner populations hospitalized with COVID-19. *Sci Rep* 2021; 11(1):6488. PMID: 33753786. [Full Text](#)

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Prisons in the United States have become a hotbed for spreading COVID-19 among incarcerated individuals. COVID-19 cases among prisoners are on the rise, with more than 143,000 confirmed cases to date. However, there is paucity of data addressing clinical outcomes and mortality in prisoners hospitalized with COVID-19. An observational study of all patients hospitalized with COVID-19 between March 10 and May 10, 2020 at two Henry Ford Health System hospitals in Michigan. Clinical outcomes were compared amongst hospitalized prisoners and non-prisoner patients. The primary outcomes were intubation rates, in-hospital mortality, and 30-day mortality. Multivariable logistic regression and Cox-regression models were used to investigate primary outcomes. Of the 706 hospitalized COVID-19 patients (mean age 66.7 ± 16.1 years, 57% males, and 44% black), 108 were prisoners and 598 were non-prisoners. Compared to non-prisoners, prisoners were more likely to present with fever, tachypnea, hypoxemia, and markedly elevated inflammatory markers. Prisoners were more commonly admitted to the intensive care unit (ICU) (26.9% vs. 18.7%), required vasopressors (24.1% vs. 9.9%), and intubated (25.0% vs. 15.2%). Prisoners had higher unadjusted inpatient mortality (29.6% vs. 20.1%) and 30-day mortality (34.3% vs. 24.6%). In the adjusted models, prisoner status was associated with higher in-hospital death (odds ratio, 2.32; 95% confidence interval (CI), 1.33 to 4.05) and 30-day mortality (hazard ratio, 2.00; 95% CI, 1.33 to 3.00). In this cohort of hospitalized COVID-19 patients, prisoner status was associated with more severe clinical presentation, higher rates of ICU admissions, vasopressors requirement, intubation, in-hospital mortality, and 30-day mortality.

Public Health Sciences

Cassidy-Bushrow AE, Burmeister C, Birbeck J, Chen Y, Lamerato L, Lemke LD, Li J, Mor G, O'Leary BF, Peters RM, Reiners JJ, Jr., Sperone FG, Westrick J, Wiewiora E, and Straughen JK. Ambient BTEX exposure and mid-pregnancy inflammatory biomarkers in pregnant African American women. *J Reprod Immunol* 2021; 145:103305. PMID: 33725526. [Full Text](#)

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Air pollution is associated with preterm birth (PTB), potentially via inflammation. We recently showed the mixture benzene, toluene, ethylbenzene, and xylene (BTEX) is associated with PTB. We examined if ambient BTEX exposure is associated with mid-pregnancy inflammation in a sample of 140 African-American women residing in Detroit, Michigan. The Geospatial Determinants of Health Outcomes Consortium study collected outdoor air pollution measurements in Detroit; these data were coupled with Michigan Air Sampling Network measurements to develop monthly BTEX concentration estimates at a spatial density of 300 m². First trimester and mid-pregnancy BTEX exposure estimates were assigned to maternal address. Mid-pregnancy (mean 21.3 ± 3.7 weeks gestation) inflammatory biomarkers (high-sensitivity C-reactive protein, interleukin [IL]-6, IL-10, IL-1β, and tumor necrosis factor-α) were measured with enzyme immunoassays. After covariate adjustment, for every 1-unit increase in first trimester BTEX, there was an expected mean increase in log-transformed IL-1β of 0.05 ± 0.02 units (P = 0.014) and an expected mean increase in log-transformed tumor necrosis factor-α of 0.07 ± 0.02 units (P = 0.006). Similarly, for every 1-unit increase in mid-pregnancy BTEX, there was a mean increase in log IL-1β of 0.06 ± 0.03 units (P = 0.027). There was no association of either first trimester or mid-pregnancy BTEX with high-sensitivity C-reactive protein, IL-10, or IL-6 (all P > 0.05). Ambient BTEX exposure is associated with inflammation in mid-pregnancy in African-American women. Future studies examining if inflammation mediates associations between BTEX exposure and PTB are needed.

Public Health Sciences

Coleman CM, Bossick AS, Zhou Y, Hopkins-Johnson L, Otto MG, Nair AS, Willens DE, and Wegienka GR. Introduction of a community health worker diabetes coach improved glycemic control in an urban primary care clinic. *Prev Med Rep* 2021; 21:101267. PMID: 33364150. [Full Text](#)

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The burden of diabetes is higher in urban areas and among racial and ethnic minorities. The purpose of this research was to evaluate the effectiveness of extending a diabetes intervention program (DIP) by engaging a team, including a community health worker (CHW), to provide care for patients to meet glycemic control, specifically in a predominantly urban, minority patient population. The DIP enrolled diabetic patients from an internal medicine clinic. A CHW facilitated the collection of glucose meter readings. The CHW coached patients on glycemic control while the CHW's registered nurse partner titrated the patient's recommended insulin dose. Subsequent HbA1c values for participants were compared to those seen at the same clinic who were not enrolled. The DIP was deployed for nine months. One hundred forty-four patients were enrolled in the DIP and 348 patients constituted the comparator group. Ninety-three DIP participants had pre- and post-intervention HbA1c values and were compared to 348 non-DIP participants. Propensity score weighted adjusted analyses suggest that participants were more likely to reduce their HbA1c values by at least 1.0% and have HbA1c values of less than 8.0% (64 mmol/mol) than non-participants (adjusted odds ratio = aOR = 1.47, 95% CI 1.26-1.71, and aOR = 1.23, 95% CI 1.06-1.43, respectively). CHW coaches as part of a team in a clinical setting improved glycemic control in a predominantly urban, minority patient population.

Public Health Sciences

Danoun OA, Zillgitt A, Hill C, Zutshi D, Harris D, Osman G, Marawar R, Rath S, Syed MJ, Affan M, Schultz L, and Wasade VS. Outcomes of seizures, status epilepticus, and EEG findings in critically ill patient with COVID-19. *Epilepsy Behav* 2021; 118:107923. PMID: 33770609. [Full Text](#)

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OBJECTIVE: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a myriad of neurological manifestations and its effects on the nervous system are increasingly recognized. Seizures and status epilepticus (SE) are reported in the novel coronavirus disease (COVID-19), both new onset and worsening of existing epilepsy; however, the exact prevalence is still unknown. The primary aim of this study was to correlate the presence of seizures, status epilepticus, and specific critical care EEG patterns with patient functional outcomes in those with COVID-19. **METHODS:** This is a retrospective, multicenter cohort of COVID-19-positive patients in Southeast Michigan who underwent electroencephalography (EEG) from March 12th through May 15th, 2020. All patients had confirmed nasopharyngeal PCR for COVID-19. EEG patterns were characterized per 2012 ACNS critical care EEG terminology. Clinical and demographic variables were collected by medical chart review. Outcomes were divided into recovered, recovered with disability, or deceased. **RESULTS:** Out of the total of 4100 patients hospitalized with COVID-19, 110 patients (2.68%) had EEG during their hospitalization; 64% were male, 67% were African American with mean age of 63 years (range 20-87). The majority (70%) had severe COVID-19, were intubated, or had multi-organ failure. The median length of hospitalization was 26.5 days (IQR = 15 to 44 days). During hospitalization, of the patients who had EEG, 21.8% had new-onset seizure including 7% with status epilepticus, majority (87.5%) with no prior epilepsy. Forty-nine (45%) patients died in the hospital, 46 (42%) recovered but maintained a disability and 15 (14%) recovered without a disability. The EEG findings associated with outcomes were background slowing/attenuation (recovered 60% vs recovered/disabled 96% vs died 96%, $p < 0.001$) and normal (recovered 27% vs recovered/disabled 0% vs died 1%, $p < 0.001$). However, these findings were no longer significant after adjusting for severity of COVID-19. **CONCLUSION:** In this large multicenter study from Southeast Michigan, one of the early COVID-19 epicenters in the US, none of the EEG findings were significantly correlated with outcomes in critically ill COVID-19 patients. Although seizures and status epilepticus could be encountered in COVID-19, the occurrence did not correlate with the patients' functional outcome.

Public Health Sciences

Graff M, Justice AE, Young KL, **Levin AM, Neslund-Dudas C, Padhukasahasram B, Rybicki BA**, et al. Discovery and fine-mapping of height loci via high-density imputation of GWASs in individuals of African ancestry. *Am J Hum Genet* 2021; Epub ahead of print. PMID: 33713608. [Request Article](#)

Although many loci have been associated with height in European ancestry populations, very few have been identified in African ancestry individuals. Furthermore, many of the known loci have yet to be generalized to and fine-mapped within a large-scale African ancestry sample. We performed sex-combined and sex-stratified meta-analyses in up to 52,764 individuals with height and genome-wide genotyping data from the African Ancestry Anthropometry Genetics Consortium (AAAGC). We additionally combined our African ancestry meta-analysis results with published European genome-wide association study (GWAS) data. In the African ancestry analyses, we identified three novel loci (SLC4A3, NCOA2, ECD/FAM149B1) in sex-combined results and two loci (CRB1, KLF6) in women only. In the African plus European sex-combined GWAS, we identified an additional three novel loci (RCCD1, G6PC3, CEP95) which were equally driven by AAAGC and European results. Among 39 genome-wide significant signals at known loci, conditioning index SNPs from European studies identified 20 secondary signals. Two of the 20 new secondary signals and none of the 8 novel loci had minor allele frequencies (MAF) $< 5\%$. Of 802 known European height signals, 643 displayed directionally consistent associations with height, of which 205 were nominally significant ($p < 0.05$) in the African ancestry sex-combined sample. Furthermore, 148 of 241 loci contained ≤ 20 variants in the credible sets that jointly account for 99% of the posterior probability of driving the associations. In summary, trans-ethnic meta-analyses revealed novel signals and further improved fine-mapping of putative causal variants in loci shared between African and European ancestry populations.

Public Health Sciences

Jones LR, Levin AM, Dai X, Datta I, Li J, Yin C, and Mi QS. MicroRNA Profile Differentiates Head and Neck Keloid and Adjacent Normal Skin Tissue. *Facial Plast Surg Aesthet Med* 2021; Epub ahead of print. PMID: 33710934. [Full Text](#)

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Public Health Sciences

Lehrberg A, Davis MB, Baidoun F, Petersen L, Susick L, Jenkins B, Chen Y, Ivanics T, Rakitin I, Bensenhaver J, Proctor E, Nathanson SD, and Newman LA. Outcome of African-American compared to White-American patients with early-stage breast cancer, stratified by phenotype. *Breast J* 2021; Epub ahead of print. PMID: 33738890. [Full Text](#)

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BACKGROUND: Breast cancer mortality rates are 39% higher in the African-American (AA) women compared to White-American (WA) women despite the advances in overall breast cancer screening and treatments. Several studies have undertaken to identify the factors leading to this disparity in United States with possible effects of lower socioeconomic status and underlying aggressive biology. **METHODS:** A retrospective analysis was done using a prospectively maintained database of a metropolitan health system. Patients were selected based on diagnosis of early-stage breast cancer between 10/1998 and 02/2017, and included women over age of 18 with clinically node-negative disease. Patients were then stratified by phenotype confirmed by pathology and patient-identified race. **RESULTS:** A total of 2,298 women were identified in the cohort with 39% AA and 61% WA women. The overall mean age at the time of diagnosis for AA women was slightly younger at 60 years compared to 62 years for WA women ($p = 0.003$). Follow-up time was longer for the WA women at 95 months vs. 86 months in AA women. The overall 5-year survival was analyzed for the entire cohort, with the lowest survival occurring in patients with triple-negative breast cancer (TNBC). Phenotype distribution revealed a higher incidence of TNBC in AA women compared to WA women (AA 16% vs. WA 10%; $p < 0.0001$). AA women also had higher incidence of HER2 positive cancers (AA 16.8% vs. WA 15.3%; $p < 0.0001$). WA women had a significantly higher distribution of Non-TNBC/HER2-negative phenotype (AA 55% vs. WA 65%; $p < 0.0001$). Furthermore, a subgroup analysis was done for a sentinel lymph node (SLN) negative cohort that showed higher rates of grade 3 tumors in AA (AA 35% vs. WA 23%; $p < 0.0001$); and higher rates of grade 1 and grade 2 tumors in WA (30% vs. 21% and 44% vs. 40%). Despite higher grade tumors in AA women, five-year overall survival outcomes in SLN-negative cohort did not differ between AA and WA women when stratifying based on tumor subtype. **CONCLUSION:** Breast cancer survival disparities in AA and WA women with SLN-negative breast cancer are diminished when evaluated at early-stage cancers defined by SLN-negative tumors. Our evaluation suggests that when diagnosed early, phenotype does not contribute to racial survival outcomes. The lower survival rate in AA women with breast cancer may be attributed to later stage biology between the two races, or underlying socioeconomic disparities.

Public Health Sciences

Li J, Gordon SC, Zhou Y, Boscarino JA, Schmidt MA, Daida YG, Rupp LB, Trudeau S, and Lu M. Sex Differences in Extrahepatic Outcomes After Antiviral Treatment for Hepatitis C. *Am J Gastroenterol* 2021; 116(3):576-583. PMID: 33399360. [Full Text](#)

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INTRODUCTION: Despite recognized differences in the rates of cardiovascular and renal disease between men and women in the general population, studies of the downstream effects of antiviral treatment for hepatitis C (HCV) have not investigated differences in outcomes based on sex. We analyzed sex differences in risk of acute coronary syndrome (ACS), end-stage renal disease (ESRD), and ischemic stroke by treatment and response in a large US-based multisite cohort of HCV patients. **METHODS:** Observation started at the HCV diagnosis date (untreated) or last antiviral treatment start (treated). Treatment selection bias was addressed using an inverse probability-weighting approach. We estimated the effect of treatment on the cumulative incidence of outcomes using the Fine-Gray method (subdistribution hazard ratios [sHR] and 95% confidence intervals [95% CI]). Death was a competing risk. **RESULTS:** Roughly 40% of 15,295 HCV patients were women. After controlling for other risk factors, sustained virological response (SVR) (interferon-based [IFN] or direct-acting antiviral [DAA]) significantly reduced risk of all outcomes, particularly among female patients. Female patients who achieved SVR after IFN-based treatment had significantly lower risk of ACS compared with male patients with SVR from either treatment type (sHR 0.45 [95% CI 0.35-0.59] vs 0.81 [95% CI 0.69-0.96, for DAA SVR] and sHR 0.72 [95% CI 0.62, 0.85, for IFN SVR]). Successful treatment seemed to be most protective against ESRD; female patients who achieved SVR were at 66%-68% lower risk than untreated patients (sHR 0.32 [95% CI 0.17-0.60 for DAA SVR] and 0.34 [95% CI 0.20-0.58 for IFN SVR]), whereas men were at 38%-42% lower risk (sHR 0.62 [95% CI 0.46-0.85 for DAA SVR] and 0.58 [95% CI 0.43-0.76 for IFN SVR]). IFN treatment failure significantly increased risk of all outcomes by 50%-100% among female patients. Compared with no treatment, female patients who experienced IFN treatment failure were at 63% increased risk of ACS (sHR 1.63 [95% CI 1.35-1.96]), almost twice the risk of ESRD (sHR 1.95 [95% CI 1.43-2.66]) and 51% increased risk of stroke (sHR 1.49 [95% CI 1.11-2.00]). **DISCUSSION:** SVR reduced the risk of extrahepatic complications, particularly in females. The significantly increased risk associated with IFN TF in women—a subset who represented roughly 10% of that group—underscores the importance of prioritizing these patients for DAA treatment irrespective of the fibrosis stage.

Public Health Sciences

Lu M, Li J, Zhou Y, Rupp LB, Moorman AC, Spradling PR, Teshale EH, Boscarino JA, Daida YG, Schmidt MA, Trudeau S, and Gordon SC. Trends in Cirrhosis and Mortality by Age, Sex, Race, and Antiviral Treatment Status Among US Chronic Hepatitis B Patients (2006-2016). *J Clin Gastroenterol* 2021; Epub ahead of print. PMID: 33780209. [Full Text](#)

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BACKGROUND: Changing US demographics and evolving chronic hepatitis B (CHB) treatments may affect longitudinal trends in CHB-related complications. We studied trends in the prevalence of cirrhosis (past or present) and incidence of all-cause mortality, stratified by patient age, sex, race, and antiviral treatment status, in a sample from US health care systems. **METHODS:** Joinpoint and Poisson regression (univariate and multivariable) were used to estimate the annual percent change in each outcome from 2006 to 2016. **RESULTS:** Among 5528 CHB patients, cirrhosis prevalence (including decompensated cirrhosis) rose from 6.7% in 2006 to 13.7% in 2016; overall mortality was unchanged. Overall rates of cirrhosis and mortality were higher among treated patients, but adjusted annual percent changes (aAPC) were significantly lower among treated than untreated patients (cirrhosis: aAPC +2.4% vs. +6.2%, mortality: aAPC -3.9% vs. +4.0%). Likewise, among treated patients, the aAPC for mortality declined -3.9% per year whereas among untreated patients, mortality increased +4.0% per year. **CONCLUSIONS:** From 2006 to 2016, the prevalence of cirrhosis among CHB patients doubled. Notably, all-cause mortality

increased among untreated patients but decreased among treated patients. These results suggest that antiviral treatment attenuates the progression of cirrhosis and the risk of death among patients with CHB.

Public Health Sciences

Rybicki BA, Sadasivan SM, Chen Y, Kravtsov O, Palangmonthip W, Arora K, Gupta NS, Williamson S, Bobbitt K, Chitale DA, Tang D, Rundle AG, and Iczkowski KA. Growth and differentiation factor 15 and NF- κ B expression in benign prostatic biopsies and risk of subsequent prostate cancer detection. *Cancer Med* 2021; Epub ahead of print. PMID: 33784024. [Full Text](#)

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Growth and differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine 1 (MIC-1), may act as both a tumor suppressor and promotor and, by regulating NF- κ B and macrophage signaling, promote early prostate carcinogenesis. To determine whether expression of these two inflammation-related proteins affect prostate cancer susceptibility, dual immunostaining of benign prostate biopsies for GDF-15 and NF- κ B was done in a study of 503 case-control pairs matched on date, age, and race, nested within a historical cohort of 10,478 men. GDF-15 and NF- κ B expression levels were positively correlated ($r = 0.39$; $p < 0.0001$), and both were significantly lower in African American (AA) compared with White men. In adjusted models that included both markers, the odds ratio (OR) for NF- κ B expression was statistically significant, OR =0.87; $p = 0.03$; 95% confidence interval (CI) =0.77-0.99, while GDF-15 expression was associated with a nominally increased risk, OR =1.06; $p = 0.27$; 95% CI =0.96-1.17. When modeling expression levels by quartiles, the highest quartile of NF- κ B expression was associated with almost a fifty percent reduction in prostate cancer risk (OR =0.51; $p = 0.03$; 95% CI =0.29-0.92). In stratified models, NF- κ B had the strongest negative association with prostate cancer in non-aggressive cases ($p = 0.03$), older men ($p = 0.03$), and in case-control pairs with longer follow-up ($p = 0.02$). Risk associated with GDF-15 expression was best fit using nonlinear regression modeling where both first ($p = 0.02$) and second ($p = 0.03$) order GDF-15 risk terms were associated with significantly increased risk. This modeling approach also revealed significantly increased risk associated with GDF-15 expression for subsamples defined by AA race, aggressive disease, younger age, and in case-control pairs with longer follow-up. Therefore, although positively correlated in benign prostatic biopsies, NF- κ B and GDF-15 expression appear to exert opposite effects on risk of prostate tumor development.

Public Health Sciences

Spradling PR, Zhong Y, Moorman AC, **Rupp LB, Lu M, Gordon SC**, Teshale EH, Schmidt MA, Daida YG, and Boscarino JA. Psychosocial Obstacles to Hepatitis C Treatment Initiation Among Patients in Care: A Hitch in the Cascade of Cure. *Hepatol Commun* 2021; 5(3):400-411. PMID: 33681675. [Full Text](#)

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There are limited data examining the relationship between psychosocial factors and receipt of direct-acting antiviral (DAA) treatment among patients with hepatitis C in large health care organizations in the United States. We therefore sought to determine whether such factors were associated with DAA initiation. We analyzed data from an extensive psychological, behavioral, and social survey (that incorporated several health-related quality of life assessments) coupled with clinical data from electronic health records of patients with hepatitis C enrolled at four health care organizations during 2017-2018. Of

2,681 patients invited, 1,051 (39.2%) responded to the survey; of 894 respondents eligible for analysis, 690 (77.2%) initiated DAAs. Mean follow-up among respondents was 9.2 years. Compared with DAA recipients, nonrecipients had significantly poorer standardized scores for depression, anxiety, and life-related stressors as well as poorer scores related to physical and mental function. Lower odds of DAA initiation in multivariable analysis (adjusted by age, race, sex, study site, payment provider, cirrhosis status, comorbidity status, and duration of follow-up) included Black race (adjusted odds ratio [aOR], 0.59 vs. White race), perceived difficulty getting medical care in the preceding year (aOR, 0.48 vs. no difficulty), recent injection drug use (aOR, 0.11 vs. none), alcohol use disorder (aOR, 0.58 vs. no alcohol use disorder), severe depression (aOR, 0.42 vs. no depression), recent homelessness (aOR, 0.36 vs. no homelessness), and recent incarceration (aOR, 0.34 vs. no incarceration). Conclusion: In addition to racial differences, compared with respondents who initiated DAAs, those who did not were more likely to have several psychological, behavioral, and social impairments. Psychosocial barriers to DAA initiation among patients in care should also be addressed to reduce hepatitis C-related morbidity and mortality.

Public Health Sciences

Suresh S, Siddiqui M, Abu Ghanimeh M, Jou J, Simmer S, Mendiratta V, Russell S, Al-Shammari M, Chatfield A, Alsheik E, Dang D, Genaw J, and Zuchelli T. Association of obesity with illness severity in hospitalized patients with COVID-19: A retrospective cohort study. *Obes Res Clin Pract* 2021; 15(2):172-176. PMID: 33653666. [Full Text](#)

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BACKGROUND: Although recent studies have shown an association between obesity and adverse coronavirus disease 2019 (COVID-19) patient outcomes, there is a paucity in large studies focusing on hospitalized patients. We aimed to analyze outcomes associated with obesity in a large cohort of hospitalized COVID-19 patients. **METHODS:** We performed a retrospective study at a tertiary care health system of adult patients with COVID-19 who were admitted between March 1 and April 30, 2020. Patients were stratified by body mass index (BMI) into obese (BMI \geq 30 kg/m²) and non-obese (BMI < 30 kg/m²) cohorts. Primary outcomes were mortality, intensive care unit (ICU) admission, intubation, and 30-day readmission. **RESULTS:** A total of 1983 patients were included of whom 1031 (51.9%) had obesity and 952 (48.9%) did not have obesity. Patients with obesity were younger ($P < 0.001$), more likely to be female ($P < 0.001$) and African American ($P < 0.001$) compared to patients without obesity. Multivariable logistic models adjusting for differences in age, sex, race, medical comorbidities, and treatment modalities revealed no difference in 60-day mortality and 30-day readmission between obese and non-obese groups. In these models, patients with obesity had increased odds of ICU admission (adjusted OR, 1.37; 95% CI, 1.07-1.76; $P = 0.012$) and intubation (adjusted OR, 1.37; 95% CI, 1.04-1.80; $P = 0.026$). **CONCLUSIONS:** Obesity in patients with COVID-19 is independently associated with increased risk for ICU admission and intubation. Recognizing that obesity impacts morbidity in this manner is crucial for appropriate management of COVID-19 patients.

Public Health Sciences

Teng H, Li C, Zhang Y, Lu M, Chopp M, Zhang ZG, Melcher-Mourgas M, and Fleckenstein B. Therapeutic effect of Cerebrolysin on reducing impaired cerebral endothelial cell permeability. *Neuroreport* 2021; 32(5):359-366. PMID: 33661804. [Full Text](#)

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Cerebrolysin has been shown to promote neurovascular protection and repair in preclinical models of stroke and neural injury and is demonstrating promise for stroke and neural injury therapeutic application in the clinic. The effect of Cerebrolysin on the human cerebral endothelial cell function has not been investigated. Using an in-vitro cerebral endothelial cell permeability assay and western blot analyses of tight junction and proinflammatory and procoagulant proteins, the present study showed that tissue plasminogen activator (tPA) and fibrin substantially impaired human cerebral endothelial cell barrier function and increased permeability, which persisted for at least 24 h. western blot analysis revealed that tPA and fibrin significantly increased proinflammatory and procoagulation proteins of intercellular adhesion molecule 1, high mobility group box 1, tumor necrosis factor α and phosphorylated nuclear factor kappa B-p65, and significantly reduced tight junction proteins zonular 1, occludin and claudin. However, Cerebrolysin significantly diminished and reversed tPA- and fibrin-impaired endothelial cell permeability, which was associated with significant reductions of tPA- and fibrin-augmented proinflammatory and procoagulation proteins and significant elevations of tPA- and fibrin-decreased tight junction proteins. The beneficial effect of Cerebrolysin appears specific because cerebroprotein hydrolysate, with a distinct peptide composition, failed to show the reduction of tPA- and fibrin-impaired permeability. These data indicate that cererbrolysin has a therapeutic effect on tPA- and fibrin-impaired cerebral endothelial cell permeability by reducing proinflammatory and procoagulation proteins and by elevating tight junction proteins.

Pulmonary and Critical Care Medicine

Chiu YW, Kao YH, **Simoff MJ**, Ost DE, Wagner O, Lavin J, Culbertson RA, and Smith DG. Costs of Biopsy and Complications in Patients with Lung Cancer. *Clinicoecon Outcomes Res* 2021; 13:191-200. PMID: 33762834. [Full Text](#)

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PURPOSE: To describe the distribution of diagnostic procedures, rates of complications, and total cost of biopsies for patients with lung cancer. **PATIENTS AND METHODS:** Observational study using data from IBM MarketScan(®) Databases for continuously insured adult patients with a primary lung cancer diagnosis and treatment between July 2013 and June 2017. Costs of lung cancer diagnosis covered 6 months prior to index biopsy through treatment. Costs of chest CT scans, biopsy, and post-procedural complications were estimated from total payments. Costs of biopsies incidental to inpatient admissions were estimated by comparable outpatient biopsies. **RESULTS:** The database included 22,870 patients who had a total of 37,160 biopsies, of which 16,009 (43.1%) were percutaneous, 14,997 (40.4%) bronchoscopic, 4072 (11.0%) surgical and 2082 (5.6%) mediastinoscopic. Multiple biopsies were performed on 41.9% of patients. The most common complications among patients receiving only one type of biopsy were pneumothorax (1304 patients, 8.4%), bleeding (744 patients, 4.8%) and intubation (400 patients, 2.6%). However, most complications did not require interventions that would add to costs. Median total costs were highest for inpatient surgical biopsies (\$29,988) and lowest for outpatient percutaneous biopsies (\$1028). Repeat biopsies of the same type increased costs by 40-80%. Complications account for 13% of total costs. **CONCLUSION:** Costs of biopsies to confirm lung cancer diagnosis vary substantially by type of biopsy and setting. Multiple biopsies, inpatient procedures and complications result in higher costs.

Pulmonary and Critical Care Medicine

Shakaroun D, Bhan A, and Ishani D. A rare case of lingual thyroid in a man. *Applied Radiology* 2021; 50(2):42-43. PMID: Not assigned. [Request Article](#)

Radiation Oncology

Barton KN, Siddiqui F, Pompa R, Freytag SO, Khan G, Dobrosotskaya I, Ajlouni M, Zhang Y, Cheng J, Movsas B, and Kwon D. Phase I trial of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for the treatment of metastatic pancreatic cancer. *Mol Ther Oncolytics* 2021; 20:94-104. PMID: 33575474. [Full Text](#)

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The safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL 12) gene therapy was evaluated in metastatic pancreatic cancer patients. In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTK(SR39) rep-hIL-12) expressing yCD/mutTK(SR39) (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL 12) was injected into tumors of 12 subjects with metastatic pancreatic cancer (T2N0M1-T4N1M1) at escalating doses (1×10^{11}), 3×10^{11} , or 1×10^{12} viral particles). Subjects received 5-fluorocytosine (5-FC) therapy for 7 days followed by chemotherapy (FOLFIRINOX or gemcitabine/albumin-bound paclitaxel) starting 21 days after adenovirus injection. The study endpoint was toxicity through day 21. Experimental endpoints included measurements of serum IL 12, interferon gamma (IFNG), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells and proliferation markers were analyzed by flow cytometry. Twelve patients received Ad5-yCD/mutTK(SR39) rep-hIL-12 and oral 5-FC. Approximately 94% of the 121 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTK(SR39) rep-hIL-12 DNA was detected in the blood of two patients. Elevated serum IL 12, IFNG, and CXCL10 levels were detected in 42%, 75%, and 92% of subjects, respectively. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTK(SR39) rep-hIL-12 administration. The median survival of patients in the third cohort is 18.1 (range, 3.5-20.0) months. The study maximum tolerated dose (MTD) was not reached.

Radiation Oncology

Glide-Hurst CK, Lee P, Yock AD, Olsen JR, Cao M, **Siddiqui F**, Parker W, **Doemer A**, Rong Y, Kishan AU, Benedict SH, Li XA, Erickson BA, Sohn JW, Xiao Y, and Wuthrick E. Adaptive Radiation Therapy (ART) Strategies and Technical Considerations: A State of the ART Review From NRG Oncology. *Int J Radiat Oncol Biol Phys* 2021; 109(4):1054-1075. PMID: 33470210. [Full Text](#)

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The integration of adaptive radiation therapy (ART), or modifying the treatment plan during the treatment course, is becoming more widely available in clinical practice. ART offers strong potential for minimizing treatment-related toxicity while escalating or de-escalating target doses based on the dose to organs at

risk. Yet, ART workflows add complexity into the radiation therapy planning and delivery process that may introduce additional uncertainties. This work sought to review presently available ART workflows and technological considerations such as image quality, deformable image registration, and dose accumulation. Quality assurance considerations for ART components and minimum recommendations are described. Personnel and workflow efficiency recommendations are provided, as is a summary of currently available clinical evidence supporting the implementation of ART. Finally, to guide future clinical trial protocols, an example ART physician directive and a physics template following standard NRG Oncology protocol is provided.

Radiation Oncology

Hathout L, Wang Y, Wang Q, Vergalaso I, **Elshaikh MA**, **Dimitrova I**, Damast S, Li JY, Fields EC, Beriwal S, Keller A, Kidd EA, Usov M, Jolly S, Jaworski E, Leung EW, Donovan E, Taunk NK, Chino J, Natesan D, Russo AL, Lea JS, Albuquerque KV, and Lee LJ. A Multi-Institutional Analysis of Adjuvant Chemotherapy and Radiation Sequence in Women with Stage IIIC Endometrial Cancer. *Int J Radiat Oncol Biol Phys* 2021; Epub ahead of print. PMID: 33677053. [Full Text](#)

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PURPOSE/OBJECTIVES: To evaluate the impact of sequence and type of adjuvant therapy for patients with stage IIIC endometrial carcinoma (EC) on outcomes. **MATERIALS/METHODS:** In a multi-institutional retrospective cohort study, patients with stage IIIC EC who had surgical staging and received both adjuvant chemotherapy and radiation treatment (RT) were included. Adjuvant treatment regimens were classified as: adjuvant chemotherapy followed by sequential RT (upfront chemo) which was predominant sequence, RT with concurrent chemotherapy followed by chemotherapy (concurrent), systemic chemotherapy before and after RT (sandwich), adjuvant RT followed by chemotherapy (upfront RT) or chemotherapy concurrent with vaginal cuff brachytherapy alone (chemo-brachy). Overall survival (OS) and recurrence-free survival (RFS) rates were estimated by Kaplan-Meier method. **RESULTS:** A total of 686 eligible patients were included with a median follow-up of 45.3 months. The estimated 5-year OS and RFS rates were 74% and 66%, respectively. The sequence and type of adjuvant therapy was not correlated with OS or RFS (adjusted $p=0.68$ and 0.84 , respectively). On multivariate analysis, black race, non-endometrioid histology, grade 3 tumor, stage IIIC2, presence of adnexal and cervical involvement were associated with worse OS and RFS (all $p<0.05$). Regardless of the sequence of treatment, the most common site of first recurrence was distant metastasis (20.1%). Vaginal only, pelvic only and para-aortic lymph node (PALN) recurrences occurred in 11 (1.6%), 15 (2.2%) and 43 (6.3%) patients, respectively. Brachytherapy alone was associated with a higher rate of PALN recurrence (15%) compared to External Beam Radiotherapy (EBRT) (5%) $p<0.0001$. **CONCLUSIONS:** The sequence and type of combined adjuvant therapy did not impact OS or RFS rates. Brachytherapy alone was associated with a higher rate

of PALN recurrence emphasizing the role of nodal radiation for stage IIIC EC. The vast proportion of recurrences were distant despite systemic chemotherapy, highlighting the need for novel regimens.

Research Administration

Kemp SB, Steele NG, Carpenter ES, Donahue KL, Bushnell GG, Morris AH, The S, Orbach SM, Sirihorachai VR, Nwosu ZC, Espinoza C, Lima F, Brown K, Girgis AA, Gunchick V, Zhang Y, Lyssiotis CA, Frankel TL, Bednar F, Rao A, Sahai V, Shea LD, **Crawford HC**, and Pasca di Magliano M. Pancreatic cancer is marked by complement-high blood monocytes and tumor-associated macrophages. *Life Sci Alliance* 2021; 4(6). PMID: 33782087. [Full Text](#)

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Pancreatic ductal adenocarcinoma (PDA) is accompanied by reprogramming of the local microenvironment, but changes at distal sites are poorly understood. We implanted biomaterial scaffolds, which act as an artificial premetastatic niche, into immunocompetent tumor-bearing and control mice, and identified a unique tumor-specific gene expression signature that includes high expression of C1qa, C1qb, Trem2, and Chil3. Single-cell RNA sequencing mapped these genes to two distinct macrophage populations in the scaffolds, one marked by elevated C1qa, C1qb, and Trem2, the other with high Chil3, Ly6c2 and Plac8. In mice, expression of these genes in the corresponding populations was elevated in tumor-associated macrophages compared with macrophages in the normal pancreas. We then analyzed single-cell RNA sequencing from patient samples, and determined expression of C1QA, C1QB, and TREM2 is elevated in human macrophages in primary tumors and liver metastases. Single-cell sequencing analysis of patient blood revealed a substantial enrichment of the same gene signature in monocytes. Taken together, our study identifies two distinct tumor-associated macrophage and monocyte populations that reflects systemic immune changes in pancreatic ductal adenocarcinoma patients.

Sleep Medicine

Greenwald MK, Moses TEH, and **Roehrs TA**. At the Intersection of Sleep Deficiency and Opioid Use: Mechanisms and Therapeutic Opportunities. *Transl Res* 2021; Epub ahead of print. PMID: 33711513. [Full Text](#)

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Due to the ongoing opioid epidemic, innovative scientific perspectives and approaches are urgently needed to reduce the unprecedented personal and societal burdens of nonmedical and recreational opioid use. One promising opportunity is to focus on the relationship between sleep deficiency and opioid use. In this review, we examine empirical evidence: (1) at the interface of sleep deficiency and opioid use, including hypothesized bidirectional associations between sleep efficiency and opioid abstinence; (2) as

to whether normalization of sleep deficiency might directly or indirectly improve opioid abstinence (and vice versa); and (3) regarding mechanisms that could link improvements in sleep to opioid abstinence. Based on available data, we identify candidate sleep-restorative therapeutic approaches that should be examined in rigorous clinical trials.

Sleep Medicine

Grivas P, Khaki AR, Wise-Draper TM, **Gadgeel SM, Hwang C, Singh SRK**, et al. Association of Clinical Factors and Recent Anti-Cancer Therapy with COVID-19 Severity among Patients with Cancer: A Report from the COVID-19 and Cancer Consortium. *Ann Oncol* 2021; Epub ahead of print. PMID: 33746047. [Full Text](#)

BACKGROUND: Patients with cancer may be at high risk of adverse outcomes from SARS-CoV-2 infection. We analyzed a cohort of patients with cancer and COVID-19 reported to the COVID-19 and Cancer Consortium (CCC19) to identify prognostic clinical factors, including laboratory measurements and anti-cancer therapies. **PATIENTS AND METHODS:** Patients with active or historical cancer and a laboratory-confirmed SARS-CoV-2 diagnosis recorded between March 17-November 18, 2020 were included. The primary outcome was COVID-19 severity measured on an ordinal scale (uncomplicated, hospitalized, admitted to intensive care unit, mechanically ventilated, died within 30 days). Multivariable regression models included demographics, cancer status, anti-cancer therapy and timing, COVID-19-directed therapies, and laboratory measurements (among hospitalized patients). **RESULTS:** 4,966 patients were included (median age 66 years, 51% female, 50% non-Hispanic white); 2,872 (58%) were hospitalized and 695 (14%) died; 61% had cancer that was present, diagnosed, or treated within the year prior to COVID-19 diagnosis. Older age, male sex, obesity, cardiovascular and pulmonary comorbidities, renal disease, diabetes mellitus, non-Hispanic Black race, Hispanic ethnicity, worse ECOG performance status, recent cytotoxic chemotherapy, and hematologic malignancy were associated with higher COVID-19 severity. Among hospitalized patients, low or high absolute lymphocyte count, high absolute neutrophil count, low platelet count, abnormal creatinine, troponin, LDH, and CRP were associated with higher COVID-19 severity. Patients diagnosed early in the COVID-19 pandemic (January-April 2020) had worse outcomes than those diagnosed later. Specific anti-cancer therapies (e.g. R-CHOP, platinum combined with etoposide, and DNA methyltransferase inhibitors) were associated with high 30-day all-cause mortality. **CONCLUSIONS:** Clinical factors (e.g. older age, hematological malignancy, recent chemotherapy) and laboratory measurements were associated with poor outcomes among patients with cancer and COVID-19. Although further studies are needed, caution may be required in utilizing particular anti-cancer therapies.

Sleep Medicine

Kalmbach DA, Cheng P, Roth T, Swanson LM, **Cuamatzi-Castelan A**, Roth A, and **Drake CL**. Examining Patient Feedback and the Role of Cognitive Arousal in Treatment Non-response to Digital Cognitive-behavioral Therapy for Insomnia during Pregnancy. *Behav Sleep Med* 2021; Epub ahead of print. PMID: 33719795. [Request Article](#)

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Objective: Insomnia affects over half of pregnant and postpartum women. Early evidence indicates that cognitive-behavioral therapy for insomnia (CBTI) improves maternal sleep and mood. However, standard CBTI may be less efficacious in perinatal women than the broader insomnia population. This study sought to identify patient characteristics in a perinatal sample associated with poor response to CBTI, and characterize patient feedback to identify areas of insomnia therapy to tailor for the perinatal experience. **Participants:** Secondary analysis of 46 pregnant women with insomnia symptoms who were treated with digital CBTI in a randomized controlled trial. **Methods:** We assessed insomnia, cognitive arousal, and depression before and after prenatal treatment, then 6 weeks postpartum. Patients provided feedback on digital CBTI. **Results:** Residual cognitive arousal after treatment was the most robust factor associated with treatment non-response. Critically, CBTI responders and non-responders differed on no other sociodemographic or pretreatment metrics. After childbirth, short sleep (<6 hrs/night) was associated with

maternal reports of poor infant sleep quality. Patient feedback indicated that most patients preferred online treatment to in-person treatment. Although women described digital CBTI as convenient and helpful, many patients indicated that insomnia therapy would be improved if it addressed sleep challenges unique to pregnancy and postpartum. Patients requested education on maternal and infant sleep, flexibility in behavioral sleep strategies, and guidance to manage infant sleep. Conclusions: Modifying insomnia therapy to better alleviate refractory cognitive arousal and address the changing needs of women as they progress through pregnancy and early parenting may increase efficacy for perinatal insomnia. Name: Insomnia and Rumination in Late Pregnancy and the Risk for Postpartum Depression URL: [clinicaltrials.gov/Registration: NCT03596879](https://clinicaltrials.gov/Registration/NCT03596879).

Surgery

Alvarez R, Stricklen A, Buda CM, Ross R, Bonham AJ, **Carlin AM**, Varban OA, Ghaferi AA, and Finks JF. Factors associated with completion of patient surveys 1 year after bariatric surgery. *Surg Obes Relat Dis* 2021; 17(3):538-547. PMID: 33334677. [Full Text](#)

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BACKGROUND: Patient-reported outcomes (PRO) obtained from follow-up survey data are essential to understanding the longitudinal effects of bariatric surgery. However, capturing data among patients who are well beyond the recovery period of surgery remains a challenge, and little is known about what factors may influence follow-up rates for PRO. **OBJECTIVES:** To assess the effect of hospital practices and surgical outcomes on patient survey completion rates at 1 year after bariatric surgery. **SETTING:** Prospective, statewide, bariatric-specific clinical registry. **METHODS:** Patients at hospitals participating in the Michigan Bariatric Surgery Collaborative are surveyed annually to obtain information on weight loss, medication use, satisfaction, body image, and quality of life following bariatric surgery. Hospital program coordinators were surveyed in June 2017 about their practices for ensuring survey completion among their patients. Hospitals were ranked based on 1-year patient survey completion rates between 2011 and 2015. Multivariable regression analyses were used to identify associations between hospital practices, as well as 30-day outcomes, on hospital survey completion rankings. **RESULTS:** Overall, patient survey completion rates at 1 year improved from 2011 (33.9% ± 14.5%) to 2015 (51.0% ± 13.0%), although there was wide variability between hospitals (21.1% versus 77.3% in 2015). Hospitals in the bottom quartile for survey completion rates had higher adjusted rates of 30-day severe complications (2.6% versus 1.7%, respectively; P = .0481), readmissions (5.0% versus 3.9%, respectively; P = .0157), and reoperations (1.5% versus .7%, respectively; P = .0216) than those in the top quartile. While most hospital practices did not significantly impact survey completion at 1 year, physically handing out surveys during clinic visits was independently associated with higher completion rates (odds ratio, 13.60; 95% confidence interval, 1.99-93.03; P = .0078). **CONCLUSIONS:** Hospitals vary considerably in completion rates of patient surveys at 1 year after bariatric surgery, and lower rates were associated with hospitals that had higher complication rates. Hospitals with the highest completion rates were more likely to physically hand surveys to patients during clinic visits. Given the value of PRO on longitudinal outcomes of bariatric surgery, improving data collection across multiple hospital systems is imperative.

Surgery

Barton KN, Siddiqui F, Pompa R, Freytag SO, Khan G, Dobrosotskaya I, Ajlouni M, Zhang Y, Cheng J, Movsas B, and Kwon D. Phase I trial of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for the treatment of metastatic pancreatic cancer. *Mol Ther Oncolytics* 2021; 20:94-104. PMID: 33575474. [Full Text](#)

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The safety of oncolytic adenovirus-mediated suicide and interleukin-12 (IL 12) gene therapy was evaluated in metastatic pancreatic cancer patients. In this phase I study, a replication-competent adenovirus (Ad5-yCD/mutTK(SR39) rep-hIL-12) expressing yCD/mutTK(SR39) (yeast cytidine deaminase/mutant S39R HSV-1 thymidine kinase) and human IL-12 (IL 12) was injected into tumors of 12 subjects with metastatic pancreatic cancer (T2N0M1-T4N1M1) at escalating doses (1×10^{11}), 3×10^{11} , or 1×10^{12} viral particles). Subjects received 5-fluorocytosine (5-FC) therapy for 7 days followed by chemotherapy (FOLFIRINOX or gemcitabine/albumin-bound paclitaxel) starting 21 days after adenovirus injection. The study endpoint was toxicity through day 21. Experimental endpoints included measurements of serum IL 12, interferon gamma (IFNG), and CXCL10 to assess immune system activation. Peripheral blood mononuclear cells and proliferation markers were analyzed by flow cytometry. Twelve patients received Ad5-yCD/mutTK(SR39) rep-hIL-12 and oral 5-FC. Approximately 94% of the 121 adverse events observed were grade 1/2 requiring no medical intervention. Ad5-yCD/mutTK(SR39) rep-hIL-12 DNA was detected in the blood of two patients. Elevated serum IL 12, IFNG, and CXCL10 levels were detected in 42%, 75%, and 92% of subjects, respectively. Analysis of immune cell populations indicated activation after Ad5-yCD/mutTK(SR39) rep-hIL-12 administration. The median survival of patients in the third cohort is 18.1 (range, 3.5-20.0) months. The study maximum tolerated dose (MTD) was not reached.

Surgery

Brescia AA, Deeb GM, Sang SLW, **Tanaka D**, Grossman PM, Sukul D, He C, Theurer PF, Clark M, Shannon FL, Chetcuti SJ, and Fukuhara S. Surgical Explantation of Transcatheter Aortic Valve Bioprostheses: A Statewide Experience. *Circ Cardiovasc Interv* 2021; Epub ahead of print. PMID: 33719506. [Full Text](#)

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BACKGROUND: Despite the rapid adoption of transcatheter aortic valve replacement (TAVR) since its initial approval in 2011, the frequency and outcomes of surgical explantation of TAVR devices (TAVR-explant) is poorly understood. **METHODS:** Patients undergoing TAVR-explant between January 2012 and June 2020 at 33 hospitals in Michigan were identified in the Society of Thoracic Surgeons Database and linked to index TAVR data from the Transcatheter Valve Therapy Registry through a statewide quality collaborative. The primary outcome was operative mortality. Indications for TAVR-explant, contraindications to redo TAVR, operative data, and outcomes were collected from Society of Thoracic Surgeons and Transcatheter Valve Therapy databases. Baseline Society of Thoracic Surgeons Predicted Risk of Mortality was compared between index TAVR and TAVR-explant. **RESULTS:** Twenty-four surgeons at 12 hospitals performed TAVR-explants in 46 patients (median age, 73). The frequency of TAVR-explant was 0.4%, and the number of explants increased annually. Median time to TAVR-explant was 139 days and among known device types explanted, most were self-expanding valves (29/41, 71%). Common indications for TAVR-explant were procedure-related failure (35%), paravalvular leak (28%), and need for other cardiac surgery (26%). Contraindications to redo TAVR included need for other

cardiac surgery (28%), unsuitable noncoronary anatomy (13%), coronary obstruction (11%), and endocarditis (11%). Overall, 65% (30/46) of patients underwent concomitant procedures, including aortic repair/replacement in 33% (n=15), mitral surgery in 22% (n=10), and coronary artery bypass grafting in 16% (n=7). The median Society of Thoracic Surgeons Predicted Risk of Mortality was 4.2% at index TAVR and 9.3% at TAVR-explant (P=0.001). Operative mortality was 20% (9/46) and 76% (35/46) of patients had in-hospital complications. Of patients alive at discharge, 37% (17/37) were discharged home and overall 3-month survival was 73±14%. **CONCLUSIONS:** TAVR-explant is rare but increasing, and its clinical impact is substantial. As the utilization of TAVR expands into younger and lower-risk patients, providers should consider the potential for future TAVR-explant during selection of an initial valve strategy.

Surgery

Ivanics T, Shubert CR, Muaddi H, Claasen M, Yoon P, Hansen BE, McCluskey SA, and Sapisochin G. Blood Cell Salvage and Autotransfusion Does Not Worsen Oncologic Outcomes Following Liver Transplantation with Incidental Hepatocellular Carcinoma: A Propensity Score-Matched Analysis. *Ann Surg Oncol* 2021; Epub ahead of print. PMID: 33778907. [Full Text](#)

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BACKGROUND: Intraoperative blood cell salvage and autotransfusion (IBSA) during liver transplantation (LT) for hepatocellular carcinoma (HCC) is controversial for concern regarding adversely impacting oncologic outcomes. **OBJECTIVE:** We aimed to evaluate the long-term oncologic outcomes of patients who underwent LT with incidentally discovered HCC who received IBSA compared with those who did not receive IBSA. **METHODS:** Patients undergoing LT (January 2001-October 2018) with incidental HCC on explant pathology were retrospectively identified. A 1:1 propensity score matching (PSM) was performed. HCC recurrence and patient survival were compared. Kaplan-Meier survival analyses were performed, and univariable Cox proportional hazard analyses were performed for risks of recurrence and death. **RESULTS:** Overall, 110 patients were identified (IBSA, n = 76 [69.1%]; non-IBSA, n = 34 [30.9%]). Before matching, the groups were similar in terms of demographics, transplant, and tumor characteristics. Overall survival was similar for IBSA and non-IBSA at 1, 3, and 5 years (96.0%, 88.4%, 83.0% vs. 97.1%, 91.1%, 87.8%, respectively; p = 0.79). Similarly, the recurrence rate at 1, 3, and 5 years was not statistically different (IBSA 0%, 1.8%, 1.8% vs. non-IBSA 0%, 3.2%, 3.2%, respectively; p = 0.55). After 1:1 matching (26 IBSA, 26 non-IBSA), Cox proportional hazard analysis demonstrated similar risk of death and recurrence between the groups (IBSA hazard ratio [HR] of death 1.26, 95% confidence interval [CI] 0.52-3.05, p = 0.61; and HR of recurrence 2.64, 95% CI 0.28-25.30, p = 0.40). **CONCLUSIONS:** IBSA does not appear to adversely impact oncologic outcomes in patients undergoing LT with incidental HCC. This evidence further supports the need for randomized trials evaluating the impact of IBSA use in LT for HCC.

Surgery

Jesse MT, Hansen B, Bruschein H, Chen G, Nonterah C, Peipert JD, Dew MA, Thomas C, Ortega AD, Balliet W, Ladin K, Lerret S, Yaldo A, Coco T, and Mallea J. Findings and recommendations from the organ transplant caregiver initiative: Moving clinical care and research forward. *Am J Transplant* 2021; 21(3):950-957. PMID: 32946643. [Full Text](#)

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Lay-caregivers are essential to the continuum of care in adult organ transplantation. However, we have a limited understanding of the experiences, exigencies, and outcomes associated with lay-caregiving for organ transplant patients. While much discussion and debate has focused on caregiver requirements in relation to transplant candidate selection, little focus has been given to understanding the needs of caregivers themselves. In response to this, the Organ Transplant Caregiver Initiative was created, and a meeting was held during October 6-7, 2019. Transplant healthcare professionals, researchers, and lay-caregivers discussed the experiences, educational needs, existing research, and research recommendations to improve the experience of lay-caregivers for adult organ transplant patients. In this report, we summarize the Organ Transplant Caregiver Initiative and meeting findings, providing a preliminary action plan to improve education, research, and advocacy for organ transplant caregivers.

Surgery

Lehrberg A, Davis MB, Baidoun F, Petersen L, Susick L, Jenkins B, Chen Y, Ivanics T, Rakitin I, Bensenhaver J, Proctor E, Nathanson SD, and Newman LA. Outcome of African-American compared to White-American patients with early-stage breast cancer, stratified by phenotype. *Breast J* 2021; Epub ahead of print. PMID: 33738890. [Full Text](#)

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BACKGROUND: Breast cancer mortality rates are 39% higher in the African-American (AA) women compared to White-American (WA) women despite the advances in overall breast cancer screening and treatments. Several studies have undertaken to identify the factors leading to this disparity in United States with possible effects of lower socioeconomic status and underlying aggressive biology. **METHODS:** A retrospective analysis was done using a prospectively maintained database of a metropolitan health system. Patients were selected based on diagnosis of early-stage breast cancer between 10/1998 and 02/2017, and included women over age of 18 with clinically node-negative disease. Patients were then stratified by phenotype confirmed by pathology and patient-identified race. **RESULTS:** A total of 2,298 women were identified in the cohort with 39% AA and 61% WA women. The overall mean age at the time of diagnosis for AA women was slightly younger at 60 years compared to 62 years for WA women ($p = 0.003$). Follow-up time was longer for the WA women at 95 months vs. 86 months in AA women. The overall 5-year survival was analyzed for the entire cohort, with the lowest survival occurring

in patients with triple-negative breast cancer (TNBC). Phenotype distribution revealed a higher incidence of TNBC in AA women compared to WA women (AA 16% vs. WA 10%; $p < 0.0001$). AA women also had higher incidence of HER2 positive cancers (AA 16.8% vs. WA 15.3%; $p < 0.0001$). WA women had a significantly higher distribution of Non-TNBC/HER2-negative phenotype (AA 55% vs. WA 65%; $p < 0.0001$). Furthermore, a subgroup analysis was done for a sentinel lymph node (SLN) negative cohort that showed higher rates of grade 3 tumors in AA (AA 35% vs. WA 23%; $p < 0.0001$); and higher rates of grade 1 and grade 2 tumors in WA (30% vs. 21% and 44% vs. 40%). Despite higher grade tumors in AA women, five-year overall survival outcomes in SLN-negative cohort did not differ between AA and WA women when stratifying based on tumor subtype. **CONCLUSION:** Breast cancer survival disparities in AA and WA women with SLN-negative breast cancer are diminished when evaluated at early-stage cancers defined by SLN-negative tumors. Our evaluation suggests that when diagnosed early, phenotype does not contribute to racial survival outcomes. The lower survival rate in AA women with breast cancer may be attributed to later stage biology between the two races, or underlying socioeconomic disparities.

Surgery

Suresh S, Siddiqui M, Abu Ghanimeh M, Jou J, Simmer S, Mendiratta V, Russell S, Al-Shammari M, Chatfield A, Alsheik E, Dang D, Genaw J, and Zuchelli T. Association of obesity with illness severity in hospitalized patients with COVID-19: A retrospective cohort study. *Obes Res Clin Pract* 2021; 15(2):172-176. PMID: 33653666. [Full Text](#)

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BACKGROUND: Although recent studies have shown an association between obesity and adverse coronavirus disease 2019 (COVID-19) patient outcomes, there is a paucity in large studies focusing on hospitalized patients. We aimed to analyze outcomes associated with obesity in a large cohort of hospitalized COVID-19 patients. **METHODS:** We performed a retrospective study at a tertiary care health system of adult patients with COVID-19 who were admitted between March 1 and April 30, 2020. Patients were stratified by body mass index (BMI) into obese (BMI ≥ 30 kg/m²) and non-obese (BMI < 30 kg/m²) cohorts. Primary outcomes were mortality, intensive care unit (ICU) admission, intubation, and 30-day readmission. **RESULTS:** A total of 1983 patients were included of whom 1031 (51.9%) had obesity and 952 (48.9%) did not have obesity. Patients with obesity were younger ($P < 0.001$), more likely to be female ($P < 0.001$) and African American ($P < 0.001$) compared to patients without obesity. Multivariable logistic models adjusting for differences in age, sex, race, medical comorbidities, and treatment modalities revealed no difference in 60-day mortality and 30-day readmission between obese and non-obese groups. In these models, patients with obesity had increased odds of ICU admission (adjusted OR, 1.37; 95% CI, 1.07-1.76; $P = 0.012$) and intubation (adjusted OR, 1.37; 95% CI, 1.04-1.80; $P = 0.026$). **CONCLUSIONS:** Obesity in patients with COVID-19 is independently associated with increased risk for ICU admission and intubation. Recognizing that obesity impacts morbidity in this manner is crucial for appropriate management of COVID-19 patients.

Undergraduate Medical Education

Battista EB, Yedulla NR, Koolmees DS, Montgomery ZA, Ravi K, and Day CS. Manufacturing Workers Have a Higher Incidence of Carpal Tunnel Syndrome. *J Occup Environ Med* 2021; 63(3):e120-e126. PMID: 33394876. [Full Text](#)

Henry Ford Health System, Detroit, Michigan (Dr Day); Wayne State University School of Medicine, Ann Arbor, MI (Mr Battista, Mr Yedulla, Mr Koolmees, Mr Montgomery, Dr Day); University of Michigan (Mr Ravi), Detroit, Michigan.

OBJECTIVE: It is unclear whether clerical or labor-type work is more associated with risk for developing work-related carpal tunnel syndrome (WrCTS). **METHODS:** National employment, demographic, and injury data were examined from the Bureau of Labor Statistics databases for the years 2003 to 2018. Injuries for clerical and labor industries were compared using linear regression, two-group t test, and one-way analysis of variance (ANOVA) analysis. **RESULTS:** WrCTS injuries are decreasing over time ($B = -1002.62$, $P < 0.001$). The labor industry demonstrated a significantly higher incidence of WrCTS when compared with the clerical industries ($P < 0.001$). Within labor industries, the manufacturing industry had the highest incidence of WrCTS over time ($P < 0.001$). **CONCLUSIONS:** Our study showed WrCTS injuries have declined over time. Additionally, our findings may suggest that the labor industry has a stronger association with WrCTS than the clerical industry.

Urology

Jiang T, Osadchiy V, Weinberger JM, Zheng MH, Owen MH, Leonard SA, Mills JN, **Kachroo N**, and Eleswarapu SV. Impact of the COVID-19 Pandemic on Patient Preferences and Decision Making for Symptomatic Urolithiasis. *J Endourol* 2021; Epub ahead of print. PMID: 33478351. [Full Text](#)

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Background: Pandemic restrictions have changed how patients approach symptomatic kidney stones. We used a mixed-methods digital ethnographic approach to evaluate social media discussions about patient concerns and preferences for urolithiasis care during the COVID-19 pandemic. **Materials and Methods:** We retrospectively analyzed kidney stone-related discussions on a large social media platform using qualitative analysis and natural language processing-based sentiment analysis. Posts were mined for demographic details, treatments pursued, and health care encounters. Pre-COVID-19 (January 1, 2020-February 29, 2020) and COVID-19 (March 1, 2020-June 1, 2020) posts were extracted from the popular online Reddit discussion board, "r/KidneyStones," which is dedicated to discussions related to urolithiasis. **Results:** We extracted $n = 649$ posts (250 pre-COVID-19, 399 COVID-19); 150 from each cohort underwent thematic analysis and data extraction. Quantitative sentiment analysis was performed on 418 posts (179 pre-COVID-19, 239 COVID-19) that described stone-related decision making before intervention. Notable discussion themes during COVID-19 focused on barriers to care and concerns about stone management. Discussants exhibited more negative and anxious tones during COVID-19, based on sentiment analysis ($p < 0.01$). Patient preferences shifted away from in-person visits and procedures ($p < 0.001$). Mean reported stone size among those visiting emergency room (ER) increased from 5.1 to 10.5 mm ($p < 0.001$). The proportion of discussants preferring conservative management with stones ≥ 10 mm increased (12.5% pre-COVID-19 vs 26% during COVID-19, $p = 0.002$). Opioid mentions increased from 9% to 27% of posts ($p < 0.001$) and were most associated with conservative management discussions. **Conclusions:** Online discussion forums provide contemporaneous insight into patients' experiences during a time when traditional patient-centered research methodologies are limited due to social distancing. During the pandemic, patients with symptomatic kidney stones expressed anxiety regarding outpatient encounters and reluctance toward procedural intervention. Patients opted instead for at-home conservative treatment beyond clinical guidelines and reserved ER visits for larger stones, potentially causing self-harm. Opioid discussions proliferated, an alarming consequence of the pandemic.

Urology

Veccia A, Carbonara U, Derweesh I, Mehrazin R, Porter J, **Abdollah F**, Mazzone E, Sundaram CP, Gonzalzo M, Mastroianni R, Ghoreifi A, Cacciamani GE, Patel D, **Marcus J, Danno A**, Steward J, Bhattu AS, Asghar A, Reese AC, Wu Z, Uzzo RG, Minervini A, Rha KH, Ferro M, Margulis V, Hampton LJ, Simone G, Eun DD, Djaladat H, Mottrie A, and Autorino R. Single stage Xi® robotic radical nephroureterectomy for upper tract urothelial carcinoma: surgical technique and outcomes. *Minerva Urol Nephrol* 2021; Epub ahead of print. PMID: 33781022. [Full Text](#)

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BACKGROUND: Radical nephroureterectomy (RNU) represents the standard of care for high grade upper tract urothelial carcinoma (UTUC). Open and laparoscopic approaches are well-established treatments, but evidence regarding robotic RNU is growing. The introduction of the Xi® system facilitates the implementation of this multi-quadrant procedure. The aim of this video-article is to describe the surgical steps and the outcomes of Xi® robotic RNU. **METHODS:** Single stage Xi® robotic RNU without patients repositioning and robot re-docking were done between 2015 and 2019 and collected in a large worldwide multi-institutional study, the ROBotic surgery for Upper tract Urothelial cancer Study (ROBUUST). Institutional review board approval and data share agreement were obtained at each center. Surgical technique is described in detail in the accompanying video. Descriptive statistics of baseline characteristics and surgical, pathological, and oncological outcomes were analyzed. **RESULTS:** Overall, 148 patients were included in the analysis; 14% had an ECOG >1 and 68.2% ASA ≥3. Median tumor dimension was 3.0 (IQR:2.0-4.2) cm and 34.5% showed hydronephrosis at diagnosis. Forty-eight% were cT1 tumors. Bladder cuff excision and lymph node dissection were performed in 96% and 38.1% of the procedures, respectively. Median operative time and estimated blood loss were 215.5 (IQR:160.5-290.0) minutes and 100.0 (IQR: 50.0-150.0) mL, respectively. Approximately 56% of patients took opioids during hospital stay for a total morphine equivalent dose of 22.9 (IQR:16.0-60.0) milligrams equivalent. Postoperative complications were 26 (17.7%), with 4 major (15.4%). Seven patients underwent adjuvant chemotherapy, with median number of cycles of 4.0 (IQR:3.0-6.0). **CONCLUSIONS:** Single stage Xi® RNU is a reproducible and safe minimally invasive procedure for treatment of UTUC. Additional potential advantages of the robot might be a wider implementation of LND with a minimally invasive approach.

Conference Abstracts

Dermatology

Bae JM, **Zubair R**, Ju HJ, **Kohli I**, Lee HN, Eun SH, **Lyons AB**, **Vellaichamy G**, Han TY, **Lim HW**, and **Hamzavi IH**. Development and validation of facial vitiligo area scoring index (F-VASI) using the fingertip unit. *Pigment Cell Melanoma Res* 2021; 34(2):436.

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Background: Facial involvement has often been evaluated separately in clinical trials, because facial involvement is not only the most critical factor in the patient's life, but also the area with the greatest response to treatment. However, no reliable measurement tools for facial vitiligo are available thus far. **Objective:** To develop and validate a practical instrument for assessing facial vitiligo. **Methods:** Facial Vitiligo Area Scoring Index (F-VASI) was measured as the sum of all fingertip units (FTUs) of each vitiligo lesion on the face. In the validation study, a total of 41 dermatologists evaluated photographs of 17 patients with facial vitiligo as F-VASI using the FTU twice at an interval of 2 weeks. **Results:** F-VASI showed remarkably high accuracy (concordance correlation coefficient: 0.937, smallest detectable change: 2.0 FTU) as well as high intra-rater reliability (intraclass correlation coefficient: 0.926) and inter-rater reliability (0.909). **Conclusion:** F-VASI is an accurate, reliable, and practical instrument for assessing the extent of facial involvement in vitiligo patients. It can be used alone to sensitively assess small scattered lesions on the face, as well as to complement the hand unit when performing VASI for generalized vitiligo.

Dermatology

Lebwohl MG, Worm M, **Stein Gold LF**, Bangert C, Schmid-Grendelmeier P, Khan T, Biswas P, DiBonaventura M, Chan G, Terry K, Valdez H, and Clibborn C. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: Results from the open-label run-in period of JADE REGIMEN. *Br J Dermatol* 2021; 184(3):e73-e74.

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Abrocitinib, an oral once-daily Janus kinase 1 selective inhibitor, administered as monotherapy at doses of 200 mg and 100 mg, was well tolerated and more effective than placebo in patients with moderate-to-severe atopic dermatitis (AD) after 12 weeks of treatment in two phase III clinical trials [JADE MONO-1 (NCT03349060) and JADE MONO-2 (NCT03575871)] and one phase IIb (NCT02780167) clinical trial. The efficacy and safety of abrocitinib in an induction maintenance paradigm has not been investigated. The objective of this study was to assess the short-term efficacy and safety of abrocitinib monotherapy in the open-label run-in period of the JADE REGIMEN study (NCT03627767). In JADE REGIMEN, patients aged ≥ 12 years with moderate-to-severe AD received abrocitinib monotherapy 200 mg for 12 weeks as part of an open-label run-in period before being randomly assigned 1 : 1 : 1 to receive abrocitinib 200 mg, abrocitinib 100 mg or placebo in a 40-week double-blind maintenance period. The analysis of efficacy in the run-in period was evaluated by measuring the proportion of patients who achieved an Investigator's Global Assessment (IGA) response of 'clear' (0) or 'almost clear' (1) with ≥ 2 - grade improvement, $\geq 75\%$ improvement in Eczema Area and Severity Index (EASI 75 response) and Peak Pruritus Numerical Rating Scale (PP-NRS) (used with permission of Regeneron Pharmaceuticals, Inc. and Sanofi) response with ≥ 4 -point improvement (PP-NRS4) at week 12. Patients who achieved IGA and EASI 75 responses during the 12-week run-in period (responders) were randomly assigned 1 : 1 : 1 to receive abrocitinib 200 mg, abrocitinib 100 mg or placebo during the 40-week maintenance period of the study; patients who did not reach this response threshold were considered nonresponders and completed the study at week 12. During the maintenance period, randomly assigned patients who experienced flares of AD (loss of $\geq 50\%$ of EASI response achieved at week 12 with an IGA score ≥ 2) entered a 12-week open-label rescue period. As part of the open-label period, 1233 patients [mean age 31.6 years; 20.0% (n = 246) aged < 18 years; male 55.5%; white 75.5%; moderate AD per IGA 59.1%; severe AD per IGA 40.9%; median EASI score 27.9; median Dermatology Quality of Life Index (DLQI) score 16.0; median Children's DLQI score 12.0] were treated with abrocitinib 200 mg once daily. A total of 120 patients (9.7%) discontinued before week 12, mostly because of adverse events [49 patients (4.0%)] and patient/parent/guardian withdrawal

[42 patients (3.4%)]. At week 12, 65.9% [95% confidence interval (CI) 63.3-68.6], 75.6% (95% CI 73.1-78.0) and 68.3% (95% CI 65.3-71.3) achieved IGA, EASI 75 and PP-NRS responses, respectively; 65.2% (95% CI 62.5-67.9) achieved both IGA and EASI 75 responses. In adolescents and adults, the week 12 response rates were 59.8% (95% CI 53.6-65.9) and 67.5% (95% CI 64.6-70.4) for IGA, 71.5% (95% CI 65.9- 77.2) and 76.6% (95% CI 73.9-79.2) for EASI 75, and 57.5% (95% CI 50.0-65.0) and 70.6% (95% CI 67.4-73.8) for PP-NRS4. During the run-in period, 820 patients (66.5%) reported AEs; 20 (1.6%) reported serious AEs, and 38 (3.1%) reported severe AEs. Overall, 798 patients (64.7%) were randomly assigned to the maintenance period at week 12. Abrocitinib monotherapy 200 mg was effective and well tolerated in adolescents and adults with moderate-to-severe AD during the 12-week run-in open-label period of JADE REGIMEN. These results support the efficacy and safety observed in the phase III JADE MONO-1 and JADE MONO-2 abrocitinib monotherapy clinical trials.

Diagnostic Radiology

Nypaver T, Miller D, Weaver M, Marin H, Lee A, Griffith B, Wang DD, and Kabbani L. Symptomatic Extracranial Carotid Disease in COVID-19 Patients Is Related to Thrombus Formation. *J Vasc Surg* 2021; 73(3):44-45.

Background: Coronavirus disease-2019 (COVID-19) has been associated with an acquired hypercoagulable condition. This study was undertaken to review the clinical manifestations of COVID-related symptomatic extracranial carotid artery disease (ECCAD) and compare the carotid plaque composition of symptomatic COVID patients to non-COVID symptomatic patients with ECCAD. Methods: All patients with neurologic manifestations attributed to ECCAD who had clinical diagnosis of COVID-19 were reviewed. The clinical presentation, outcome, and carotid plaque characteristics of all patients were reviewed, and compared to symptomatic ECCAD patients prior to the COVID era (Table). Plaque composition was determined by analysis of calcium volume (mm³) within the carotid lesion with computed tomography angiography (CTA) using VitreaCore (version 6.7.6001.1) with manual outlining of calcium within the carotid lesions. Results: Between the period of March 28 and April 12, 2020, seven patients with COVID-19 were admitted with cerebrovascular manifestations (all ischemic strokes) related to carotid bifurcation lesions. Five patients were documented to have COVID-19 by nasal polymerase chain reaction, and two were clinically diagnosed. Two patients had significant clot in the contralateral carotid (Fig). In six of the COVID patients (86%), their presenting symptom was the stroke, whereas one patient developed a stroke 24 hours after being admitted with respiratory symptoms. Three patients underwent procedural intervention: one with an open carotid thromboendarterectomy and two with macrovascular distal embolization, underwent percutaneous mechanical thrombectomy. The remaining four patients were treated with anticoagulation alone. Seven consecutive patients with strokes secondary to ECCAD were selected from the pre-COVID era for comparison (Fig). The calcium plaque volume was significantly lower in the COVID patients compared to non-COVID patients, 84 mm³ (mean) compared to 401 mm³ (mean) (P = .02). Conclusions: In COVID patients presenting with strokes and concomitant ipsilateral extracranial carotid lesions, there is more thrombus burden and less calcification than in typical carotid atherosclerotic lesions. This analysis reinforces that the underlying pathology of this COVID-related clinical entity is one of hypercoagulability.

Hematology-Oncology

Girard N, Bazhenova L, Minchom A, Ou S, **Gadgeel S**, Trigo J, Viteri S, Li G, Mahadevia P, Londhe A, Backenroth D, Li T, and Bauml JM. MA04.07 Comparative Clinical Outcomes for Patients with NSCLC Harboring EGFR Exon 20 Insertion Mutations and Common EGFR Mutations. *J Thorac Oncol* 2021; 16(3):S145-S146.

Introduction: Approximately 85–90% of the mutations seen in EGFR-mutant non-small cell lung cancers (NSCLCs) are common mutations (cEGFR), Exon 19 deletions and Exon 21 L858R. Up to 10% of EGFR-mutant NSCLC harbors Exon 20 insertion mutations (Exon20ins). We conducted a retrospective cohort study using real-world data to compare clinical outcomes between patients harboring Exon20ins and cEGFR. Methods: This retrospective cohort study included patients from the Flatiron Health database (1 January 2011 through 31 May 2020) who had advanced NSCLC. The objectives of the study were to assess the prognostic value of Exon20ins compared with cEGFR (start date of first-line therapy as the index date) and the effect of tyrosine kinase inhibitor (TKI) treatment between the groups (start date of

first TKI line as the index date). Analysis was stratified by line of TKI use. Endpoints included real-world overall survival (rwOS), progression-free survival (rwPFS), and time to next therapy (rwTTNT) and were analyzed using multivariable Cox proportional hazards model and summarized by Kaplan-Meier method. Results: Among 62,464 patients with advanced NSCLC, 181 with Exon20ins and 2833 with cEGFR met eligibility criteria. Population demographics between the groups were comparable with minor exceptions. With median 34-month follow-up, Exon20ins was associated with a 75% increased risk of death (adjusted hazard ratio [adjHR] of 1.75 [95%CI, 1.45–2.13]; $p < 0.0001$); median rwOS was 16.23 (95%CI, 11.04–19.38) for Exon20ins and 25.49 months (95%CI, 24.48–27.04) for cEGFR (Table). The estimated 5-year survival rate for Exon20ins is 8% compared with 19% for cEGFR. The predictive value of TKI treatment, stratified by line, was assessed in 76 Exon20ins and 2749 cEGFR patients who were treated with TKIs. With median 20.6-month follow-up, there was a 170% increase in risk of progression or death associated with Exon20ins (adjHR of 2.7 [95% CI, 2.06–3.55]; $p < 0.0001$); median rwPFS was 2.86 months (95%CI, 2.14–3.91) compared with 10.45 months (95%CI: 10.05–10.94) for cEGFR. Furthermore, there was a 170% increased risk of death (adjHR of 2.70 [95% CI, 2.04–3.57]; $p < 0.0001$) associated with Exon20ins; median rwOS was 7.46 months (95%CI, 5.45–13.34) for Exon20ins and 25.49 months (95%CI, 24.28–26.81) for cEGFR (Table). Conclusion: Patients with Exon20ins have a worse prognosis compared with patients with cEGFR. Furthermore, EGFR TKI treatment was substantially less effective for patients with Exon20ins, as the risk of disease progression and mortality was higher compared with patients with cEGFR. These findings highlight the need for new treatment options for Exon20ins. [Formula presented] Keywords: Exon20ins, Prognostic, Predictive

Hematology-Oncology

Spigel DR, Rodríguez-Abreu D, Cappuzzo F, Velcheti V, Ganti AK, Johnson D, Govindan R, Antonia S, Besse B, Altan M, Edelman M, Ramalingam S, Felip E, **Gadgeel S**, Juan-Vidal O, Gupta A, Currie S, Lin W, Tagliaferri M, and Reck M. P77.04 PROPEL: A Phase 1/2 Trial of Bempegaldesleukin (NKTR-214) Plus Pembrolizumab in Lung Cancer and other Advanced Solid Tumors. *J Thorac Oncol* 2021; 16(3):S636-S637.

Introduction: Checkpoint inhibitors (CPIs), are now part of standard treatment in many advanced solid tumors, including metastatic non-small cell lung cancer (NSCLC). However, novel, more effective CPI combinations are needed to broaden, deepen, and prolong responses, especially for patients with poor prognostic features or negative predictive clinical factors for CPI benefit, including programmed death-ligand 1-negative (PD-L1[-]) status. Bempegaldesleukin (BEMPEG; NKTR-214) is a first-in-class CD122-preferential interleukin-2 pathway agonist that directly activates and expands effector T cells and natural killer cells over immunosuppressive regulatory T cells. BEMPEG plus CPI combination has demonstrated promising efficacy and can convert PD-L1(-) tumors to PD-L1(+) in patients with various solid tumors.(1,2) Given the early efficacy data and favorable safety profile of BEMPEG plus nivolumab, PROPEL will evaluate the clinical benefit, safety and tolerability of BEMPEG combined with another CPI, pembrolizumab (PEMBRO). Here, we present the updated methodology and protocol for the enrolling PROPEL study.(3) Methods: This phase 1/2 multinational trial evaluates BEMPEG plus PEMBRO in patients with locally advanced or metastatic solid tumors. During dose escalation (US only), ~40 patients with various advanced solid tumors (first- and second-line melanoma, NSCLC, urothelial carcinoma, head and neck squamous cell carcinoma, and hepatocellular carcinoma; regardless of PD-L1 status) will be treated with escalating doses of BEMPEG plus PEMBRO according to a 3+3 or step-up design. During dose expansion (global), ~58 patients with previously untreated advanced or metastatic NSCLC will be enrolled, and stratified based on PD-L1 status (<1%, 1-49%, and >50% staining on tumor cells by immunohistochemistry [for France only, patients with PD-L1 ≤49% will be excluded]). The primary objectives of the dose escalation are to evaluate safety and tolerability and determine the maximum tolerated dose/recommended phase 2 dose for BEMPEG in combination with PEMBRO. The primary objective of the dose expansion is objective response rate (by RECIST 1.1) in first-line metastatic NSCLC. Enrollment is ongoing (NCT03138889). References: 1. Diab A, et al. *J Immunotherapy Canc* 2019;7(1 suppl):3006; 2. Siefker-Radtke A, et al. *J Clin Oncol* 2019;37(7 suppl):388; 3. Reck M, et al. Poster presented at ESMO 2019; Poster 127TiP. Keywords: Immunotherapy, Immune Checkpoint Inhibition

Hematology-Oncology

Wood C, Lopez G, Zhao L, Li M, Surya N, Patel S, Grogan M, Bertino E, Shields P, He K, Carbone D, Otterson G, Presley C, Pannecouk B, Kalemkerian G, Schneider B, **Gadgeel S**, Ramnath N, Owen D, and Qin A. P78.05 Patterns of irAE During First Line Pembrolizumab for NSCLC: Incidence, Risk Factors, and Impact on Clinical Outcome. *J Thorac Oncol* 2021; 16(3):S639-S640.

Introduction: Pembrolizumab monotherapy is the preferred treatment option for patients with stage IV non-small cell lung cancer (NSCLC) with programmed death-ligand 1 (PD-L1) tumor expression $\geq 50\%$ and no actionable driver mutations. There is little real world data on immune-related adverse events (irAEs) with first-line pembrolizumab. In this study, we aim to better understand irAE incidence, risk factors, and impact on clinical outcome in treatment naïve patients receiving first-line pembrolizumab therapy. Methods: We conducted a multicenter, retrospective study of patients with treatment-naïve NSCLC and a PD-L1 expression of $\geq 50\%$ treated with first line pembrolizumab monotherapy between June 2016 and January 2020. irAEs were determined by treating physician diagnosis and lack of alternative etiologies. Risk factors for irAE occurrence were determined using a logistic regression model. Overall survival (OS) was measured from the date of therapy initiation to death or the last point of follow-up. Survival was estimated by the Kaplan-Meier method. Cox proportional hazards were used to determine the association between irAE and OS while treating irAE as a time-dependent variable. $P < 0.05$ was considered significant. Results: In our cohort of 153 patients, the median age was 66 years old (range 41-90); 37% of patients were female, 76.4% of patients had adenocarcinoma, and 21.5% had squamous cell carcinoma. Median follow-up time was 12 months. irAEs occurred in 65 patients (42.4%) with 23 (15.1%) developing irAE CTCAE grade ≥ 3 . The most common high grade irAEs were pneumonitis (n=9), colitis (n=6), and hepatitis (n=2). Higher risk for irAE was associated with current tobacco use or cessation of tobacco use < 6 months prior to treatment start (odds ratio [OR] 2.27, 95% confidence interval [CI] 1.14-4.52, $P=0.02$), prior or concurrent radiation therapy (OR 2.03, 95 %CI 1.06-3.90, $P=0.03$), neutrophil-lymphocyte ratio (NLR) > 5 prior to starting therapy (OR 2.33, 95% CI 1.19-4.56, $P=0.01$), and longer course of pembrolizumab treatment (OR 1.039 per cycle, 95% CI 1.009-1.070, $p=0.011$). There was no difference in OS between patients who experienced low grade irAEs (< 3) and those who did not develop irAEs (HR=0.391, 95% CI 0.124-1.231, $p=0.1325$) while those who developed high grade irAEs (≥ 3) had worse OS (HR 2.419, 95% CI, 1.117-5.243, $p=0.021$). Of patients who developed any grade irAEs, those who discontinued pembrolizumab therapy after irAE were found to have worse OS than those who continued therapy (HR 3.178, 95% CI 1.14-8.83, $p=0.03$). Conclusion: Risk factors for the development of irAEs during first-line pembrolizumab included current or recent smoking status, NLR > 5 prior to treatment start, prior or concurrent radiation therapy, and longer exposure to therapy. Higher grade irAEs and those events leading to discontinuation were associated with worse OS, and no OS benefit was observed in patients with lower grade adverse events. Our study identifies patients at high risk for irAEs who may benefit from closer monitoring during therapy. The lack of survival benefit from irAE in NSCLC patients with high PD-L1 expression has not previously been reported and warrants further investigation. Keywords: Pembrolizumab, immune related adverse events, Non small cell lung cancer

Radiation Oncology

Higgins K, Hu C, Ross H, Jabbour S, Kozono D, Owonikoko T, **Movsas B**, Solberg T, Xiao C, Williams T, Welsh J, Simko J, Wang X, Mohindra N, Hsu C, Stinchcombe T, and Bradley J. P48.02 NRG Oncology/Alliance LU005: Chemoradiation vs. Chemoradiation Plus Atezolizumab in Limited Stage Small Cell Lung Cancer. *J Thorac Oncol* 2021; 16(3):S499-S500.

Introduction: Limited stage small cell lung cancer (LS-SCLC) is treated with standard of care platinum/etoposide (EP) and thoracic radiation therapy (TRT) with curative intent, however the majority of patients are not cured and median overall survival is approximately 30 months. Addition of atezolizumab to chemotherapy in extensive stage SCLC has improved progression free and overall survival in a non-curative setting leading to hope that addition of an immune checkpoint inhibitor to standard chemoradiotherapy could benefit LS-SCLC patients. LU005 is a randomized phase II/III trial of standard concurrent chemoradiation with or without atezolizumab for patients with LS-SCLC. Methods: Patients are randomly assigned in a 1:1 ratio to standard EP chemotherapy with concurrent TRT (45 Gy BID or 66 Gy QD) with or without atezolizumab beginning concurrently with TRT, and continued every 3 weeks for up to

12 months. Eligible patients have LS-SCLC, PS 0-2, adequate organ function, no concerning comorbidities (including no active autoimmune disease) and are eligible for TRT. Patients are randomized prior to their second cycle of EP and thoracic radiation begins with the second overall cycle of chemotherapy (first cycle of study therapy) in both treatment arms. Prophylactic cranial radiation (PCI) is recommended for patients who respond to treatment. The phase II/III primary endpoints are progression free (PFS) and overall survival (OS) respectively. Secondary endpoints include objective response rates, local and distant disease control, and quality of life/patient reported outcomes assessment. Translational science component includes blood and tissue based immune related assays. Results: This study activated in May 2019. 120 of 506 planned patients have been accrued as of 8/20/2020. Keywords: Limited stage small cell lung cancer, chemoradiation, atezolizumab

Surgery

Nypaver T, Miller D, Weaver M, Marin H, Lee A, Griffith B, Wang DD, and Kabbani L. Symptomatic Extracranial Carotid Disease in COVID-19 Patients Is Related to Thrombus Formation. *J Vasc Surg* 2021; 73(3):44-45.

Background: Coronavirus disease-2019 (COVID-19) has been associated with an acquired hypercoagulable condition. This study was undertaken to review the clinical manifestations of COVID-related symptomatic extracranial carotid artery disease (ECCAD) and compare the carotid plaque composition of symptomatic COVID patients to non-COVID symptomatic patients with ECCAD. Methods: All patients with neurologic manifestations attributed to ECCAD who had clinical diagnosis of COVID-19 were reviewed. The clinical presentation, outcome, and carotid plaque characteristics of all patients were reviewed, and compared to symptomatic ECCAD patients prior to the COVID era (Table). Plaque composition was determined by analysis of calcium volume (mm³) within the carotid lesion with computed tomography angiography (CTA) using VitreaCore (version 6.7.6001.1) with manual outlining of calcium within the carotid lesions. Results: Between the period of March 28 and April 12, 2020, seven patients with COVID-19 were admitted with cerebrovascular manifestations (all ischemic strokes) related to carotid bifurcation lesions. Five patients were documented to have COVID-19 by nasal polymerase chain reaction, and two were clinically diagnosed. Two patients had significant clot in the contralateral carotid (Fig). In six of the COVID patients (86%), their presenting symptom was the stroke, whereas one patient developed a stroke 24 hours after being admitted with respiratory symptoms. Three patients underwent procedural intervention: one with an open carotid thromboendarterectomy and two with macrovascular distal embolization, underwent percutaneous mechanical thrombectomy. The remaining four patients were treated with anticoagulation alone. Seven consecutive patients with strokes secondary to ECCAD were selected from the pre-COVID era for comparison (Fig). The calcium plaque volume was significantly lower in the COVID patients compared to non-COVID patients, 84 mm³ (mean) compared to 401 mm³ (mean) (P = .02). Conclusions: In COVID patients presenting with strokes and concomitant ipsilateral extracranial carotid lesions, there is more thrombus burden and less calcification than in typical carotid atherosclerotic lesions. This analysis reinforces that the underlying pathology of this COVID-related clinical entity is one of hypercoagulability.

HFHS Publications on COVID-19

Cardiology/Cardiovascular Research

Kerrigan DJ, Brawner CA, Ehrman JK, and Keteyian S. Cardiorespiratory Fitness Attenuates the Impact of Risk Factors Associated With COVID-19 Hospitalization. *Mayo Clin Proc* 2021; 96(3):822-823. PMID: 33673935. [Full Text](#)

Cardiology/Cardiovascular Research

Spertus JA, Birmingham MC, Butler J, Lingvay I, **Lanfear DE**, Abbate A, Kosiborod ML, Fawcett C, Burton P, Damaraju CV, Januzzi JL, and Whang J. Novel Trial Design: CHIEF-HF. *Circ Heart Fail* 2021; 14(3):e007767. PMID: 33724883. [Full Text](#)

Dermatology

Freeman EE, McMahon DE, Lipoff JB, Rosenbach M, Desai SR, Fassett M, French LE, **Lim HW**, Hruza GJ, and Fox LP. Cold and COVID: Recurrent Pernio during the COVID-19 Pandemic. *Br J Dermatol* 2021; Epub ahead of print. PMID: 33657646. [Full Text](#)

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Rozenstein A, **Griffith BD**, and Ruchman RB. Residency Match During the COVID-19 Pandemic: The Clear and Present Danger of the Remote Interview. *J Am Coll Radiol* 2021; 18(3 Pt A):438-441. PMID: 33129766. [Full Text](#)

Emergency Medicine

Illg Z, Muller G, Mueller M, Nippert J, and Allen B. Analysis of absolute lymphocyte count in patients with COVID-19. *Am J Emerg Med* 2021; 46:16-19. PMID: 33706251. [Full Text](#)

Gastroenterology

Suresh S, Siddiqui M, Abu Ghanimeh M, Jou J, Simmer S, Mendiratta V, Russell S, Al-Shammari M, Chatfield A, Alsheik E, Dang D, Genaw J, and Zuchelli T. Association of obesity with illness severity in hospitalized patients with COVID-19: A retrospective cohort study. *Obes Res Clin Pract* 2021; 15(2):172-176. PMID: 33653666. [Full Text](#)

Hematology-Oncology

Grivas P, Khaki AR, Wise-Draper TM, **Gadgeel SM, Hwang C, Singh SRK**, et al. Association of Clinical Factors and Recent Anti-Cancer Therapy with COVID-19 Severity among Patients with Cancer: A Report from the COVID-19 and Cancer Consortium. *Ann Oncol* 2021; Epub ahead of print. PMID: 33746047. [Full Text](#)

Infectious Diseases

Altibi AM, Pallavi B, Liaqat H, Slota AA, Sheth R, Al Jebbawi L, George ME, LeDuc A, Abdallah E, Russell LR, Jain S, Shirvanian N, Masri A, and Kak V. Characteristics and comparative clinical outcomes of prisoner versus non-prisoner populations hospitalized with COVID-19. *Sci Rep* 2021; 11(1):6488. PMID: 33753786. [Full Text](#)

Infectious Diseases

Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, Fadel R, Morrison A, Kenney RM, Alangaden G, Ramesh M, and Mor G. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics* 2021; Epub ahead of print. PMID: 33693506. [Full Text](#)

Internal Medicine

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Internal Medicine

Jiwani RA, and **Rehana RW**. Cough to Dyspnea to Acute Respiratory Distress Syndrome. *Am J Med Sci* 2021; 361(3):396-397. PMID: 33097195. [Full Text](#)

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Garcia de Mattos Barbosa M, Liu H, Huynh D, Shelley G, Keller ET, Emmer BT, Sherman EJ, Ginsburg D, Kennedy AA, Tai AW, Wobus CE, Mirabelli C, Lanigan TM, **Samaniego M**, Meng W, Rosenfeld AM, Luning Prak ET, Platt JL, and Cascalho M. IgV somatic mutation of human anti-SARS-CoV-2 monoclonal antibodies governs neutralization and breadth of reactivity. *JCI Insight* 2021; Epub ahead of print. PMID: 33769311. [Full Text](#)

Neurology

Aboul Nour H, **Affan M**, **Mohamed G**, **Mohamud A**, **Schultz L**, **Latack K**, **Brady M**, **Scozzari D**, Haddad Y, **Katramados A**, **Bou Chebl A**, and **Ramadan AR**. Impact of the COVID-19 Pandemic on Acute Stroke Care, Time Metrics, Outcomes, and Racial Disparities in a Southeast Michigan Health System. *J Stroke Cerebrovasc Dis* 2021; 30(6):105746. PMID: 33780695. [Full Text](#)

Neurology

Danoun OA, Zillgitt A, Hill C, Zutshi D, Harris D, Osman G, Marawar R, Rath S, Syed MJ, Affan M, **Schultz L**, and **Wasade VS**. Outcomes of seizures, status epilepticus, and EEG findings in critically ill patient with COVID-19. *Epilepsy Behav* 2021; 118:107923. PMID: 33770609. [Full Text](#)

Neurology

Nguyen TN, Haussen DC, Qureshi MM, **Chebl A**, et al. Decline in subarachnoid haemorrhage volumes associated with the first wave of the COVID-19 pandemic. *Stroke Vasc Neurol* 2021; Epub ahead of print. PMID: 33771936. [Full Text](#)

Pharmacy

Draghici S, Nguyen TM, Sonna LA, Ziraldo C, Vanciu R, **Fadel R**, **Morrison A**, **Kenney RM**, **Alangaden G**, **Ramesh M**, and Mor G. COVID-19: disease pathways and gene expression changes predict methylprednisolone can improve outcome in severe cases. *Bioinformatics* 2021; Epub ahead of print. PMID: 33693506. [Full Text](#)

Public Health Sciences

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Sleep Medicine

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Surgery

Nypaver T, Miller D, Weaver M, Marin H, Lee A, Griffith B, Wang DD, and Kabbani L. Symptomatic Extracranial Carotid Disease in COVID-19 Patients Is Related to Thrombus Formation. *J Vasc Surg* 2021; 73(3):44-45.

Surgery

Suresh S, Siddiqui M, Abu Ghanimeh M, Jou J, Simmer S, Mendiratta V, Russell S, Al-Shammari M, Chatfield A, Alsheik E, Dang D, Genaw J, and Zuchelli T. Association of obesity with illness severity in hospitalized patients with COVID-19: A retrospective cohort study. *Obes Res Clin Pract* 2021; 15(2):172-176. PMID: 33653666. [Full Text](#)

Urology

Jiang T, Osadchiy V, Weinberger JM, Zheng MH, Owen MH, Leonard SA, Mills JN, **Kachroo N**, and Eleswarapu SV. Impact of the COVID-19 Pandemic on Patient Preferences and Decision Making for Symptomatic Urolithiasis. *J Endourol* 2021; Epub ahead of print. PMID: 33478351. [Full Text](#)