

Fusion

A student-led research publication of the George Washington University School of Medicine and Health Sciences | Spring 2021, Volume XIV

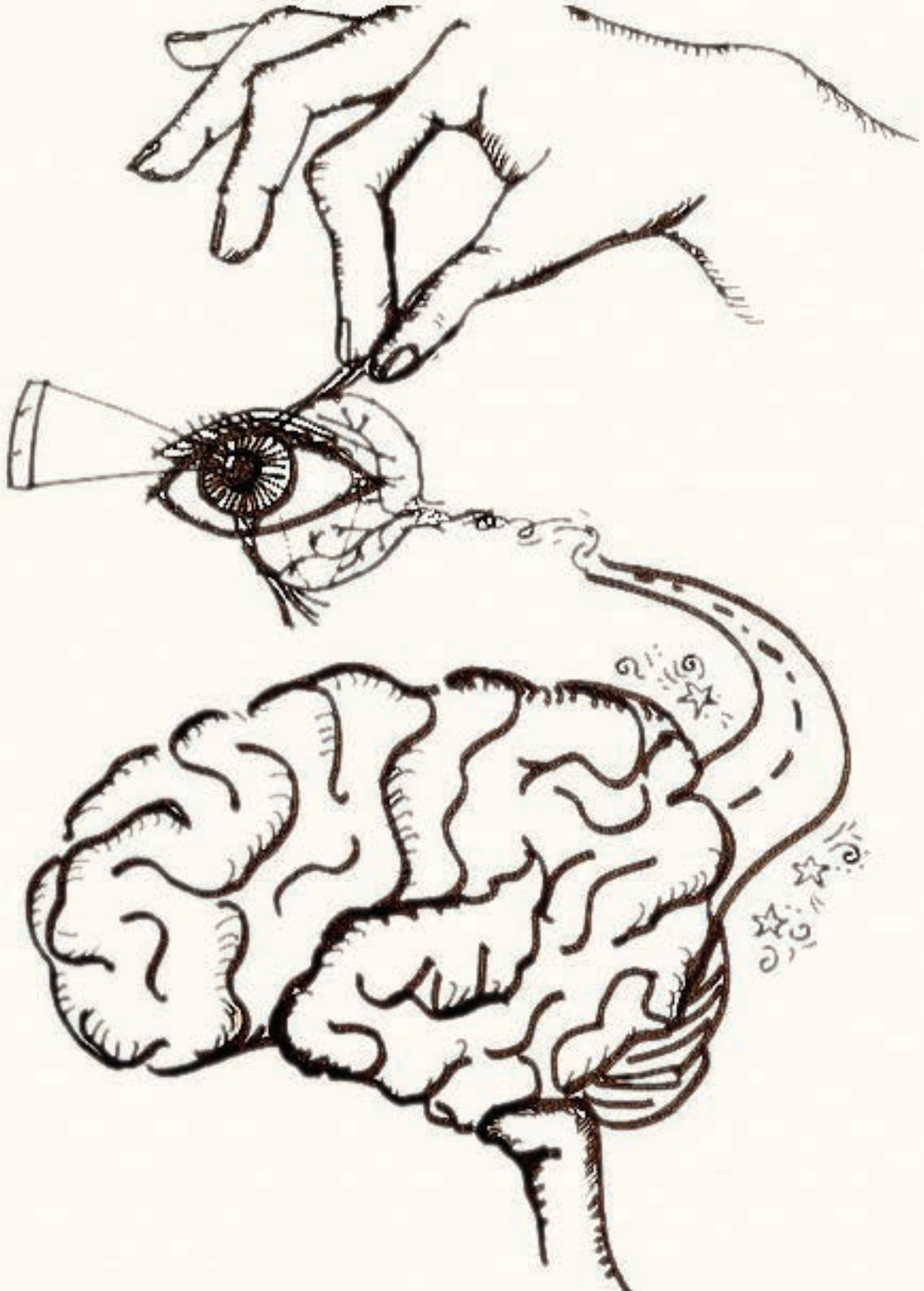


Table of Contents:

WILLIAM H. BEAUMONT RESEARCH PRIZE WINNERS

The William Beaumont Research Awards are given to three students for outstanding research accomplishments from work submitted for publication in Fusion, the student-run research magazine at GW School of Medicine and Health Sciences.

The recipients of the 2021 William Beaumont Research Awards are:

- **El Shatnofy, Muhammad:** Variations in PIEZO1 rs62048221 Associated with Strength and Anthropometric Measures in Young Adults, **p. 8**
- **Ganguli, Sangrag:** Screening for Small Molecule Modulators of RIG-I and MDA5 Using a Functional and Biochemical Assay, **p. 10**
- **Ali, Issa:** Predicting Deletion of Chromosomal Arms 1p/19q in Low-Grade Gliomas from MR Images using Machine Intelligence, **p. 33**

BASIC SCIENCE

Chiu, Anthony: CRISP-View: A Database of Functional Genetic Screens Spanning Multiple Phenotypes. p. 7

El Shatnofy, Muhammad: Variations in PIEZO1 rs62048221 Associated with Strength and Anthropometric Measures in Young Adults. ... p. 8

Falk, Zachary: Reproducibility of RNA-Seq Methods in Evaluating Blood RNA Biomarkers of Coronary Artery Disease. p. 9

Ganguli, Sangrag: Screening for Small Molecule Modulators of RIG-I and MDA5 Using a Functional and Biochemical Assay. p. 10

Pertsovskaya, Vera: Environmental Enrichment Promotes Developmental Myelination Through Adulthood. p. 12

Shancer, Zoë: SARS-CoV-2 Specific T-cell Epitopes and in Silico HLA Restriction Predictions. p. 14

CLINICAL PRACTICE INNOVATION, PUBLIC HEALTH, AND HEALTH POLICY

Green, Clare K.: The Association of H-Index and Academic Rank among Full-Time Academic Orthopaedic Trauma Surgeons Affiliated with Fellowship Programs. p. 16

Green, Clare K.: Variation in State and Federal Reimbursement in the Treatment of Upper Extremity Fractures. p. 18

Kolodner, Rebecca: Qualitative Experiences of Person-centered Maternity Care among Mexican and Chinese Immigrants in California. p. 20

Levy, Bennett R.: Economic Impact of Thrombectomy: Relationship of Socioeconomic Disparities with Timely Access to Stroke Care. p. 22

Liu, Matthew: The Development of a Global Health Dermatologic Surgery Training Program in Durban, South Africa. p. 24

Metri, Samer and Calabria, Emily: Medical Cannabis Education Among Health Care Trainees: A Scoping Review. p. 26

Tovar, Matthew A. and Pita, Mario A.: Mapping the Road to Intervention: A Systematic Review of Homeless Health Care Research. p. 27

Tovar, Matthew A.: Characterizing Injury Patterns of Casualties in Bombings Related to Terrorism in the Military and Civilian Populations. p. 29

Yeroushalmi, Samuel: Consumer Attitudes and Behaviors on Medical Cannabis in Dermatology. p. 31

Yeroushalmi, Samuel: Patient Experiences with Teledermatology during the COVID-19 Pandemic: A Survey. p. 32

Fusion

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ON THE COVER: Illustration by Dara Baker, MD '21, who received an NIH Medical Student Research program fellowship to support her research and matched at the University of Illinois Eye and Ear Infirmary for ophthalmology.

CLINICAL RESEARCH | ONCOLOGY

Ali, Issa: Predicting Deletion of Chromosomal Arms 1p/19q in Low-Grade Gliomas from MR Images Using Machine Intelligence. p. 33

Chalif, Eric J.: Malignant Pineal Parenchymal Tumors in Adults: A National Cancer Database Analysis. p. 34

Fu, Melinda: Impact of Varian Histology on Occult Nodal Metastasis after Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Review of the National Cancer Database. p. 36

Pelaez, Guido David: Evaluation of Selective HDAC6 Inhibition as a Potentiator of Antigen-Targeted Immunotherapy in Diffuse Large B-Cell Lymphoma. p. 38

Reddy, Akshay: The Impact of Adjuvant Chemotherapy on Oncologic Outcomes of Patients with Locally Advanced Bladder Adenocarcinoma: An Analysis of the National Cancer Database. p. 40

Wynne, Michael: Comparison of Perioperative Characteristics and Outcomes for Minimally Invasive vs Open Retroperitoneal Lymph Node Dissection for the Treatment of Testicular Cancer: A NSQIP Analysis. p. 41

CLINICAL RESEARCH | SURGERY AND ANESTHESIA

Adams-Mardi, Cyrus P.: Robotic-Assisted Laparoscopic Approach to Radical Cystectomy Mitigates Surgical Complications in Patients with Preoperative Malnutrition. p. 43

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Ceneri, Nicolle: A Contemporary Analysis: Presenting Symptoms in Patients with a Vascular Ring and Predictors of Symptom Resolution After Surgical Repair p. 44

Ceneri, Nicolle: Cardiovascular Surgical Outcomes of Patients with Heterotaxy Syndrome and Predictors of Mortality in the Current Era p. 46

Cho, Kevin and Shah, Aribah: Is Epidural Analgesia Necessary for Unilateral Hip Reconstruction in Children with Neuromuscular Conditions? p. 47

Crowder, Hannah R.: Facial Nerve Dysfunction after Mandibular Distraction Osteogenesis for Robin Sequence p. 48

Martinez, Paul F.: Radiosurgery for Brain Metastases from Ovarian Cancer: An Analysis of 25 Years' Experience with Gamma Knife Treatment p. 49

Pat, Vivien: A Retrospective Analysis of Trigger Point Injections in the Management of Post-surgical Pain in Patients Who Had Anterior Cervical Surgery p. 51

Rashid, Waleed: Masculinized Male Chest Contouring: Creating the Armor Plate p. 52

Ricotti, Robert: Increased Complication Rates in Octogenarians Undergoing Same-Day Discharge Following Total Knee Arthroplasty: A Matched Cohort Analysis. p. 54

Shah, Aribah and Cho, Kevin: Evaluating Postoperative Immobilization Following Hip Reconstruction in Children with Neuromuscular Conditions. p. 55

CLINICAL RESEARCH | EMERGENCY MEDICINE AND CRITICAL CARE

Burke, Morgan: Pediatric Transfusion-Associated Hyperkalemic Cardiac Arrest p. 57

Iyer, Sneha: Autonomic Tone in Preterm Infants Correlates with Morbidity of Prematurity p. 58

Keswani, Meghana: Deadly Duo: A Curious Case of Cardiogenic Shock p. 59

Newton, Sophia: Factors Associated with Clinical Severity in Emergency Department Patients Presenting with Symptomatic SARS-CoV-2 Infection p. 61.

Quan, Theodore: Utilization of Quinolones in the Emergency Department, 2005-15 p. 62

Ratnaseelan, Aarane: Determining Whether an Individual's Age or Comorbidities is Superior in Predicting Mortality in COVID-19 Patients p. 63

Jett, Alex; Marcinkowski, Bridget; and Srinivasa, Nandan: Evaluation of Thromboelastography in Patients with Gastrointestinal Bleeding p. 64

CLINICAL RESEARCH | OTHER

Khilnani, Aneka: Retrospective Review Characterizing the CNH Vulvar Dermatology Clinic p. 66

Baker, Dara: Topical DUREZOL® (difluprednate ophthalmic emulsion) 0.05% Challenge Prior to IntraVitreous Administration of Corticosteroid Analogues – DIVCA p. 67

Dobbs, Wyn: The Role of Regulatory T-Cells in Exercise-Induced Exacerbation in Chikungunya Arthritis Patients p. 68

Fierbaugh, Paige A.: Treatment Rate of Methotrexate vs Medicinal Plants or Alternative Medicine Therapies for Patients with Chronic Arthritis After Chikungunya p. 69

Gupta, Vrinda: Pregnancy and Child Outcomes Following Fetal Intracranial Hemorrhage p. 70

Gupta, Puneet: Residual Gastric Volume Prior to Bedside Percutaneous Endoscopic Gastrostomy Tube Placement: Do We Need to Hold Tube Feeds Prior to Peg Tube Placement? p. 72

Kallik, Christina: Association of Medication Mismanagement with Hospital-Related Complications in Patients with Parkinson's Disease p. 74

Manjunath, Jaya: Atopic Dermatitis is Associated with Multiple Behavioral Problems in United States Children p. 76

Shwe, Wendy: Agenesis of the Corpus Callosum: A Retrospective Study on Fetal and Postnatal Outcomes p. 77

Vaziri, Tina: Increased Caspase-1 Activation in the Setting of COVID-19 Disease p. 78

TRANSLATIONAL RESEARCH

Herur-Raman, Aalap: An Anatomical Study of the Foramen of Monro: Implications in Management of Pineal Tumors Presenting with Hydrocephalus p. 80

GW MEDICAL STUDENT RESEARCH



MEDICAL STUDENT RESEARCH OPPORTUNITIES

A number of competitive scholarship programs are available to assist in funding exceptional projects in health care and medicine, including diversity targeted fellowships, the Jean L. Fourcroy M.D. Research Award, Health Services Scholarships, the Lazarus Family Scholarship Program, and the WT Gill Fellowship, among others.

In 2020, 22 students won a Gill Summer Research Fellowship and 65 students received a Health Services Scholarship, which are internally funded programs that provide stipend support for medical student research in the summer.

For a list of SMHS student research funding opportunities, timelines, and application tips visit the website smhs.gwu.edu/research/research-workforce/medical-student-research/medical-student-funding-opportunities.

CHAUDHRY RECEIVES 2020 SPECK AWARD



The 2020 recipient of the recipient of the annual Doris DeFord Speck, BA '41, and George Speck, MD '41 Endowed Prize for outstanding accomplishments in medical student research was **Sharjeel Chaudhry, MD '20**. Chaudhry demonstrated an exceptional record of research accomplishment throughout his years at medical school. Chaudhry also received the prestigious Sarnoff Cardiovascular

Fellowship, which supported his research on the role of coagulation factor XII in arterial clot formation at Beth Israel Deaconess Medical Center under the mentorship of Robert Flaumenhaft. This work led to several first author and co-author publications, presentations at national meetings, and supported the award of an additional \$1 million dollars in funding from Bayer Pharmaceutical.

ALMEIDA RECEIVES AMERICAN BRAIN TUMOR ASSOCIATION FELLOWSHIP

Neil Almeida, MSIV, earned a competitive fellowship from the American Brain Tumor Association, and the Carolyn Kuckein student fellowship from the Alpha

Omega Alpha honor society in support of his research. He also received a Beaumont Research Award for outstanding research accomplishments



Neil Almeida, MSIV

METEOR PROGRAM

The Mentored Experience to Expand Opportunities in Research (METEOR) program is a competitive fellowship for underrepresented-in-medicine students. For more information, visit the website smhs.gwu.edu/academics/md-program/admissions/METEOR.

Research plans were extensively disrupted this year due to the COVID-19 epidemic. However, medical students demonstrated considerable ingenuity and flexibility in modifying plans to involve research goals that could be accomplished remotely. In addition, as shown in this photo of students participating in collecting samples for laboratory testing, medical students were extensively involved in community outreach and support to Washington, D.C., residents affected by the epidemic.



ASH MINORITY MEDICAL STUDENT AWARD

Guido Pelaez, MSIII, a recipient of a fellowship from the METEOR program, will have a chance to build on his passion for research after being chosen for the American Society of Hematology (ASH) 2020 Minority Medical



Guido Pelaez, MSIII

Student Award Program. Pelaez is investigating ways to improve antibody-directed immunotherapy in B-cell lymphoproliferative disease under the supervision of Alejandro Villagra, PhD, assistant professor of biochemistry and molecular medicine at SMHS and a researcher in the GW Cancer Center, and Christopher Hourigan, MD, DPhil, an investigator at the National Institutes of Health.

WALTER FREEMAN RESEARCH WINNER

Keirsten Snyder, MD '20, won the 2020 recipient of the Walter Freeman award. The annual award is given to the graduating senior who submits the best scientific paper based on original research.

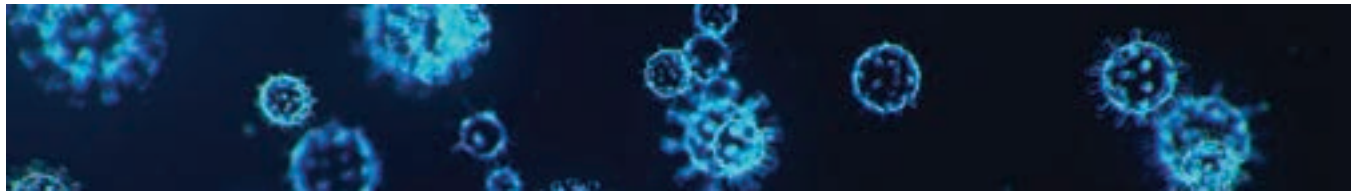


Keirsten Snyder, MD '20



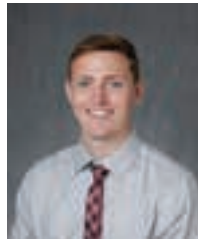
WT GILL FELLOW

Noor Diab, MSII, BS '19, won the 2020 WT Gill Fellowship to continue her research on the epigenetic regulation of cancer pathogenesis, under the mentorship of Katherine Chiappinelli, PhD, assistant professor of microbiology, immunology, and tropical medicine. This work was initiated while Diab was an undergraduate at GW and the picture (on left) above shows her in the lab prior to COVID-19 masking precautions.

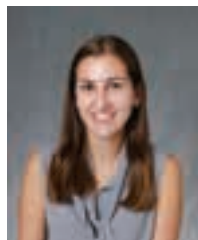


Beaumont Society President's Letter

In an effort to highlight some of the impressive work undertaken by medical students at The George Washington University (GW) School of Medicine and Health Sciences (SMHS), we, the co-presidents of the William H. Beaumont Medical Research Honor Society, proudly present the 2021 edition of *Fusion*. The official research journal of the GW SMHS, *Fusion* is a student-led publication that aims to circulate the research achievements of GW medical students to provide a forum to communicate their findings and also to illustrate the broad spectrum of research conducted at GW. This edition received over 50 submissions for publication, which far surpasses the previous record high for a single year, which is a testament to student engagement and a burgeoning research environment at our institutions. We believe that the rich diversity of opportunities in



Zachary Falk, MSII



Zoe Shancer, MSII

research offered at GW is reflected in the various disciplines represented in this edition, which include work in basic science, clinical medicine, translational research, medical education, public health, and health policy.

This year especially, we are humbled and inspired by the efforts of our SMHS colleagues, who not only navigated the typical challenges in conducting research but also had to contend with the COVID-19 pandemic that has so greatly affected us all. Abstracts were submitted from students of each of the four MD classes and several submissions directly investigated the impact of COVID-19 on clinical practice, which demonstrates the flexibility and determination of both the students and their principal investigators in adapting to the rapidly evolving research landscape and producing quality work that will benefit our society.

While we are disappointed that 2020 forced us to miss the in person interactions of last spring's Medical Student Research Day, which was changed to an on-line format, we are pleased that Beaumont was able to adapt and remotely deliver our workshop talk series for the first year class and plan to develop 2021 Medical Research Day into an interactive and virtual format. These outlets are essential to the development and

refinement of research skills for members of all classes and we are delighted to play a role in this process. It is clear that in recent years, the trajectory of student involvement in research has decidedly increased, which is strong evidence that GW is committed to providing opportunities for its students and cementing its reputation as a university entrenched in investigation and discovery.

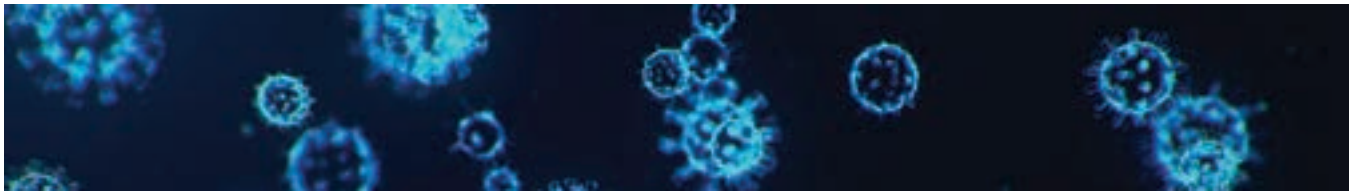
We would like to thank our mentors, especially our faculty advisor David Leitenberg, MD, PhD, associate professor of microbiology, immunology, and tropical medicine at the GW SMHS, and medical director of flow cytometry and immunology at Children's National Hospital, and Thomas Kohout, director of publications at GW SMHS, for their guidance and assistance with this publication. We would also like to thank the *Fusion* co-leaders and editorial board members (listed in the table of contents) for their contributions to this work.

We hope you enjoy reading this edition of *Fusion* and that you will consider contributing to the journal next year!

Zachary Falk and Zoe Shancer

Co-Presidents, William H. Beaumont Medical Research Honor Society





Letter from the Editors

As future clinicians, we have a responsibility not only to our patients but also in our significant contributions to the advancement of science and development of scientific thinking. Without scientific research, the crucial link between our modern knowledge of medicine and the intricacies of patient care would simply not exist. Here at the George Washington University (GW) School of Medicine and Health Sciences (SMHS), research plays an everyday role in the lives of our students as they work to improve health care in numerous ways, all while moving one step closer to solidifying their own careers as future physician-scientists.

As co-directors of the Fusion Editorial Board, we are pleased to present the 2021 edition of Fusion, a student-run research publication that highlights the diversity of research conducted by our very own medical students at GW SMHS. The



Alice Chen, MSI



Isabel Park, MSI

articles presented in this journal span a wide range of research disciplines, including basic science, clinical medicine, public health, among others. As a research journal, Fusion's primary goal is to provide an outlet through which students have the opportunity to proudly showcase their research to their peers and the general GW community. Beyond that, Fusion aims to fulfill the goals of the broader William H. Beaumont Medical Research Honor Society, which serves as a forum for students to learn about peer research and share research experiences with one another. This year, the top Fusion abstracts were selected to receive the prestigious William Beaumont Research Award and present their research at GW Medical Student Research Day held in May. This initiative is designed to further exemplify the accomplishments of our students and represent their commitment to advancing the health care field in different areas of focus.

The breadth and depth of student research evident in our quality abstract submissions speaks to the diverse interests of GW medical students, and we hope readers become inspired to develop research interests of their own and join the flourishing GW SMHS research community in the near future. We also hope that

this journal initiates more discourse surrounding the importance of novel translational and clinical research and its impact on health care overall.

This edition would not have been made possible without the collective help and support of several distinguished people. We would like to give special thanks to our mentor David Leitenberg, MD, PhD, associate professor of microbiology, immunology, and tropical medicine at the GW SMHS, and medical director of flow cytometry and immunology at Children's National Hospital, for his guidance as senior researcher and advisor of Fusion. We would also like to thank Thomas Kohout, director of publications at GW, SMHS, and Beaumont Society Co-Presidents Zachary Falk and Zoe Shancer, for their continued support and involvement with the publication of this edition. We are grateful to the Editorial Board members (listed on the Table of Contents) for their efforts and contributions to the journal.

We hope you enjoy this edition of Fusion. We encourage you to contribute to the journal in our next issue!

Co-Directors:

Alice Chen, MSI

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David Leitenberg MD, PhD, associate professor of microbiology, immunology, and tropical medicine at SMHS, and medical director of flow cytometry and immunology at Children's National Hospital

Performance Inspite of the Pandemic

To say it has been a challenging year is an understatement. The COVID-19 pandemic affected our personal and professional lives in a myriad of ways. This was especially true of our medical students pursuing research activities. Because of COVID-19-related restrictions on student access to laboratory and clinical facilities, as well as changes in clinical practice which affected patient participation in clinical trials, carefully considered research plans were significantly affected if not disrupted all together.

In light of these challenges, I am very proud of the research accomplishments described in this year's edition of *Fusion*. Students demonstrated remarkable flexibility and adapted to COVID-19-related restrictions on research activity by focusing on what was feasible and changing plans accordingly. For example, students developed new skills in informatics and applied that to the development and statistical analysis of clinical data-bases as well as to the analysis of genomic and proteomic data. I was particularly struck by how our students responded to the pandemic by participating in COVID-19-related community health efforts combined with COVID-19-related research. Several of our students were instrumental in developing databases to

collect clinical and laboratory information related to COVID-19-related illnesses and response to therapy. Some of this research has already been assembled and published in peer-reviewed journals and information continues to be collected and analyzed in ongoing longitudinal research.

As can be seen in the pages of *Fusion*, medical student research activity at GW is thriving and reflects a broad range of research interests including basic science research, clinical research, as well as research in public health and health policy. Data from our most recent graduating class, indicated that 89% of students participated in research while a student in medical school, and 65 percent of students report publishing a peer-reviewed manuscript, which compares to a national average of 55%. This is a credit to the efforts of our students and very importantly our faculty mentors, who are essential for this productivity. Congratulations to all for your success!

David Leitenberg MD, PhD

associate professor of microbiology, immunology, and tropical medicine at SMHS, and medical director of flow cytometry and immunology at Children's National Hospital



CRISP-view: A Database of Functional Genetic Screens Spanning Multiple Phenotypes

Anthony Chiu,
MSII

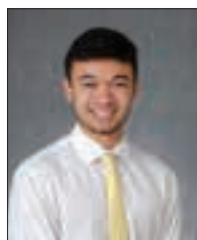
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The pairing of CRISPR/Cas9 gene editing with next-generation sequencing technology has enabled the scientific community to amass large volumes of genetic knock-out data on numerous cancer cell lines, particularly within the last decade. As a result, computational methods can be applied to correlate cell survival and proliferation with individual genes across a cancer cell's entire genome.¹ This presents a major opportunity to probe large-scale genetic data for potential therapeutic targets. However, effectively analyzing and comparing these immense datasets poses a significant challenge.

The Model-based Analysis of Genome-wide CRISPR/Cas9 Knockout with Visualization of CRISPR Screens (MAGeCK-VISPR) is an algorithm and visualization tool previously developed to determine novel essential genes and pathways from CRISPR screening experiments.² It assigns a numerical “beta-score” to genes in order to rank

their essentiality in cell survival and proliferation.² MAGeCK-VISPR is a downloadable software which can be executed on the command line, and it is currently one of the most favored and highly cited analytical models used for this purpose. The aim of this project was to leverage this software to build a comprehensive, standardized database of CRISPR screening data for the exploration and visualization of functional genes across multiple cancer types.

Raw data was retrieved from publicly-available genome-wide CRISPR screening data sets and was processed using the MAGeCK-VISPR algorithm. We performed systematic analysis on all data sets to assign numerical scores for the determination of essential genes. All samples were annotated with fields for cell line, organism, treatment, controls, and sgRNA library used for knock-out. The data was organized and uploaded into a publicly available database containing 10,321 human samples and 825 murine samples from 167 papers as of September 2020. Data is presented on a web-interface which allows researchers to search by cell line, tissue type, and treatment conditions. Positively and negatively selected genes are ranked by beta-scores computed by the MAGeCK-VISPR algorithm, and can be easily visualized along with quality control metrics and sample metadata on the interface. This database, entitled CRISP-view, currently represents the most comprehensive database of

CRISPR screening data to date.³

The construction of CRISP-view offers a rich landscape of genetic data on numerous cancer cell lines. The standardization of analysis from raw data sets, which allows comparability between previously incomparable samples, as well as the expansive volume of data are major strengths providing opportunity for further investigation. Future work will apply data mining and machine-learning approaches to this accumulation of genetic “big data” to better understand cancer genetics and search for therapeutic targets.

The construction of CRISP-view offers a rich landscape of genetic data on numerous cancer cell lines.

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Variations in PIEZO1 rs62048221 Associated with Strength and Anthropometric Measures in Young Adults



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Osteoporosis is a chronic disease characterized by low bone density, disrupted bone microarchitecture, and an increased risk for fractures.¹ While epidemiological studies have linked skeletal loading with osteogenic responses, insufficient research has explored the molecular mechanisms underlying the mechanical forces influencing bone mineral density (BMD).^{1,2} Several genetic variants of PIEZO1, a mechanically activated ion channel, have been associated with decreased BMD and increased fracture risk.^{2,3} The purpose of this study was to explore musculoskeletal phenotypes associated with the PIEZO1 single nucleotide polymorphism (SNP), rs62048221, in two cohorts of healthy young adults.

Cohorts: The Assessing Inherited Markers of Metabolic Syndrome in

the Young (AIMMY) was comprised of the University of Calgary subgroup, with healthy Caucasian young adults (n=111; 61 males, 50 females; ages 18-35) and the Howard University subgroup with African American young adults (n=75; 21 male, 54 female, ages 18-25) who were recruited as part of a study to identify genetic variants associated with risk factors for metabolic syndrome. Functional Single Nucleotide Polymorphism Associated with Human Muscle Size and Strength (FAMuSS) was comprised of healthy young adult Caucasians (n=370; 148 male, 222 female, ages 17-40) who participated in a strengthening program of their non-dominant (ND) arm for three months.

Genotyping: This study used the Applied Biosystems QuantStudio 7 Flex Real-Time PCR System and Applied Biosystems Taqman Allelic Discrimination Assays in genotyping the FAMuSS and AIMMY cohort DNA samples. Statistical Analysis: All SNPs were tested for Hardy Weinberg equilibrium (HWE), and age adjustments were made for each result. Analysis of covariance (ANCOVA), using additive genetic models, was used to test relationships among SNP genotypes and phenotypes for bone quality. Statistically significant associations underwent post-hoc pairwise comparisons and p-values were adjusted using the Sidak method. IRB: This study was approved by the Children's National Hospital Institutional Review Board.

The genotype distribution for rs62048221 of PIEZO1 was in Hardy Weinberg equilibrium in the FAMuSS and HU-AIMMY cohorts. Among females in the FAMuSS cohort, homozygous variants in rs62048221 were significantly correlated with

lower baseline one arm strength (p=0.0161) and percent change in one arm strength (p=0.0214) in the non-dominant arm. These associations were not found in males in the FAMuSS cohort. In the AIMMY cohort, the TT genotype of rs62048221 in females was associated with a lower hip circumference compared to heterozygous females (p=0.0298).

CONCLUSIONS: This study expands the known role of the PIEZO1 SNP rs62048221 in musculoskeletal health and bone development. The T allele of rs62048221 has been associated with decreased BMD in UK Biobank samples.² This study demonstrated a new association between the T allele and baseline one arm strength and percent change in one arm strength in the non-dominant arm among females in the FAMuSS cohort. This association was not observed for males in the FAMuSS cohort nor among males or females in the AIMMY cohort. The decrease in arm strength may help explain the results of past researchers, who associated polymorphisms in mechanosensitive genes with decreased distal radius and forearm BMD.^{4,5} Further research is warranted to explore the biological mechanisms underlying the influence of rs62048221 on BMD. Elucidation of PIEZO1 and other genetic variants that impact bone mineral density would be useful in planning exercise and care regimens for those at higher risk of fracture through their genetic variants.

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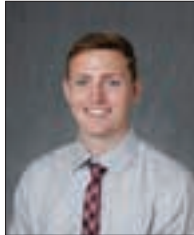
Reproducibility of RNA-Seq Methods in Evaluating Blood RNA Biomarkers of Coronary Artery Disease

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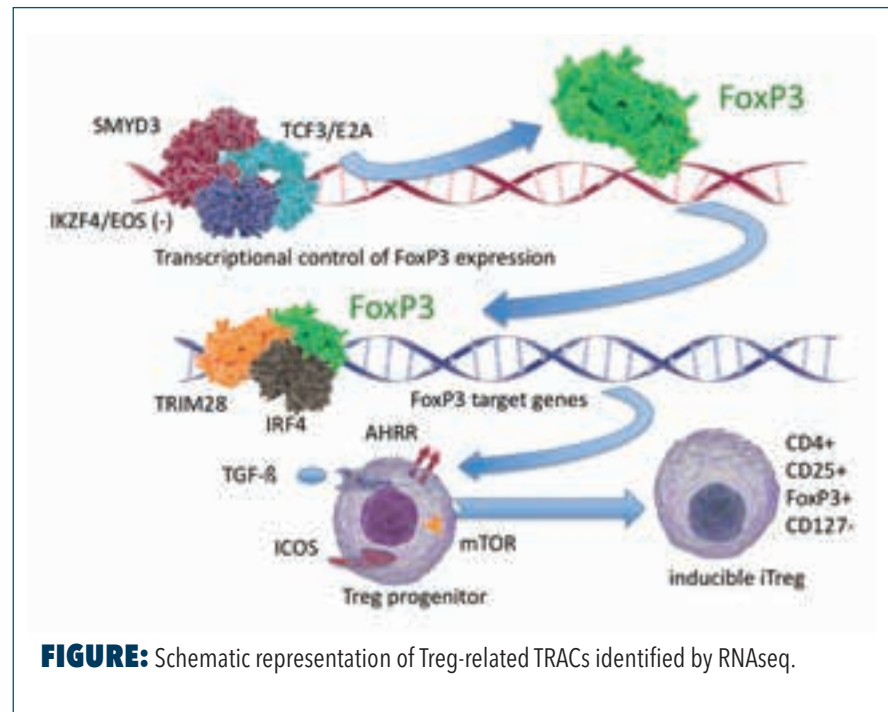
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Cardiovascular disease remains the major cause of death in developed countries, with atherosclerosis leading to approximately 650,000 myocardial infarctions (MI) each year in the United States.¹ While the current diagnostic gold standard for coronary artery disease (CAD) is coronary angiography via cardiac catheterization, less invasive blood tests identifying a regulatory T-cell (Treg) imbalance have shown impressive sensitivity and specificity for CAD.² Whole blood RNA analyses via single-molecule next-generation sequencing (NGS) of RNA (RNAseq) have identified transcripts associated with CAD (TRACs) that illustrate an mRNA signature of a Treg-like defect in CAD patients (Figure 1). Results have been variable, however, based on the specific single molecule sequencer product employed. The prospect of an accurate and reliable blood test to predict the development of atherosclerosis excites many and would fundamentally alter the diagnostic landscape for CAD.



The objective of the study was to determine the degree of reproducibility among the primary techniques previously used to identify and quantify the Treg imbalance underlying atherosclerosis. Specifically, we examined the single molecule sequencers from SeqLL and Illumina. Determining the degree of reproducibility of these sequencers would enable investigators to discern superior techniques and ultimately empower clinicians and to make use of the most reliable methods.

Whole blood RNA was analyzed by single-molecule next-generation sequencing (NGS) of RNA (RNA-Seq) to identify TRACs in a discovery group and a validation

group presenting for coronary catheterization. Whole blood RNA was depleted of ribosomal RNA (rRNA) and then sequenced on a SeqLL Single Molecule Sequencer. The resulting short reads were aligned to the human transcriptome and the number of reads per kilobase of exon per million (RPKM) was determined and compared between groups by a combined fold-change/p-value filter. This model was replicated in an additional study, and an identical design was undertaken using a sequencer from Illumina, and transcript reads were analyzed by sequencer product.

Sequencing identified a profile of Treg imbalance in patients with even

Continued on p. 10

mild coronary stenosis (>20%) as confirmed on coronary angiography. The SeqLL platform identified a subset of 39 transcripts highly-associated with CAD that were replicated in a follow-up study ($p < 0.001$), while the Illumina follow-up study displayed minimal meaningful overlap with its initial findings.

Conclusion: The SeqLL sequencing platform of amplification-free, single molecule sequencing seems to be more reproducible than the amplification-dependent Illumina NextSeq. Future investigations will be directed toward establishing a clinically relevant amplification-free method of quantifying RNA in patient blood.

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Screening for Small Molecule Modulators of RIG-I and MDA5 Using a Functional and Biochemical Assay

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The vertebrate immune system has receptors that recognize a wide range of viral nucleic acids during an infection and elicit a robust anti-viral response. Retinoic acid-inducible gene-I (RIG-I) and Melanoma Differentiation-Associated protein 5 (MDA5) are two such pattern recognition receptors (PRRs) that stimulate a type I interferon (IFN) response against a variety of double stranded ribonucleic acid (dsRNA).¹ While proper functioning of these receptors is critical for reducing viral spread, mis-regulation of MDA5 or RIG-I can result in autoinflammatory conditions such as Systemic Lupus Erythematosus (SLE), Aicardi-Goutières syndrome (AGS), and Singleton-Merten syndrome (SMS).²

Previous research suggests that the ATPase active site of these receptors acts as an allosteric modulation

site, playing a role in altering the confirmation of RIG-I and MDA5 and thereby affecting their signaling activity.³ Our group has examined several mutations in the ATPase site that result in loss of the ATPase activity. While the dsRNA binding capabilities remained intact, these mutants displayed significant changes in signaling activity. Half of these mutant proteins showed a hyper-signaling phenotype, while the other half displayed a complete loss of signaling. This finding has been our rationale for targeting the ATPase site with small molecule intervention. In this study, we have used a biochemical assay to screen for thousands of small

molecules to identify potential hits that inhibit the ATP hydrolysis capabilities of RIG-I and MDA5. These hits were then further characterized using cell-signaling and cell-free assays to delve into the mechanism of inhibition. More specifically, these assays served to identify whether downstream mediators in the RIG-I and MDA5 pathways were inhibited or activated by the compounds.

MDA5 and RIG-I were recombinantly expressed in a strain of E. coli. These cells were lysed, and the proteins were purified using affinity and size-exclusion chromatography. RNA was prepared using in vitro transcription with bacteriophage

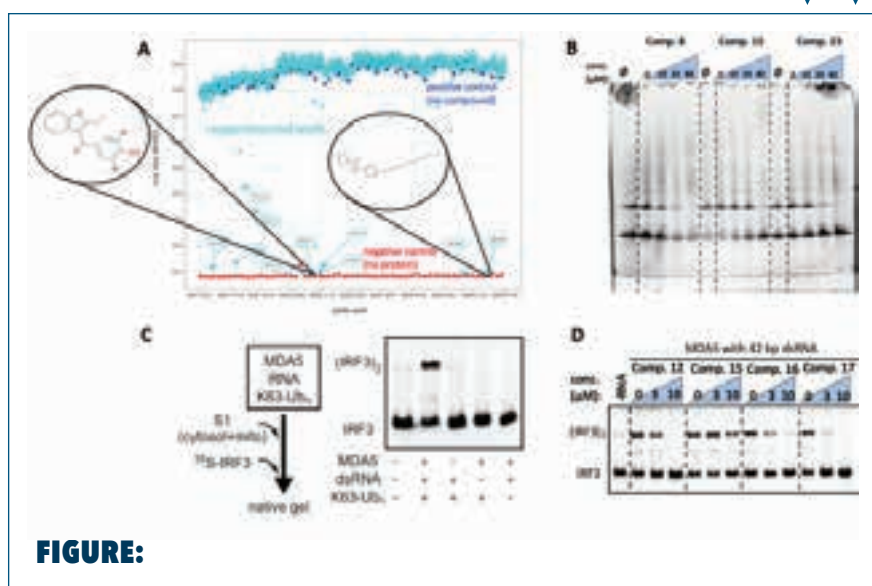


FIGURE:



RNA polymerase and gel electrophoresis. The ATP hydrolysis assay was implemented in screening thousands of small molecules from various libraries. The reaction was initiated when a mixture of RNA and ATP was added to pre-incubated protein and compounds. The optical densities of the samples were then measured to gauge ATP hydrolysis. After initial screening, electrophoretic mobility shift assay (EMSA) was performed by incubating MDA5, RIG-I, RNA, and the small molecule compounds. Gel electrophoresis with SYBR gold staining was used to determine how these compounds influence RNA binding. Finally, IRF3 dimerization (downstream transcription factor) was studied to assess whether the compounds upregulate or down-regulate the MDA5/RIG-I signaling pathway.

Compounds were numbered rather than named to maintain confidentiality. After the compound screening, “hits” were classified as compounds that were successful in inhibiting ATP hydrolysis (Figure A). The EMSA showed that some compounds were able to interrupt protein-RNA binding at high doses of the compound (Figure B). IRF3 dimerization occurs only when the protein and RNA are both present, and dimerization indicates an activation of the downstream signaling process (Figure C). Illustrated in Figure D, certain compounds were able to interrupt the IRF3 dimerization, indicating that these compounds were successful in inhibiting the MDA5 signaling cascade. Compounds such as Compound 17 were especially potent in inhibiting this step even at lower concentrations.

Conclusions: Among the hits were inhibitors of several known enzymes such as certain dehydrogenases, Cytochrome P40, topoisomerase, and cyclooxygenase. Identifying inhibitors these pathways has implications in therapy for autoinflammatory conditions. Future experiments will implement additional cell-based assays to further characterize the hits.

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Environmental Enrichment Promotes Developmental Myelination Through Adulthood

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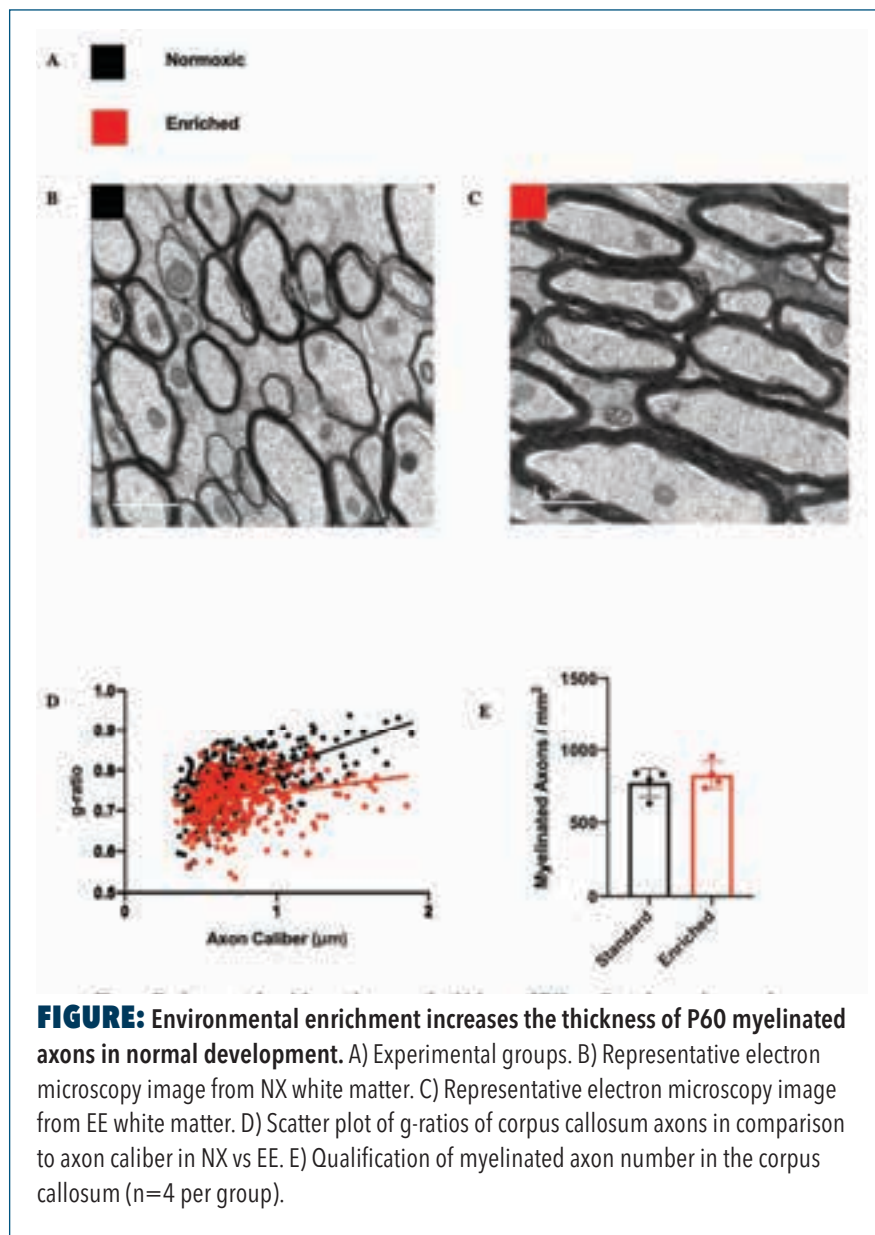
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The well documented plasticity of the mammalian brain suggests a role for environmental experience in modulating brain development.¹ Indeed, environmental enrichment (EE) has been championed as a robust and non-invasive approach to augment white matter health.^{1,2} This experimental paradigm, which exposes animals to increased social interactions, novel stimuli, and voluntary exercise, is a powerful promoter of neuroplasticity that leads to functional improvement in neurological injury models, such as premature birth.^{1,2} Recent work has demonstrated that this neuroplasticity increases activity-regulated changes in myelin forming cells, including oligodendrocyte precursor cell (OPC) proliferation, oligodendrogenesis, and modulations in the thickness and number of myelinated axons.³⁻⁵ We previously reported that early and continuous EE attenuates cellular, behavioral, and ultrastructural deficits caused by hypoxic brain injury by stimulating oligodendrocyte maturation, myelination, and



functional recovery.¹ While the value of an EE intervention after adult injury has been demonstrated,² the utility of EE in normal development, especially in glial development, has not been fully elucidated. Here, we aimed to understand whether EE affects normal developmental myelination through adulthood.

Mice were randomly assigned to be housed in an enriched environment or standard environment cages. The enriched environment condition

consisted of clear Plexiglas cages (24 cm W x 20 cm H x 46 cm L) that had either wooden blocks or metal link chains hanging from the roof, a running wheel, a series of plastic "habit-trails" of different configurations, and several balls and other objects spread over the floor. These objects were changed every 3 days to preserve novelty. The standard environment protocol consisted of smaller cages (16 cm W x 13 cm H x 37 cm L) without any of the novel objects that

mice housed in an enriched environment had. Furthermore, while control mice were reared in groups of 2-5 animals per cage, mice housed in an enriched environment were reared in groups of 8-12 animals per cage. Immunohistochemistry and electron microscopy analysis was performed. An inclined beam-walking test was used to examine differences in sub-cortical white matter myelination between experimental and control groups. The time that it took each mouse to reach the target at the top of the inclined beam as well as the number of foot slips was documented. Analysis was performed at postnatal day (P) 60.

We first assessed the effects of prolonged EE on OPCs and proliferating OPCs versus normoxic (NX) controls and found no changes in oligodendrogenesis in response to EE. To examine effects of myelination at the ultrastructural level, we performed electron microscopy analysis on the corpus callosum of P60 mice. In comparison to NX mice, EE mice

had axons with thicker myelin, as indicated by lower g-ratio values (Figure). Furthermore, enriched mice had improved motor coordination on a beam walking test, as demonstrated by the decreased number of foot slips. No significant difference between groups was noted for the amount of time that it took to reach the target.

Conclusions: The cellular, ultra-structural, and behavioral experiments conducted in this study demonstrate that prolonged EE, comprised of enhanced exposure to novel stimuli, socialization, and locomotor activity, can increase developmental myelination and lead to functional improvement in behavior. Hence, EE can play a beneficial role in normal development. Future research should work towards translating EE protocols into clinical interventions for improving locomotor function.

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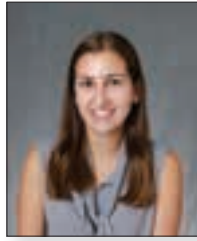
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SARS-CoV-2 specific T-cell Epitopes and in Silico HLA restriction Predictions

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Understanding T-cell responses to SARS-CoV-2 is crucial for the development of vaccines and adoptive immunotherapy. The HLA presentation of antigenic peptides in particular is essential for generating robust T-cell responses against SARS-CoV-2, which may affect susceptibility to and severity of SARS-CoV-2 infection. The purpose of this study was to determine whether SARS-CoV-2-specific T-cell epitopes identified in convalescent patients are predicted to be restricted through a wide range of both class I and class II HLA molecules. The study also aimed to determine the stability of SARS-CoV-2 predicted epitopes.

T-cell epitope mapping of structural proteins was done using mini-pools containing 5–12 peptides each, with responses measured via IFN- γ ELISpot. Once SARS-CoV-2 specific T-cell epitopes were identified, predictive algorithms were used to determine HLA restriction predictions for each epitope of membrane, spike, nucleocapsid and envelop proteins.

The predictive algorithms used were NetMHCIIpan and MARIA, which provide percent rank scores, normalizing prediction scores by comparing epitopes to a set of random peptides.^{1,2} The stability of SARS-CoV-2 predicted epitopes was determined through identification of and comparison to known SARS-CoV-2 genetic variants in available literature.

T-cell epitopes within the C-terminus of membrane protein were identified at amino acids (AA) 144–163 and 173–192, which were recognized by 8 and 6 convalescent donors respectively. Mapping of spike epitopes demonstrated three regions at AA 57–75, 205–224, and 449–463, which were recognized by 3 donors. Mapping of nucleocapsid epitopes revealed two regions at AA 257–271 and 313–335, which were recognized by three donors.

All membrane epitopes were predicted to be MHC Class II restricted. In silico analysis suggested restriction of these epitopes through HLA-DR11, DR7, DQ3, and DQ7. Nucleocapsid epitopes between AA 257–271 were predicted to be Class II restricted. Strong binders included HLA-DPA1*02:01 and HLA-DPBr*14:01. Two nucleocapsid epitopes between AA 313–335 were Class I restricted. Five spike epitopes were predicted to be Class II restricted through HLA-DRBr*03:01, HLA-DRB3*01:01, HLA-DPA1*01:03, HLA-DPBr*02:01.

One known SARS-CoV-2 genetic variant within membrane protein, T175M, overlaps with predicted peptide 44. One nucleocapsid variation, T271I, overlaps with predicted epitope 65. Two known spike mutations overlap with predicted epitopes: N74K mutation with peptide 15 and S221W with peptide 53.

Conclusions: In silico analysis predicted HLA restriction of membrane protein epitopes through alleles which are present in approximately 50% of the population.³ Identified membrane, nucleocapsid, and spike epitopes appear to be genetically stable, as known variants are point mutations that do not overlap with anchor residues. Further study is needed to better understand the biologic activity of SARS-CoV-2 T-cells of various restrictions. It will be critical to determine if there are risk associations with specific HLA types.

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Table 1: Identified Class II Epitopes in Membrane, Nucleoprotein, and Spike proteins and predicted HLA restrictions

Membrane										
Peptide sequence	Amino acid location	Subject	HLA-DRB1	HLA-DRB3	HLA-DRB4	HLA-DRB5	HLA-DQA1	HLA-DQB1	HLA-DPA1	HLA-DPB1
LRGHLRAGPHLGRG	144-159	257	07:01, 11:04	02:02	01:03		02:01, 05:01	03:01, 03:03	01:03, 02:01	03:01, 03:03
		262	07:01, 11:01	02:02	03:01		02:01, 05:01	02:02, 03:01	01:03, 03:01	04:01, 11:01
		265	11:04, 15:02	02:02	01:01, 01:03	01:02	01:03, 05:01	03:01, 06:01	01:03, 02:01	02:01, 14:01
		270	11:04, 15:01	02:02			01:02, 05:01	03:01, 06:02	01:03, 02:01	04:01, 14:01
LRAGHHLGRCDKD	145-163	257	07:01, 11:04	02:02	01:03		02:01, 05:01	03:01, 03:03	01:03, 02:01	03:01, 03:03
		265	11:04, 15:02	02:02	01:01, 01:03	01:02	01:03, 05:01	03:01, 06:01	01:03, 02:01	02:01, 14:01
SRTLSTYYKLGASQRV	173-188	262	07:01, 11:01	02:02	01:01		02:01, 05:01	02:02, 03:01	01:03, 03:01	04:01, 11:01
		265	11:04, 15:02	02:02	01:01, 01:03	01:02	01:03, 05:01	03:01, 06:01	01:03, 02:01	02:01, 14:01
		269	12:01, 15:01	02:02	01:01	01:01	01:02, 05:01	03:01, 05:01	01:03, 01:03	02:01, 04:01
		270	11:04, 15:01	02:02			01:02, 05:01	03:01, 06:02	01:03, 02:01	04:01, 14:01
		273	03:02, 15:02	01:02	01:01, 01:03	02:02	01:02, 04:01	04:02, 05:02	02:02, 02:02	01:01, 01:01
		275	01:01, 03:01	01:01	01:01, 01:03		01:01, 05:01	02:01, 05:01	01:03, 01:03	02:01, 02:01
STYYKLGASQRVAGDS	177-182	262	07:01, 11:01	02:02	01:01		02:01, 05:01	02:02, 03:01	01:03, 03:01	04:01, 11:01
		269	12:01, 15:01	02:02	01:01	01:01	01:02, 05:01	03:01, 05:01	01:03, 01:03	02:01, 04:01
		273	03:02, 15:02	01:02	01:01, 01:03	02:02	01:02, 04:01	04:02, 05:02	02:02, 02:02	01:01, 01:01
		275	01:01, 03:01	01:01	01:01, 01:03		01:01, 05:01	02:01, 05:01	01:03, 01:03	02:01, 02:01
LGASQRVAGDSQFAA	181-195	275	01:01, 03:01	01:01	01:01, 01:03		01:01, 05:01	02:01, 05:01	01:03, 01:03	02:01, 02:01
Nucleoprotein										
KPRQRRTATKAYNYI	257-271	276	04:01, 07:01	01:01	01:03		03:01, 05:05	03:01, 03:02	02:01, 02:01	14:01, 14:01
AFQMSRIGMEVTPS	313-327	270	11:04, 15:01	02:02			01:02, 05:01	03:01, 06:02	01:03, 02:01	04:01, 14:01
Spike										
PFSSNVTFHAIHVS	57-71	259	03:01, 13:01	01:01	01:03		01:03, 05:01	02:01, 06:03	01:03, 01:03	04:01, 04:01
NYTFHAIHVSQTNG	61-75	259	03:01, 13:01	01:01	01:03		01:03, 05:01	02:01, 06:03	01:03, 01:03	04:01, 04:01
SKHTPNLVRDLPGD	205-219	291	03:01, 04:01	01:01	01:03		03:01, 05:01	02:01, 03:02	01:03, 01:03	02:01, 03:01
PNLVRDLPGDPSAL	209-223	273	03:02, 16:02	01:02	01:01, 01:03		01:02, 04:01	04:02, 05:02	02:02, 02:02	01:01, 01:01
		291	03:01, 04:01	01:01	01:03		03:01, 05:01	02:01, 03:02	01:03, 01:03	02:01, 03:01
YNYLYRLFRKSNLKP	449-463	291	03:01, 04:01	01:01	01:03		03:01, 05:01	02:01, 03:02	01:03, 01:03	02:01, 03:01

Red: strong binder (<2). Green: Weak binder (2-10)

Table 2: Identified Class I Epitopes in Nucleoprotein and predicted HLA restrictions

Peptide sequence	Amino acid location	Subject	HLA-A	HLA-B	HLA-C
MSRIGMEVTPSGTWL	317-331	270	24:02, 26:01	40:01, 44:05*	02:02, 03:04
GMEVTPSGTWLTYTG	321-335	270	24:02, 26:01	40:01, 44:05*	02:02, 03:04

Red: strong binder (<2). Green: Weak binder (2-10). * Predicted B*44:05 peptide: GMEVTPSGTW

The Association of H-Index and Academic Rank Among Full-Time Academic Orthopaedic Trauma Surgeons Affiliated with Fellowship Programs

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Research productivity has traditionally been a key determinant for professional advancement within academic medicine.¹ In the past, productivity has been assessed using simple numeric measures such as publications and citation counts. However, these metrics only measure quantity and are unable to provide insight regarding the quality of a researcher's publications. In recent years, there has been a push to move past these simple measures of productivity.^{1,2} J. E. Hirsch first proposed the H-index in 2005 as a bibliographic metric to objectively assess the quality of a researcher's publications.³ While originally developed for use in the natural sciences,³ its association with academic rank has since been validated by studies within a variety of both medical and surgical specialties.^{4,5} To our knowledge, no prior studies have evaluated academic impact by orthopaedic trauma surgeons on faculty at fellowship training programs. The purpose of this study is to assess the association

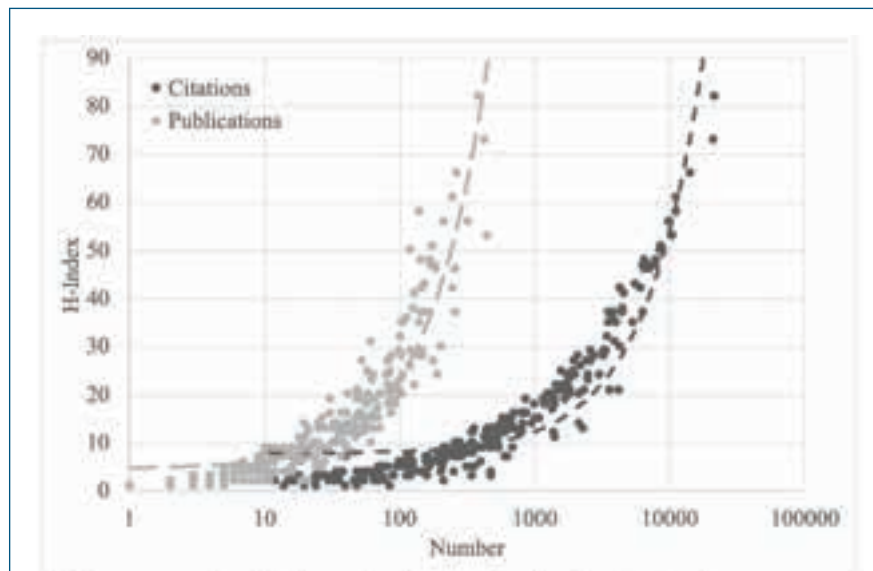


FIGURE 1: H-Index versus number of citations and publications plotted on logarithmic scale.

between H-index and academic rank within this cohort.

This is a cross-sectional study of full-time orthopaedic surgeons affiliated with orthopaedic trauma association (OTA) fellowship programs in the United States. The study population was constructed by querying the Orthopaedic Trauma Association (OTA) website to obtain a complete record of all OTA-affiliated orthopaedic traumatology fellowship training programs. A total of 62 programs were identified. For each program, the department website was used to generate a list of faculty members with primary appointments. The

H-indices of 322 orthopaedic traumatologists from 57 OTA fellowship programs were organized and calculated. Additionally, the total number

[O]ur findings indicate that H-index, number of citations, and number of publications are strongly correlated with academic rank among full-time orthopaedic trauma surgeons affiliated with fellowship training programs.

of publications, academic rank, and fellowship training pedigree were also collected. Data normality was assessed using the Shapiro-Wilk test. Variance was assessed using Kruskal-Wallis test for non-parametric data that were not normally

distributed due to skew and outliers. Post-hoc analysis on non-normally distributed data was performed using Mann-Whitney test with Bonferroni correction. Median differences for non-normal data were determined by Hodges-Lehman estimation.

Overall, these 322 surgeons have published 14,822 publications. The total H-index for this group of surgeons is 4,136. Number of publications is a stronger predictor of H-index than number of citations ($p < 0.0001$). Number of publications, number of citations, and H-Index tend to increase with academic rank ($p < 0.001$). There exists no significant trend with respect to affiliated training amongst the various academic ranks. Orthopaedic trauma versus other orthopaedic sub-specialty fellowship training is not a predictor of academic rank ($p = 0.11$). There exist no geographical differences with regards to academic rank and training affiliation ($p = 0.79$). There is no statistical difference in research productivity for those with affiliated training pedigree versus those not affiliated with respect to number of publications ($p = 0.44$), number of citations ($p = 0.62$), and H-Index ($p = 0.59$).

In conclusion, our findings indicate that H-index, number of citations, and number of publications are strongly correlated with academic

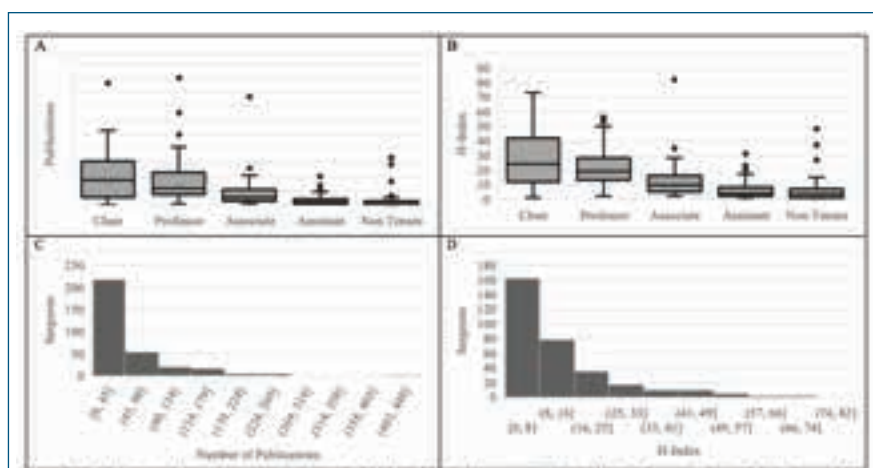


FIGURE 2: Number of publications by academic rank in box-and-whisker (A) and histogram (C) plots. H-index by academic rank in rank in box-and-whisker (B) and histogram (D) plots.

rank among full-time orthopaedic trauma surgeons affiliated with fellowship training programs. While research productivity is not the only benchmark for achievement in academic medicine, it has historically been considered a key determinant for professional advancement. Our findings suggest the H-index may be a useful metric for evaluating academic impact within the field of orthopaedic trauma surgery.

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Variation in State and Federal Reimbursement in the Treatment of Upper Extremity Fractures

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The purpose of this study is to compare MCR and MCD reimbursement rates for 12 orthopaedic procedures performed to treat common fractures of the upper extremity. Upper extremity injuries account for approximately 10% of traumas presenting to emergency departments in the United States and represent a significant source of health care spending.¹ Secondary to both a growing population and increasing life expectancy, it is also anticipated that more Americans will continue to enroll in Medicare (MCR) and Medicaid (MCD).^{2,3} Given the increasingly large number of patients covered by government-run healthcare programs, it is critical that a sufficient number of orthopaedic surgeons participate with these payers. However, MCD is a federal-state program, and the guidelines put forth by the Centers for Medicare and Medicaid Services (CMS) allow for each state to determine access and MCD reimbursement rates.⁴ Large discrepancies have been reported between MCD and MCR reimbursement for identical procedures.⁵ Such inconsistencies in reimbursement may act as a barrier to MCD patients gaining access to timely orthopaedic care.

Twelve orthopaedic procedures

TABLE 1: Medicaid, Medicare, and Medicare Wage Index Adjusted Medicaid Reimbursement. Data presented as Mean \pm SD, MedianS with range, and coefficient of variation for reimbursement.

Procedure	Mean (SD)	Median (Range)	Coefficient of Variation
Medicare Reimbursement			
Shoulder Arthroplasty	1473.9(93.55)	1467.93(1353.37-1929.14)	0.06
Shoulder Hemiarthroplasty	1218.63(77.23)	1212.69(1119.53-1590.95)	0.06
Proximal Humerus ORIF	894.26(56.53)	887.26(822.65-1159.20)	0.06
Total Elbow Arthroplasty	1477.59(496.77)	1467.63(1355.55-1929.40)	0.07
Distal Humerus ORIF	943.11(46(1.88)	934.22(865.29-1222.61)	0.07
Radial Head ORIF	662.68(143.4)	654.36(607.29-850.56)	0.07
Radial Head Arthroplasty	692.48(45.36)	685.71(635.78-894.61)	0.07
Radial Head Excision	515.78(432.85)	510.08(472.55-661.27)	0.06
Humeral Shaft ORIF	891.18(56.68)	883.53(818.32-1151.96)	0.06
Humeral Shaft IMN	871.37(66(55.43)	864.27(799.55-1129.60)	0.06
Olecranon ORIF	661.41(32(42.14)	654.93(606.05-849.00)	0.06
Clavicle ORIF	729.42(64(46.41)	723.33(669.27-940.61)	0.06
Total	919.88(308.62)	862.11(472.55-1929.40)	0.34
Medicaid Reimbursement			
Shoulder Arthroplasty	1181.26(321.56)	1136.48(515.5-2219.63)	0.27
Shoulder Hemiarthroplasty	944.24(244.09)	933.46(515.5-1830.52)	0.26
Proximal Humerus ORIF	659.77(189.48)	644.74(211-1333.75)	0.29
Total Elbow Arthroplasty	1141.79(308.93)	1122.65(846.95-2219.93)	0.27
Distal Humerus ORIF	676.13(208.64)	684.31(211-1406.02)	0.31
Radial Head ORIF	483.54(140.66)	486.33(151-978.64)	0.29
Radial Head Arthroplasty	561.65(166.9)	544.5(242.29-1123.7)	0.3
Radial Head Excision	396.45(107.61)	387.54(134-760.84)	0.27
Humeral Shaft ORIF	664.08(192.34)	671.92(211-1325.43)	0.29
Humeral Shaft IMN	676.1(175.25)	664.45(211-1299.7)	0.26
Olecranon ORIF	497.83(145.75)	502.59(128.88-976.84)	0.29
Clavicle ORIF	507.8(165.08)	511.5(151-1082.25)	0.33
Total	701.08(328.41)	612.66(128.88-2219.93)	0.47
Medicare Wage Index Adjusted Medicaid Reimbursement			
Shoulder Arthroplasty	1083.24(192.91)	981.72(537.15-2802.06)	0.36
Shoulder Hemiarthroplasty	874.96(177.65)	769.3(449.12-2310.85)	0.36
Proximal Humerus ORIF	603.08(240.22)	550.71(234.97-1683.73)	0.4
Total Elbow Arthroplasty	1047.73(391.67)	929.95(483.44-2802.44)	0.37
Distal Humerus ORIF	624.48(255.01)	579.26(234.97-1774.96)	0.41
Radial Head ORIF	447.08(175.79)	406.22(18.15-1235.44)	0.39
Radial Head Arthroplasty	518.2(191.36)	458.66(252.47-1299.43)	0.37
Radial Head Excision	366.79(134.89)	326.74(149.23-960.88)	0.37
Humeral Shaft ORIF	613.1(236.59)	558.77(234.97-1673.22)	0.39
Humeral Shaft IMN	624.85(223.74)	564.92(234.97-1640.74)	0.36
Olecranon ORIF	458.96(177.81)	417.44(134.29-1233.16)	0.39
Clavicle ORIF	470.07(201.98)	440.61(161.15-1366.23)	0.43
Total	642.94(339.28)	551.21(134.29-2802.44)	0.53

performed for the treatment of common upper extremity fractures were selected for analysis. The 2020 MCR reimbursement rate was collected for each procedure for each state from the Medicare Physician Fee Schedule Database. MCD reimbursement rates were obtained from each state's physician fee schedule database. Reimbursement rates were then compared by assessing the ratio of MCD to MCR, the dollar difference in MCD to MCR reimbursement, and the difference per relative value unit (RVU) to adjust for the difference in procedure complexity.^{2,3} The range of variation in MCD reimbursement

and MCR wage index-adjusted MCD reimbursement was calculated, as well as the coefficient of variation. Comparisons in reimbursement were calculated using coefficient of variation and student T tests to evaluate the differences between the mean MCD and MCR reimbursements.

There was statistically significant difference in reimbursement rates between MCR and MCD for all 12 procedures, with MCD reimbursing on average 46.5% less than MCR. In 40 states, MCD reimbursed less than MCR for all 12 procedures. Regarding the dollar difference per RVU, MCD paid on average \$18.03 less per RVU

than MCR. There was substantial variation in reimbursement per RVU, ranging from \$69.22 less per RVU (New Jersey, radial head ORIF) to \$45.47 more per RVU (Illinois, radial head arthroplasty) for MCD. The coefficient of variation for MCD reimbursement ranged from 0.26 (shoulder hemiarthroplasty and humeral shaft IMN) to 0.33 (clavicle ORIF). This is in stark contrast with the significantly lower variability observed in MCR reimbursement, which ranged from 0.06 to 0.07 for all procedures.

The findings of this study call attention to the significant variability in reimbursement that exists among state MCD programs for 12 orthopaedic procedures commonly used to treat fractures of the upper extremity. This exceeded the variation seen in MCR reimbursement for the same group of procedures. Additionally, MCD reimbursement was significantly lower than MCR for all 12 procedures. Such discrepancies may act as a barrier, preventing many MCD patients from accessing timely orthopaedic care. Implementing more uniform and robust reimbursement

TABLE 2: Dollar differences between Medicaid and Medicare reimbursement. Data presented as a Mean \pm SD, Median (range) with range and percent difference. Negative values indicate lower Medicaid reimbursement when compared to Medicare.

	Mean (SD)	Median (range)	% Difference	P value	Coefficient of Variation
Dollar Difference between MCD and MCR					
Shoulder Arthroplasty	-393.83(316.85)	-397.75 (1020.78-663.33)	-34.49(42.41)	<0.001	-1.08
Shoulder Hemiarthroplasty	-275.95(216.95)	-268.43(800.92-339.37)	-38.07(39.95)	<0.001	-0.86
Proximal Humeral ORIF	-244.64(183.89)	-234.87(1768.77-174.55)	-51.23(66.62)	<0.001	-0.73
Total Elbow Arthroplasty	-336.94(303.61)	-324.20(81073.11-290.53)	-46.73(58.42)	<0.001	-0.81
Distal Humeral ORIF	-248.73(208.46)	-246.24(820.19-384.65)	-57.64(73.68)	<0.001	-0.78
Radial Head ORIF	-180.01(140.51)	-155.53(878.69-378.08)	-57.60(67.61)	<0.001	-0.78
Radial Head Arthroplasty	111.79(167.66)	127.93(488.96-425.63)	-34.27(44.05)	<0.001	-1.27
Radial Head Excision	-120.03(107.71)	-120.59(434.51-99.87)	-62.35(56.95)	<0.001	-0.9
Humeral Shaft ORIF	-228.29(193.29)	-205.73(785.32-373.47)	-49.78(64.7)	<0.001	-0.84
Humeral Shaft IMN	-196.43(173.71)	-193.94(741.64-170.1)	-40.14(55.72)	<0.001	-0.88
Clavicular ORIF	-344.46(145.65)	-342.15(477.21-377.84)	-57.07(83.88)	<0.001	-0.89
Clavicle ORIF	-222.79(163.56)	-205.58(649.44-341.64)	-65.16(85.27)	<0.001	-0.72
Total	-221.62(111.87)	-192.81(8773.11-463.31)	-46.53(63.26)	<0.001	-0.89

models may increase access to care for the millions of MCD beneficiaries in the United States.

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Qualitative Experiences of Person-centered Maternity Care among Mexican and Chinese Immigrants in California

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Improving high quality, respectful
maternity care is a global priority
to advance maternal and neonatal
health.¹ Globally, mistreatment of
women during maternity care is

widespread. Recent data from the
United States (US) suggest that one
in six women reported experiencing
one or more types of mistreatment.²
Immigrant women, in particular, face
a myriad of assaults to their basic civil
rights, potentially leading to lower
health status. Despite lower access to
prenatal care and increased reports of
discrimination, stigma, and infringe-
ments on reproductive rights, the
maternity care experiences of immi-
grant women remain understudied.
This article extends the literature
of person-centered maternity care
(PCMC) by applying recently vali-
dated measures and frameworks to a
US context.^{3,4} Specifically, this study
focuses on Mexican and Chinese
immigrant women, two of the largest

immigrant populations in the U.S.

The Research on Immigrant
Health and State Policy Study is a
convergent parallel mixed methods
study examining the lived experiences
of Latino and Asian immigrants in
California. Semi-structured, in-depth
interviews were conducted from
August 2018 to August 2019 with
Mexican and Chinese women living
in Los Angeles or Orange County
who gave birth within the past two
years. Interviews (n=18) were con-
ducted by nine bilingual interviewers,
transcribed, and subsequently coded.
Coded data were mapped onto the
domains of PCMC.

Women described several prefer-
ences when establishing prenatal care,
including provider qualifications, lin-
guistic, and ethnic concordance. Most
Chinese women who actively sought a
specific provider cited linguistic and
ethnic concordance as their main
criteria. Across ethnicity, county, and
immigration status, women shared
the expectation that more difficul-
ties arose for those who did not speak
English.

Almost all participants spoke of
an overall positive experience, yet
the majority of women pinpointed
instances of mistreatment. Negative
experiences ranged from long wait
times to acts of disrespectful care such
as denial of necessary medical care.
Many women described specific nega-
tive encounters such as feeling rushed,
judged, and blamed by providers.

Translation services were often
quoted as unavailable or flawed.
However, Mexican women, overall,
reported greater ease of accessing
translation services or bilingual pro-
viders compared to Chinese partici-
pants. For women who spoke English
well, or attended clinics with bilingual
staff or adequate translation services,

TABLE: Participant Characteristics

	Mexican n=10	Chinese/ Taiwanese n=8	Total n=18
Age (years)			
Mean	38	34.4	36.4
≤30	2	3	5
31-40	2	4	6
>40	6	1	7
Legal Status			
Naturalized	1	1	2
Permanent Resident	0	5	5
Work Permit	3	1	4
Overseas Born Citizen	0	1	1
Undocumented	6	0	6
Time in US (years)			
Mean	20	11.9	16.4
County			
LA	5	5	10
OC	5	3	8
Undocumented family or friends			
	10 (100%)	3 (37.5%)	13 (72.2%)

language and cultural concordance were not defining features in their perception of care.

Some women utilized informal support systems to enhance communication such as enlisting a family member to assist in translating or using available technology to overcome language barriers. Chinese women, in particular, were more likely to utilize these strategies to enhance their care experience.

To our knowledge, this study is the first to apply concepts of PCMC to a US context, particularly among immigrant women. Our findings are in line with other research that suggests poor patient-centered care among communities of color in the U.S.⁵

There is significant overlap with our study findings and the experiences of lower status women in international contexts. However, it

is also important to highlight areas that may be uniquely specific to the US immigrant context. These include judgements related to fertility, language challenges, and preferences for cultural concordance with providers.

Understanding immigrant experiences of respectful maternity care can offer insight to clinicians and policy-makers, and contextualize the future of patient-centered care research and its intersection with immigrant life in the U.S.

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Economic Impact of Thrombectomy: Relationship of Socioeconomic Disparities with Timely Access to Stroke Care

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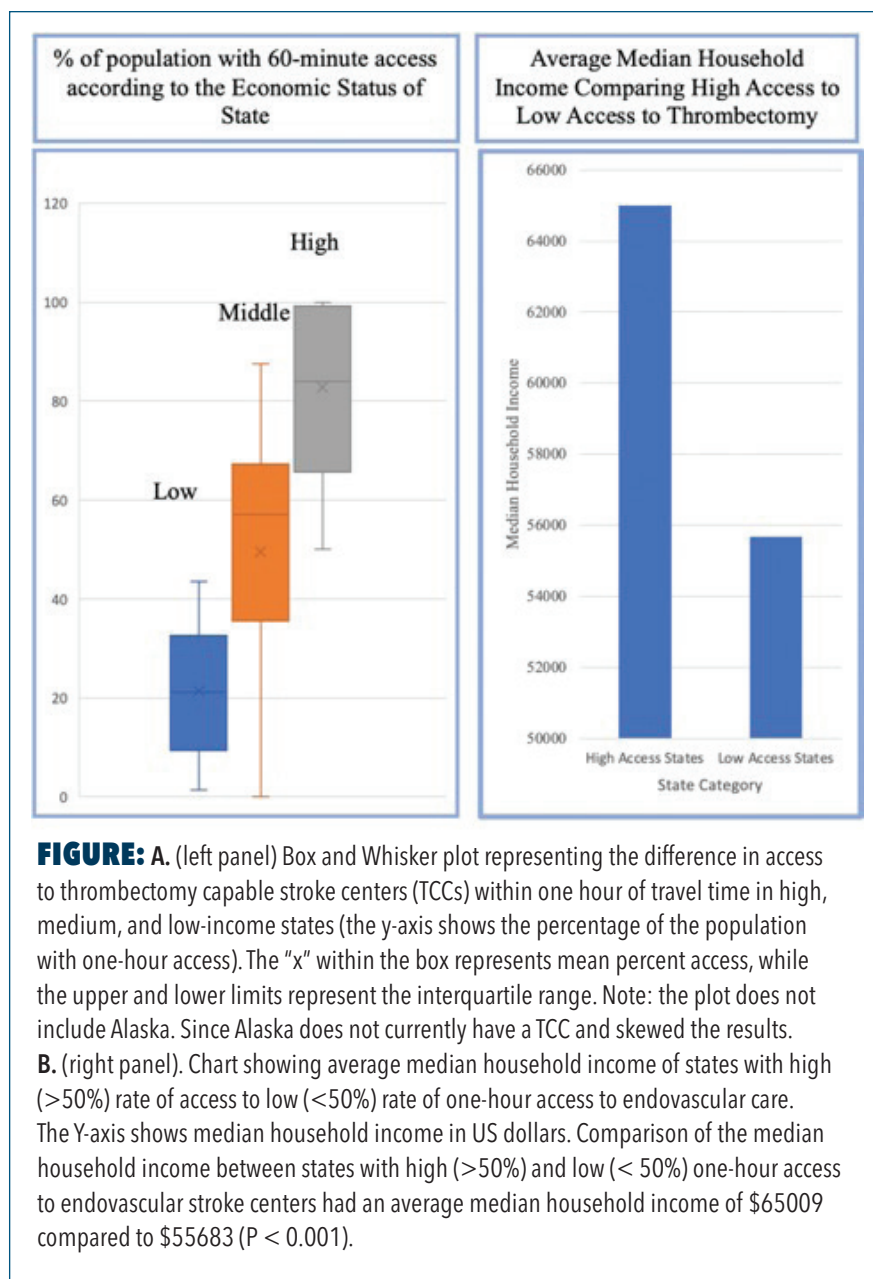
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In the last five years, mechanical thrombectomy has revolutionized the standard of care for patients suffering from acute stroke.¹ The cost of mechanical thrombectomy procedures has been shown to cost more than traditional medical therapy.² Still, the mechanical thrombectomy procedure for acute stroke contributes to a greater cost-effective outcome in terms of quality-adjusted life years (QALY) and reduces the cost of long-term stroke care.² The gain of additional QALY translates into cost effectiveness which has been shown across various countries and different types of health and economic systems across the world. Given the fact that clinical outcomes are strongly dependent on time to recanalization (removing the blood clot), it is important to examine the socioeconomic disparity of geographic living distance from thrombectomy capable stroke centers as related to patient outcomes. Currently, there is no literature comparing patient outcomes from thrombectomy to median income levels and geographic living distance from accredited thrombectomy capable stroke hospitals. In this study we performed a comprehensive literature review to understand the cost



effectiveness of mechanical thrombectomy in a global context. We additionally estimated timely access (less than one hour) to thrombectomy capable stroke centers (TCCs) and evaluate the relationship of access with socio-economic status using US Census, median household income and ambulance data. We further demonstrate that timely access to stroke care is imperative for optimal

outcomes, and such access varies by socioeconomic geography. To help improve stroke outcomes nationally and standardize access to care, more stroke centers could be developed in geographical locations with lower median income.

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ABBREVIATIONS:

Quality-adjusted life years (QALY), thrombectomy capable stroke centers (TCCs). United States of America (USA), US Dollar(USD), Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME), Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials(HERMES), Mechanical Embolus Removal in Cerebral Ischemia (MERCI), Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE)

TABLE: Table. Different studies showing Cost/QALY gained and data sources used

Study	Country	Clinical trial used for data source	Incremental Ratio of endovascular treatment (Cost / QALY gained)
Kunz et al., 2016	USA	Hermes Collaboration, meta-analysis (Goyal et al.)	\$3110 (2016)
Shireman et al.	USA	SWIFT PRIME	\$4881 (USD 2015)
Leppert et al., 2015	USA	MR CLEAN	\$14 137 (USD 2012)
Patil et al., 2009	USA	MERCI study	\$12 120 (USD 2008)
Kim et al., 2011	USA	Multi-MERCI study	\$16 001 (USD 2009)
Nguyen-Huynh et al., 2011	USA	Multi-MERCI study	\$9386 (USD 2009)
Achit et al., 2017	France	THRACE	€ 14,881
Kabore et al., 2019	France	SWIFT PRIME	€ 14,715
Bouvy et al., 2013	Netherlands	Expert panel opinion	€ 1922 (Euros 2010)
Ganesalingam et al., 2015	United Kingdom	Hermes Collaboration, meta-analysis (Goyal et al.)	\$11 651 (USD 2013)

The Development of a Global Health Dermatologic Surgery Training Program in Durban, South Africa

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The annual incidence of malignant melanoma in South Africa is amongst the highest rates in the world at 4.76 per 100,000 persons overall and up to 19.2 per 100,000 in whites.¹ While South Africa has the highest number of medical schools in Sub-Saharan Africa, surgical training for dermatologists has historically been limited. The Global Health Dermatologic Surgery (GHDS) Training Program was developed to provide dermatologic surgery curriculum and training to the registrars (residents), and consultants (attending physicians), at the Nelson Mandela School of Medicine (NMSOM) in Durban, South Africa.

We conducted a prospective qualitative study of the 15 total training trips from 2014–19. The Institutional Review Board of the Nelson R. Mandela School of Medicine at the University of KwaZulu-Natal approved this study. Patients were screened for inclusion in this study by local dermatologists and were scheduled for a procedure. Throughout the program, the following were recorded in a REDCap database: tracking of type of procedures, postoperative complication rates (hematoma, infection, dehiscence, pain, and sero-sanguinous discharge), and patient satisfaction surveys. Surgeons phoned patients if they did not show up for follow-up. In addition, consultant/registrar surgical knowledge was

TABLE 1: Patient and Operative Characteristics at the Nelson Mandela Hospital, 2014–19

Characteristics	No.	%
Pre-operative Diagnosis (n=362)		
Keloid	86	23.76
BCC	78	21.55
Sebaceous cyst	24	6.63
Neurofibroma	19	5.25
Hydrocystoma	16	4.42
Dermoid cyst	16	4.42
Epidermoid Cyst	15	4.14
SCC	13	3.59
Other	74	20.44
Procedures (n=387)		
Excision		
Simple Excision	286	73.90
Excisional Biopsy/Disc Excision	26	6.72
ED&C	7	1.81
Shave Excision	4	1.03
Excision & Injection, steroid	4	1.03
Biopsy		
Biopsy	31	8.01
Shave biopsy	2	0.52
Punch Biopsy	1	0.26
Injection		
Injection, steroid	3	0.78
Injection, bleomycin & Cryotherapy	1	0.26
Injection, 5FU	1	0.26
Other	21	5.43
Reconstruction (n=147)		
Primary Closure	142	96.60
Flaps	6	4.08
Incorporated into other repair	3	2.04
Grafts	1	0.68

assessed by pre- and post-didactic assessments.

Seventeen volunteer surgeons (four surgeons made multiple trips) taught and supervised a total of 21 registrars and consultants over the 15 trips between 2014–18. They

evaluated 362 patients and 387 procedures were performed. Of the 299 patients who followed-up at one week, 236 (78.93%) had no complications at all. 30 (10.03%) patients had reported infections of the surgical site. Dehiscence of the surgical site

TABLE 2: Complications and satisfaction survey results of patients who returned for one week follow up

Outcome	No. (%)
Complications	(n=299)
No Complications	236 (78.93)
Infection	30 (10.03)
Other	15 (5.02)
Dehiscence	12 (4.01)
Hematoma	5 (1.67)
Seroma	1 (0.33)
Satisfaction survey result	
Site Appearance	(n=259)
"Very Satisfied"	123 (47.49)
"Satisfied"	113 (43.63)
"Indifferent, No opinion"	17 (6.56)
"Not Satisfied"	6 (2.32)
Site Feel	(n=258)
"Very Satisfied"	115 (44.57)
"Satisfied"	124 (48.06)
"Indifferent, No opinion"	12 (4.65)
"Not Satisfied"	7 (2.71)

was noted in 12 (4.01%) patients and hematomas reported in five (1.67%) patients. On a 1–4 scale, the mean scores for both site appearance and site feel was 3.37, indicating the most patients were “satisfied” to “very satisfied” for their surgical site’s appearance and feel at 1-week post operation. Dermatologic surgery knowledge and competencies were assessed using a 40-point test. Consultants and registrars significantly improved their scores on the post-didactic assessments; the difference in the posttest scores was 23.4 points ($p = .003$, 95% confidence interval 10.9, 35.9).

Short term dermatologic medical service trips, in which a visiting dermatologist provides care to an underserved group for a short period of time, provide poor long-term outcomes and may not be cost-effective.^{2,3} However, long-term educational programs with a focused clinical scope may establish cost-effective long term means of improving care.⁴ The GHDS training program shares goals with other international medical missions, such as providing robust cultural

and educational exchange, but with the primary goal of long term self-fulfilling sustainable surgical training, thereby establishing the NMSOM as a training hub for sub-Saharan Africa for future dermatologists.

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Medical Cannabis Education Among Health Care Trainees: A Scoping Review

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It was previously demonstrated that health care professionals would like additional education on medical cannabis.¹ However, there has not yet been a review of the status of medical cannabis curriculum for allied health care trainees worldwide. Given that future health care workers will be placed on the forefront of patient care, they must be prepared to counsel patients. This study was designed to address this gap in knowledge.

Methods: A search syntax was generated and the PubMed, ERIC, CINAHL, and Web of Science databases were searched for relevant articles. A gray literature search of Google Scholar, MedEd, Medline, and the Proquest Dissertations and Theses section was also performed. All titles and abstracts were screened. Selected articles were subsequently screened using pre-determined inclusion and exclusion criteria.

Results: Allied health care trainees lacked sufficient knowledge about medical cannabis and did not feel prepared to counsel patients on this subject. They expressed a growing interest in medical cannabis and would like more standardized education on the topic. Faculty and deans at various institutions agreed on the need to educate students on the subject and aimed to implement courses on medical cannabis or expand their existing curricula.

Conclusions: While the medical cannabis landscape is developing,

medical and allied health students are not properly educated and knowledgeable on this emerging field of clinical care. The findings suggest that the implementation of competency-based curricula on medical cannabis is essential for allied health care

While the medical cannabis landscape is developing, medical and allied health students are not properly educated and knowledgeable on this emerging field of clinical care.

trainees to have the appropriate level of knowledge to counsel and educate their patients.

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Mapping the Road to Intervention: A Systematic Review of Homeless Health Care Research

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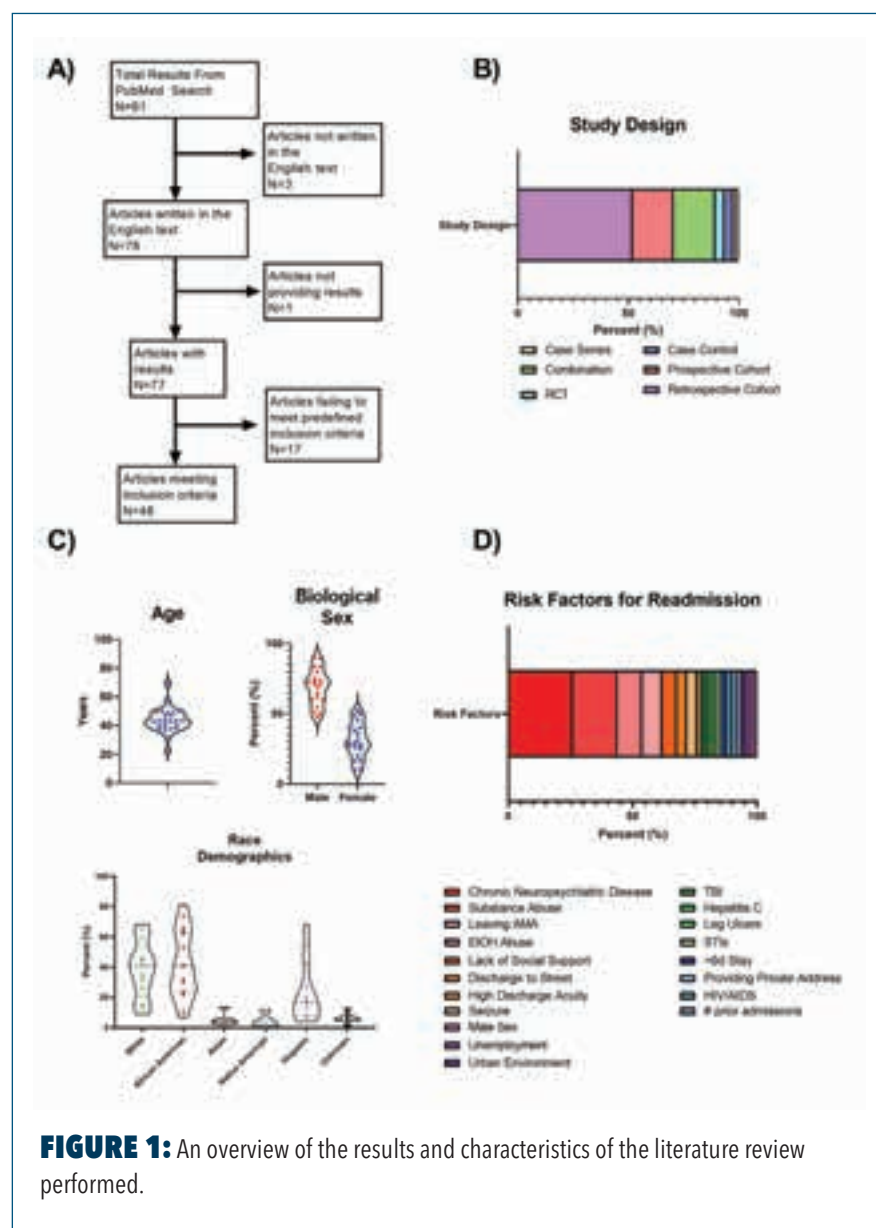
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Homelessness presents significant barriers to health care and is associated with increased hospitalizations.¹ Interventions aimed at improving care transitions and facilitating access to stable housing are key to reducing hospital visits and readmissions.² The state of homeless health care and its associated costs are important areas of public health research as these investigations provide essential data needed to motivate targeted interventions such as medical respite programs.² Here we present a systematic review of investigations into the state of homeless health care, focusing on risk factors for hospital readmission, demographics, and the most commonly used study designs. All together, we aim to more clearly define a roadmap for future research.

Methods: The literature search



was carried out using standardized PRISMA criteria, using the PubMed database and the MeSh terms: “(Homeless Persons) AND (Readmission).” The references of retrieved articles were reviewed for identification of additional relevant studies. Primary inclusion criteria were defined as the article investigating either homeless readmission rate, causes of homeless readmission, or risk factors for homeless readmission. Abstracts not meeting these

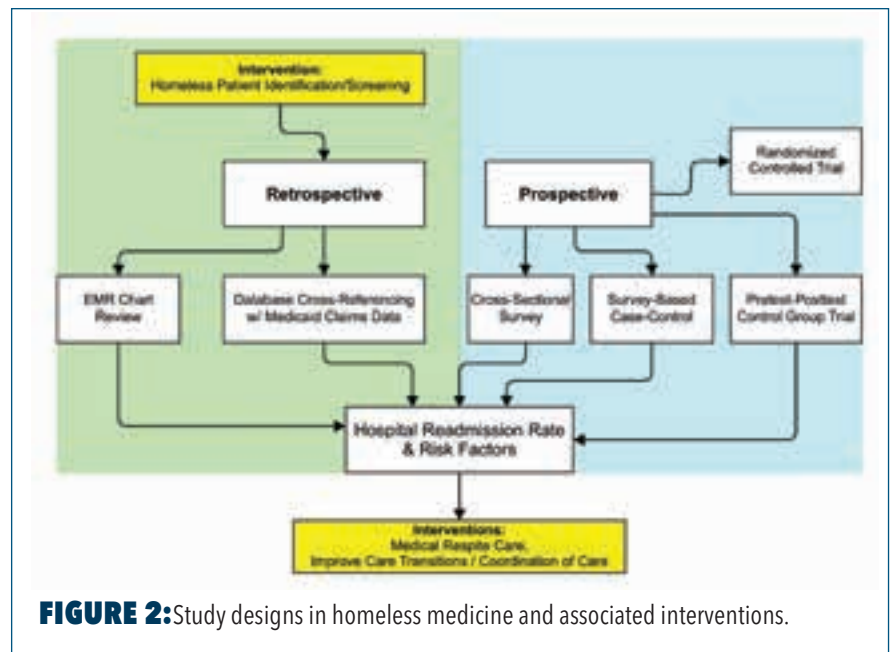
criteria were excluded. Article data was then extracted, aggregated, and analyzed. Statistical and numerical analysis was performed in GraphPad v8 statistical software package.

Results: The literature search returned a total of 81 articles. As shown in Figure 1.A, 33 articles were excluded. Figure 1.B shows the majority of articles (52%, n=25) were a retrospective cohort study. Other study designs

Continued on p. 28

included prospective cohort (18.7%, n=9), randomized control trial (4.2%, n=2), case control (4.2%, n=2), case series (2.1%, n=1), and hybrid/combinatorial design (18.7%, n=9). A total of 1,748,550 patients experiencing homelessness were described amongst the 48 articles. Figure 1.C summarizes demographic data collected in this study. Approximately 60% of that cohort identified as male with a mean age of 39 years old. Race distribution among the cohort was 38% Caucasian, 40% African American, 5% Asian, 4% Native American, and 28% Hispanic. Twenty broad themes of risk factors [Figure 1.D] were identified for patient readmission, with the most commonly mentioned risk factors being chronic neuropsychiatric disease (mentioned in 26% of 39 articles that analyzed risk factors), illicit drug abuse disorder (18%), and alcohol abuse disorder (10%).

Discussion: Retrospective designs were by far the most commonly used. A 2017 systematic review tabulated the ways in which numerous retrospective studies identified homeless patients by information found in patient charts.³ Identification criteria for homeless patients was widely heterogeneous between studies and the lack of reliable standardization was noted to be a significant drawback towards data interpretation across multiple retrospective investigations. Our finding that retrospective designs are most commonly used in the study of homeless medicine highlights the importance of implementing standardized homeless screening tools in the hospital setting [Figure 2]. Fundamental to studying homeless



health care is the ability to reliably identify homeless patients.⁴

Our review also revealed a new methodology for investigating homeless health care.⁵ Racine et al. collected homeless person Medicaid identification numbers from a non-profit database and matched the IDs to the Massachusetts Medicaid claims database. This revealed detailed person-level homeless health care utilization information such as city-wide hospitalizations, ED visits, expenditures, and diagnoses all without relying on patient chart information. Not all cities have access to similar databases required to replicate these analyses, but Homeless Management Information Systems, which are found more commonly, may prove to be a useful tool for designing similar database-matching investigations.

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Characterizing Injury Patterns of Casualties in Bombings Related to Terrorism in the Military and Civilian Populations

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*** Disclaimer:** The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the United States Government.

Introduction: Explosions and bombings remain real threats that have the capacity to quickly create thousands of casualties with devastating injuries (see Figure 1 a,b). Because of this, the medical community needs to remain ready to respond to these high-stress

... [T]he fatality rates from neurological injury are approximately equal; therefore, the data suggest injuries sustained in the setting of helmet protection are more likely to be survivable.

events. To date, few articles have summarized key details of blast injury profiles in terrorist bombings globally, and no studies have analyzed the difference in blast injury profiles between Military and Civilian populations. Thus, the primary aim of this study¹

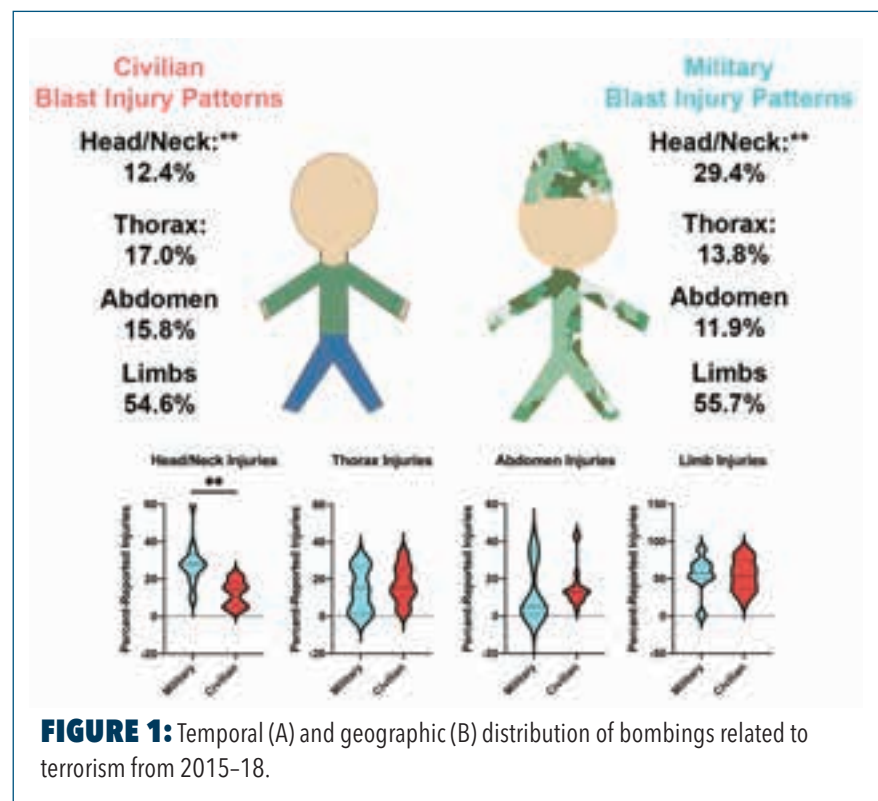


FIGURE 1: Temporal (A) and geographic (B) distribution of bombings related to terrorism from 2015–18.

was to perform a literature review and meta-analysis of all articles reporting on blast injury trauma with the ultimate goal of ascertaining differences in injury profiles reported between Military and Civilian casualties. Such data can be implemented for disaster preparation and education in medical facilities worldwide.

Methods: The literature search was designed and executed (per PRISMA guidelines) to compare blast injury patterns between Military and Civilian casualties following terrorist bombing. The search was performed using selected MeSH search terms. Injury pattern data was extracted and stratified into Abbreviated Injury Scale (AIS) body region numerical descriptors for the

head/neck (1,3), thorax (4), abdomen (5), and extremities (7,8). Data means were then calculated for each AIS-defined region and then compared between articles describing Military populations versus those describing Civilian populations. Statistical analysis was performed in GraphPad Prism v8 statistical software package (San Diego, California). Data sets were initially scrutinized for normality, then assessed for statistically significant differences (defined as $\alpha < 0.05$) using Welch's t-test of unequal variance. Error within the data sets were reported as a 95% Confidence Interval (CI).

Results: The literature search revealed a total of 806 articles (342 Military, 464 Civilian), with 28 (10 Military, 18 Civilian) meeting all inclusion criteria. A total of 33,387 unique injuries were reported ($n=18,711$

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Military, n=14,676 Civilian) in these articles. Figure 1 shows that there are several differences in injury patterns. In both populations, AIS regions 7,8 were most affected by bombings, followed by AIS 1,3, AIS 5, then AIS 4. In addition, there was a significant difference between injuries reported in AIS regions 1+3 reported between the Military and Civilian populations ($p=0.00632$). There were also marginally lower reports of thoracoabdominal injuries in the Military population compared to Civilians, but outliers in both data sets make statistical conclusions difficult. There were no significant differences in victim age, reports of limb injuries, or proportion of instantaneous fatalities in either population.

Conclusions: Given that Military members typically wear protective body armor and ballistic helmets when exposed to a blast, it was unexpected to see a higher number of head and neck injuries. Even though there are increased reports of head and

neck injuries, the fatality rates from neurological injury are approximately equal; therefore, the data suggest injuries sustained in the setting of helmet protection are more likely to be survivable. Ultimately this implies that in a given blast MCI, the Military Treatment Facility receiving casualties might actually see a higher number of patients with blast neurotrauma compared to Civilian hospitals. Though this hypothesis requires further investigation, this finding emphasizes the importance

of neurotrauma stabilization and the importance of intimate integration of the neurosurgical service in the preparation and response phases of mass casualty scenarios related to terrorism bombings.

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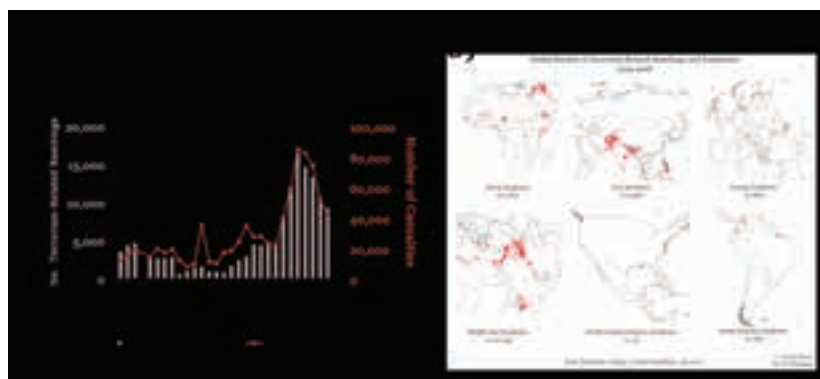


FIGURE 2: Blast injury patterns and differences between Military and Civilian personnel.

Consumer Attitudes and Behaviors on Medical Cannabis in Dermatology

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Access to medical cannabis products (MCPs) has rapidly increased due to changing regulatory landscapes.¹ However, literature on consumer behaviors and attitudes with regards to dermatologic use is limited, and therefore we sought to address this gap.²

Methods: A survey was emailed via SurveyMonkey's platform to users 18 and older of their rewards panel asking about usage patterns and beliefs regarding MCP use to treat dermatologic conditions.

Results: 504 adults completed our survey (92.1% response rate) with a relatively consistent distribution of age and gender. 17.6% of respondents used an over-the-counter (OTC) cannabis product without dermatologist recommendation (NROTC: non-recommended, over-the-counter) to treat a skin condition. The most common indications were acne (28.4%), psoriasis (26.1%) and atopic dermatitis (22.7%) (Figure) and the most common route of administration (ROA) was topical (64.7%). Of those who had seen a dermatologist (66.3%), 15.3% used an OTC product per their dermatologist's recommendation (DROTC: dermatologist recommended, over-the-counter), most commonly for

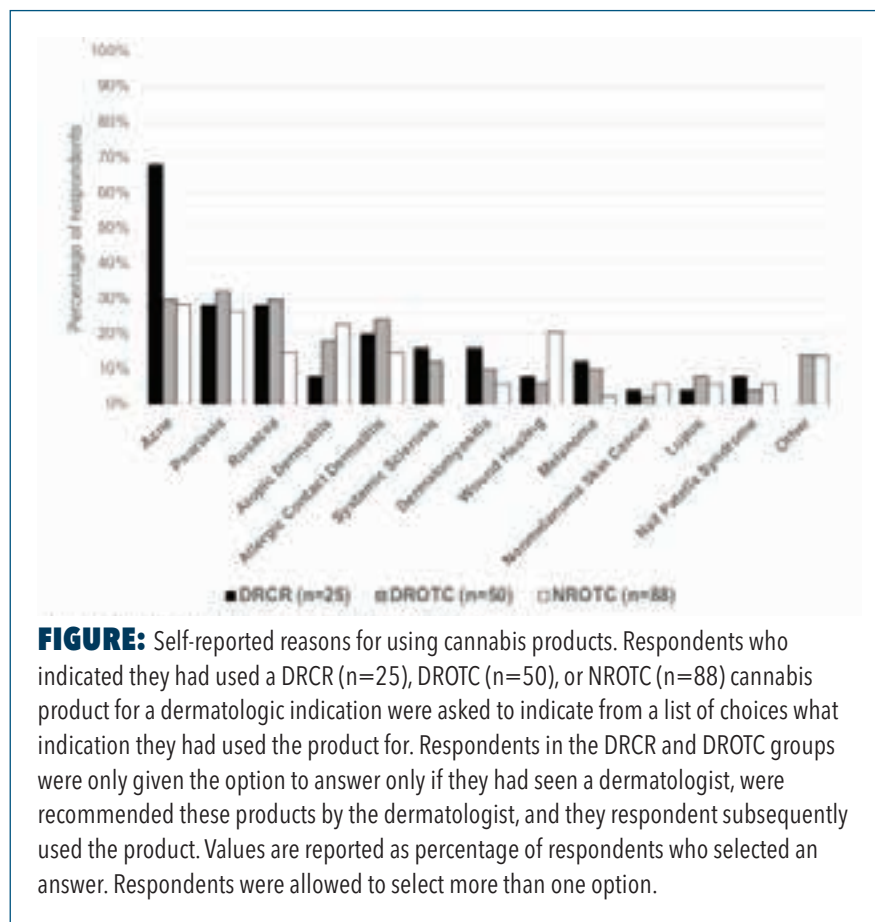


FIGURE: Self-reported reasons for using cannabis products. Respondents who indicated they had used a DRCR (n=25), DROTC (n=50), or NROTC (n=88) cannabis product for a dermatologic indication were asked to indicate from a list of choices what indication they had used the product for. Respondents in the DRCR and DROTC groups were only given the option to answer only if they had seen a dermatologist, were recommended these products by the dermatologist, and they respondent subsequently used the product. Values are reported as percentage of respondents who selected an answer. Respondents were allowed to select more than one option.

psoriasis (32%), rosacea (30%), and acne (30%) (Figure) and the most common ROA was topical (62.5%). 7.8% of those who had seen a dermatologist used an MCP which required a Department of Health-approved card per their dermatologist's recommendation (DRCR: dermatologist recommended, card requiring), most commonly for acne (68%), psoriasis (28%), and rosacea (28%) (Figure) and the most common ROA was ingestion (50%) per their dermatologist's recommendations. 11.8% of respondents were not comfortable seeing a dermatologist who recommended MCPs and 6.4% of respondents disapproved the use of cannabinoids for dermatologic indications.

Conclusion: This survey shows that consumers use cannabis products for numerous dermatologic conditions.

Inflammatory disorders such as acne, psoriasis, atopic dermatitis, and rosacea were among some of the conditions being most frequently treated by cannabis products. It is important to note that current literature on the subject is limited, and the benefits and risks of use are not well understood. Physicians should be aware of common barriers to initiating treatment with MCPs, such as skepticism and poor understanding, as well as cost and legality issues. Given the interest in medical cannabis for dermatologic use as shown by this study, it is important for dermatologists to stay up to date with the scientific and legal landscapes in order to best serve patient needs. It is important to understand and inform patients who may seek out

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cannabis products that recognized, evidence-based treatments currently remain the standard of care, though MCPs may be a suitable option for

patients who are interested in alternative therapies.

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Patient Experiences with Teledermatology During the COVID-19 Pandemic: A Survey

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The COVID-19 pandemic has drastically changed the practice of dermatology as social distancing guidelines have led to a shift from in-office care to virtual telehealth (teledermatology).¹ We aimed to determine patient satisfaction, perceived barriers, as well as indications for teledermatology appointments during the COVID-19 pandemic.

Methods: A survey was sent out via SurveyMonkey's online platform to the George Washington University Medical Faculty Associates' Department of Dermatology patients who were 18 years and older and attended telehealth appointments during the COVID-19 pandemic.

Results: Out of 894 invitations sent, 168 patients completed our survey (18.8% response rate). The most common reasons for making a telehealth appointment were for a new rash (11.6%), eczema (9.8%), and psoriasis (9.1%) (Figure). The most common reasons respondents liked telehealth

were because of time efficiency (81.1%), not requiring transportation (74.2%), and maintaining social distancing (73.6%). The most common reasons respondents did not like telehealth were due to lack of physical touch (26.8%) and feeling they received an inadequate assessment (15.7%). Very few patients reported that they were unlikely to undertake another telehealth visit (9.94%) or recommend a telehealth visit to others (6.92%).

Conclusion: As the COVID-19 pandemic continues to affect millions of patients who require dermatology care, telehealth proves to be an effective and useful modality to bring care to patients during this public health emergency. The majority of patients who had telehealth encounters with our dermatology department found a telehealth visit to be an adequate substitute for an in-person visit. Major

reported drawbacks include patients feeling like they did not receive an adequate examination or did not have any physician touch though these were still reported in a minority of patients. Overall, the convenience and efficacy of telehealth as well as its ability to maintain separation while social distancing recommendations are in place make it an effective way for dermatologists to continue to provide quality and safe care during the pandemic as well as during potential future public health crises.

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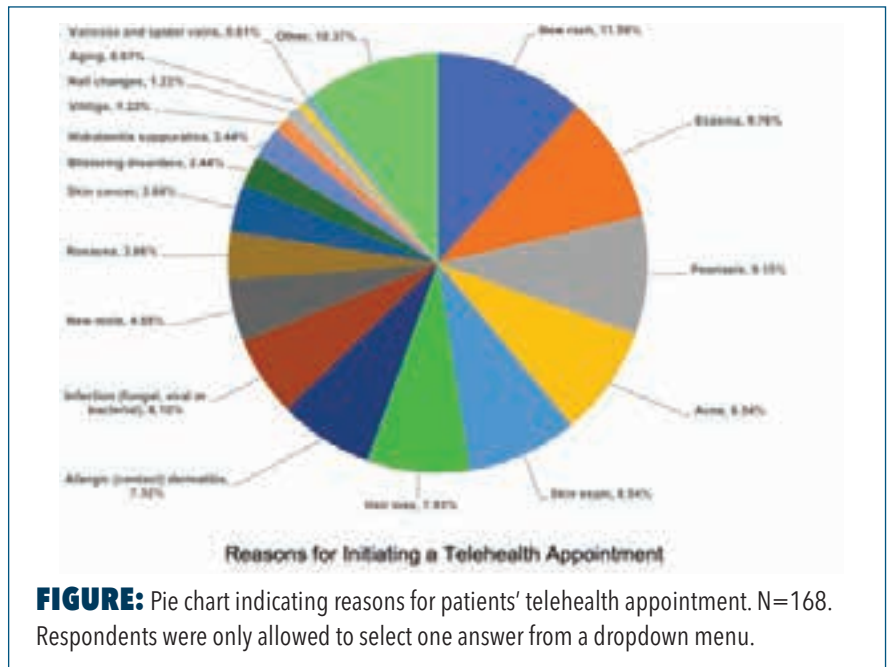


FIGURE: Pie chart indicating reasons for patients' telehealth appointment. N=168. Respondents were only allowed to select one answer from a dropdown menu.

Predicting Deletion of Chromosomal Arms 1p/19q in Low-Grade Gliomas from MR Images Using Machine Intelligence

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Several studies have linked co-deletion of chromosome arms 1p/19q in low-grade gliomas (LGG) with positive response to treatment and longer progression-free survival. Hence, predicting 1p/19q status is crucial for effective treatment planning of LGG. In this study, we predict the 1p/19q status from MR images using convolutional neural networks (CNN), which could be a non-invasive alternative to surgical biopsy and histopathological analysis. Our method consists of three main steps: image registration, tumor segmentation, and classification

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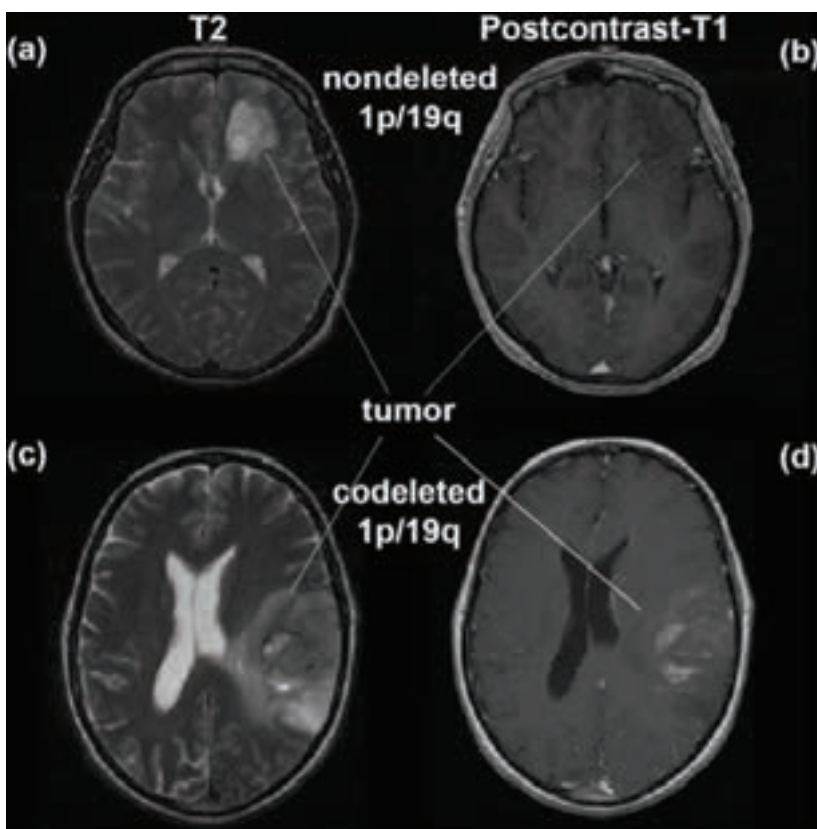


FIGURE 1: An example of low-grade glioma with and without 1p/19q codeletion. Images a and b show T2 and post contrast T1 for non-deleted 1p/19q. Images c and d show T2 and post contrast T1 for codeleted 1p/19q.



FIGURE 2: A flowchart of the multi-scale CNN architecture. Blue box is the input image. Yellow boxes are convolutional layers. Green boxes are rectified linear units (ReLU), activations. Red Boxes are max pooling layers. Purple boxes are fully connected layers, plus a softmax binary classifier. Cyan circle shows the output label.

of 1p/19q status using CNN. We included a total of 159 LGG with three image slices each who had biopsy-proven 1p/19q status (57 non-deleted and 102 co-deleted) and preoperative postcontrast-T₁ (T₁C) and T₂ images. We divided our data into training, validation, and test sets. The training data was balanced for equal class probability and was then augmented with iterations of random translational shift, rotation, and horizontal and

vertical flips to increase the size of the training set. We shuffled and augmented the training data to counter overfitting in each epoch. Finally, we evaluated several configurations of a multi-scale CNN architecture until training and validation accuracies became consistent. The results of the best performing configuration on the unseen test set were 93.3% (sensitivity), 82.22% (specificity), and 87.7% (accuracy). Multi-scale CNN with their self-learning capability provides promising results for predicting

1p/19q status non-invasively based on T₁C and T₂ images. Predicting 1p/19q status non-invasively from MR images would allow selecting effective treatment strategies for LGG patients without the need for surgical biopsy.¹

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Malignant Pineal Parenchymal Tumors in Adults: A National Cancer Database Analysis

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In the absence of randomized trials for adult pineal parenchymal tumors (PPT), we use a national database to evaluate treatment trends and the survival impact of surgery, radiation, and chemotherapy.

Methods: The National Cancer Database was queried for adult patients with histologically confirmed PPT diagnosed from 2004 to 2016. Univariate and multivariate Cox regressions were used to evaluate the prognostic impact of covariates. Kaplan-Meier survival curves

were generated for comparative subanalyses.

Results: A total of 202 patients met inclusion criteria. A plurality of pineoblastoma (PB) patients were treated with trimodal therapy (43.6%, 24/55) (Figure 1). Pineal parenchymal tumor of intermediate differentiation (PPTID) patients were most commonly treated with either surgery alone (35.1%, 47/134) or with surgery and radiation (32.8%,

44/134) (Figure 1). Factors associated with improved overall survival on multivariable analysis included younger patient age, female sex, lower comorbidity score, receipt of surgery, and receipt of radiation (each $p < .05$). Receipt of chemotherapy was not associated with survival. Subanalyses revealed that the effect of radiation on survival was most prominent in PB patients and in PPTID patients who had not received surgery

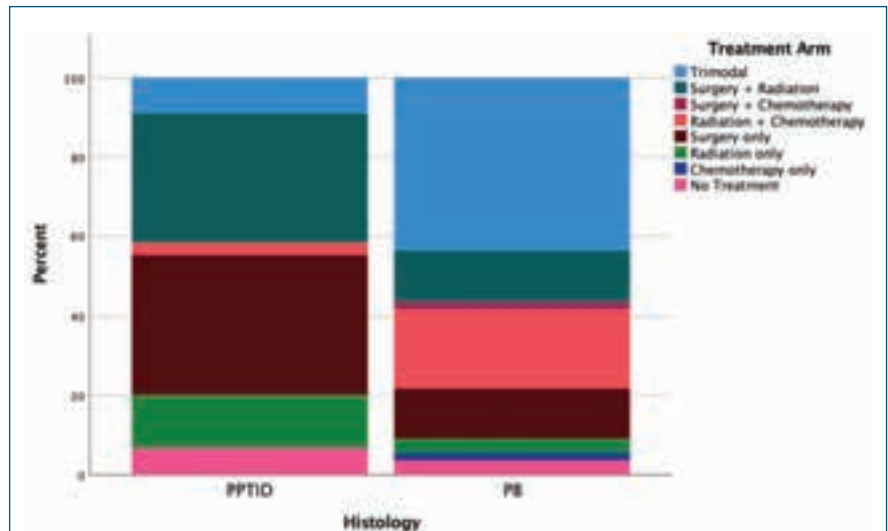


FIGURE 1: Stacked Bar Graph of Treatment Trends for PB and PPTID. PB is most commonly treated with surgery and adjuvant chemoradiation. PPTID is most commonly treated with surgery alone or with surgery and adjuvant radiation.

(Figure 2). No survival benefit of adjuvant radiation was demonstrated in surgically treated PPTID patients (Figure 2).

Conclusions: Currently, there is a paucity of data regarding treatment outcomes for adult PPT tumors, and this is the largest study to date.^{1,2} While radiotherapy and surgery were found to increase survival in all PPT patients, there was no survival benefit of adjuvant radiation in surgically treated PPTID. This suggests overtreatment of many PPTID adult patients with radiotherapy.

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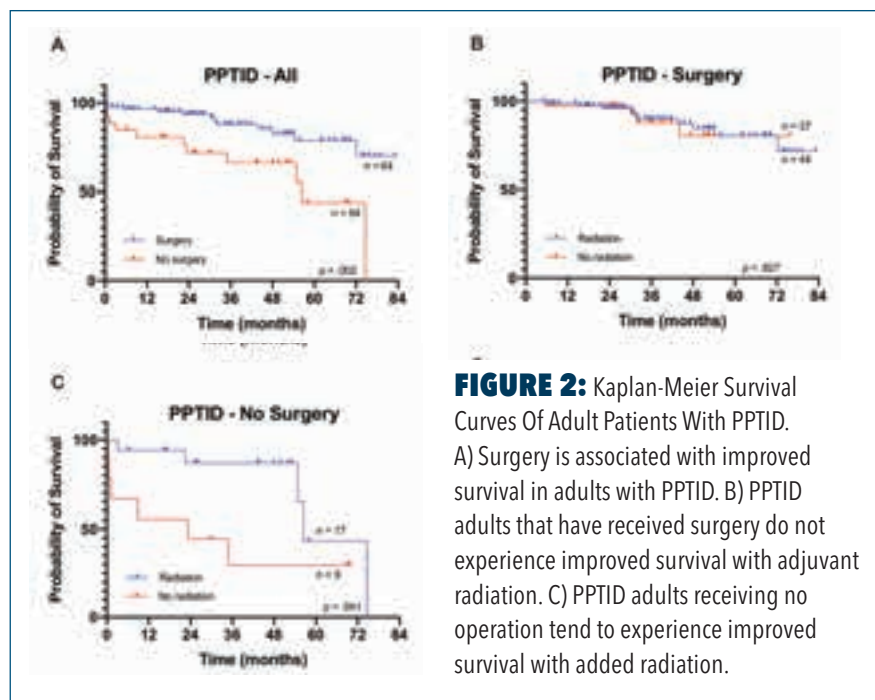


FIGURE 2: Kaplan-Meier Survival Curves Of Adult Patients With PPTID. A) Surgery is associated with improved survival in adults with PPTID. B) PPTID adults that have received surgery do not experience improved survival with adjuvant radiation. C) PPTID adults receiving no operation tend to experience improved survival with added radiation.

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Impact of Variant Histology on Occult Nodal Metastasis after Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Review of the National Cancer Database

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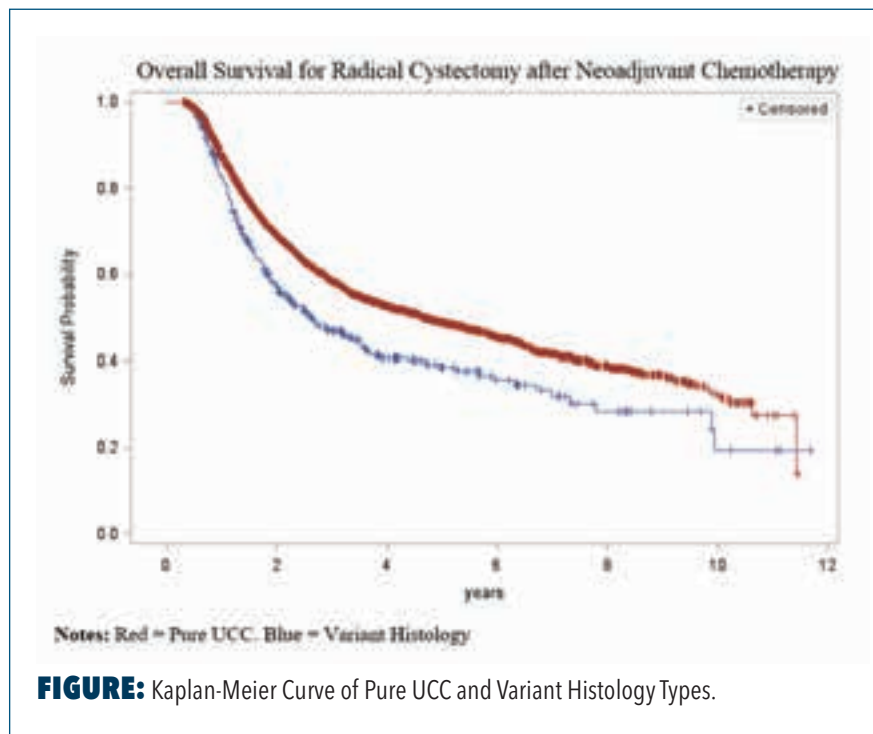
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Variant histology accounts for 30% of bladder urothelial carcinoma cases. Variant histology is associated with a higher incidence of locally advanced disease and occult regional lymph node metastasis.¹ Neoadjuvant chemotherapy (NAC) is the gold-standard treatment for resectable cT2-4 disease as it achieves pathologic complete response in select patients at the time of radical cystectomy (RC). Post-hoc analysis of a landmark randomized trial has demonstrated preserved chemosensitivity and even pT0 status in the setting of variant histology. While there is much interest in the role of bladder preservation for such patients, the observation of pT0N+ pathology in patients who undergo subsequent RC has prompted concerns about this approach.² The aim of this study is to analyze how variant histology impacts pathologic downstaging after NAC.

A retrospective cohort analysis of 5,335 cT2-4NoMo patients who underwent NAC and RC between 2004 and 2016 was performed using the National Cancer Database (NCDB). These patients were stratified by



histological type into pure urothelial cell carcinoma (UCC) and variant groups (i.e. neuroendocrine, micropapillary, squamous, etc.) using the WHO ICD-O classification. The rate of pathologic downstaging to \leq pT1 was analyzed, along with concomitant persistent pN+ status. Overall survival was analyzed using Kaplan-Meier estimation and multivariable Cox-proportional hazards regression, stratified by histology type. Multivariable models were adjusted for confounding demographic and clinicopathologic variables.

Of the cases, 7.9% were variant histology while 92.1% were pure UCC. Pure UCC was associated with significantly better unadjusted survival with a 5-year survival rate

of 48.8% compared to 38.5% in the variant group ($p < 0.001$). After adjusting, UCC was associated with significantly decreased mortality hazard relative to variant histology

Our study showed that the propensity for distant spread contributed to significantly worse survival outcomes in the variant histology group.

(aHR=0.75; $p < 0.001$). UCC had lower adjusted odds of being pN+ (aOR=0.60, $p < 0.001$), specifically pN2 (aOR=0.57) and pN3 (aOR=0.40). Node-positive variant histology patients demonstrated higher node positive count compared to pure UCC (median 3 vs 2 nodes, $p < 0.001$).

Our study showed that the propensity for distant spread contributed to significantly worse survival outcomes in the variant histology group. Patients with variant histology were more likely to harbor occult regional lymph node metastasis in the setting of intravesical pathologic complete response (pTo). Although micropapillary histology was more likely to be downstaged to pTo, the increased likelihood of residual nodal disease reinforces the role of surgical consolidation after NAC for these patients. On the other hand, neuroendocrine histology may allow for successful bladder preservation after chemotherapy given its higher downstaging to pToNo. RC with thorough pelvic lymph node dissection remains the gold-standard for surgical consolidation after NAC, especially in cases of variant histology.

TABLE:

Outcome	Mixed Histology (n=419)	Pure UCC (n=4916)	Adjusted Odds Ratio (95% CI)	p-value
Path Node Status			Reference	-
0	311 (74.2%)	4030 (82.0%)		
1	36 (8.6%)	366 (7.5%)	0.75 (0.51 – 1.11)	0.146
2	55 (13.1%)	426 (8.7%)	0.57 (0.41 – 0.79)	<0.001
3	17 (4.1%)	94 (1.9%)	0.40 (0.23 – 0.70)	0.001
Path Node +	108 (25.8%)	886 (18.0%)	0.60 (0.47 – 0.77)	<0.001
Downstage to pT0	110 (26.3%)	1269 (25.8%)	0.99 (0.75 – 1.31)	0.948
Complete Downstage to pT0N0	104 (24.8%)	1235 (25.1%)	1.04 (0.78 – 1.38)	0.815
Partial downstage to pT0 pTa pT1	45 (10.7%)	689 (14.0%)	1.25 (0.89 – 1.75)	0.192
Any pT downstage	155 (37.0%)	1958 (39.8%)	1.13 (0.89 – 1.44)	0.317
Downstage pT0N1-3	6 (1.4%)	34 (0.7%)	0.53 (0.20 – 1.37)	0.190

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Evaluation of Selective HDAC6 Inhibition as a Potentiator of Antigen-Targeted Immunotherapy in Diffuse Large B-Cell Lymphoma

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Patients with aggressive diffuse large B-cell lymphoma (DLBCL) who fail initial combination therapy, may undergo second-line treatment with curative intent; however, treatment involves high-dose chemotherapy and autologous stem cell transplantation, which is reserved only for eligible candidates.¹ One-third of candidates will proceed with high-dose therapy with durable remission rates limited to approximately 25%.¹

Clearly, there exists a population of patients in need of new treatments. Hope may be found in anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, which has garnered wide success in the treatment of pre-B-cell acute lymphoblastic leukemia (ALL).^{2,3} Although CAR T-cell therapy has not had the same level of success in DLBCL, results remain encouraging and demonstrate a need for further research. Additionally, clinical studies of bispecific anti-CD19xCD3 or anti-CD20xCD3 monoclonal antibodies have shown similar promise.⁴

Despite the excitement surrounding antigen-targeted immunotherapies, these novel treatments face critical obstacles. Patients receiving CAR T-cell therapy or bispecific

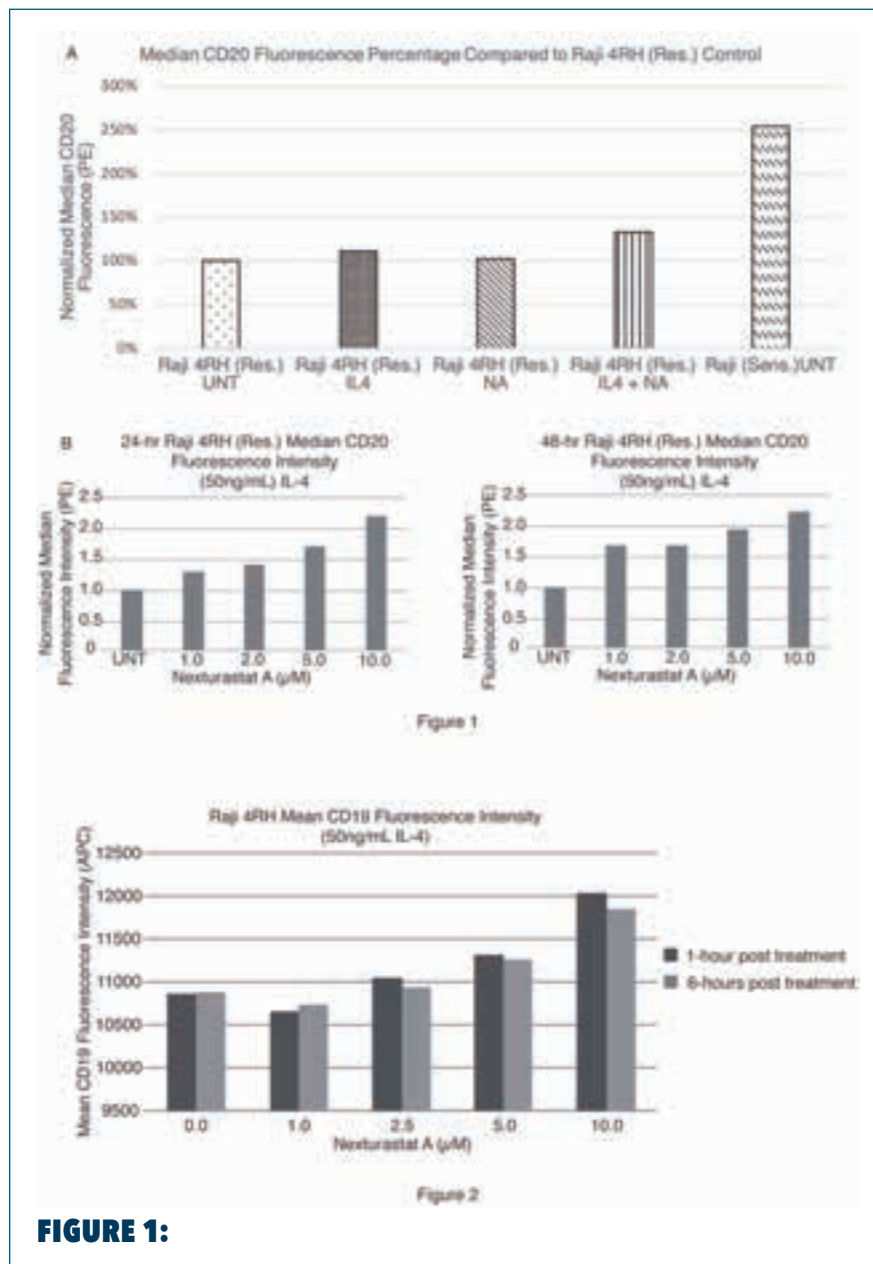


FIGURE 1:

monoclonal antibodies might only benefit from brief remissions or may never enter remission at all.^{2,3} Similar to existing treatments, CAR T-cell therapy is challenged by resistance and failure of long-term disease remission.^{2,3}

One reason may be antigen loss. Several studies have demonstrated the generation of escape variants lacking

the targeted CD19 or CD20 antigens when under the selective pressure of immunotherapy. A theorized mechanism for this is interrupted protein translocation, supported by observations of CD20 trafficking disruption in rituximab-resistant B-cell cancers.⁴

Histone deacetylase 6 inhibitors (HDAC6i) have been well characterized as modulators of protein

trafficking and have been shown to upregulate the expression of CD20 on B-cell tumor lines.^{4,5} Achieving a similar effect with CD19 expression may offer a new avenue for potentiating anti-CD19 CAR T-cell platforms, particularly because immunotherapy studies have shown that only a small diminution of surface antigen may be sufficient for treatment failure.³

Through our studies, we investigated the effect of HDAC6i on surface expression of CD19 and CD20 in rituximab-resistant (CD20-low) Raji4RH cells. Raji4RH cells were treated with either 50 ng/mL IL-4, 5 μ M of the HDAC6i, Nexturastat A (NextA), or a combination thereof for 48 hours. Untreated Raji4RH cells and untreated Raji cells (CD20-high) were used as controls. HDAC6i in combination with IL-4 increased CD20 expression in rituximab-resistant Raji4RH cells (Figure 1a). Later, at concentrations of 10 μ M, HDAC6i achieve a 2-fold increase in CD20 surface expression as reported by median fluorescence intensity compared to the untreated control (Figure 1b). Next, rituximab-resistant Raji4RH cells were treated with 50 ng/mL IL-4 and increasing doses of NextA for 24 hours. (Figure 2). When examining mean CD19 fluorescence, we observed an increase, although modest, in CD19 surface expression at 1-hour and 6-hours post-treatment.

Our results establish that HDAC6is can increase CD20 expression in CD20-low B-cells and suggest a strong potential for HDAC6i to function as a positive modulator of CD20 expression in the setting of resistant disease. Additionally, our studies suggest that there exists an interaction between HDAC6 function and CD19 surface expression. These results are promising as even slight changes in surface expression of antigen targets can greatly influence immunotherapy response. However, further optimization of treatment

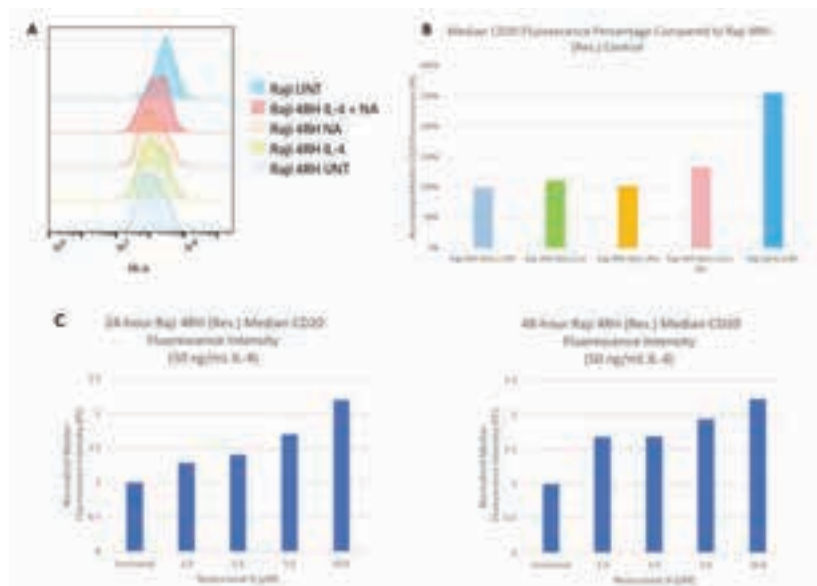


FIGURE 2:

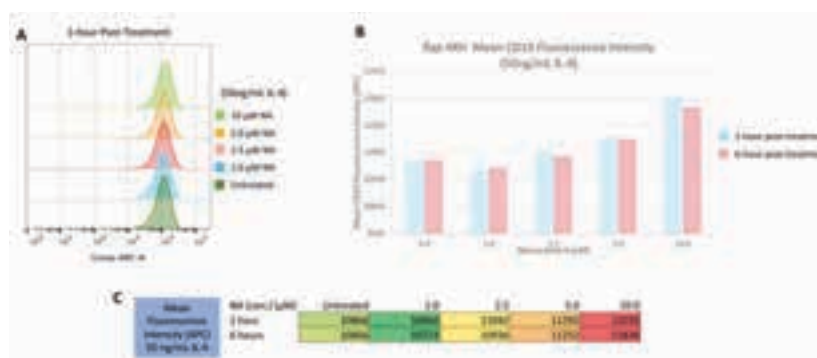


FIGURE 3:

dosing and cytokine combination is necessary, warranting the need for future studies.

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The Impact of Adjuvant Chemotherapy on Oncologic Outcomes of Patients with Locally Advanced Bladder Adenocarcinoma: An Analysis of the National Cancer Database

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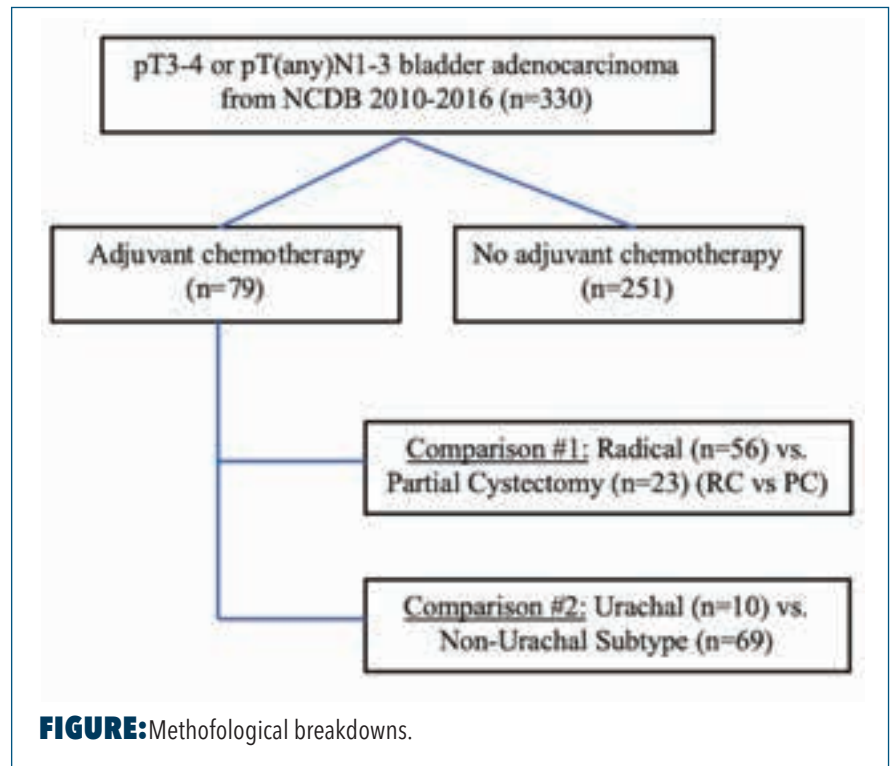
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Adenocarcinoma of the bladder is an especially rare histological subtype of bladder neoplasms, accounting for approximately 0.5-2% of diagnoses in the United States.¹ These tumors can be further classified based on origin from the urachus, an embryologic structure that functions to connect the developing bladder to the allantois. In up to one-third of individuals, remnants of these developmental tissues may persist and serve as a potential location for malignancy. Importantly, there is little consistent evidence regarding the treatment of both non-urachal and urachal adenocarcinomas.² Although radical cystectomy (RC) is often considered the standard of care for both locally advanced urachal and non-urachal adenocarcinomas, there is a paucity of data providing conclusive guidance regarding any additional management options that may be of benefit in such an uncommon histological bladder neoplasm.³ Specifically, the relatively poor prognosis associated with locally advanced bladder adenocarcinoma necessitates investigation of the utility of adjuvant chemotherapy (AC) and



risk stratification of those who would benefit from such systemic therapy. This study seeks to evaluate the oncologic and surgical outcomes of those with locally advanced disease treated with and without AC.

Methods: A retrospective cohort analysis was performed using the National Cancer Database from 2006 to 2016. Patients with non-metastatic locally advanced pT3-4 or pT(any)N1-3 primary bladder adenocarcinoma who received AC only or did not receive AC after radical or partial cystectomy (PC) were included. The AC cohort was further sub-stratified by surgery type (PC versus RC) and disease origin (urachal versus non-urachal subtypes) (Figure). Survival, oncologic, and surgical outcomes were compared between cohorts.

Results: Inclusion criteria identified 79 AC patients and 251 no AC patients. Of the 79 patients who received AC,

23 had PC procedure, 56 had RC procedure, 10 had urachal origin and 69 had non-urachal origin. Receipt of AC was significantly higher in RC relative to PC (27.6% vs 18.1%; $p = 0.049$). Urachal vs. non-urachal subtype did not impact receipt of AC (25.3% vs 17.5%; $p = 0.214$), but urachal subtype was associated with improved overall survival compared to non-urachal (47% vs 18%; HR = 0.37; $p = 0.04$). Although receipt of AC was significantly associated with higher odds of positive margins (46% vs 23%; odds ratio = 2.85; $p < 0.01$), no difference in overall survival was detected between the AC and no AC cohorts (23% vs 19%; hazards ratio [HR] = 0.98; $p = 0.91$). Of note, independent of AC, PC was associated with improved survival compared to RC (51% vs 12%; HR = 0.25; $p < 0.01$).

Conclusions: There is no detected survival benefit to the use of a

non-standardized AC regimen in locally advanced bladder adenocarcinoma. Within the AC treated population, survival outcomes suggest that urachal subtype may confer survival advantage and that those patients selected for PC tend to have improved survival. Although employing a national dataset, statistical power was limited given the rarity of this disease.

Further investigation is warranted on a larger scale in order to assess the impact of AC regimen, afford proper patient selection, and enhance risk stratification for oncologic outcomes.

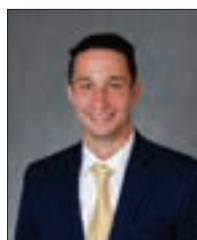
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Comparison of Perioperative Characteristics and Outcomes for Minimally Invasive vs Open Retroperitoneal Lymph Node Dissection for the Treatment of Testicular Cancer: A NSQIP Analysis

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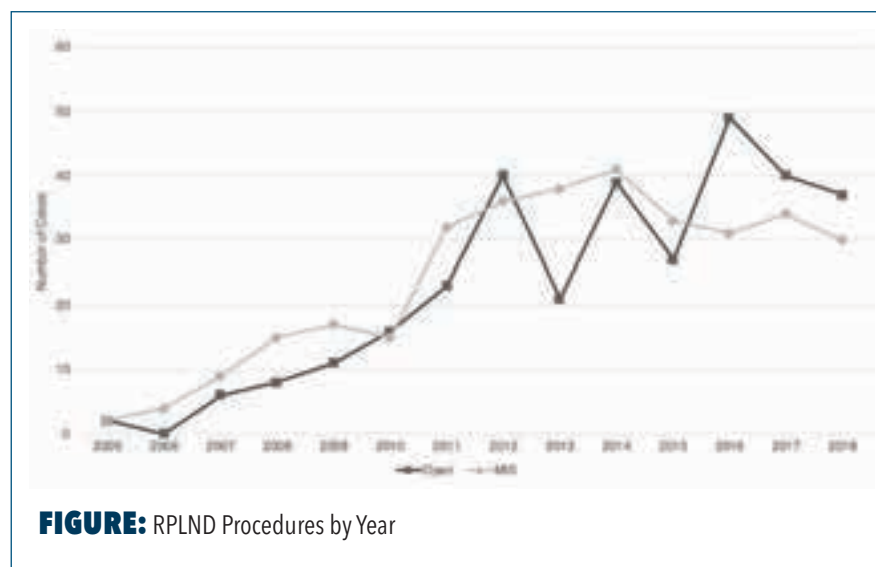


FIGURE: RPLND Procedures by Year

Testicular cancer is the most common solid tumor in young men ages 20 to 34 years old.¹ Primary retroperitoneal lymph node dissection (RPLND) is an established post-orchietomy treatment option for men with clinical stage I and IIA/B non-seminomatous germ cell tumors (NSGCTs).^{1,2} Open RPLND is currently considered the gold standard approach for low stage NSGCT; however, it is a major abdominal procedure associated with significant morbidity and prolonged hospital stays.^{3,4} A minimally invasive surgical (MIS) approach seeks to afford patients similar oncologic outcomes with decreased morbidity. Outcomes in robotic and laparoscopic RPLND for the management of NSGCT have been studied in recent case series, however limited data currently exists directly comparing outcomes in MIS versus open

RPLND. As such, the present study queries the National Surgical Quality Improvement Program (NSQIP) database to assess 30-day perioperative outcomes and characteristics for MIS vs open RPLND along with trends over time.

The NSQIP database (2005–18) was queried for patients with non-disseminated testicular cancer ± retroperitoneal lymph node involvement. Patients with distant metastasis, a history of chemotherapy, or a history of radiation therapy were excluded. Chi-square, Fisher's exact test, independent samples t-test, and Mann-Whitney U test were used to identify unadjusted associations and potential confounding covariates.

Multivariable logistic regression and multivariable generalized linear models were used to analyze independent associations between treatment approach and perioperative outcomes. Trends over time were analyzed by way of Spearman's rank correlation coefficient analysis, ρ . All statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) with a two-sided p-value < 0.05 considered statistically significant.

Inclusion criteria identified 646 patients; 337 (52.2%) with MIS treatment and 309 (47.8%) with open treatment. Compared to open, MIS RPLND was significantly associated

Continued on p. 42

TABLE: Multivariable Analysis for Perioperative Outcomes

30-Day Outcome	Open (n=309)	MIS (n=337)	Unadjusted p-value	aOR (95% CI) or β (SE)	Multivariable p-value
Superficial SSI	4 (1.3%)	2 (0.6%)	0.433	0.87 (0.12 – 6.34)	0.89
Bleeding Transfusion	23 (7.4%)	13 (3.9%)	0.047	1.19 (0.54 – 2.62)	0.672
Mortality	–	3 (0.9%)	0.25	NE	–
Return to OR	5 (1.6%)	9 (2.7%)	0.359	1.07 (0.28 – 4.12)	0.927
Acute Care Stay >30 day	–	1 (0.3%)	0.999	NE	–
Reoperation	4 (1.3%)	6 (1.8%)	0.754	0.96 (0.19 – 4.69)	0.955
Readmission	18 (5.8%)	20 (5.9%)	0.953	0.96 (0.44 – 2.14)	0.928
C. Difficile	1 (0.3%)	3 (0.9%)	0.625	NE	–
Operative Time Mean \pm SD	274 \pm 124	147 \pm 118	<0.001	-35 (9)	<0.001
Length of Hospital Stay Median (Q1, Q3)	4 (3, 6)	1 (0, 5)	<0.001	-0.41 (0.07)*	<0.001

aOR=adjusted odds ratio for MIS vs open; CI=confidence interval; β =parameter estimate; SE=standard error; OR=operating room; SSI=surgical site infection; NE=not estimable due to too few events; SD=standard deviation; Q1=first quartile; Q3=third quartile; * β (SE) natural logarithm transformed for nonparametric distribution before reverse transform for interpretation.

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with older age, non-White race, diabetes, hypertension, weight loss >10% 6 months prior to surgery, and lymph node involvement (all respective $p < 0.05$). There was a trend level association between MIS RPLND and a higher proportion of chronic steroid use, pre-operative transfusion, and higher American Society of Anesthesiologists (ASA) classification (all respective $p < 0.1$). Multivariable analysis detected no significant difference in rates of superficial surgical site infection, 30-day mortality, unplanned return to OR, acute care stay > 30 days, reoperation, readmission, or C. Difficile complications. MIS RPLND was significantly

associated with 35 ± 9 minute shorter adjusted operative time and $51\% \pm 7\%$ shorter adjusted hospital stay (respective $p < 0.05$) (Table). RPLND volume has increased since 2005 ($p = 0.724$; $p = 0.003$) with the open approach being utilized more often in recent years ($p = 0.101$; $p = 0.013$) (Figure).

MIS RPLND demonstrated comparable perioperative outcomes to open RPLND with decreased length of hospital stay, despite higher burden of comorbidities. Although lymph node yield could not be assessed within the limitations of NSQIP, the shorter operative time of MIS reinforces the importance of thorough dissection and adherence to template-based or full bilateral dissection as indicated, regardless of the surgical modality.

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Robotic-Assisted Laparoscopic Approach to Radical Cystectomy Mitigates Surgical Complications in Patients with Preoperative Malnutrition

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There is growing evidence of the adverse impact of preoperative malnutrition and hypoalbuminemia on perioperative and postoperative complications following radical cystectomy (RC) for the treatment of muscle-invasive bladder cancer. A robotic-assisted laparoscopic approach to RC is becoming more widely used and, based on its reduced perioperative morbidity, could potentially be a preferable surgical modality for patients with nutritional deficits. Prior studies examining the impact of malnutrition on outcomes after RC have not explored the influence of surgical modality. This investigation will evaluate the associations of robot-assisted surgical approach with perioperative and 30-day postoperative complications after RC. It will also evaluate the effects of preoperative malnutrition and hypoalbuminemia on perioperative and 30-day postoperative complications after RC in the study cohort.

Methods: Retrospective review of the American College of Surgeons

(ACS) National Quality Improvement Database (NSQIP) identified patients who underwent RC with postoperative diagnosis of bladder cancer and non-disseminated disease (2005–18).^{1,2} Surgical approach was categorized as open vs. robotic/laparoscopic. Given there is not a universally accepted definition of “malnutrition” we analyzed the data in multiple ways to explore our hypotheses. The analysis was performed using a composite group (low serum albumin (<3.5g/dL), 10% 6-month preoperative weight loss, or BMI <18.5 kg/m²) as well as a separate analysis for hypoalbuminemia only and there was not a significant difference in outcomes. Therefore, for this investigation, malnourishment was defined as either having low serum albumin (<3.5g/dL), 10% 6-month preoperative weight loss, or BMI <18.5 kg/m². Multivariable logistic regression and generalized linear models were used for categorical and continuous outcomes, respectively, to characterize the association between robotic-assisted surgical approach and 30-day perioperative/postoperative complications following RC compared to non-robotic operations.

Results: Of 7,974 patients identified, 730 (9.3%) were robotic-laparoscopic and 7235 (90.7%) were open. There were 1370 (17.2%) malnourished patients and 6604 (82.8%) non-malnourished. In the 739 robotic cases, 102 (13.8%) were malnourished. Malnourished patients were more

likely to be older, female, current smokers, have COPD and higher American Society of Anesthesiology (ASA) score. Regarding perioperative complications, malnourishment was associated with greater preoperative transfusions, systemic sepsis, peri/postoperative bleeding transfusions, 30-day mortality, postoperative C. difficile infection rate, and hospital length of stay — despite actually shorter operative time. In non-malnourished patients: robotic approach was associated with lower adjusted odds of bleeding transfusion (aOR=0.39), return to OR (aOR=0.55), and fewer adjusted

The typical benefits seen with robotic surgery translate to malnourished patients, although they are still prone to longer hospital stay than their adequately nourished counterparts.

days from operation to discharge (β [SE]= -1.3[0.3]) compared to open (all respective $p < 0.05$). In malnourished patients: robotic approach was associated with lower adjusted odds of bleeding transfusions (aOR=0.51) and fewer adjusted days from operation to discharge (β [SE]= -5.2[1.1]) compared to open (all respective $p < 0.05$).

Conclusions: Robotic-laparoscopic approach to RC mitigated two of the postoperative complications associated with malnutrition: bleeding transfusions and days from

Continued on p. 44

operation to discharge. The typical benefits seen with robotic surgery translate to malnourished patients, although they are still prone to longer hospital stay than their adequately nourished counterparts. Further improvements in perioperative pathways are needed to optimize the experience of malnourished

patients undergoing radical cystectomy, especially given the observed association with other high risk comorbidities. These findings highlight the fact that a robotic approach to RC may be preferable for patients with preoperative nutritional deficits.

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A Contemporary Analysis: Presenting Symptoms in Patients with a Vascular Ring and Predictors of Symptom Resolution After Surgical Repair

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Vascular rings are rare congenital anomalies of the aortic arch which result from inappropriate embryologic regression of the paired branchial arches. The term "vascular ring" indicates vascular anomalies that encircle the intrathoracic portion of the esophagus and trachea.¹ Vascular rings can cause respiratory or gastrointestinal symptoms due to compression of these structures, which are expected to improve with surgical division. Advances in imaging technology have resulted in early detection in asymptomatic patients. This poses new challenges for management of patients with known vascular rings. We sought to analyze the presence

and patterns of symptoms associated with vascular rings, including severity and time to symptom onset from birth, and to determine predictors of symptom resolution after surgery.

Methods: Single-center, 10-year retrospective review of all patients diagnosed with isolated vascular rings between January 2010 and December 2019. Vascular rings were classified as either double aortic arch (DAA) or right aortic arch with left ligamentum arteriosum (RAA) by

echocardiography. Respiratory and GI symptoms were examined for their possible influence on surgical intervention and stratified using a severity score.

Results: One hundred patients with isolated complete vascular ring met inclusion criteria. Thirty-four patients (34%) had a DAA and sixty-six (66%) had RAA. Seventy-five patients (75%) were diagnosed after presenting with respiratory or gastrointestinal symptoms; twenty-five

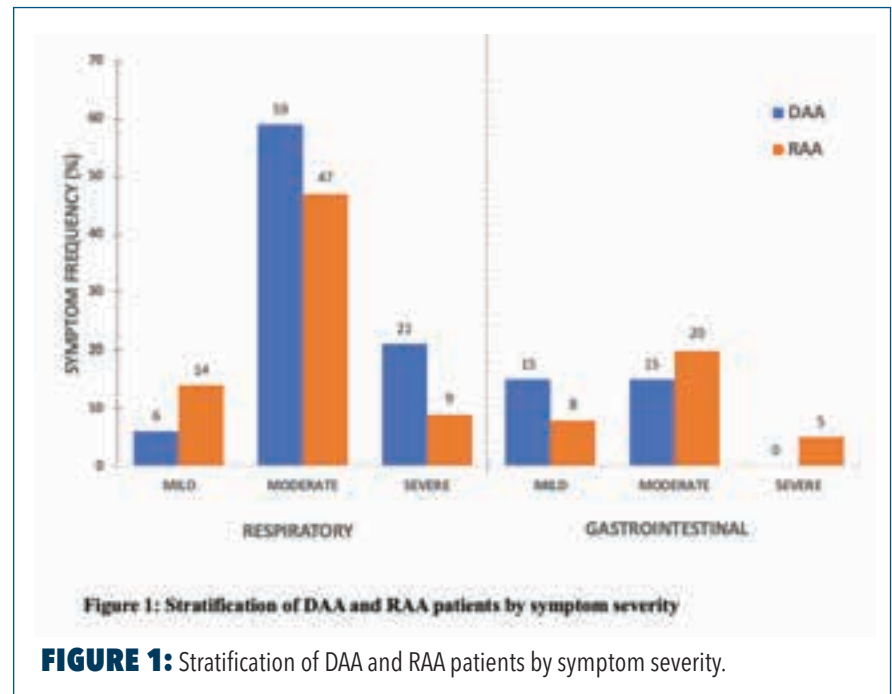
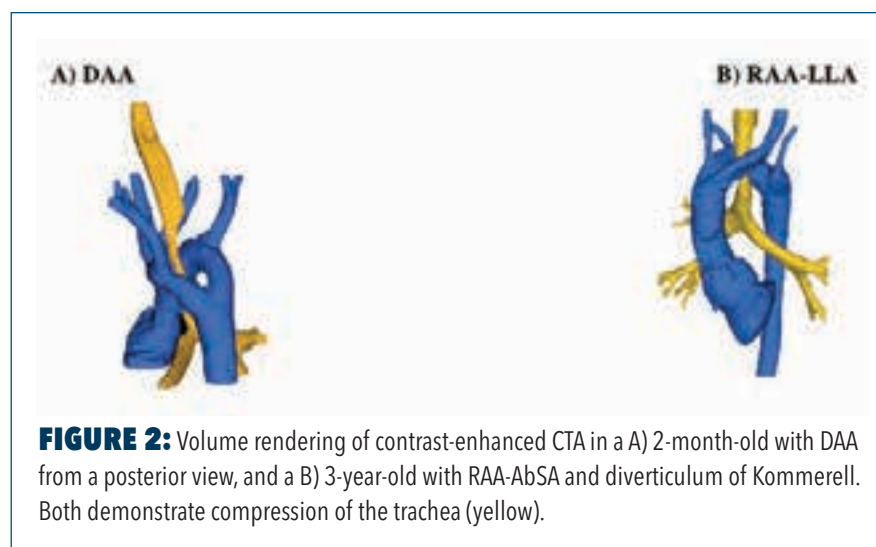


FIGURE 1: Stratification of DAA and RAA patients by symptom severity.

(25%) were asymptomatic at presentation, diagnosed incidentally. Symptoms were stratified by severity (Figure 1) and respiratory symptoms were found to be more frequent, regardless of arch anatomy.

Seventy-four patients (74%) underwent surgical division of the vascular ring, out of which 99% (73/74) were symptomatic. Forty-two patients (63%) with RALL (n=42) received surgical intervention compared to thirty-two patients (94%) with DAA. Chi-square analysis found moderate/severe respiratory symptoms predictive of surgery in patients with a RALL (OR 6.0, $p = 0.002$). At a median follow-up of 2.2 years, incidence of overall symptoms decreased significantly in patients who underwent surgical division ($p < 0.001$); only 28 patients (39%) exhibited persistent symptoms. The incidence of respiratory symptoms, including stridor and recurrent respiratory infections, as well as GI symptoms, decreased significantly in the postoperative period ($p < 0.001$). There was no change in the incidence of asthma symptoms in patients undergoing surgical intervention ($p = 0.808$). Neither age at operation ($p = 0.158$) nor the anatomic type of the ring ($p = 0.332$) were predictive of symptom resolution. The presence



of airway narrowing on pre-operative bronchoscopy or computed tomography resolved significantly postoperatively (62%, $p < 0.001$). Incidence of recurrent respiratory infections was higher in the patients with residual tracheal narrowing after surgical division (3/20 vs 0/54; $p = 0.02$). Survival was 100% (74/74).

Conclusions: Surgical division of the vascular ring leads to resolution of obstructive symptoms in the vast majority of patients, with the exception of symptoms of asthma. Patients with symptomatic isolated vascular rings should be offered surgical intervention; those who present predominantly with symptoms of asthma may

not benefit from surgery. Although RALL is more common than DAA, the latter are more likely to undergo surgical intervention regardless of symptom severity. Presence of postoperative residual tracheal narrowing predicts a persistence of respiratory tract infections, but not other symptoms. A coordinated multidisciplinary investigation of obstructive respiratory and gastrointestinal symptoms is necessary for early diagnosis of vascular rings and appropriate referral for surgical intervention.

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Cardiovascular Surgical Outcomes of Patients with Heterotaxy Syndrome and Predictors of Mortality in the Current Era

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Heterotaxy syndrome may be defined as a spectrum of abnormally discordant organ situs resulting from aberrant left-right axis determination in the thoracic and abdominal cavities.¹ The abnormal degree of thoracic and abdominal visceral symmetry is associated with complex intracardiac abnormalities, which may require cardiovascular surgery early in life. We sought to analyze outcomes of patients with heterotaxy syndrome undergoing cardiovascular surgical repair, with a focus on univentricular palliation vs full biventricular repair, and to determine predictors of mortality.

Methods: A single-center, 10-year retrospective review of all patients diagnosed with heterotaxy syndrome who underwent cardiovascular surgical repair from January 2008 to December 2017. Diagnosis of heterotaxy syndrome was based upon evaluation of thoracoabdominal situs by echocardiography. Patients were classified as either single ventricle (SV) or biventricular (BV) according to their functional anatomy after repair. Univariate and multivariable Cox regression analysis and Kaplan-Meier analysis for survival were performed.

Results: Eighty-two patients with heterotaxy syndrome met inclusion criteria. Fifty-five patients (67%) underwent SV palliation and twenty-seven (33%) underwent complete BV

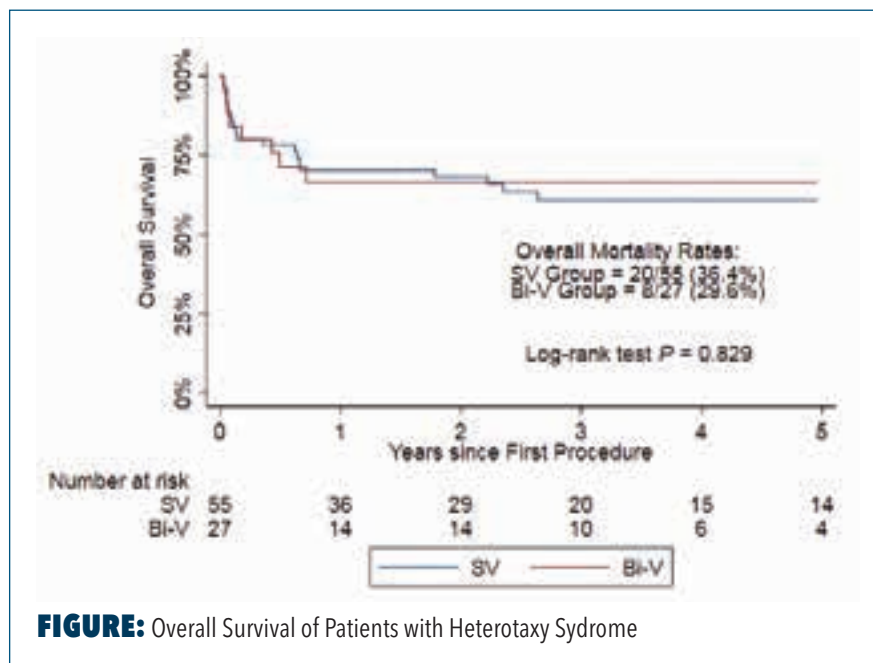


FIGURE: Overall Survival of Patients with Heterotaxy Syndrome

repair. Patient mortality in the entire cohort was 34% (28/82) including 36% (20/55) for SV palliation and 30% (8/27) for BV repair. Interstage mortality among SV patients was 29% after stage 1 (12/46), 17% after stage 2 (7/42), and 4% after stage 3 (1/23). Among all heterotaxy patients, independent risk factors for mortality included pre- or post-operative ECMO (HR=10.4; 95% CI: 4.3-25.4; P<0.001), TAPVR (HR=4.3; 95% CI: 1.7-10.8; P=0.002), and body weight <2500g (HR=2.4; 95% CI: 1.0-5.4; P=0.041). Among patients undergoing SV palliation, significant multivariable risk factors for mortality included ECMO (HR=11.0; 95% CI: 3.6-34.2; P<0.001) and TAPVR (HR=7.0; 95% CI: 2.3-21.7; P=0.001). Pulmonary vein stenosis was a significant univariate predictor of mortality among all heterotaxy patients (HR=3.0; 95% CI: 1.4-6.4; P=0.005) and in the subgroup of SV patients (HR=4.0; 95% CI: 1.7-9.7; P=0.002). Overall survival of all heterotaxy patients was 66% (54/82) at a median follow-up time of 2.2 years (0.4-4.1) from the first operation (Figure).

Conclusions: Despite advancements in perioperative care and refinement of cardiovascular operative techniques, there is still considerable mortality in children with heterotaxy syndrome in the current era. Significant risk factors for mortality in these patients include body weight <2500g, TAPVR, and ECMO, which may help to further inform surgical decision-making. Surgeons should proceed with caution in patients with pulmonary vein stenosis, as this is a significant predictor of mortality irrespective of the functional cardiac anatomy after repair. There was comparable observed survival after the first procedure, though objective overall long-term survival was higher in those who received complete biventricular repair. Further understanding of this complex patient population is needed to overcome poor prognostic factors and improve overall long-term survival.

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Is Epidural Analgesia Necessary for Unilateral Hip Reconstruction in Children with Neuromuscular Conditions?

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Proximal femur and pelvic osteotomies are commonly used to correct spastic hip dislocations in children with cerebral palsy (CP). Treatment of postoperative pain, in these often cognitively impaired children, is challenged by difficulty self-reporting pain.^{1,2,3} While undertreated pain causes suffering, overtreatment can precipitate respiratory compromise in this vulnerable population.^{1,3,4} In patients with CP undergoing spine surgery, epidural analgesia has been shown to decrease intensive care unit admissions due to respiratory decompensation.⁴ Thus many centers are also using epidural anesthesia for children undergoing lower extremity surgery.

Epidural analgesia is often continued for 2–3 days, during which time a Foley catheter is left in place until the epidural catheter is discontinued.⁵ Neural-blockade in unilateral surgeries often delays physical therapy, further delaying patient discharge. This study sought to determine if there was a difference in pain control between the use of epidural analgesia versus non-epidural pain control modalities

for patients with neuromuscular conditions undergoing unilateral hip reconstruction. Additionally, we sought to quantify differences in length of stay between the two populations.

Methods: Following approval from the Institutional Review Board, we performed a retrospective chart review of pediatric hip reconstructive procedures in which either epidural or non-epidural analgesia was administered for postoperative pain relief. We identified patients who underwent unilateral or bilateral proximal femoral osteotomies, pelvic osteotomies, or hip open reductions from Jan. 01, 2009 to Dec. 2, 2019, which yielded 227 patients. We excluded patients who had a revision surgery and those without neuromuscular conditions. The final cohort consisted of 82 cases that met all criteria, of which 66 underwent unilateral procedures. Demographics, laterality of surgery, postoperative pain control modality, duration of pain control modality, and length of stay at hospital were recorded. Pain scores were recorded using the FLACC pain scale.

Results: Of the patients undergoing unilateral procedures, 37 used non-epidural pain-control modalities, and 29 used epidural analgesia. The average ages of the epidural group and non-epidural group were 8.82 years and 10.61 years, respectively. The epidural group had median, mean, high, and low pain scores for the length of their stay of 3.5, 3.45, 5.93, and 1.31, respectively. The epidural group had a mean length of stay of 6.34 days. The non-epidural group had median, mean, high, and low pain scores for the length of their stay of 3.43, 3.62, 6.27, and 1.77, respectively. The non-epidural group had a mean length of stay of 4.41 days. An unpaired t-test was used to analyze the data, and there were no significant differences in

median ($p=0.84$), mean ($p=0.52$), high ($p=0.54$), and low ($p=0.09$) pain scores between the epidural and non-epidural groups. There was also no significant difference ($p=0.09$) in the length of stay between the groups.

Conclusion: There were no significant differences in pain scores or length of stay between the epidural and non-epidural groups.

Significance: These results suggest that patients undergoing unilateral hip reconstruction do not benefit from epidural analgesia when compared to non-epidural pain control modalities. We are hopeful that this will allow practitioners to standardize postoperative pain control in this patient population.

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Facial Nerve Dysfunction after Mandibular Distraction Osteogenesis for Robin Sequence

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Mandibular distraction osteogenesis (MDO) is a staged intervention frequently used to address airway obstruction in infants with Robin Sequence (RS). Facial nerve dysfunction (FND) is a well-known but poorly documented complication that may occur during device placement/osteotomies, active distraction/lengthening, consolidation, and/or device removal. The aim of our study was to precisely and fully document this adverse event in our recent experience to identify possible risk factors that may be associated with this increasingly popular surgical airway procedure.

Methods: A retrospective review of a prospectively gathered database was performed to identify patients with RS that underwent MDO at our institution from March 2013 to June 2020. We included all infants

who did not exhibit FND, had early resolution of FND, or had FND with at least three months follow-up after device removal. Basic demographic data and factors potentially related to FND were documented, including onset, laterality, time to resolution, and incidence of long-term palsy.

Results: 23 patients with RS were included in the analysis. 56.5% of patients were female and the majority of patients had an associated syndromic diagnosis (65.21%, n=15). Average age at the time of device placement was 2.4 months. Mean latency, distraction and consolidation phase were 1.9 days, 19.1 days, and 82.1 days, respectively. Mean distraction rate was 1.2 mm/day. FND was documented in 39.1% (n=9) of patients, six of which were temporary. The majority of FND cases occurred during the distraction phase and one FND during the consolidation period. FND persisted in 3 patients for a mean of 25 months after device removal. All FND cases involved the marginal mandibular branch, with one patient presenting with additional involvement of zygomatic branch. FND was not detected immediately

following distractor placement/osteotomies or device removal.

Conclusions: FND associated with MDO for infants with RS is not uncommon. Our study demonstrated that most cases of FND occurred during the active distraction phase, likely due to a stretch injury of the marginal mandibular branch. While the majority of FND cases are transient, a small proportion may persist. Future studies must

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aim to characterize risk factors for FND, as well as identify strategies for mitigating the risk of this adverse event.

Objective: This study is the first to characterize the prevalence of permanent and transient facial nerve dysfunction experienced by a cohort of RS patients following MDO at a single institution in recent years.

Radiosurgery for Brain Metastases From Ovarian Cancer: An Analysis of 25 Years' Experience with Gamma Knife Treatment

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Cerebral metastases from gynecological tumors are rare and usually develop late in the course of the disease. The incidence of brain metastases in ovarian cancer is between 1% and 3% with a recent increase likely related to earlier diagnosis with modern imaging techniques (CT, MRI, PET) and more effective systemic therapies allowing prolongation of the patient's life.^{1,2} Life expectancy in these patients is poor. Typically, the treatment of brain metastasis in patients with ovarian cancer has consisted of a multimodal approach including surgery, radiation, and chemotherapy. Whole brain radiation therapy (WBRT) for brain metastases has not changed its poor prognosis and very short survival. Stereotactic radiosurgery (SRS) is becoming a new paradigm in the management of these patients, in which high doses of collimated radiation are delivered by a linear accelerator or by a Gamma Knife.

A retrospective analysis of all patients with ovarian cancer treated with Gamma Knife SRS (GKRS) at outpatient centers from October 1993 to January 2019 was performed.

TABLE:

Characteristics	Median (range)	Mean (range)	Total Number	Percentage
Age (years)	60 (39-79)	60 (39-79)		
KPS %	90	88		
90			7	78%
80			2	22%
No. of brain metastases	2 (1-11)	3 (1-11)		
1	-	-	4	44%
>2	-	-	5	56%
Location of brain metastases			45	
Supratentorial	-	-	29	64%
Infratentorial	-	-	16	36%
Tumor volume at GKRS (cm ³)	1.9 (0.4-30.3)	3.9		
Prescribed dose (Gy)	17	15.8		
Previous treatment	-	-	9	100%
Radiotherapy				
Chemotherapy	-	-	9	100%
Resection of primary	-	-	9	100%
Surgery of metastatic disease	-	-	2	22%
WBRT	-	-	1	12%
Follow-up time (months)	50	54		

Inclusion criteria included tissue-confirmed diagnosis of epithelial ovarian cancer with evidence of brain metastases as diagnosed by computed tomography (CT) and magnetic resonance imaging (MRI). Karnofsky score (KPS), age at diagnosis, radiosurgery dose, and survival time were analyzed. Of 872 women diagnosed and treated for brain metastases in the center, nine had primary ovarian cancer (1.03%). At presentation six of the nine patients had a KPS of 90%, one with 80% and two patients had no documented score. The median age at first treatment was 57 years old.

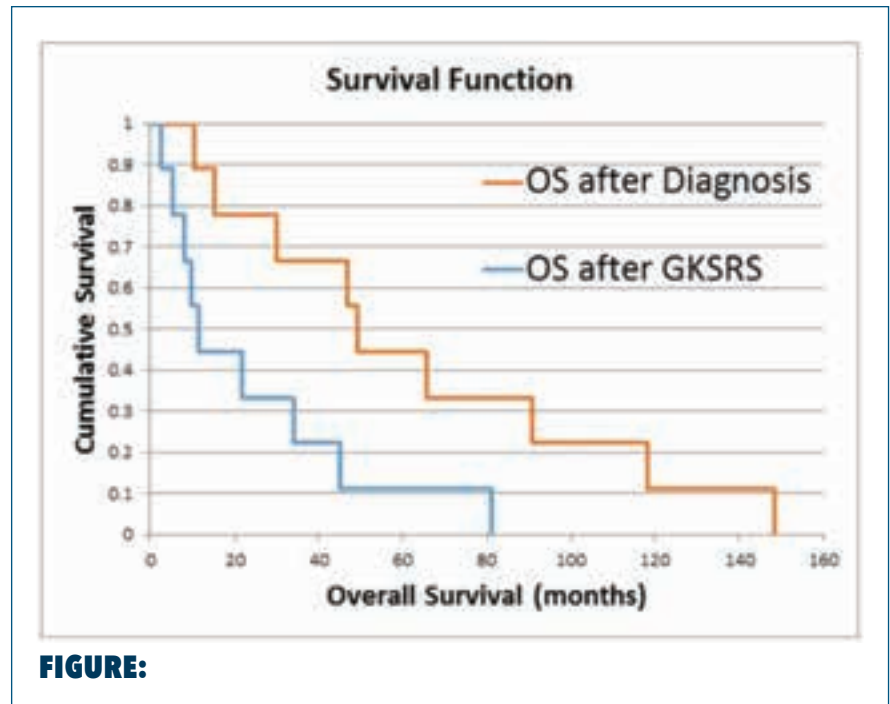
Radiosurgery in these patients was done by GKRS that delivers a high-dose fraction radiation to the target using Cobalt-60 as the radioactive source. A stereotactic frame fixed to the patient's head resulted in unsurpassed accuracy and precision. A brain MRI with contrast was obtained immediately prior to the treatment. The following organs at risk were contoured: brainstem, optic chiasm, optic nerves, lens and any other of pertinent structure. Forty-two metastases were treated

Continued on p. 50

with 16 procedures in the nine patients.

In this group of patients, the interval between diagnosis of ovarian carcinoma and development of brain metastases ranged from -1.0 to 125.5 months with a median of 31.5 months. The -1.0 stands for one patient whose brain metastasis was found prior to the primary tumor. The median overall survival time estimate from original diagnosis of ovarian cancer (OS2) was 48 months, ranging from 10.6 to 148.4 months. The median overall survival after GKRS (OS1) was 10.6 months ranging from 2.5 to 81.1 months.

Although this study should be interpreted with caution because of the limited number of patients, our results are in accordance with the current published literature. In general, the median survival after diagnosis of brain metastases is usually six months; nevertheless, better survival can be achieved when multimodality therapy



is used. GKRS is a valuable modality for management of brain metastases that is minimally invasive and well tolerated.

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A Retrospective Analysis of Trigger Point Injections in the Management of Post-surgical Pain in Patients Who Had Anterior Cervical Surgery

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The opioid epidemic has launched the United States into a public health crisis, resulting in a greater emphasis on non-opioid multimodal pain control methods. At our institution, postoperative posterior neck stiffness and myofascial pain is a common concern after anterior cervical surgery (ACS), likely due to prolonged intraoperative positioning in neck extension. Studies have shown successful analgesic outcomes of trigger point injections with local anesthetic for generalized myofascial pain.^{1,2} This retrospective pilot study aimed to evaluate whether trigger point injections with bupivacaine decrease postsurgical pain compared with traditional therapies in patients undergoing ACS and thereby decrease the amount of opioid medication used.

Methods: We retrospectively reviewed all ACS cases from January 2019 to March 2020 at a single university hospital. We identified patients who received trigger point injections with 0.25% bupivacaine (TP) versus standard care (SC). In the TP group, only one TP was performed and administered in multiple locations along the bilateral trapezii and rhombi

TABLE: Primary outcomes of anterior cervical surgery patients receiving postoperative standard pain control versus trigger point injection at multiple time points.

Outcome	Standard Care (n=47)	Trigger Point Injection (n=28)	p-value
OME	(mg)	(mg)	
6 hours	32±2.8 (n=47)	22±3.0 (n=28)	0.025*
12 hours	54±5.1 (n=29)	37±10.5 (n=9)	0.18
24 hours	78±7.1 (n=27)	58±18.9 (n=6)	0.35
VAS			
6 hours	3.4±0.4 (n=47)	3.3±0.4 (n=28)	0.78
12 hours	5.3±0.6 (n=29)	4.2±1.3 (n=9)	0.45
24 hours	5.4±0.6 (n=27)	3.2±1.5 (n=6)	0.21

Data presented as Mean±Standard Deviation, OME: Oral Morphine Equivalent, VAS: Visual Analog Scale, * p-value was <0.05

by an anesthesiologist. Patients were excluded if TP was performed >3 hours from surgery, if patient was in recovery for opioid use disorder, underwent a posterior approach, staged surgery, or sustained cervical trauma. The primary outcomes were pain control through the Visual Analog Scale (VAS) and calculated oral morphine equivalents (OME) taken at 6, 12, and 24 hours postoperatively. Secondary outcomes included length of stay. Statistical analysis was performed, and p-values were based on Welch's t-test.

Results: There were 137 patients who received anterior cervical surgery (100 SC, 37 TP), and 62 were excluded. A total of 75 (47 SC, 28 TP) patients were included in this study. The average age of patients was 56 years old. The average OME at 6 hours was significantly lower when comparing SC vs TP (32 vs 22, p=0.025). There was no significant difference in average VAS at all time points and average OME at 12 and 24 hours (Table). 50% of patients were discharged by 18 hours.

Discussion: Within six hours of the postoperative period, TP led to significantly lower opioid consumption, without affecting overall pain level. Therefore, in this retrospective study, TP is an effective alternative opioid-sparing method of pain control for myofascial neck pain in the immediate postoperative period after ACS. This is an important consideration for pain control management during the opioid epidemic.

Limitations of this retrospective study were the small number of study participants, that many patients were discharged before 18 hours, and that some may have been on chronic pain therapy. Using the lessons learned here, a prospective double-blinded randomized controlled study will be designed and conducted to compare with the results of this retrospective study. Additionally, future studies can continue to ascertain effectiveness while also assessing for safety and generalizability across other types of surgeries.

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Masculinized Male Chest Contouring: Creating the Armor Plate

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Many male patients have desired elimination of their feminine-appearing breast, termed gynecomastia. These patients have desired maximal flattening of their chest. We present a new set of patients who instead desire a more muscular-appearing chest than a gynecomastia repair that is interposed on a chiseled abdominal contour. In contrast to the former set of patients, these patients desire bulking of their breasts with a bolder-appearing armor plate look. We present an alternative to traditional gynecomastia repair which involves a novel approach to chest contouring creating a flat, yet bold, pentagonal-shaped breast with linear borders utilizing both fat and gland removal as well as strategic fat grafting back into the chest to create an armor plate appearance.

Methods: This study reviews the technique of chest optimization on a cohort of 38 males with ages ranging from 21 to 62 years old (average, 37.5 years old). Patients are treated with a combination of intra-muscular and subcutaneous fat grafting strategically to create a pentagonal-shaped

chest with bold and linear borders (Figure 1). Intramuscular fat injection is performed along the vertical medial line. This injection of fat into the pectoralis muscle performed simultaneously with gynecomastia repair allows for masculine appearance of the chest. Fat graft amount ranges between 60 and 350 cc injected to each chest side (average, 150 cc). Tumescant solution is used to infiltrate and aspirate (roughly 2–4 mL of solution for each milliliter of aspirated volume). Average infiltration varies between 100–300 (right) and 100–280 (left) with an average of 150 (both right and left). Fat graft is grafted into the pectorals (10 cc injected into single

prominent inscription). Photographs are taken at the 3- to 4-month mark for each patient. No complications were found in all cases.

Results: Below, we have demonstrated three cases of an armor male chest contour interposed on a harmonious masculinized abdominal contour. All patients, 6-month post-surgery, demonstrate a pentagonal shaped chest with bold and linear borders (Figures 2). Patients were monitored, and no complications were experienced.

Conclusion: The armor plate chest appearance provides a more masculine male chest appearance. We represent this alternative approach

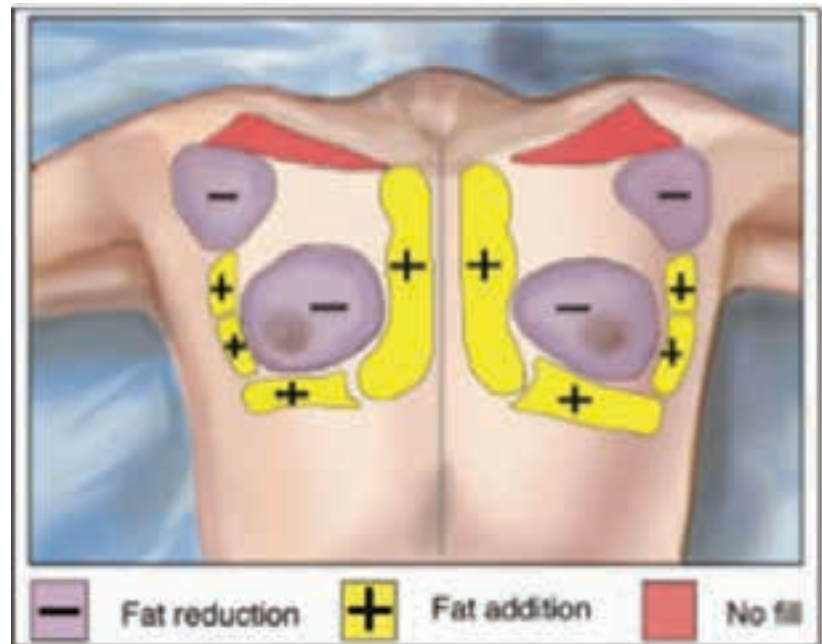


FIGURE 1: Preoperative markings of chest masculinization protocol. Plus signs indicate regions where fat is added, whereas minus signs indicate regions fat will be subtracted. This strategic placement of fat helps us to create a pentagonal-shaped chest with bold and linear borders.

to traditional gynecomastia repair technique since it achieves a more muscular-appearing chest contour that is more harmonious on a male patient undergoing abdominal etching. Further monitoring and precise evaluation of patients will expand on the evaluation of fat-cell survival and needed to determine the efficaciousness of this technique.

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FIGURE 2: Male chest contouring to create a masculinized armor plate appearance. A 34-year-old male three months following ultrasound-assisted liposuction of the abdomen, lateral chest, pubic region, and fat grafting to the chest. Patient demonstrates linear chest borders post-operation creating a more masculinized appearance.

Increased Complication Rates in Octogenarians Undergoing Same-Day Discharge Following Total Knee Arthroplasty: A Matched Cohort Analysis

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Same-day discharge pathways may increase patient satisfaction and reduce overall costs in total knee arthroplasty (TKA).^{1,2} These pathways offer potential advantages but have not been thoroughly evaluated in potentially at-risk populations, such as in patients ≥ 80 years old.³ The purpose of this study was to compare 90-day complications and mortality following same-day discharge after primary TKA in patients ≥ 80 years old and those < 80 years old.

Methods: Patients who underwent unilateral TKA, were discharged on postoperative day 0, and had a minimum 90-day follow-up were identified in a national insurance claims database (PearlDiver Technologies) using CPT code 27447. These patients were stratified into two cohorts based upon age: 1) non-octogenarians (< 80 years old) and 2) octogenarians (≥ 80 years old). These cohorts were propensity matched based upon sex, Charlson Comorbidity Index, and obesity status. Univariate analysis was performed to determine differences in 90-day complications and mortality between the two cohorts.

TABLE: Univariate analysis of 90-day complications following same-day discharge after total knee arthroplasty.

Category	Total (n = 2222)	Octogenarians (n = 1111)	%	Non- octogenarians (n = 1111)	%	p-value
Renal Failure	144	82	7.38%	62	5.58%	0.084
Anemia	429	227	20.43%	202	18.18%	0.179
Arrhythmia w/ afib	347	231	20.79%	116	10.44%	<0.001
Arrhythmia w/o afib	155	93	8.37%	62	5.58%	0.009
Bleeding complication	20	12	1.08%	8	0.72%	0.368
Blood Transfusion	108	59	5.31%	49	4.41%	0.324
Cellulitis	69	41	3.69%	28	2.52%	0.111
MI	135	65	5.85%	70	6.30%	0.657
Pneumonia	74	50	4.50%	24	2.16%	0.002
Stroke	53	34	3.06%	19	1.71%	0.037
Death	63	30	2.70%	31	2.79%	0.896
DVT	77	39	3.51%	38	3.42%	0.907
Heart Failure	200	117	10.53%	83	7.47%	0.012
Pulmonary Embolism	49	26	2.34%	23	2.07%	0.665
Respiratory Complication	32	17	1.53%	15	1.35%	0.722
UTI	263	159	14.31%	104	9.36%	<0.001
Sepsis	41	23	2.07%	18	1.62%	0.431

*Bold values indicate statistical significance. Afib: atrial fibrillation; MI: myocardial infarction; DVT: deep vein thrombosis; UTI: urinary tract infection.

Results: In total, 1,111 patients were included in each cohort. Both cohorts were successfully matched, with no observed differences in matched parameters for demographics or comorbidities. There was no significant difference in 90-day mortality between the two cohorts ($p=0.896$). However, octogenarians were at significantly increased risk of postoperative atrial fibrillation (20.8% vs. 10.4%; $p<0.001$), pneumonia (4.5% vs. 2.2%; $p=0.002$), and urinary tract infection (14.3% vs 9.4%; $p<0.001$) compared to the non-octogenarian cohort.

Conclusion: Relative to matched controls, octogenarians are at significantly increased risk of medical complications within 90 days following same-day primary TKA, including cardiac arrhythmias, pneumonia, and urinary tract infection. Clinicians should place emphasis on

the increased risk of these complications when counseling patients and should practice careful patient selection when performing same-day TKA in the octogenarian population.

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Evaluating Postoperative Immobilization Following Hip Reconstruction in Children with Neuromuscular Conditions

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Hip disorders, such as hip subluxation, dislocation, and developmental dysplasia of the hip, affect approximately one-third of children with cerebral palsy (CP).¹ These disorders result from a combination of spastic muscles placing abnormal forces on the hip joint, resulting in subluxation and bony deformities.² Treatments include non-operative (physical therapy, orthotics, medications) and operative management.³ Femoral and acetabular reconstructive surgeries are the primary surgical interventions for hip disorders in CP patients, but there is no consensus on postoperative immobilization method.⁴

Postoperative protocols following hip reconstruction in children with CP include physical therapy, cast immobilization (hip spica, Petrie cast), abduction pillows, and pain management. Cast immobilization is used to achieve stability and prevent early dislocation but poses risk of serious orthopaedic complications.⁵ Currently, postoperative immobilization method is determined

by surgeon preference. This study sought to inform postoperative protocol by evaluating the effects of several methods of postoperative immobilization in patients with neuromuscular conditions following hip reconstruction and determining which postoperative immobilization technique leads to the fewest number of complications.

Methods: Following approval from the Institutional Review Board, we performed a retrospective chart review of pediatric hip reconstructive procedures in which either a spica cast, Petrie cast, or abduction pillow was placed for postoperative hip immobilization. We identified patients who underwent unilateral or bilateral proximal femoral osteotomies, pelvic osteotomies, or hip open reductions from 01/01/2009 - 12/02/2019, which yielded 227 patients. We excluded patients who had a revision surgery and those without neuromuscular conditions. The final cohort consisted of 82 cases that met all criteria. Demographics, laterality of surgery, type of procedure, postoperative hip immobilization technique, and 30-day postoperative complications were recorded. Complications were defined as readmission to hospital for a respiratory or orthopedic issue, including but not limited to re-dislocation or loss of surgical fixation. Additionally, we included soft-tissue complications, such as pressure ulcers or any superficial or deep wound infection.

Results: Of the 82 patients, 32 received spica casting, 35 received Petrie casting, and 15 received an

abduction pillow. Within the spica group, 23% underwent hip procedures, 10% underwent femur procedures, and 67% underwent combined hip and femur procedures. Of these procedures, 53% included an open reduction. Within the Petrie group, 6% underwent hip procedures, 17% underwent femur procedures, and 77% underwent combined hip and femur procedures. Of these procedures, 60% included an open reduction. Within the abduction pillow

These results suggest that patients with neuromuscular conditions undergoing hip reconstruction do not additionally benefit from spica or Petrie casting in the setting where an open reduction is not performed.

group, 13% underwent hip procedures, 47% underwent femur procedures, and 40% underwent combined hip and femur procedures. Of these procedures, 7% included an open reduction. The complication rates, as defined in the methods section, were 21.9% for the spica cast group, 17.1% for Petrie cast, and 13.3% for abduction pillow. A chi-squared test was used to analyze the data, and there was no significant difference in complication rates among spica cast, Petrie cast, or abduction pillow groups ($p=0.76$).

Conclusion: There was no significant difference in complication rates among the three methods of immobilization.

Continued on p. 56

Significance: These results suggest that patients with neuromuscular conditions undergoing hip reconstruction do not additionally benefit from spica or Petrie casting in the setting where an open reduction is not performed. We are hopeful that this will allow practitioners to standardize postoperative hip immobilization in this patient population.

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Pediatric Transfusion-Associated Hyperkalemic Cardiac Arrest

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Transfusion-associated hyperkalemic cardiac arrest (TAHCA) is an adverse outcome associated with red blood cell (RBC) transfusion. During refrigerated storage, RBCs undergo a series of morphological, functional, and metabolic changes that are collectively termed 'the red blood cell storage lesion.' The RBC storage lesion occurs in part to a progressive increase in extracellular potassium as cation transporters, including Na⁺/K⁺ ATPase, are impaired during

hypothermic storage. Blood product irradiation further increases extracellular [K⁺], as it increases the permeability of the RBC membrane. Consequently, rapid or large volume transfusions can predispose patients to hyperkalemia and electrical instabilities, including cardiac arrest.

Objective: We aimed to review the literature on the incidence of transfusion-associated hyperkalemia, highlight the association with cardiac electrical instabilities, and identify potential mitigation strategies to reduce the risk of hyperkalemia in transfused pediatric patient populations.

Results: We identified 21 case reports of TAHCA in pediatric patients. Hyperkalemia and cardiac electrical instabilities were more commonly reported in pediatric patients if blood products were transfused quickly, were delivered directly to the heart without adequate time for electrolyte equilibration, or when blood products had accumulated extracellular potassium due to prolonged storage or following irradiation. We note that hyperkalemia and/or TAHCA may be underreported due to incomplete hemovigilance reporting systems.¹ Collectively, the 21 reports suggest that the risk of hyperkalemia may

be mitigated by using fresh blood products, reducing storage time after blood product irradiation, and implementing of post-transfusion manipulations that wash or remove excess extracellular potassium.

Conclusion: Advances in transfusion medicine have improved the quality of RBCs during storage; despite these advances, vulnerable patient populations experience trans-

Advances in transfusion medicine have improved the quality of RBCs during storage; despite these advances, vulnerable patient populations experience transfusion-associated hyperkalemia.

fusion-associated hyperkalemia. Mitigation strategies may help to reduce the risk of TAHCA, which is associated with poor short-term survival rate following rapid blood administration.²

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Autonomic Tone in Preterm Infants Correlates with Morbidity of Prematurity

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An appropriately mature autonomic nervous system (ANS) is key for transition from the intrauterine to

seem to influence ANS development to term in a preterm population with a relatively low level of prematurity-related complications.¹ GA at birth may therefore have less impact on ANS development than previously thought. Prior studies investigating ANS maturation in preterm infants have predominantly involved infants with higher levels of prematurity-related complications,^{1,2} so it may be that ANS development in the preterm infant is more related to medical comorbidities than birth GA. Given recent evidence that GA at birth may have less impact on ANS maturation than previously thought, we hypothesized that the medical complexity

of preterm infants correlates with ANS maturation. For the purposes of this study, we considered medical complexity to include any of the following at any time during admission: culture positive

infection, necrotizing enterocolitis (NEC) diagnosis, presence of a patent ductus arteriosus requiring medical or surgical intervention or hemodynamic instability requiring pressors, brain injury on head ultrasound including periventricular leukomalacia and intraventricular hemorrhage grade 3 or 4, and need for mechanical ventilation/intubation.

In this study, we set out to determine the degree to which complications of prematurity impact ANS development by comparing 114 preterm infants (birth GA ≤ 33 weeks) divided into two groups with differing levels of complications of prematurity. Group 1 included infants

without significant complications of prematurity, while group 2 included infants with medical or surgical complications of prematurity. Weekly electrocardiogram (ECG) data was assessed from admission to neonatal intensive care units (NICU) discharge. ANS tone was determined by heart rate variability (HRV) analysis in time and frequency domains. Normalized low frequency, alpha 1, and root mean square 1 characterized sympathetic tone, while normalized high frequency characterized parasympathetic tone. Median regression with a group by time interaction term was used to model ANS maturation across days of life and evaluate any differences in maturation rates between groups.

Overall, we found that cohorts of preterm infants with differing levels of medical complexity show differences in their ANS development, specifically for time-domain metrics of HRV. The results indicated that medical comorbidities, and, perhaps, the negative experiences associated with illness, do impact the trajectory of ANS development in preterm infants. Understanding how medical complexity impacts ANS development in preterm infants may lead to future advances in NICU care.

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Understanding how medical complexity impacts ANS development in preterm infants may lead to future advances in NICU care.

extrauterine environment at birth,¹ and abnormal ANS development has been linked to neurodevelopmental, neuropsychiatric, and cardiovascular outcomes later in life. The ANS undergoes a critical period of maturation during the latter half of gestation and during the early neonatal period. Previous studies have found that preterm birth and subsequent maturation in the extrauterine environment can impact ANS development.^{1,2} However, it is likely that multiple factors impact ANS development in the extrauterine environment beyond gestational age (GA) at birth. Our group recently showed that duration of extrauterine development did not

Deadly Duo: A Curious Case of Cardiogenic Shock

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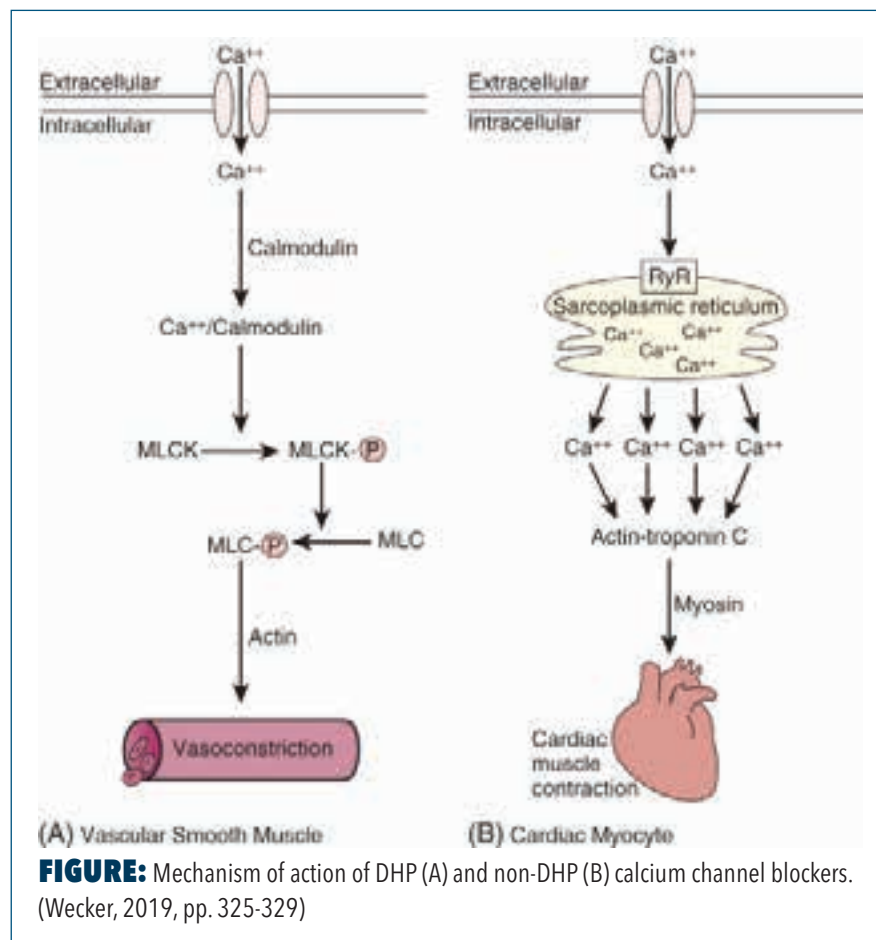
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A 52-year-old male with a past medical history significant for hypertrophic cardiomyopathy (HCM), atrial fibrillation, hypertension, and hyperlipidemia presented to an outside hospital for pre-syncope episodes. Prior to presentation, he was experiencing persistent, symptomatic palpitations with heart rates in the 110s, and his verapamil dose was increased from 120mg to 240mg daily. In addition, the patient was also being managed with metoprolol tartrate 100mg BID, amiodarone, and rivaroxaban. The patient arrived at the hospital with shortness of breath, cyanosis, hypotension, and bradycardia. He endorsed alcohol use the day before with burning abdominal pain and weakness at that time. He was subsequently intubated, paced, and required pressor support with norepinephrine and epinephrine. His verapamil was also held at this time. His labs are listed in the table below. Given his worsening liver function tests, and a Model for End-Stage Liver Disease (MELD) Score of 39, he was transferred to a transplant center for evaluation for liver transplant. Liver biopsy was consistent with hypoxic injury. Extensive workup for other etiologies of liver failure, including viral hepatitis panel, and autoimmune hepatitis panel were



all negative. The patient's liver function continued to improve over the course of his hospitalization without need for transplant, but renal function did not recover, and he was transferred to our facility for hemodialysis initiation. He continued to remain in atrial fibrillation over the course of the hospitalization with heart rate sustained in 140s bpm. His metoprolol tartrate dose was increased to 125mg BID for better rate control. His hospital course was otherwise complicated by Klebsiella ventilator-acquired pneumonia (VAP) and post-traumatic stress disorder (PTSD) from the protracted hospital course.

Discussion: Verapamil is a calcium channel blocker commonly used to treat hypertension and provide rate control for atrial fibrillation/flutter. It has a strong affinity for

both myocardial and vascular smooth muscle, allowing it to exert its effects not only on the musculature of the heart but also on arterioles throughout the body. The therapeutic mechanism is primarily vasodilation, along with suppressing cardiac contractility, sinoatrial node automaticity, and atrioventricular node conduction.¹

While this potent vasodilation is effective in treating patients with hypertension, it also poses a significant risk profile when taken at doses over the therapeutic range, most notably causing bradycardia, hypotension, conduction disturbances, and escape rhythms. When progressive, hypotension and bradycardia can eventually lead to cardiogenic shock.¹

Combination therapy is very commonly used to manage

Continued on p. 60

various medical conditions; however, polypharmacy inherently increases the risk of adverse events. Cardiogenic shock has been reported as a rare complication associated with the use of verapamil and beta-blockers. Verapamil produces a state of myocardial depression, which is usually not problematic due to a compensatory sympathetic reflex.² However, the co-administration of beta-blockers blunts this compensatory mechanism, potentiating myocardial depression, thus posing an increased risk for cardiogenic shock.³

The aforementioned principles outline the risks posed when taking doses over the threshold for therapeutic treatment.⁴ The case presented here remains unique as the dosage for both the metoprolol and verapamil were within the therapeutic range. Therefore, while rare, it is important to up-titrate these medications with caution and consider the risk for cardiogenic shock with potential for end-organ

TABLE: Laboratory Results

BUN	71
Cr	7.2
BUN/Cr	9

Tbili	1.6
AST	13,112
ALT	9,553

Adenovirus	-
Coxsackie A	-
Coxsackie B	-
Babesiosis	-
ANA	-

VZV	+
EBV	+
Quant Gold	-
HSV IgM	-
HSV PCR	-

PT	57.2
INR	6.42
PTT	42.9

Troponin I	0.047
Lactic Acid	8.2
LDH	47,222

Anti-HAV	-
Anti-HBV	-
Anti-HCV	-
Anti-HDV	-
Anti-HEV	-

damage even when delivered within the therapeutic window.

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Factors Associated with Clinical Severity in Emergency Department Patients Presenting with Symptomatic SARS-CoV-2 Infection

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Objective: To measure the association of race, ethnicity, comorbidities, and insurance status with need for hospitalization of symptomatic Emergency Department (ED) patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

Methods: This study is a retrospective case-series of symptomatic patients presenting to a single ED with laboratory-confirmed SARS-CoV-2 infection from March 7 to Aug. 9, 2020. We collected patient-level information regarding demographics, public insurance status (Medicare or Medicaid), comorbidities, level of care and mortality using a structured chart review. We compared demographics

and comorbidities of patients who were (1) able to convalesce at home, (2) required admission to general hospital ward, (3) required admission to intensive care unit (ICU), or (4) died within 30 days of the index visit. Multivariable and univariable logistic regression analyses were performed to report adjusted odds ratios (aOR) and the associated 95% confidence intervals (95% CI) with hospital admission versus ED discharge home and need for intensive care unit (ICU) admission versus general hospital ward admission.

Results: In total, 993 patients who presented to the ED with symptoms were included in the analysis with 370 (37.3%) patients requiring hospital admission and 70 (7.1%) patients requiring ICU care. Patients requiring admission were more likely to be Black or African American, to be Hispanic or Latinx, or to have public insurance (either Medicaid or Medicare.) In multivariable logistic regression analysis comparing which patients required hospital admission, Black race (aOR 1.4, 95% CI 0.7-2.8) and Hispanic ethnicity (aOR 1.1, 95% CI 0.5-2.0) were associated less with need for admission than public insurance (Medicaid: aOR 3.4, 95% CI 2.2-5.4; Medicare: aOR 2.6, 95% CI 1.2-5.3; Medicaid and Medicare: aOR 3.6 95% CI 2.1-6.2) and the presence of hypertension (aOR 1.8, 95% CI 1.2-2.7), diabetes (aOR 1.6, 95% CI 1.1-2.5), obesity (aOR 1.7, 95% CI 1.1-2.5), heart failure (aOR 3.9, 95% CI 1.4-11.2), and hyperlipidemia (aOR 1.8, 95% CI 1.2-2.9) were identified as independent predictors of hospital admission. When comparing those who needed ICU admission versus general hospital ward admission, Medicaid (aOR 2.2, 95% CI 1.0-5.1) and Medicare (aOR 2.0 95% CI 0.7-5.8) were associated with

ICU admission but Black patients were less likely (aOR 0.6 95% CI 0.1 - 2.4) and Hispanic patients were weakly (aOR 1.05 95% CI 0.54 - 2.02) associated with ICU admission.

Conclusion: Comorbidities and public insurance are predictors of more severe illness for patients with SARS-CoV-2. This study suggests that the disparities in severity seen in coronavirus (COVID-19) among Black and Hispanic patients may be attributable, in part, to low socioeconomic status and chronic health conditions.

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Utilization of Quinolones in the Emergency Department, 2005–15

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Quinolones are antibiotics used for a wide array of infections.^{1,2} Nevertheless, their side effects have resulted in changes in quinolone administration by providers.³ In this study, the trend of quinolone utilization over the years in the emergency department (ED) was analyzed.

A review of the National Hospital Ambulatory Medical Care Survey (NHAMCS) database was performed. Using drug codes provided by the Centers for Disease Control and Prevention (CDC), all patients 18 years and older who were administered or prescribed quinolones were identified between 2005 and 2015. Bivariate and multivariate statistical analyses were used to analyze the demographics, payment source, and hospital disposition of the study population. Reasons for ED visit and final diagnoses were also examined.

In 2005, quinolone was administered during 2.8 million visits, accounting for 2.4% of all ED visits.

From 2005 to 2009, quinolone utilization experienced an average relative increase each year of 4.5%. From 2010–2015, quinolone use had an average relative decrease each year of 3.2%. In 2015, quinolone was administered during 2.7 million visits (1.9% of all ED visits, $P < 0.0001$).

Quinolone use decreased in both young adults, ages 18–44, and middle adults, ages 45–64 (20.1% and 1.5%, $P < 0.0001$), whereas its use increased in older adults, ages 65+ (1.8%, $P < 0.0001$). Quinolone utilization increased for males (1.3%, $P < 0.0001$) and decreased for females (10.8%, $P < 0.0001$), with its use more common in females (56.8%–59.9%). Quinolone use increased in patients with Medicare and Medicaid (2.7% and 18.7%, $P < 0.0001$), while its use decreased in those with self-pay and private insurance (13.0% and 41.9%, $P < 0.0001$). Compared to the patients in 2005, the patients in 2015 who received quinolones had increased odds of returning to the ED within 72 hours after discharge (OR 0.7, 95% CI 2.8–9.1, $P < 0.0001$). The patients in 2015 were also less likely to be admitted to the hospital (OR 1.2, 95% CI 19.1–36.4, $P < 0.0001$). The most common reason for visit where quinolone was used

was abdominal pain (9.2%–11.7%). The most common final diagnosis was urinary tract infection (12.9%–15.5%).

EDs are prescribing less quinolones for their patients due to their side effects and black box warnings, such as altered mental status and aortic rup-

EDs are prescribing less quinolones for their patients due to their side effects and black box warnings, such as altered mental status and aortic ruptures. Future research should focus on concomitant increase in other drugs to replace quinolones in the ED.

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Determining Whether an Individual's Age or Comorbidities is Superior in Predicting Mortality in COVID-19 Patients

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To date, the SARS-CoV-2 coronavirus (COVID-19) has rapidly killed over a million people worldwide.¹ Researchers identified elderly age and various comorbidities as early risk factors for mortality. Patterns observed in Wuhan and early cases in the United States indicate that the risk of death increases in those over 65 years old, as well as individuals in any age group with comorbidities, including diabetes, heart disease, and clotting disorders.² In fact, the study reported that the mortality rate for COVID-19 patients is 7% in people with diabetes, 10% in people with heart disease, and 15% in people ≥ 80 years old. Additionally, for those with cancer, hypertension, or chronic respiratory disease, the mortality rate rises to 6% from 1% in the general population.² Due to the influx of patients requiring hospitalization and advanced airway management (e.g., intubation and mechanical ventilation), many hospitals faced supply shortages early on in the pandemic. In resource limited settings overwhelmed by a heavy infection burden, such as various regions of Italy, reports

emerged of rationing ventilators and even withholding life-saving interventions from individuals over a certain age cut-off.³ This begs the question of whether healthy elderly individuals have increased mortality over their younger counterparts with comorbid conditions. The Charlson Comorbidity Index (CCI) is a popular risk adjustment tool for 10-year survival in patients. However, applying the CCI to COVID-19 patients has not yet been probed. The objective of this study was to determine whether age or the CCI is superior in predicting mortality in COVID-19 patients.

Methods: Between March and July 2020, a prospective registry containing all COVID-19 admissions to the George Washington University Hospital was created. A receiver operator characteristic (ROC) curve was created for both age and CCI as a predictor of mortality. Data was then divided into age brackets with a breakdown of CCI quartiles for each bracket.

Results: In total, 369 patients were studied. Mean age was 61.5 years and CCI was 3.91. The ROC curve for CCI yielded an Area under the Curve (AOC) of 0.6476 (0.57–0.72), while that for age yielded an AOC of 0.6737 (0.60–0.75). ROC contrast estimation of these two predictors did not indicate that one was significantly better than the other. When age groups were analyzed by CCI, there were certain healthy older age groups with better survival than their younger, comorbid counterparts. For example, ≥ 91 -year-olds with a lower quartile CCI (0–5,6) had a 0–33.3% mortality rate. This is better than 81–90-year-olds with a

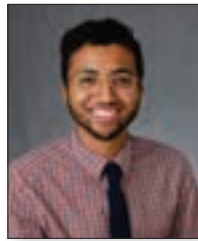
CCI of 7 (57.1%) or CCI ≥ 9 (75%) and even mortality rates in 61–70-year-olds with a CCI of 5–6 (53.8%) and 7–10 (50.0%).

Conclusions: Both age and CCI are significant predictors of mortality for the population represented in this registry. Comparing the two did not show a significant mortality difference. However, our study suggests that one must reconsider withholding treatment from the healthy elderly population, as these patients may have better survival than their younger, but more comorbid, counterparts. Data may be confounded by our institution admitting transfers from outside institutions and more elderly patients being made DNR/DNI or CMO than younger patients. Further studies are needed to evaluate these trends and to possibly look at the entire COVID-19 population in Washington, D.C., rather than just those admitted to the hospital.

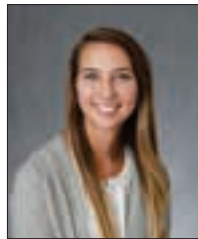
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Evaluation of Thromboelastography in Patients with Gastrointestinal Bleeding



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Thromboelastography (TEG) is a low-cost, point-of-care diagnostic test used to quantitatively assess platelet function, clot formation, and fibrinolysis. TEG is increasingly employed to guide transfusion therapy in trauma and surgical cases to decrease mortality and blood product transfusion.^{1,2} These populations are distinctly different from the medical population, which carries different comorbidities, risk factors and baseline antiplatelet/anticoagulant use. The most common subset of medical patients with acute bleeding are those with gastrointestinal bleeding (GIB). To our knowledge, the utility of TEG in patients with GIB is not

TABLE 1: Blood Product Utilization in TEG and non-TEG patients

	TEG	Non-TEG
All Patients		
Mean pRBC - Days 0 and 1**	2.93	5.622
Mean FFP - Days 0 and 1**	0.469	2.49
Mean All Products ^a - Days 0 and 1**	3.59	9.09
Negative Binomial Regression		
Mean All Products ^a - Days 0 and 1**	4	6.42

^a pRBC plus cryoprecipitate plus platelets plus fresh frozen plasma (FFP)

** $p < 0.01$

well described to date. We sought to assess whether TEG has a benefit in patients with clinically significant GIB by examining blood product utilization.

Methods: A retrospective chart review was performed on patients who were admitted between 01/01/2017 and 12/30/2019 to our intensive care unit with an ICD 10 diagnosis code of “hematemesis” (K92.0), “melena” (K92.1), or “gastrointestinal hemorrhage, unspecified” (K92.2). Patients greater than 18 years of age were included in the study if they had a clinically significant GIB, defined as receiving an administration of a blood transfusion for the GI bleed.³ After this initial stratification, patients were excluded from the study if they were DNR/DNI and/or comfort care status on admission, had received a documented blood transfusion in the preceding two weeks, presented as a trauma, had respiratory failure or mechanical ventilation on admission, had a history

of a transfusion-dependent anemia or hematological disorder, had a left ventricular assist device, were in cardiac arrest on admission, or had presumed shock from a non-hemorrhagic etiology.

Results: TEG patients had significantly greater numbers of total blood products (packed red blood cells (pRBC), cryoprecipitate, platelets,

The use of TEG for patients presenting with GIB resulted in increased pRBC and FFP transfusions without any change in clinical outcomes as compared to the standard of care.

and fresh frozen plasma (FFP)) transfused than the non-TEG patients during GIB days 0 and 1 (mean 9.09 vs. 3.59, $p < 0.01$). This difference was primarily driven by differences in pRBC (mean 5.622 vs. 2.93, $p < 0.01$) and FFP (mean 2.49 vs. 0.469, $p < 0.01$). Cryoprecipitate (mean 0.295 vs. 0.015, $p < 0.01$) and platelet usage (mean 0.688 vs. 0.18, $p < 0.01$) in

TEG patients was also significantly higher than in non-TEG patients on bleed days 0 and 1. Multivariate analysis revealed that TEG patients still received a greater total number of blood products during GIB days 0 and 1 compared to non-TEG patients (mean 6.42 [95% CI 4.48–8.36] vs. 4.00 [95% CI 3.19–4.80], $p < 0.01$) even when controlled for the following covariates: vasopressor use, sex, race, age, total comorbidities, shock index, hemoglobin on admission, platelet level, hemorrhage control, alcohol abuse, cirrhosis, abdominal surgeries, cerebrovascular disease, and malignancy (Table 1). The clinical outcomes for patients in the TEG and non-TEG arms were not significantly different for most parameters (Table 2).

Conclusions: The use of TEG for patients presenting with GIB resulted in increased pRBC and FFP transfusions without any change in clinical outcomes as compared to the standard of care. Our findings underscore the need for a randomized controlled trial to further elucidate the role of TEG in medical patients before routine adoption of its use in these patients.

TABLE 2: Patient Clinical Outcomes

	Non-TEG (n)	TEG (n)
Total	194	61
ICU length of stay (days)	2.77	3.53
Development of Respiratory Failure n (%)	45 (23.2)	19 (31.1)
Mechanical Ventilation Requirement* n (%)	26 (13.4)	16 (26.2)
AKI n (%)	39 (20.1)	10 (16.4)
Renal Replacement Therapy n (%)	4 (2.10)	1 (1.64)
Discharge Destination n (%)		
Home	137 (70.6)	40 (65.6)
Death	16 (8.25)	7 (11.5)

* $p < 0.05$

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Retrospective Review Characterizing the Children's National Hospital Vulvar Dermatology Clinic

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This study aims to characterize the diseases seen in a multispecialty pediatric dermatology-gynecology vulvar clinic at Children's National Hospital (CNH) in Washington, D.C. Though dermatologic findings involving the vulva may present to a variety of practices, ranging from pediatric primary care, dermatology, gynecology, or urology, few training programs provide significant training on the interdisciplinary knowledge needed to accurately diagnose pediatric vulvar dermatologic diseases. To our knowledge, very few multispecialty clinics bring together dermatology and gynecology, especially in a pediatric setting. Based on experience in our multidisciplinary pediatric dermatology-gynecology vulvar clinic, we aim to highlight the benefits of a multispecialty clinic and showcase the conditions diagnosed, managed, and treated. Additionally, we will explore relevant epidemiological factors seen in this patient population.

Methods: We conducted a retrospective review of 180 patient charts from pediatric patients seen at the joint dermatology-gynecology clinic at

CNH, at least once between January 2016 and June 2020. Data collected from the charts included patient diagnosis, demographics, vulvar symptoms, and prior care related to the patient's vulvar symptoms. Data was entered into a RedCap database and analyzed.

Results: Among the 180 patients seen (mean age 6.89 \pm SD 4.63), the three most common conditions seen in the clinic are as follows: pediatric vulvar lichen sclerosis (PVLS) (69.9%), vitiligo (21.69%), and vulvovaginitis (21.69%). In total, 83 conditions were evaluated in this multispecialty clinic. Approximately 17.8% of patients with pediatric lichen sclerosis and 38.9% of patients with vitiligo were misdiagnosed at least once. On average, from the time of symptom onset to a diagnosis, those with PVLS waited 14.58 months and those with vitiligo waited 10.29 months until diagnosis. Of those with PVLS who first received a misdiagnosis, 92.8% of the time the diagnosis was made outside of the dermatology-gynecology clinic. Of those with vitiligo who first received a misdiagnosis, 75.0% of the time the diagnosis was made outside of the dermatology-gynecology clinic. In the paper, epidemiological factors for the clinic as a whole and for the three most common diseases are discussed.

Conclusion: Our study addresses a gap in published information on pediatric vulvar symptoms and patient characteristics in a multispecialty dermatology-gynecology interdisciplinary clinic. The chart review

highlights the variety of conditions seen and complexity of care faced in a pediatric dermatology-gynecology clinic, with emphasis on the risk for a delay in diagnosis when vulvar symptomatology is diagnosed in patients seen outside of a dermatology-gynecology clinic initially. Enhanced training at the pediatric primary care level is needed to help guide clinicians in accurately diagnosing pediatric vulvar complaints.

Keywords: Pediatric dermatology, pediatric gynecology, multispecialty clinic, pediatric vulvar lichen sclerosis, vitiligo, vulvovaginitis, vulvar care.

Our study addresses a gap in published information on pediatric vulvar symptoms and patient characteristics in a multispecialty dermatology-gynecology interdisciplinary clinic.

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Topical DUREZOL® (difluprednate ophthalmic emulsion) 0.05% Challenge Prior to IntraVitreous Administration of Corticosteroid Analogues – DIVCA

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Ocular corticosteroids are ubiquitous medications used to treat a wide variety of conditions that were previously vision-threatening, including uveitis, diabetic macular edema (DME) and retinal vein occlusion (RVO). Despite the therapeutic value of these medications, they often induce the elevation of intraocular pressure (IOP), leading to progressive ocular nerve damage and, in some cases, to corticosteroid-induced glaucoma.

For patients in the general population without glaucoma, an estimated one-third of the population may be considered “steroid responders,” indicating that treatment with a steroid would lead to an increase in IOP.¹ Of the two primary formulations of ocular steroids, topical and intravitreal, the latter often results in clinically significant IOP elevation, threatening vision. Although certain risk factors have been identified as predictors for corticosteroid response,

the variability of outcomes among individual patients continues to render the decision to initiate intravitreal corticosteroid treatment difficult.

One method for assessing an individual’s potential risk of developing a steroid response following intravitreal injection may be the evaluation of that patient’s IOP following the administration of a topical corticosteroid. Of the topical corticosteroids available on the market, Durezol (difluprednate) is one of the most potent, contributing to its utility as an adequate challenger to elicit steroid response. Thus, we hypothesized that we could identify intravitreal steroid responders as individuals who experienced elevated IOP following administration of Durezol topical corticosteroid.

A prospective cohort study of 29 patients diagnosed with DME or RVO over four years (2016-20) was conducted. IOP was measured at baseline and at four weekly intervals following topical corticosteroid treatments. After a two-week washout period, intravitreal corticosteroid injection was administered, IOP was then measured at three intervals post-injection: 2-4; 4-8; 8-12 weeks. After excluding nine patients with incomplete steroid courses, linear models and corresponding plots

were generated for 20 patients using R open-source software. Baseline IOP was not a statistically significant predictor of IOP elevation after treatment. Regressing average IOP for the four weeks following intravitreal injection compared with the average IOP for the 3-week intervals following topical corticosteroid administration yielded an estimated slope of 0.72 with 95% CI of (0.46, 0.99) and $R^2 = 0.57$.

For patients in the general population without glaucoma, an estimated one-third of the population may be considered “steroid responders,” indicating that treatment with a steroid would lead to an increase in IOP.¹

This study suggests that post-topical corticosteroid IOP response is a good predictor of the post-intravitreal corticosteroid IOP response, independent of baseline IOP, making it a potentially useful screening process for predicting steroid responders.

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The Role of Regulatory T-Cells in Exercise-Induced Exacerbation in Chikungunya Arthritis Patients

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Chikungunya virus (CHIKV) is an arbovirus that causes fever, rash, myalgia, arthralgia and persistent arthritis. CHIKV arthritis is symmetric with relapsing-remitting symptoms mirroring rheumatoid

Our studies are consistent with recent Treg depleted murine models of arthritis showing that voluntary running might play a role in switching off the Treg-mediated resolution of arthritis leading to increased joint inflammation.³

arthritis. In our prior published study of a different cohort, we found that 39% of CHIKV arthritis patients reported relapses of CHIKV arthritis due to exercise.¹ The underlying mechanism of exercise-induced viral arthritis (EIVA) relapses is unknown. The objective of this analysis is to examine the regulatory T-cell (T-reg) immune response related to CHIKV arthritis flares.

Methods: On hundred twenty-four Colombian patients with a history of CHIKV infection four years prior were enrolled (approved by The George Washington University Institutional Review Board#121611 and the Clinica de la Costa IRB, Colombia (FWA IORG0008529)). Eleven patients were excluded from the analysis due lack of serologic confirmation of CHIKV infection (n=9), lack of blood sample (n=1), or lack of information on exercise effects (n=1). One hundred thirteen cases were analyzed. Demographic factors and measures of arthritis disease severity are reported. Flow cytometry of

T-cells was performed on a BD Celesta flow cytometer (BD Biosciences, San Jose, CA) and analyzed in FlowJo 10 (TreeStar Inc., Ashland, OR). We compared outcomes in CHIKV patients with (n = 38) vs. without (n = 75) EIVA using t-tests to assess means and the Fisher's exact test and chi-squared to evaluate categorical variables (SAS 9.3).

Results: CHIKV cases were predominantly middle-aged Mestizo females with at least secondary school education without history of arthritis prior to CHIKV infection. 33.6% of the CHIKV cases reported worsening arthritis with exercise. EIVA patients reported higher global assessments of arthritis disease ranging from 0-100 (71.2±19.7 vs. 59.9±28.0, p=0.03). Phlebotomy obtained under resting conditions revealed that patients with

worsening arthritis from exercise had lower levels CD4+ T-cells (149,556±78,196 vs. 186,457±92,167, p= 0.04), and lower ratios of Tregs/CD4+ T-cells (1.95±0.73 vs. 2.4±1.29, p = 0.04).

Conclusions: These findings suggest that relative decreases in Treg populations in patients with CHIKV arthritis may contribute to arthritis flares during exercise. Treg cells are stimulated by exercise in humans and are suggested to play an acute anti-inflammatory role.² Our studies are consistent with recent Treg depleted murine models of arthritis showing that voluntary running might play a role in switching off the Treg-mediated resolution of arthritis leading to increased joint inflammation.³ Studies of exercise challenge in this population are needed to further define the immunologic relationship between CHIKV arthritis and exercise.

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Treatment Rate of Methotrexate vs Medicinal Plants or Alternative Medicine Therapies for Patients with Chronic Arthritis After Chikungunya

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Chikungunya virus (CHIKV) is a mosquito-borne virus that causes persistent arthritis in approximately one-fourth of patients.¹ Preliminary data suggests that alteration of regulatory T cell function may play a role in CHIKV arthritis flares. There is currently no standard treatment for this arthritis. The objective of this analysis is to determine what treatments are being used currently by patients and which of those treatments are associated with control of arthritis symptoms in a Latin American cohort.

We performed a cross-sectional analysis of self-reported medication use and symptom relief among 114

patients affected by CHIKV infection from Atlántico, Colombia for years prior. This study was approved by the ethics committee of the Clinica de la Costa (FWA IORG0008529) and The George Washington University (#121611).

All participants in the study were mestizo in ethnicity. One hundred four of 114 patients (91%) reported years of persistent arthritis attributed to their CHIKV infection from infection 4–5 years prior. Participants reporting persistent arthritis were predominately women with a mean age of 48. Of those with persistent arthritis, 26% reported using medicinal plants or alternative medicine therapies. However, of those that reported having their symptoms controlled, methotrexate and medicinal plants were the most commonly used therapeutics. Only 66% of patients with arthritis reported that the therapies they were using were able to control their symptoms. The most commonly used medications were paracetamol/acetaminophen (94%) and NSAIDS (81%) — and the least commonly used was methotrexate (1%).

With the results showing a better control of symptoms in patients taking methotrexate or medicinal plants, versus other treatment therapies, further trials are needed to investigate effectiveness of methotrexate, medicinal plants and alternative medicine therapies to determine pathophysiology and efficacy in alphaviral arthritis. Analysis of the longest follow-up of the largest

cohort of patients with relapsing-remitting chikungunya arthritis in Latin America demonstrates a lack of arthritis symptom control in over one third of patients. Over one fourth of patients reported using medicinal plants however little is known about the mechanism of action of various local medicinal plant therapies such as including *Plantago major* L. and *Terminalia catappa* L. in the treatment of CHIKV arthritis. Although both French and Brazilian guidelines both advise use of methotrexate in the treatment of chronic

Analysis of the longest follow-up of the largest cohort of patients with relapsing-remitting chikungunya arthritis in Latin America demonstrates a lack of arthritis symptom control in over one third of patients.

CHIKV arthritis, there is no standard evidence-based guidelines for the treatment of CHIKV arthritis in Colombia and very few patients were using immunomodulating therapy.²

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Pregnancy and Child Outcomes Following Fetal Intracranial Hemorrhage

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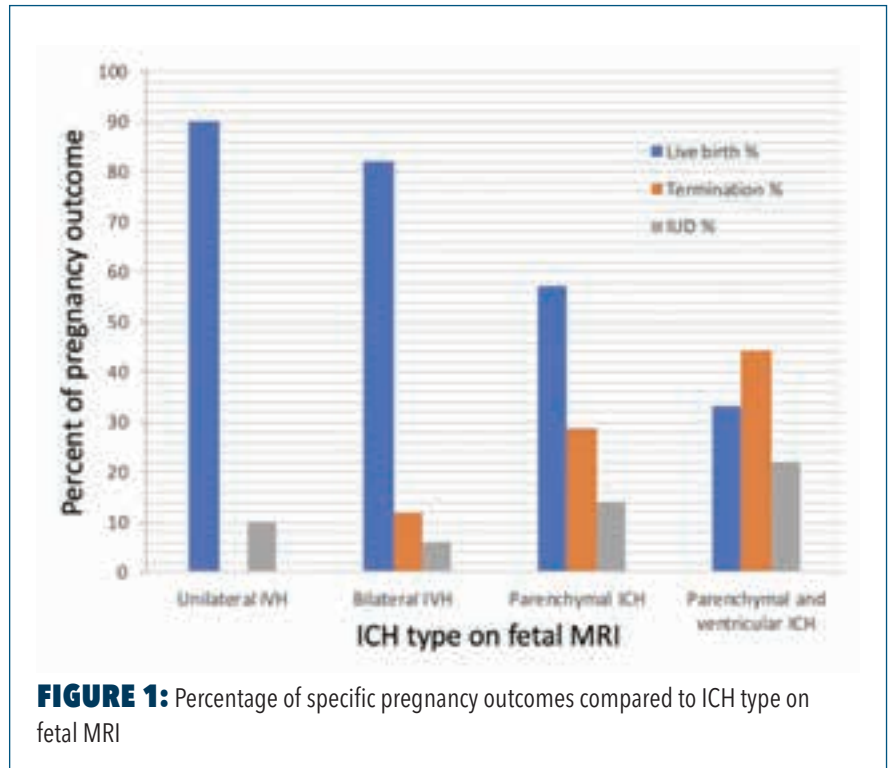
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Fetal intracranial hemorrhage (ICH) is a rare condition, with an estimated incidence of 0.5-0.9 per 1000 pregnancies, that has potentially severe consequences.¹ Previous studies on fetal ICH show it has a 40% mortality in utero or within the first month of life and less than 50% of survivors are neurodevelopmentally normal.² Existing literature defines fetal ICH and outcome based on prenatal ultrasound, however fetal MRI is increasingly used for clinical prenatal diagnosis and may aid in detection.³ Our objective was to understand pregnancy and child outcomes following fetal ICH when diagnosed by fetal MRI.

We performed a retrospective study of all cases of fetal ICH diagnosed by fetal MRI at Children's National Prenatal Pediatrics Institute from 2012 to 2020. Maternal characteristics, prenatal and postnatal imaging, ICH type, pregnancy outcome, and infant/child developmental progress were recorded. Abnormal postnatal outcomes were categorized as: mild for hypertonia or physical/occupational therapy without intellectual disability or language delays; moderate for intermediate multi-domain developmental delays; severe if non-ambulatory, non-verbal, or significant intellectual disability.

We identified 57 cases with ICH on fetal MRI. The mean (SD) maternal age was 31.1(6.9) years, gestational age



at fetal evaluation was 28.1(5.3) weeks, and birth gestational age was 38.2(1.3) weeks. Pregnancy outcomes consisted of 75% (n=43) live births, 14% (n=8) termination of pregnancy, and 11% (n=6) intrauterine demise (IUD). Of the ICH types, 81% (n=46) were intraventricular hemorrhage (IVH), 28% (n=16) were intraparenchymal and 16% (n=9) were both. Ventriculomegaly was the most common additional finding on fetal MRI, seen in 49% of patients.

From unilateral IVH to both parenchymal and ventricular ICH, there were 63% fewer live births and 55% more IUD (Figure 1). 86% of live born infants were followed clinically for 1.8 (1.6) years. Neurodevelopmental outcome was

normal in 57%, mildly abnormal in 24%, moderately abnormal in 14%, and severely abnormal in 5%. From unilateral IVH to parenchymal ICH, there were 34% more patients with

Fetal MRI description of ICH location may aid in pregnancy outcome prediction and relates to postnatal neurodevelopmental outcomes.

normal neurodevelopment (Figure 2). 30% required physical therapy and 11% had epilepsy. In five cases, an etiology was identified; 3 had abnormal placental findings and 2 had genetic findings (FNAIT and COL41A mutation).

Our findings demonstrate that pregnancy and child outcomes following fetal ICH diagnosed on fetal

MRI have a wider spectrum of outcomes than previously recognized. Following fetal ICH, 75% of pregnancies result in live birth and 81% of infants present with either normal neurodevelopment or mild neurodevelopmental delays that require physical and/or occupational therapy.

Fetal MRI description of ICH location may aid in pregnancy outcome prediction and relates to postnatal neurodevelopmental outcomes. A lower proportion of adverse pregnancy outcomes was seen with unilateral IVH, and this proportion increased as the hemorrhage became more extensive (from unilateral to bilateral) and involved different areas in the brain (from ventricles to parenchyma). The higher proportion of normal neurodevelopment seen with parenchymal ICH may be a result of the lower sample size of survivors seen with this hemorrhage. Our current findings help to provide data on fetal ICH and postnatal outcome that can be used to improve counseling to expectant mothers. Further studies

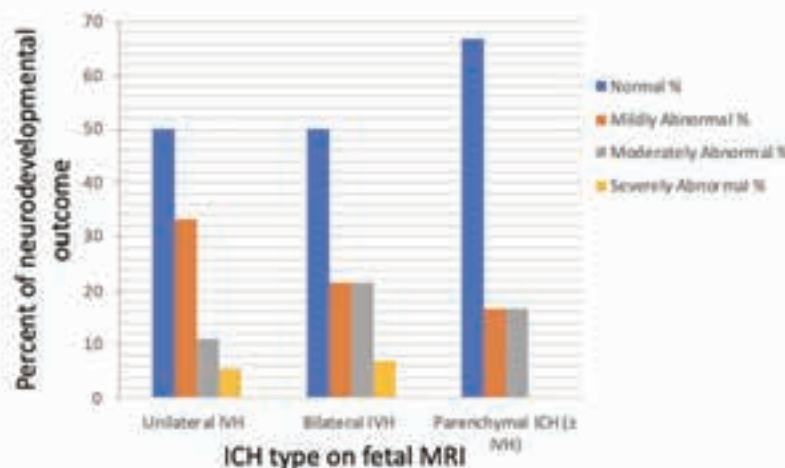


FIGURE 2: Percentage of specific neurodevelopmental outcomes compared to ICH type on fetal MRI

should evaluate fetal ICH location, size, and timing in relation to prognosis for specific postnatal outcomes.

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Residual Gastric Volume Prior to Bedside Percutaneous Endoscopic Gastrostomy Tube Placement: Do We Need to Hold Tube Feeds Prior to Peg Tube Placement?

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Percutaneous endoscopic gastrostomy (PEG) has been widely used for the long-term feeding of patients with a functional gastrointestinal system that are otherwise unable to intake solid or liquid food. There is currently no consensus regarding

Our “NPO on-call” strategy led to a median time difference of 60 minutes between stopping tube feeds and insertion of the endoscope for PEG.

the length of time that tube feeds should be held prior to bedside PEG tube placement in adult patients. The traditional dictum of holding tube feeds (NPO) at midnight the night prior to PEG placement is not borne out in the scientific literature and may put critically ill patients at risk of further malnutrition due to interrupted enteral tube feeding.¹ However, it is not known whether withholding tube feedings for a shorter time than the current standard is safe. This

possibility is supported, in part, by the decreased NPO time required in infants and children, even though their smaller stomachs and shorter esophagi increase the possibility of aspiration from a full stomach. Due to this ambiguity, our study aims to investigate if using an “on-call” NPO strategy that minimizes the length of holding tube feeds prior to PEG placement is safe by recording gastric residual volume (GRV) prior to PEG tube placement and assessing peri-procedural outcomes. We hypothesize that there is less than 100 ml GRV and no complications related to leakage of gastric contents using this strategy.

Here, we describe our experience using the “NPO on-call” strategy for holding tube feeds prior to PEG tube placement for seventeen ICU patients and describe its safety. Continuous tube feeds were held only when the surgical team was at the bedside and ready to begin the procedure. A tracheostomy was performed prior to PEG. GRV and peri-procedural outcomes were recorded. Patient

characteristics and results are summarized in Table 1. The median time from stopping tube feeds to insertion of the endoscope was 60 minutes (30, 115 IQR) and the median amount of GRV was 0 ml (0, 0 IQR). PEG was successfully performed on all patients and there were no post-procedure complications such as peritonitis or aspiration.

Enteral nutrition delivery is commonly interrupted in ICU patients, often due to airway management,

digestive intolerance, and need for diagnostic procedures.² Moreover, ICU patients are already in a state of elevated energy expenditure due to the metabolic needs of the body under stress and critical illness.¹ These factors together can lead to large differences between the caloric needs of patients and the calories actually delivered to them.² Low caloric intake, especially in ICU patients, can lead to an increased risk of nosocomial bloodstream infections, hospital length of stay, and risk of ventilator-associated pneumonia.^{3,4} Furthermore, caloric deficits in ICU patients are associated with the occurrence of sepsis, adult respiratory distress syndrome, and renal failure.⁵ In order to reduce the occurrence of these risks, interruptions in enteral nutrition need to be minimized. This understanding led to the adoption of “NPO on-call” withholding of tube feeding at GW to minimize the time of interrupted feeding.

Our “NPO on-call” strategy led to a median time difference of 60 minutes between stopping tube feeds and insertion of the endoscope for PEG. This is significantly less time relative to the current standard practice of 8-16 hours. Given that these seventeen patients also had a median GRV of 0 ml and no PPD-1 complications, our findings highlight that the prolonged NPO time is not necessary to performing endoscopy and PEG placement safely.

In conclusion, our findings indicate that minimizing time for which tube feeds are held prior to PEG using an “NPO on-call” strategy is a safe practice and may prevent delay to enteral nutrition.

TABLE: Patient characteristics and results

BMI, body mass index; EGD, esophagogastroduodenoscopy; GRV, Gastric Residual Volume; LOS, length of stay; NPO, nulla per os; PEG, percutaneous endoscopic gastrostomy; PPD-1, post-procedure day 1; TFR, tube feed rate;

Age	Sex	BMI	Hospital LOS (days)	TFR (mL/hr)	NPO-EGD time difference (min)	GRV (mL)	PEG Completed	PPD-1 Complications
60	M	26	25	50	10	0	Yes	None
73	F	28.6	18	40	719	0	Yes	None
83	F	23.5	11	42	100	0	Yes	None
45	F	21.5	12	54	155	0	Yes	None
52	M	35.9	15	130	60	200	Yes	None
71	M	51.1	14	54	30	0	Yes	None
59	F	31.7	19	50	10	0	Yes	None
62	F	27.2	28	58	20	0	Yes	None
76	M	32.3	8	40	525	0	Yes	None
62	M	33.1	14	42	11	0	Yes	None
94	F	19.9	16	54	98	5	Yes	None
57	F	24.3	11	50	210	0	Yes	None
31	M	24.5	5	30	115	5	Yes	None
77	M	34.5	8	58	80	0	Yes	None
62	F	27.2	25	58	50	0	Yes	None
74	M	36.7	15	29	44	0	Yes	None
79	F	28.7	15	45	45	0	Yes	None

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Association of Medication Mismanagement with Hospital-Related Complications in Patients with Parkinson's Disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting over six million people worldwide.¹ PD is defined by reduced dopaminergic neurotransmission in the basal ganglia causing motor symptoms of tremor, rigidity, bradykinesia, and postural instability, as well as non-motor symptoms ranging from autonomic dysfunction to cognitive decline. PD requires complex medication management to maintain the delicate balance of striatal dopamine to treat motor and non-motor symptoms. Maintaining this regimen is challenging in the inpatient setting. Medication errors involving mistimed PD medications and use of contraindicated medications, such as neuroleptics or other dopamine-blocking agents, are common in hospitalized PD patients.² Medication mistiming has previously been shown to be associated with longer lengths of stay and more complications.³ However, limited data exists examining the relationship between use of contraindicated medications and hospital outcomes in the PD population.

We aimed to investigate the incidence of medication mismanagement in hospitalized PD patients at The George Washington University

TABLE 1: Comparison of baseline characteristics and outcome measures between PD and non-PD patients

Variable	Control patients (n=1308)	PD patients (n=377)	p-value
Female %	443 (33.9%)	120 (31.8%)	0.460
Age	74.7 ± 9.4	75.3 ± 9.7	0.315
Length of Stay, days, median (Q1, Q3)	4 (2, 9)	10 (6, 20)	<0.001
30-day readmission	165 (12.6%)	96 (25.5%)	<0.001
Falls	24 (1.8%)	10 (2.7%)	0.320
Delirium	44 (3.4%)	24 (6.4%)	0.009

Hospital (GW Hospital) and explore the potential relationship of medication mismanagement on lengths of stay, 30-day readmission rates, falls, and delirium. We performed a retrospective chart review of PD patients admitted to the GW Hospital between January 2015 and January 2020. Lengths of stay, 30-day readmission rates, falls, and delirium incidences among PD patients were compared to age (± 2 years), sex, and diagnosis-related group (DRG)-matched non-PD controls. Subsequently, a comprehensive chart review was done to identify specific medication errors in the PD cohort. Medication errors were grouped into 2 categories: mistimed administration of PD medications by more than 30 minutes and use of contraindicated medications. Statistical analyses were performed to determine whether medication errors were associated with lengths of stay, 30-day readmission rates, falls, and delirium.

Three hundred seventy seven PD patients were included in this study.

The most common reasons for admission were degenerative nervous system disorder, septicemia, and urinary tract infection. Compared to controls, PD patients had approximately doubled lengths of stay ($p < 0.001$), 30-day readmission rates ($p < 0.001$), and delirium incidences ($p = 0.009$). No differences were observed between

Our analysis suggests that medication mismanagement of PD patients at this center is prevalent, and the use of contraindicated medications is associated with longer lengths of stay and higher delirium incidents.

PD and control cohorts regarding falls ($p = 0.320$) (Table 1). Medication mistiming occurred in 88.1% of PD patients. 14% of PD patients were prescribed a contraindicated medication, and those patients experienced significantly longer lengths of stay ($p < 0.001$) and had significantly more

delirium incidences ($p=0.001$). No statistically significant differences were observed in 30-day readmission rates ($p=0.248$) or falls ($p=0.408$) (Table 2). The most commonly used contraindicated medications were haloperidol (38.18%), prochlorperazine (14.55%), and metoclopramide (12.73%).

Our analysis suggests that medication mismanagement of PD patients at this center is prevalent, and the use of contraindicated medications is associated with longer lengths of stay and higher delirium incidents. This supports several reports in the literature regarding the frequency of medication mismanagement in hospitalized PD patients and its potential impact.²⁻⁵ Further analysis will need to be conducted to specifically assess the impact of medication mistiming on lengths of stay, 30-day readmission rates, and hospital complications, as this seems to be a common occurrence. Notably, our study could not assess whether increased delirium incidences in the PD cohort were a result of using contraindicated medications or if contraindicated medications were used to treat delirium. Nonetheless, this

TABLE 2: Comparison of outcome measures in PD patients who did or did not receive contraindicated medications

Outcome	No contraindicated medications (n=339)	Contraindicated medications (n=55)	p-value
Length of Stay, days, median (Q1, Q3)	10 (5, 18)	16 (8, 28)	<0.001
30-day readmission	90 (26.5%)	10 (20.6%)	0.248
Falls	10 (2.9%)	-	0.408
Delirium	16 (4.7%)	10 (18.2%)	0.001

study represents an important step in addressing the quality of care hospitalized PD patients receive and serves as a starting point for creating and implementing mitigation strategies to improve the care of PD patients.

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Atopic Dermatitis is Associated with Multiple Behavioral Problems in United States Children

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Atopic dermatitis (AD) is a chronic, inflammatory skin disease associated with intense itch, sleep disturbance, psychosocial distress, and symptoms of anxiety and depression.¹ All of these sequelae of AD may negatively impact the emotional health and social functioning in children, and ultimately lead to behavioral problems. We aimed to understand the association between AD and aberrant childhood behaviors.

Data were analyzed from the Fragile Families and Child Wellbeing

Study, a longitudinal birth cohort study of 4898 children in 20 U.S. cities.² AD was associated with the ≥ 75 th percentile of mean behavioral scores at 5 years (multivariable logistic regression; adjusted odds ratio [95% confidence interval]: 1.51 [1.18-1.93]), 9 years (1.62 [1.32-1.99]) and 15 years (1.44 [1.17-1.76]).

There was significantly increased behavioral problems at age 15 when AD persisted at ages 5, 9 and 15 (Poisson regression; adjusted risk ratio [CI95]: 1.17 [1.01-1.35]), ages 5 and 15 (1.33 [1.08-1.63]) and ages 9 and 15 (crude risk ratio [CI95]: 1.27 [1.03-1.56]). AD was associated with 12 aberrant behaviors, particularly fighting (repeated measures logistic regression; adjusted odds ratio [CI95]: 1.40 [1.15-1.70]), physically attacking people (1.38 [1.09-1.76]), being sullen (1.31 [1.15-1.49]), worrying (1.41 [1.23-1.61]), and threatening others (1.35 [1.08-1.70]). AD at age 15 was associated with ≥ 75 th percentile of the Child Behavior Checklist (CBCL)

subscales: anxious/depressed (aOR [CI95]: 1.44 [1.16-1.78]), withdrawn (1.40 [1.11-1.77]), attention problems (1.33 [1.09-1.63]), social problems (1.39 [1.13-1.72]) and aggressive (1.49 [1.22-1.82]). Significant two-way interactions were present between AD and sleep as predictors of underactivity (4.31 [3.06-6.08]), being threatening (aOR [CI95]: 3.42 [2.20-5.34]), being sullen (3.86 [2.74-5.43]) and nervousness (4.56 [3.29-6.32]).

Conclusion: Childhood AD, particularly persistent disease with sleep disturbances, was associated with a wide range of behavioral problems in US children and/or adolescents.

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Agensis of the Corpus Callosum: A Retrospective Study on Fetal and Postnatal Outcomes

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Agensis of the corpus callosum (ACC), complete or partial, is one of the most common brain malformations, occurring in 1:4000 live births, and results in a wide spectrum of clinical outcomes.¹ Fetal MRI is increasingly utilized to discern corpus callosum abnormalities that are unable to be fully assessed with ultrasonography.² This study aims to describe the spectrum of fetal brain abnormalities in ACC cases diagnosed by fetal MRI, determine the frequency of postnatal confirmation by brain MRI of fetal cases, and understand pregnancy and postnatal outcomes.

Methods: Patient medical records from Children's National Hospital's Cerner database from Jan. 1, 2012 to June 30, 2019 with a referral for a possible brain abnormality (ACC, cavum septum pellucidum abnormality, and/or ventriculomegaly), prenatal neurological consultation, complete fetal MRI, and confirmed ACC (partial or complete type) on imaging were included. Data on maternal medical and obstetric history, prenatal testing, prenatal imaging, labor and delivery, neonatal birth history, and postnatal evaluations/outcomes were recorded. Cases were defined as isolated if ACC

TABLE: Participant Characteristics

	Mexican n=10	Chinese/ Taiwanese n=8	Total n=18
Age (years)			
Mean	38	34.4	36.4
≤30	2	3	5
31-40	2	4	6
>40	6	1	7
Legal Status			
Naturalized	1	1	2
Permanent Resident	0	5	5
Work Permit	3	1	4
Overseas Born Citizen	0	1	1
Undocumented	6	0	6
Time in US (years)			
Mean	20	11.9	16.4
County			
LA	5	5	10
OC	5	3	8
Undocumented family or friends			
	10 (100%)	3 (37.5%)	13 (72.2%)

was the only brain finding. Cases were defined as complex if there were significant brain findings in addition to ACC: ventriculomegaly/hydrocephalus, posterior fossa malformation, or malformation of cortical development. Each case was categorized as partial or complete ACC and isolated or complex ACC, and group comparisons on outcomes were analyzed.

Results: We evaluated 127 pregnant women-fetal dyads by fetal MRI at 25.8 ± 5.3 weeks gestation. Forty-five (36%) had isolated-complete ACC, 17 (13%) had isolated-partial ACC, 46 (36%) had complex-complete ACC, and 19 (15%) had complex-partial ACC based on fetal MRI.

Pregnancy outcome was live birth in 75, termination in 36,

and intrauterine demise in three. Seventy-one of 75 live births had postnatal evaluations; 59 had postnatal imaging (56 brain MRI; three head ultrasound). In 40 of 59 (68%) cases, postnatal imaging confirmed the prenatal ACC finding; 19 cases had differing prenatal and postnatal imaging results. In them, 12 were identified as isolated-complete ACC prenatally and were changed to complex-complete (n=10) or isolated-partial (n=2) ACC postnatally. Two cases were identified as complex-complete prenatally and were changed to isolated-complete ACC postnatally. Children with partial or complete ACC had similar rates of communication and/or motor

Continued on p. 78

delays (44%); however, seizures were more common in partial ACC cases (26% vs. 17%). Complex ACC cases had poorer outcomes than isolated ACC cases, with complex cases having more delivery complications (44% vs. 16%), NICU admissions (69% vs. 28%), dysmorphisms in postnatal evaluations (67% vs. 27%), hearing abnormalities (20% vs. 5%), seizures (33% vs 11%), and hydrocephalus (26% vs 0%).

Conclusions: Children with complex ACC demonstrate a poorer neurologic outcome compared to children with isolated ACC. Fetal MRI can help to differentiate isolated and complex abnormalities of the corpus callosum and is a useful tool to guide prenatal counseling and postnatal neurologic care.

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IRB: PR000012833 – Retrospective Analysis of Fetal and Neonatal Corpus Callosum Abnormalities in the Fetal Medicine Institute

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Increased Caspase-1 Activation in the Setting of COVID-19 Disease

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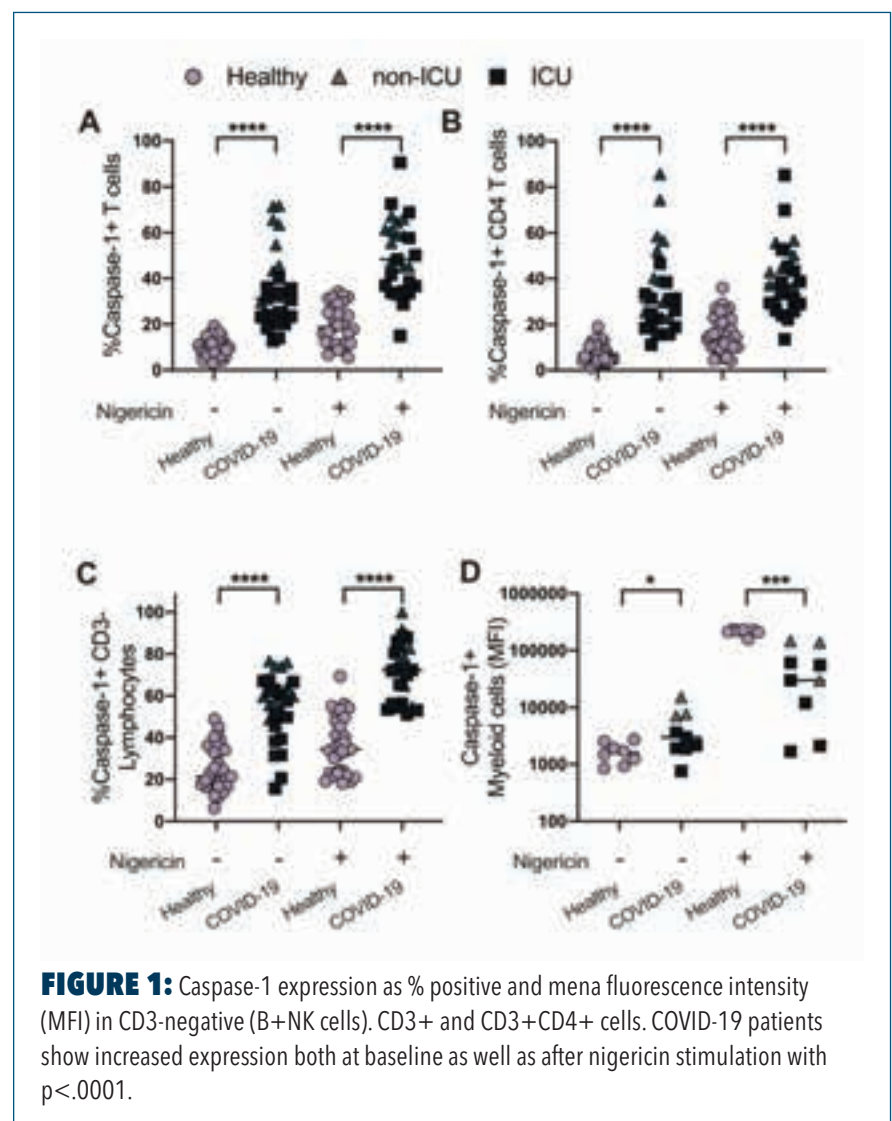


The latest threat to global health is the ongoing outbreak of Coronavirus Disease 2019 (COVID-19). Previous studies have made it increasingly clear that the innate immune system is a critical player in a patient's response to COVID-19 infection. Further, the disease-causing virus SARS-CoV-2 is a positive-sense RNA virus and is therefore, speculated to be recognized by RNA-sensing pattern recognition receptors of the innate immune system. Finally, cytokine levels of IL1- β and LDH are found to be elevated in patients with COVID-19, which are cytosolic proteins that require release by inflammasome activation and membrane rupture, respectively.¹ In this study, our lab shows that excessive caspase-1 inflammasome activation contributes to inflammation in the setting of COVID-19.

Blood samples were obtained from patients that tested positive for COVID-19 by RT-PCR as well as samples from COVID-19 negative,

healthy controls. Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood using a ficoll gradient and centrifugation,

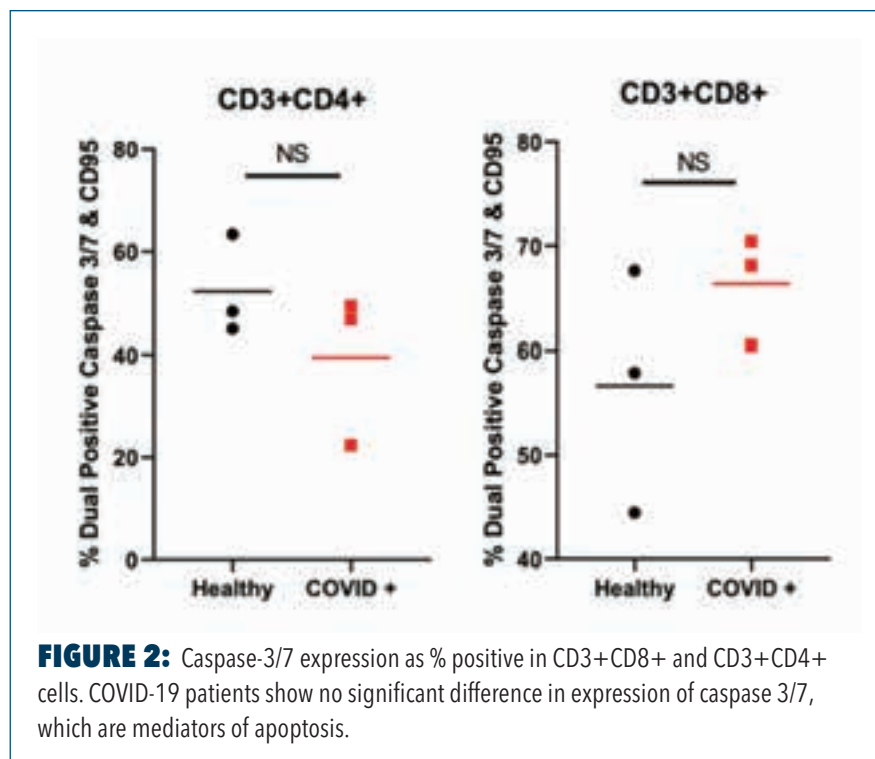
and subsequently stained with a mix of fluorescent-conjugated antibodies. A FAM-FLICA Caspase-1 and 3/7 Assay Kit was used to assess



caspase expression by flow cytometry. Samples were run on the Canto Cytometer and files were analyzed using FCS Express software.

Our experiments found that caspase-1 expression was elevated in COVID-19 patients compared to healthy controls, with highest levels seen in ICU patients compared to non-ICU patients (Figure 1). In order to show that there is distinct elevation in the pyroptotic pathway without elevation in the other caspases involved in the programmed apoptotic pathway, we also looked at caspase-3 and caspase-7 expression in isolated PBMCs. Indeed, there was no statistical difference in expression of these proteins between COVID-19 patients and healthy controls (Figure 2).

Our findings indicate that COVID-19 patients may have excessive activation of pyroptosis through the caspase-1 inflammasome. Future experiments aim to better understand the consequence of this aberrant inflammasome activation on the immune system and possibly on red blood cell function. Our lab



has performed in vitro experiments on whole blood using a pan-caspase inhibitor to show that caspase-1 levels can successfully be attenuated and hopes to explore this drug in a phase I clinical trial for the treatment of patients with COVID-19.

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An Anatomical Study of the Foramen of Monro: Implications in Management of Pineal Tumors Presenting with Hydrocephalus

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For pineal tumors presenting with hydrocephalus, simultaneous endoscopic third ventriculostomy (ETV) and tumor biopsy is commonly used as the initial step in management.^{1, 2, 4, 5} To analyze the restriction which the foramen of Monro poses to this procedure, one must start with a detailed description of the microsurgical anatomy of the foramen in living subjects. However, the orientation and shape of the foramen of Monro make this description difficult with conventional imaging techniques.^{3, 5}

Method: Virtual reality technology was applied to MRIs of 30 living subjects without hydrocephalus, as well as to MRIs of 16 patients with hydrocephalus, to generate precise anatomical models with sub-millimeter accuracy. The morphometry of the foramen of Monro

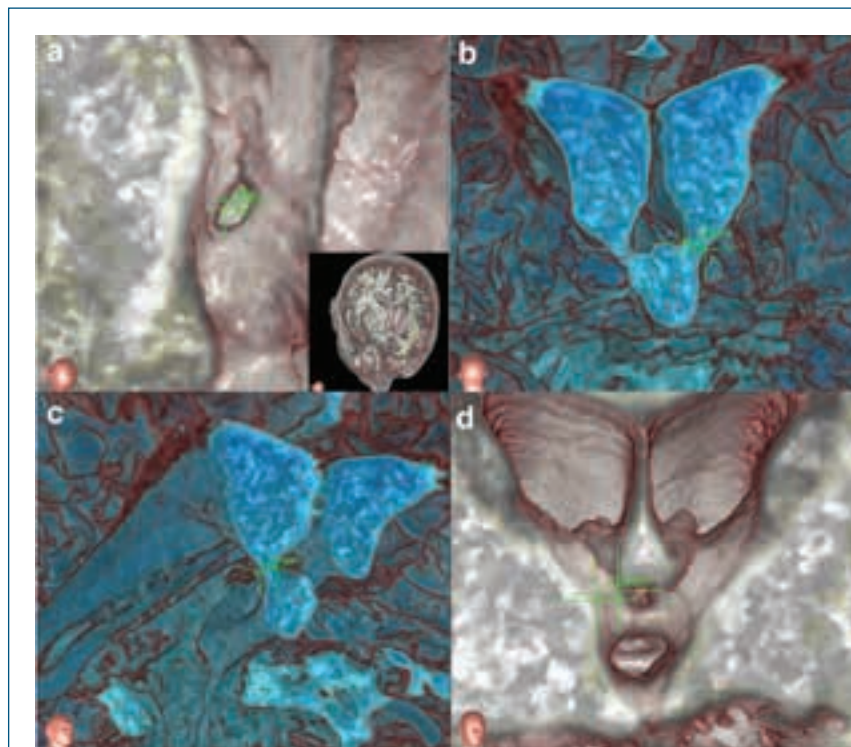


FIGURE 1: Measuring the dimensions of the Foramen of Monro. In this example, the short axis is measured (a). To start the measurement, a preliminary ruler was implanted using the top-down view on the foramen. Inset—orientation view of the top-down view along the axis of the foramen. This ruler was then examined for placement and accuracy in multiple angles in 3D space, with the ventricle and foramen first as empty spaces and then as a solid “cast” (b and c). Every foramen was measured in this fashion and data recorded only when confirmation of the correct and precise placement of the ruler was obtained (d).

was studied in each group. In addition, displacement of the margins of the foramen was studied in detail for simultaneous ETV and pineal tumor biopsy through a single burr hole.

Results: In 30 normal subjects, the foramen of Monro had oval-shaped openings averaging 5.23 mm². The foramen was larger in people above age 55 (average 7.19mm² over 55, versus 3.28 mm² under 55, $p = 0.007$) and larger on the left side compared to the right in 73% of study subjects (average 5.93 mm² left, versus 4.52 mm² right, $p = 0.002$). For 16 patients

with clinical presentation of hydrocephalus, the average opening was 32.6 mm². Simulated single burr hole simultaneous ETV and pineal tumor biopsy was performed in 10 specimens. Average displacement of the posterior and anterior margins of the foramen was 5.71 mm and 5.76 mm, respectively. However, maximum displacement reached 9.3 mm posteriorly and 10 mm anteriorly.

Conclusions: The foramen of Monro is an oval-shaped cylinder that changes in size and orientation in the hydrocephalic patient. If universally

applied to all patients regardless of foramen and tumor size, ETV/biopsy can displace structures around the Foramen of Monro up to 1 cm, which can potentially lead to neurological damage. Careful pre-operative assessment is critical to determine if a single burr hole approach is safe.

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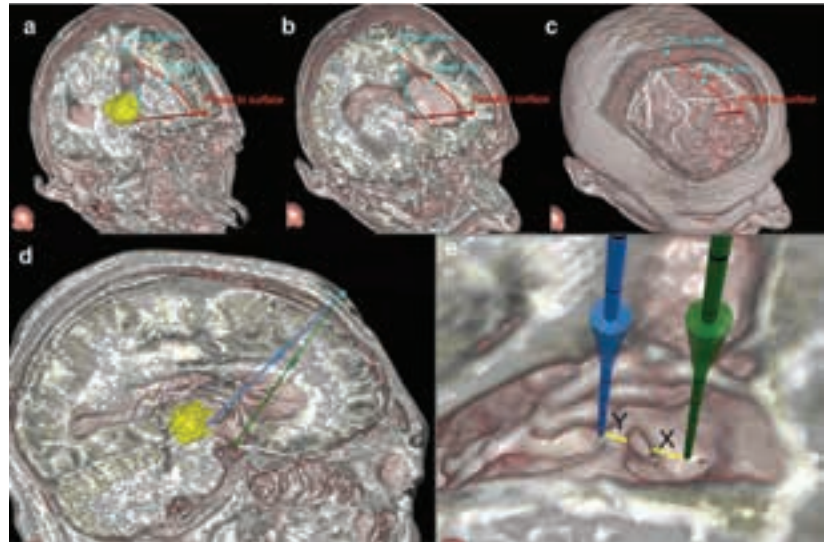
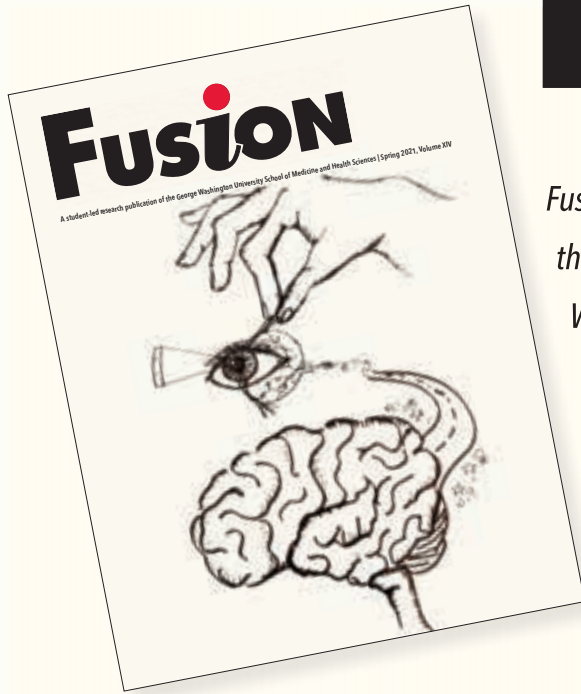


FIGURE 2: Generating the trajectories and measuring the displacement of the Foramen of Monro. Ideal trajectories extended from the pineal tumor and tuber cinereum (a), through the center of the foramen of Monro (b), to the surface (c). The study entry (SE) was then calculated by finding the midpoint of the exits points of the ideal trajectories (c). Biopsy (blue) and ETV (green) trajectories were then projected from the SE back to the targets (d). Examining the foramen of Monro with these trajectories in close-up, the anterior displacement (X) and posterior displacement (Y) were measured (e).

Fusion



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