Prevalence of unexplained left ventricular hypertrophy in the Yale New Haven Health System

Avinainder Singh, MD, MMSc and Edward J. Miller, MD, PhD

Background: Left ventricular hypertrophy (LVH) is a clinical finding commonly identified on EKG or echocardiography during routine clinical care. The etiology of LVH is varied and can range from physiologic processes such as athlete's heart, increased afterload states such as hypertensive heart disease and aortic stenosis, to infiltrative cardiomyopathies. Identifying the exact etiology of LVH carries a prognostic importance as targeted therapies can be instituted.

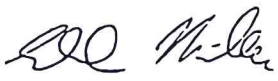
Specific Aim: Develop a method for large-scale data analytics to describe the prevalence of LVH and identify the proportion of patients with unexplained LVH across the YNHHS.

Methods: This was a retrospective cohort study which included adult outpatients who underwent transthoracic echocardiography at any site across the YNHHS from January 2020 to December 2020. Data was collected using the YNHHS LumeDx imaging repository. Only the first complete transthoracic echocardiogram was included, limited echocardiograms or those where wall thickness measurements could not be obtained were excluded. LVH was defined as interventricular septum or left ventricular posterior wall thickness of ≥ 13 mm on 3-D or M-mode scanning during transthoracic echocardiogram. Severity of LVH was further graded as mild (13-14.9 mm), moderate (15-16.9mm) and severe (≥ 17mm) using the maximal wall thickness. LVH was attributed to the following etiologies when present: hypertension (BP ≥ 140/90) and aortic stenosis (moderate or severe valvulopathy). Data was analyzed using STATA version 16.1. Categorical variables are reported as frequencies and proportions, and compared with the chi-square or Fisher exact test, as appropriate. Continuous variables are reported as means or medians and compared with the Student's t-test or the Mann-Whitney test, as appropriate. A 2-sided p value <0.05 was considered significant. The Yale IRB approved the study.

Results: A total of 36,039 patients met inclusion criteria, of which 5,121 (14.2%) met study criteria for LVH. Patients with LVH were significantly older (median age 71 vs. 66 years, p<0.001) and less likely to be female (27.8% vs. 54.4%, p<0.001). Patients with LVH also had marginally lower ejection fractions (62% vs. 63%, p<0.001), higher RV systolic pressures (27.3 mmHg vs. 25.9 mmHg, p<0.001) and more likely to have diastolic dysfunction (78.6% vs. 57%, p<0.001). Among patients with LVH, hypertension was present in 1924 (37.6%) and moderate to severe aortic stenosis in 473 (9.2%), whereas 2896 (56.6%) patients did not have the aforementioned risk factors to explain LVH.

Conclusion: Nearly 1 in 7 patients undergoing echocardiography met criteria for LVH. However, 56% of patients with LVH did not have any clinically evident risk factors for LVH. Further studies are warranted to phenotype such patients with unexplained LVH and screen for underlying infiltrative cardiomyopathies.

Avinainder Singh (Resident)



Edward J. Miller (Faculty Mentor)

High prevalence of prolonged QTc in adults and children with Williams syndrome

Benjamin D. Brink MD MS, Richard Feinn PhD, Beth Kozel MD PhD, Eric Yu MD, Sampat Sindhar BS, Julie He MD, Charles Rouse MD, Rachel Lampert MD, Barbara Pober MD*, Robert W. Elder MD*
*contributed equally as senior authors

Background: Williams syndrome (WS) occurs in 1 in 8,000 live births. The risk of sudden cardiac death is 25 to 100 times greater in WS than in the general population. Prolongation of the corrected QT interval (QTc) is a known risk of sudden cardiac death and previous literature suggested that pediatric WS patients have increased prevalence of QTc prolongation. The objective of this study was to independently determine the frequency of prolonged QTc among children and adults with WS.

Methods: A retrospective chart review was done of WS patients seen at Yale-New Haven Hospital (YNHH), Massachusetts General Hospital (MGH), and Washington University School of Medicine (WUSM) from July 16, 1971 to August 1, 2016. EKGs were obtained of all consecutive patients with the diagnosis of WS seen in Cardiology clinics (YNHH) or in Genetics clinic by one of the co-authors and on whom at least 1 readable EKG was available. Among WS patients with 2 or more EKGs, the most recent ones up to a maximum of 3 were reviewed. A control set of EKGs was created by selecting a single EKG from children and adults evaluated in Cardiology clinics at YNHH primarily for non-cardiac chest pain or an innocent murmur. Control EKGs were intended primarily to mitigate observer bias. Indications for excluding an EKG, either WS or control, included non-sinus rhythm, bundle branch block (QRS >120ms), or known QT syndrome gene mutation. EKGs were analyzed after they were de-identified, randomly sorted, and equally divided into two groups. Each group contained a mix of control and WS EKGs, and the reader was blind to patient diagnosis. Each group of EKGs was read by two cardiologists. Each reader measured the QT, JT, and RR intervals for one cardiac depolarization/ repolarization in 3 separate locations in standard leads. QTc was calculated using established methods using two different formulas: the Bazett formula ($QTcB = QT/\sqrt{RR}$) and the Fridericia Formula ($QTcFri = QT/\sqrt[3]{RR}$). QTc prolongation was defined as QTc $\geq$ 460ms.

Results: 280/296 (95%) EKGs and 147/155 (95%) WS patients were included. 123 EKGs from 123 control patients were included in the analysis. WS patients had a higher mean QTc than controls calculated by both the Bazett (444ms vs 417ms, $p<0.001$) and Fridericia formulas (413ms vs 402ms, $p<0.001$). WS patients had a higher mean heart rate compared to controls (96 bpm vs 76 bpm, $p<0.001$). In addition, WS patients with prolonged QTc had a higher heart rate than WS patients without prolonged QTc (100 bpm vs 86 bpm, $p<0.001$). Just over a third of patients with WS (52/147 =34.4%) and 5/123 (4%) controls had one or more EKGs with a prolonged QTc ≥460ms when calculated by the Bazett formula. The Fridericia formula demonstrated a much lower frequency with 8/147 (5.4%) of patients with WS having QTcF ≥ 460ms and none of the controls had prolonged QTcF. In the 52 patients with WS who had a prolonged QTcB≥ 460ms, 32 of them (62%) had more than one EKG available for analysis. Twenty-one (21/32=66%) patients with WS had multiple EKGs with not all EKGs prolonged. Patients with WS with a prolonged QTc had a statistically higher heart rate than patients with WS without a prolonged QTc.

Conclusion: In our study, adult and pediatric patients with WS have a 34.4% prevalence of prolonged QTc when calculated by the Bazett formula but only 5% when calculated using the Fridericia formula. Evidence suggests that heart rate and what formula is used to calculate QTc matter significantly in evaluating QTc prolongation in this population and further research is needed.

Benjamin D. Brink, MD

Benjamin D. Brink, MD

Authors: Bethany Canver, MD, MSW; Katie Clark, MSPH; Alayna Liptak, APRN-BC; Jeanette M. Tetrault, MD; Stephen Holt, MD, MS

Title: Preparing primary care physicians to treat addiction: inclusion of addiction training during internal medicine residency

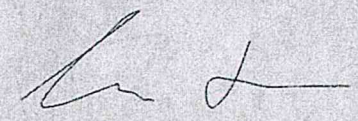
Background: People with substance use disorders (SUD) disproportionately interface with the healthcare system. Physicians in general internal medicine (GIM) lack comfort and skills required to manage SUD which leads to a dearth of providers willing and able to treat SUD. Given the prevalence of SUD, interventions to increase provider skill and comfort are needed.

Objective: We evaluated the impact of a multi-faceted, longitudinal addiction medicine curriculum embedded within an internal medicine residency on graduates' clinical practices and comfort level treating SUD.

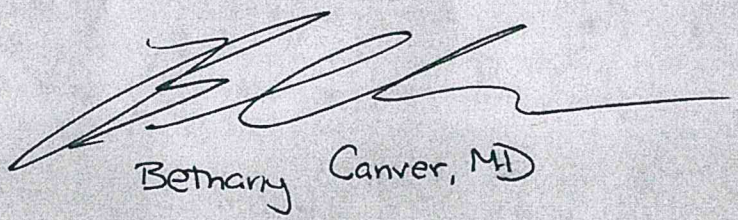
Methods: A survey was emailed to all GIM graduates from a single academic primary care residency program who graduated between 2016-2018 (n=53). The survey assessed pharmacotherapy prescribing habits since residency, comfort with SUD pharmacotherapy, overall comfort treating SUD, and experience correcting stigmatizing language or providing guidance to colleagues on the care of patients with SUD.

Results: 60% of graduates (n=32) responded to the survey. 90% (n=29) perceived themselves as more comfortable treating patients with SUD than their colleagues. All graduates felt comfortable using medications to treat SUD. 84% (n=27) perceived themselves as more comfortable using pharmacotherapy to treat SUD than their colleagues. Since completing residency, 62.5% (n=20) prescribed medications for alcohol use disorder and 46.8% (n=15) prescribed medications for opioid use disorder. 68% (n=22) corrected stigmatizing language heard in the workplace. 59% (n=19) had been asked by a colleague for guidance on diagnosis or management of SUD.

Conclusions: A recent survey suggested that the majority of primary care providers have little interest in caring for patients with SUD, however, recent graduates of a single residency program with a robust, structured, required, longitudinal addiction medicine training experience all reported a willingness to treat patients with SUD. Additionally, they reported comfort with prescribing pharmacotherapy for SUD, had taken an active role in reducing SUD-related stigma, and served as a resource for colleagues and trainees. Future research should identify the specific features of a residency program experience that are most essential to building a primary care workforce willing to care for patients with SUD.



Stephen Holt, MD



Title: Impact of Reaching Full Enteral Nutrition Early in the Mechanically Ventilated Adult Population

Camilla Powierza, MD, Melissa Knauert, MD, PhD

Background: Early enteral nutrition support in critically ill adult patients is thought to improve mortality and infectious morbidity. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, therefore, recommend initiation of early enteral nutrition in critically ill adults. However, the ideal rate of tube feeds (full feeds versus trophic feeds) and mode of administration (continuous versus intermittent) remains unclear and understudied.

Specific Aim: To evaluate the relationship between improving time to reach full enteral nutrition and clinical outcomes in critically ill mechanically ventilated adult patients.

Hypothesis: Reaching 70% of goal enteral nutrition earlier in admission will be associated with decreased mortality.

Methods: We conducted a retrospective cohort study of mechanically ventilated, adult patients receiving enteral nutrition admitted to our hospital's two medical intensive care units (MICU) between 2013 and 2019. We included patients age 18-99 years who were intubated within 24 hours of MICU admission. We excluded patients with tracheostomy present on admission, requiring chronic enteral nutrition, transferred from an intensive care unit of a differing specialty or hospital, and admitted post-cardiac arrest with subsequent devastating neurologic impairment leading to withdrawal of care. Our primary outcome was all-cause in-hospital mortality. Secondary outcomes included time to reach >70% of daily goal enteral nutritional caloric intake ("goal EN"), MICU length of stay, hospital length of stay, and ventilator-free-days.

Results: We identified 1367 patients that met eligibility criteria within our two MICUs. Our cohort was 52% male, had a mean age of 64 years (SD 0.4 years), mean APACHE II score of 25 (SD 0.2), and mean BMI of 30 (SD 0.3). The most common primary diagnoses were acute respiratory failure (53%), septic shock (18%), and cardiogenic shock (8%). We found it took a mean 3.7 days (SD 1.4 days) for patients to reach goal EN, and 53% of our sample population never reached goal EN within the first 8 days. Reaching goal EN did not lead to a significant decrease in all-cause in-hospital mortality (p=0.16).

Conclusion: Initiation of full enteral nutrition early was not associated with mortality reduction in the critically ill mechanically ventilated adult population, although the trend towards significance suggests our hypothesis may be true in a subset of critically ill patients. Thus, further evaluation of secondary outcomes and subgroup analysis are currently underway.

Resident's signature

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Title: Significance of Repeated 1R Rejections in Heart Transplantation
Authors: Christine Hsueh, Laurine Bow, Lynn Wilson, Lavanya Bellumkonda

Aim: 1R rejection is commonly seen in routine post-transplant biopsies, but the significance of repeated 1R rejection is unclear. Our aim was investigate patients with this rejection and we hypothesized that it was not associated with adverse outcomes.

Methods: We conducted a retrospective analysis of patients transplanted between July 2008 and December 2014 at our center. A total of 1,128 biopsies were performed in 69 patients. Each patient on an average had 16 biopsies.

Results: 14 patients had grade 0 on all their biopsies, 22 had grade 1 on one or two of their biopsies, 30 had grade 1 on three or more of their biopsies. Three patients had grade 2 on their initial biopsy and were excluded from the study. Compared to grade 0, presence of grade 1 rejection and repeated occurrence of grade 1 rejection, did not predict increased risk of mortality or progression to grade 2 or grade 3 rejection. Grade 1 rejection and repeated occurrence of grade 1 rejection did not predict development of de novo donor specific antibodies or graft failure as defined by decrease in ejection fraction to less than 55%.

	Grade 0 N=14	Grade 1 (1-2biopsies)n=22	Grade 1 (3 or more biopsies)n=30	P value
Age	50±14	52±15	54±11	0.57
Donor Age	41±13	38±14	30±12	0.015
BMI	24±3.3	26±4	28±5	0.015
Male Sex	57%	82%	67%	0.26
LVAD Bridge	36%	32%	36%	0.831
Blood Type				0.391
O	29%	27%	43%	
A	57%	36%	23%	
B	14%	27%	23%	
AB	0%	9%	10%	
Etiology of CMP				0.457
Ischemic	21%	32%	47%	
Non-ischemic	43%	46%	37%	
Other	36%	23%	17%	

Table 1. Baseline characteristics

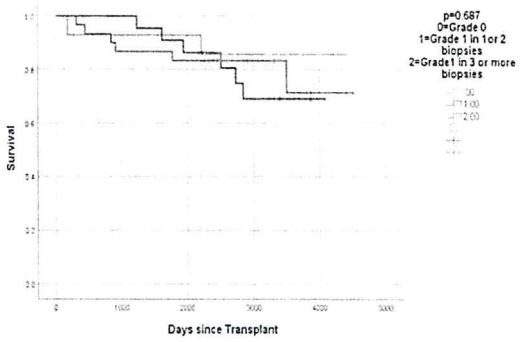

Table 2. Kaplan-Meier Curve by Grade

Conclusion: Grade 1 rejection or presence of repeated grade 1R was not associated with adverse outcomes. There was no difference in subsequent grade 2 or grade 3 rejection, development of denovo donor specific antibodies, graft failure and mortality in patients with grade 1 compared to grade 0 rejection.

3/7/2021

Assessment of the impact of an SGLT-2 inhibitor on cancer prevalence:

Curtis Perry, MD/PhD, Rachel Perry, PhD

Background: Obesity is one of the most important factors affecting cancer in the world, promoting the increasing the morbidity and mortality of more than a dozen tumor types. One promising avenue of research involves hyperinsulinemia as a crucial mediator of the relationship between obesity and cancer. Hyperinsulinemia independently associates with increased morbidity and mortality in several cancer types, suggesting the importance of further studying the role of hyperinsulinemia in the obesity-associated cancers, and the lack of effect predicted in non-obesity-associated cancers.

Specific Aim: Does treatment with an SGLT2 inhibitor reduce the risk of obesity-associated cancer?

Hypothesis: Treatment with an SGLT2 inhibitor will decrease the risk of obesity-associated cancer but have no effect on risk of non-obesity-associated cancers.

Methods: Identify all patients in the YNHH Epic ecosystem diagnosed with type 2 diabetes AND any solid cancer AND all those treated with canagliflozin or dapagliflozin or empagliflozin from 3/13 to until 12/2020. For estimation of sample size, SlicerDicer (an Epic tool) was used to estimate 1210 of these subjects fit the selection criteria. An IRB approved JDAT request for (C01.-C80. AND E11.)) AND (canagliflozin or dapagliflozin or empagliflozin) patients was submitted and awaiting return. While awaiting the JDAT data set, SlicerDicer was used to attempt to estimate the odds ratio of subjects with a type 2 diabetes diagnostic code having one of several solid tumor diagnostic codes compared to subjects with those diagnoses and the addition of an SGLT2 inhibitor prescription.

Results: In the SlicerDicer exploratory analysis of obesity associated cancer, 43 subjects had a breast cancer diagnostic code as well as type 2 diabetes and a SGLT2i prescription compared to 9858 subjects with diagnostic codes for type 2 diabetes and breast cancer alone, for an odds ratio of 0.063 (95% CI: 0.047 to 0.085, P<0.0001). Likewise, 35 subjects had a colon cancer diagnostic code as well as type 2 diabetes and a SGLT2i prescription compared to 1933 subject with diagnostic codes for type 2 diabetes and colon cancer alone, for an odds ratio of 0.2629 (95% CI: 0.19 to 0.36, P<0.0001). However, non-obesity associated cancer metastatic melanoma had 4 subjects had a metastatic melanoma diagnostic code as well as type 2 diabetes and a SGLT2i prescription compared to 209 subjects with diagnostic codes for type 2 diabetes and metastatic melanoma alone, for an odds ratio of 0.278 (95% CI: 0.1 to 0.75, P=0.011). Likewise, similarly non-obesity associated lung cancer had 4 subjects had a lung cancer diagnostic code as well as type 2 diabetes and a SGLT2i prescription compared to 209 subjects with diagnostic codes for type 2 diabetes and lung cancer alone, for an odds ratio of 0.126 (95% CI: 0.08 to 0.20, P<0.0001).

Conclusions: Intriguing odds ratio differences in both obesity associated, and non-obesity associated cancers observed in SlicerDicer await investigation with individual subject data to ensure complete and accurate diagnostic coding, as well as temporal association.

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Changing Practices and Outcomes in Patients Presenting to the Emergency Department with Gastrointestinal Bleeding

Cynthia Tsay, M.D., Dennis Shung, M.D., Loren Laine, M.D.

Background: Gastrointestinal bleeding (GIB) is the most common gastrointestinal diagnosis requiring hospital-based care in the United States (U.S.) and the fifth most common gastrointestinal reason for an emergency department (ED) visit. In 2014, GIB resulted in over 500,000 hospitalizations, almost $5 billion in hospital related costs and nearly 11,000 deaths. While the case fatality rate from GIB remains low, around <5% even among older adults, assessing trends in GIB related to patient characteristics, management, mortality, and cost can inform clinical practice and policy

Specific Aim: To determine characteristics, dispositions, and outcomes of patients presenting to the ED with GIB in the U.S. and identify epidemiologic trends in mortality, red blood cell (RBC) transfusion, and ED utilization over the last 12 years using a large administrative database.

Hypothesis: We postulated that despite more complex patients, the advent of new guidelines recommendations since 2006 (e.g., discharge of very low-risk patients from ED, implementation of restrictive transfusion strategy) influenced practice resulting in changes in clinical outcomes such as decreased mortality, decreased transfusions, and decreased hospital admissions.

Methods: The Nationwide Emergency Department Sample for 2006 and 2018 was used to identify all adult patients with a primary discharge diagnosis of GIB based on International Classification of Disease codes and categorized by location of GIB (upper, lower, or unspecified). This database includes data throughout patients' entire stay in the ED and hospital (if admitted). Baseline characteristics and risk factors included age, gender, geographic location, income quartile, primary insurance and Charlson Comorbidity Index (CCI). Disposition outcome was discharge from the ED (vs. hospital admission or observation), and clinical outcomes (over entire time in ED and hospital) were RBC transfusion, endoscopic hemostatic intervention, and in-hospital mortality. Univariate and multivariate logistic regression were performed using STATA to identify risk factors in 2018.

Results: Weighted estimates representative of a national sample included 692,953 cases of GIB in 2006 and 870,781 in 2018 with similar gender, age, geographic distribution, income quartile, and primary insurance. As compared to 2006, patients presenting to the ED in 2018 had more comorbidities (CCI≥7: 8% v 3%) yet were more likely to be discharged from the ED (39% v 30%), and less likely to receive RBC transfusions (21% v 27%). The proportion presenting with upper (32% v 34%), lower (30% v 30%) and unspecified GIB (38% v 36%) in 2018 remained unchanged compared to 2006. Overall mortality decreased in 2018 to 1.1% from 2%. Multivariate analysis demonstrated ED discharge was associated with female sex (OR 1.20, 95% CI 1.17-1.23), lower age (OR 0.96, 95% CI 0.96-0.96), fewer comorbidities (OR 0.24 95% CI 0.24-0.26), and geographic location (OR>1 for all regions compared to Northeast). Transfusion, endoscopic intervention, and mortality were associated with older age (OR 1.03 95% CI 1.03-1.03; OR 1.02 95% CI 1.02-1.02; OR 1.04 95% CI 1.04-10.4), male sex (OR 0.96 95% CI 0.94-0.99; OR 0.79 95% CI 0.77-0.81; OR 0.90 95% 0.82-0.98), and increased comorbidities (OR 3.26 95% CI 3.14-3.39; OR 3.05 95% CI 2.92-3.21; OR 8.79 95% CI 7.83-9.87).

Discussion: Patients presenting with GIB are now more likely to be discharged from the ED and less likely to be admitted or receive RBC transfusion than in 2006 despite an increase in comorbidities--possibly reflecting uptake of recent guideline recommendations. Factors associated with discharge from the ED include lower number of comorbidities, lower age, female sex, and living outside the Northeast.

Cynthia Tsay
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Loren Laine Digitally signed by Loren Laine Date: 2021.03.22 12:01:02 -04'00'
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Research Summary Abstract

Title: Post-Acute Care Patterns in Heart Failure Patients

Elisabeth Wong, MD, Erica Spatz, MD

Background: As the United States' healthcare system is trending towards value-based rather than fee-for-service payments, physicians and healthcare administrators are faced with adapting to new policies and reimbursement methods. With the Affordable Care Act of 2010, bundled payments were proposed to reduce healthcare cost while maintaining, if not improving, quality of care. The cardiovascular field continues to be a major focus of these policies as cardiac conditions are a leading cause of healthcare admissions and costs. Congestive heart failure is a major subset of cardiac conditions, accounting for significant healthcare resources. Currently, bundled payments for heart failure are offered on a voluntary basis to healthcare administrations and would include bundled payments for a 90-day period including initial admission, post-acute care, and associated readmissions. With the ever-shifting landscape of health care policy, it remains unclear how these programs will affect heart failure care and costs. Post-acute care is a large component of bundled care for patients admitted for congestive heart failure, with up to 55% of these patients being discharged to post-acute care. Medicare spends significant amounts of money on post-acute care, sometimes as much as on initial hospitalizations. Given the significant role of post-acute care in congestive heart failure care and cost, investigating the patient level factors such as sex and race that contribute to outcomes regarding post-acute care patterns in congestive heart failure is critical for understanding the components contributing to heart failure bundled payments; this understanding could help healthcare administrators and policy makers to further develop and apply these programs.

Specific Aims: (1) To understand patterns in post-acute care for heart failure patients across sex and race; (2) To analyze outcomes among advanced heart failure therapies and post-acute care including readmission rates, mortality, and cost of care across sex and race

Hypothesis: There are discrepancies among race and sex in terms of heart failure post-acute care patterns and overall outcomes during 90-day bundle periods

Methods: The study is a retrospective analysis of Medicare data. The MEDPAR data set has three subsets (hospital, skilled nursing facility, home health aide). A unique identifier is used for patients to allow for data to be extracted and linked across these different care settings. Variables of hospital stay (i.e. cardiologist involvement, length of stay, physical therapy consult, and advanced therapies) and outcomes (i.e. readmission and mortality rates) are extracted from the data set based on billing data (i.e. ICD10 coding). Additionally, the pattern of patients' settings after hospital discharge are extracted. These measures are compared across race and sex.

Results: Unfortunately, our project was stalled in the setting of the COVID-19 pandemic. Our collaborators, who have access to the CMS MEDPAR data set, were furloughed during the pandemic. This made it so that we did not have access to the data required to reach our aims. Although some of the collaborators are now no longer furloughed, they have had to prioritize research involving COVID-19 studies instead of this heart failure project since their return.

Conclusions: Despite the need to stall this project, it remains important to explore post-acute care motifs at a patient level across sex and race over the 90-day period after discharge from acute hospitalization for congestive heart failure. Research in this area will help to build understanding of characteristics that play a role in post-acute care in congestive heart failure patients which, in turn, will help healthcare administrations and policy makers better recognize the factors that will contribute to outcomes in bundled payment systems.

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Lower Gastrointestinal Syphilis: Literature Review and Case Series

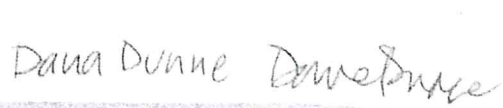
Elizabeth Ferzacca, MD; Dana Dunne, MD, MHS

Background. Syphilis infections are increasing globally. Lower gastrointestinal syphilis (LGIS) is a rare manifestation of early syphilis transmitted through anal sexual contact. Misdiagnosis of LGIS as inflammatory bowel disease may result from clinician under-awareness.

Methods. We searched the literature for articles describing cases of LGIS, and identified additional cases diagnosed within our institution. Data were extracted from the articles and medical records and analyzed to provide a summative account.

Results. 54 cases of LGIS were identified in 39 articles published between 1958 and 2020. 8 additional cases were diagnosed at our institution between 2011 and 2020, totaling 62 cases. All cases were described in men and transwomen aged 15 to 73 years. 50 (93%) individuals endorsed having sex with men. In 26 cases (52%) individuals were HIV co-infected. LGIS presented most commonly with hematochezia (67%) and anal pain (46%). The most common physical exam findings were rectal mass (38%), lymphadenopathy (31%), and rash (26%). Non-treponemal titers ranged from 1:2-1:1024. Of the 52 cases in which endoscopy was reported, 22 (42%) showed anorectal mass and 18 (35%) showed anorectal ulcer. In 44 cases (75%), histopathology revealed a chronic inflammatory infiltrate with a prominent lymphocyte component (45%) and/or plasma cells (36%). 78% of specimens to which a tissue stain was applied were positive for spirochetes.

Conclusions. LGIS should be suspected in men and transwomen presenting with a lower gastrointestinal symptom or mucosal abnormality. A sexual history must be elicited and guide testing. Misdiagnosis can delay treatment and threatens patient and public health.

Elizabeth Ferzacca  Dana Dunne 

The use of FDG-PET imaging for evaluation of myocardial viability at Yale New Haven Hospital: Patient characteristics and outcomes.

Golsa Joodi, Edward J Miller

Background: In patients with chronic ischemic cardiomyopathy, revascularization of viable myocardium results in contractile function recovery. Given risks associated with low yield interventions in this population, accurate identification of viable myocardium prior to revascularization is important. Different modalities have been previously used to identify viability, among which FDG-PET has shown the greatest sensitivity for predicting recovery.

Specific Aim: We aimed to describe the use of FDG-PET viability imaging in Yale New Haven Hospital, as well as the characteristics and outcomes of patients undergoing these studies.
Hypothesis: We hypothesized that interpreting FDG-PET imaging with a quantitative approach using standardized uptake values (SUVs) may provide additive value in identifying viable myocardium.

Methods: We retrospectively queried YNHH information systems to identify all FDG-PET viability studies performed during 8/1/2016-12/31/2019, as well as patient demographics, risk factors, invasive coronary angiography, echocardiography and FDG PET imaging data. Statistical analysis and correlations between variables were performed using SPSS. Subgroup analyses included comparison between patients that had revascularization (PCI and/or CABG) versus those treated medically. Changes in left ventricular function were assessed from echocardiograms obtained closest to the FDG-PET study and within 30 to 270 days of initial viability imaging (if performed). FDG-PET images were re-analyzed using a standardized uptake value (SUV) approach, including regional SUVs in vascular territories. SUV values were compared to angiographic severity of CAD, regional resting myocardial blood flow, and regional functional recovery after revascularization.

Results: Over the period of study, 98 patients (mean age 68, 79.6% male) underwent viability evaluation using FDG-PET (index study). Cardiovascular risk factors were prevalent among patients, and guideline directed medications were used at a reasonably good rate (beta blockers 72.4%%, neurohormonal blockade 61.3%). Forty-three patients (44%) had echocardiograms both prior to (average baseline EF 28.7%), as well as within 1-9 months (within average 162 days) after the index study (average follow-up EF 37.2%). Approximately half of these patients (N=22) underwent revascularization, including CABG in 9, and PCI in 13 patients. Ejection fraction increased by 9.6% (95% CI 4.9-14.4), 11.8% (95% CI 2.0- 21.7), 8.1% (95% CI 2.6- 13.6), and 7.2 (95% CI 2.1-12.2) among those who had any revascularization, CABG, PCI, or no revascularization, respectively. As expected, higher frequency of viability (90.9%) was reported on the FDG-PET by readers among those who subsequently underwent revascularization. Similarly, higher frequency of scar (66.7%) was reported among those without revascularization. The data regarding predictive ability of quantitative PET data for functional recovery is currently being analyzed.

Conclusions: Patients with evidence of viability who underwent revascularization had improvement in contractile function. While numerically there was more improvement among revascularized patients, there was no significant difference among these patients and those who were managed medically. This might in part be explained by relatively good rate of guideline directed medication use among our study

population. Future investigations will compare SUV-based FDG-PET interpretation as a predictor of contractile function improvement.

Resident's signature

Mentor's signature

Research in Residency Abstract

Comparison of Computed Tomography-Based Assessment of Mitral Annular Calcification to Transthoracic Echocardiography

Resident: Jakob Park, MD. **Mentors:** David Hur, MD; Lissa Sugeng, MD.

Background: Mitral annular calcification (MAC) is common disease with a prevalence of up to 42% and associated with increased stroke and death. The typical assessment by transthoracic echocardiography (TTE) is qualitative visual rating (VR), but this technique is user-dependent and lacks a gold standard for grading. While echocardiography allows for accurate assessment of hemodynamic properties across the mitral valve, cardiac computed tomography (CT) imaging is hypothesized to be more useful in quantifying calcifications by virtue of being highly sensitive to radio-dense materials. The purpose of this study is to standardize grading of MAC and compare TTE-based assessment of MAC with CT.

Specific Aim: To compare MAC assessed by CT versus transthoracic echocardiography (TTE).

Hypothesis: The primary hypothesis is that there will be a correlation of MAC assessed by CT and TTE .The secondary hypothesis is that CT will detect more MAC than TTE-based methods.

Methods: The analysis is a retrospective analysis of 60 patients with non-contrast CT and TTE prior to aortic valve replacement or mitral valve (MV) repair. MAC was assessed on TTE by VR (none, mild, moderate, severe), a previously described echo calcium score (ECS), and systematic MAC grading (SMAC). TTE-based MV parameters were recorded. CT data were measured for calcium volume (MACV) via proprietary software (Visage Imaging) by an independent rater with 3D regions of interest in the MV area.

Results: Mean age was 77 ± 11; 42% of patients were female. MACV for tertile-based groups were divided as follows: no calcification (0 mm^3, N = 16, lowest tertile (8 – 423 mm^3, N = 15), middle tertile (427 – 1972 mm^3, N = 15), highest tertile (1999 – 11647 mm^3, N = 14). CT detected MAC in a notable portion of patients without MAC by TTE-derived methods: in 16 of 29 patients (55%) by VR, in 5 out of 15 (33%) by ECS, and in 5 out of 16 (31%) by SMAC. Fifteen of 22 patients (68%) with mild MAC by VR had middle or high-tertile MAC on CT. MACV-derived categories reclassified 65%, 60%, and 54% of patients compared with VR, ECS, and SMAC grading by TTE, respectively. There were also differences in hemodynamic properties of the mitral valve with incremental MACV categories: higher MV velocity, higher transmitral gradient, and higher E/e'. Except E/e', trends were independent of TTE-based MAC analysis and significant after adjusting for mitral regurgitation or stenosis.

Conclusion: TTE has limited ability to detect mild MAC compared with CT. In our study of patients undergoing TAVR, we found that CT-based volumetric MAC assessment is feasible, sensitive, and can guide the creation of quantitative thresholds to better standardize assessement of MAC. This highly reproducible technique was more sensitive than TTE in detecting mild MAC. Higher MACV by CT was associated with increasingly abnormal MV flow and diastology.

Jakob Park

Jakob Park David Hur Lissa Sugeng

Research in Residency Summary Abstract

Title: Practice Patterns and Real-Life Outcomes for Patients with Acute Promyelocytic Leukemia

Jan Philipp Bewersdorf, MD and Amer M. Zeidan, MBBS, MHS

Background: Despite being having an excellent prognosis for long-term survival, a substantial proportion of patients (pts) with acute promyelocytic leukemia (APL) succumb early to hemorrhagic and thrombotic complications. Little is known about the patterns of care and clinical outcomes of patients with APL in the United States outside of the controlled trial setting.

Specific Aim: To describe practice patterns and outcomes of patients with newly diagnosed APL in real-world practice and to identify prognostic factors associated with adverse outcomes

Hypothesis: Patients treated in larger, higher-volume hospitals and with a risk-stratified (i.e. ATRA + arsenic trioxide for low-risk and ATRA + anthracycline for high-risk disease) treatment approach in line with guidelines have a better outcome than patients treated at smaller institutions and with other treatments not consistent with treatment recommendations.

Methods: APL pts included in the Vizient Clinical Database/Resource Manager (CDB/RM™), which includes patient demographics, hospital characteristics, charge-level medication usage, laboratory, procedure and mortality data from academic health centers and affiliated hospitals, were identified by ICD-10 code (C92.40). Pts were excluded if information on discharge disposition or medication administration were missing. Primary outcome was a composite of in-hospital death or discharge to hospice. Pearson's Chi-square test and multivariable logistic regression were used to examine associations between patient, hospital, and treatment characteristics with the primary outcome.

Results: We identified 1635 pts treated at 132 hospitals. Mean patient age was 52.1 years with 607 (37.1%) of patients being ≥60 years. Based on white blood cell (WBC) count of >10 G/L, 23.1% of patients were classified as high-risk. The majority of pts was treated with ATRA + arsenic trioxide (ATO; 862 pts; 52.7%). However, 249 pts (15.2%) did not receive ATRA, while 63 pts (3.8%) and 180 pts (11.0%) received ATRA as monotherapy or for <3 days, respectively.
188 pts (11.5%) died in the hospital and 27 pts (1.7%) were discharged to hospice. In bivariate analyses age ≥60 years, ATRA monotherapy or for <3 days, admission laboratory abnormalities (WBC ≥10 G/L, coagulation abnormalities), ICU admission, and intubation were associated with adverse outcomes. In multivariate analyses, mortality rates were higher for older age, WBC ≥10 G/L, ATRA monotherapy, ATRA + anthracycline or ATRA <3 days. Risk factors for ICU admission were similar.

Conclusions: A substantial proportion (13.2%) of adults treated for newly-diagnosed APL in this large inpatient dataset died or were discharged to hospice, which is substantially higher than in clinical trials (3-8.5%). Age≥60 years, WBC ≥10, ATRA monotherapy, ATRA + anthracycline or ATRA <3 days were associated with higher odds of adverse outcomes (death, hospice, ICU admission). Hospital and demographic factors other than age were not associated with adverse outcomes.

Resident's signature Jan Bewersdorf 3/8/2021

Mentor's signature Amer Zeidan 2/16/2021

Impact of an Automatic Palliative Care Consultation Trigger on Healthcare Utilization in Patients with Relapsed/Refractory Acute Myeloid Leukemia

Jenny Xiang
Mentors: Kerin Adelson, Elizabeth Prsic, Thomas Prebet

Background: Patients with relapsed/refractory acute myeloid leukemia (AML) have poor outcomes and high levels of healthcare utilization at end of life. Palliative care remains underused in hematology despite high symptom burden. Questions remain regarding how best to integrate palliative care for high-risk hematology patients. Previous standardized palliative care consultations in solid tumor oncology led to decreased healthcare use. We conducted a prospective cohort study evaluating automatic palliative care consultation triggers for patients admitted to a tertiary academic center with advanced phase AML.

Method: Criteria were developed for all hospitalized patients with hematologic malignancy and included: 1. persistent disease after ≥ 2 lines of therapy, 2. length of stay (LOS) >7 days for symptom management, 3. ECOG performance status > 2, and 4. refractory GVHD after 3 lines of therapy. Patients with relapsed/refractory AML were included if they met criteria 1. A palliative care nurse coordinator performed chart review of admitted patients 1-2 times/week from June to December 2020 on the inpatient hematology floor at Smilow Cancer Hospital and contacted the primary team when patients met eligibility. Baseline patient characteristics and healthcare outcomes were compared with the same AML population admitted pre-intervention (June to December 2019). Fisher t-tests were used to compare differences in patient characteristics, palliative care consultation, and healthcare use.

Results: A total 110 admitted patients were eligible (64 admissions in the pre-intervention period and 46 admissions in the post-intervention period). Baseline patient and disease characteristics were similar, including mean age at admission (60.4 vs 60.9 years, p=0.848), gender (64% vs 59% male, p=0.691), prior transplant (56% vs 52%, p=0.702), and AML risk stratification (67% vs 78% adverse risk, p=0.283). In the post-intervention group, 61% of eligible patients were screened. Of the screened patients, 54% received a palliative care consult, 18% were declined by the primary team, 14% were marked as not eligible, and 14% did not have consult with reason unspecified. Overall, palliative care consults increased in the post-intervention group (22% vs 43%, p=0.021). There was a significant increase in advance care planning and/or advanced directive documentation post-intervention (13% vs 28%, p=0.049). There was no differences in pre- and post-intervention groups in LOS (12.13 vs 12.33 days, p=0.941), 30 day readmissions (52% vs 39%, p=0.557), critical/intermediate care escalation (22% vs 13%, p=0.318) and non-palliative chemotherapy post-discharge (48% vs 39%, p=0.246).

Conclusions: An automatic palliative care referral intervention is feasible and doubled palliative care use in patients with relapsed/refractory AML, a group with high mortality and high healthcare utilization. Our intervention improved documentation of advance care planning. Although there were directional reductions in other healthcare use measures as would be expected, the differences were not statistically significant, likely due to the small sample sizes leading to the study being underpowered

Resident Signature

Mentor Signature

Research In Residency Research Summary

Title: Coronary Artery Calcium Assessment to Rule Out Obstructive Coronary Artery Disease Among Patients with Stable and Acute Chest Pain: A Systematic Review and Meta-Analysis

Resident: Justin Pacor, MD **Mentor:** Edward J. Miller, MD PhD, FASNC, FACC

Background: There is little consensus on whether absence of coronary artery calcium (CAC) can identify patients with CP who can safely avoid additional downstream testing. We conducted a systematic review and meta-analysis investigating the utility of CAC assessment for ruling out obstructive coronary artery disease (CAD) among patients with stable and acute chest pain (CP) with predominantly a low-to-intermediate risk of obstructive CAD undergoing coronary computed tomography angiography (CCTA).

Specific Aim: To determine if CAC can be used to rule out obstructive CAD on CCTA in patients with chest pain.

Hypothesis: Absence of CAC in patients with chest pain is associated with a low likelihood of obstructive CAD and low likelihood of major adverse cardiovascular events (MACE).

Methods: We searched online databases (PubMed, MEDLINE) for original research articles published between 2005 and 2020 examining the relationship between CAC and obstructive CAD (≥50% coronary luminal narrowing) on CCTA among patients with stable and acute CP.

Results: A systematic review of published articles revealed 19 articles including 79,903 patients with stable CP and 12 articles including 7,184 patients with acute CP undergoing simultaneous CAC assessment and CCTA. Overall, 45% (95% CI: 40%-50%) of patients with stable CP and 58% (95% CI: 49%-67%) of patients with acute CP had CAC=0. The negative predictive values (NPV) for CAC assessment ruling out obstructive CAD were 96% (95% CI: 94-98%) and 97% (95% CI: 94-100%) among patients with stable and acute CP, respectively. Additionally, the prevalence of non-obstructive CAD among those with CAC=0 was 13% (95% CI: 10%-16%) among those with stable CP and 10% (95% CI: 7%-14%) among those with acute CP. CAC=0 predicted a low incidence of MACE among patients with acute CP (0.65% over 1 month follow up) and stable CP (0.49% annual incidence).

Conclusions: Among over 87,000 patients with stable and acute CP undergoing CCTA with predominantly a low-to-intermediate risk of obstructive CAD, the absence of CAC was associated with a very-low prevalence of either obstructive or non-obstructive CAD, and a low incidence of MACE. These findings support the role of CAC=0 in a value-based healthcare delivery model as a "gatekeeper" for more advanced testing.

Justin Pacor

Resident Signature

Mentor Signature

Improving Resident Development in Using EPAs Through an Educational Video

Kate Penziner, MD, Katie Gielissen, MD

Background: AAMC Core EPAs (Entrustable Professional Activities) for entering residency have been described and published; however it is still unclear how to best disseminate information about workplace-based assessments (WBAs) like EPAs to residents who will be performing assessments. As part of the AAMC Pilot program, the Yale School of Medicine Internal Medicine Clerkship has transitioned to using an EPA framework to facilitate formative WBAs during clinical clerkships. The majority (over 75%) of feedback collected on students using the EPAs has been submitted by residents; however, no formal development has been done to ensure residents understand the construct of EPAs or are providing meaningful feedback to students. There is a national need for resident development on these EPAs and specifically on how to train residents in robust WBAs of these EPAs.

Specific Aim: To assess the effect of an educational video on resident understanding of the terminology surrounding EPAs and application of entrustment scales to WBAs.

Hypothesis: An educational video will improve resident's knowledge of EPA frameworks and create construct alignment in applying these frameworks via entrustment scales.

Methods: A short video describing EPAs and their application was developed and sent to residents in the Yale Internal Medicine, Primary Care, and Combined Internal Medicine-Pediatrics residencies via email. Participation was voluntary. Participants completed short surveys to assess their knowledge and skills regarding EPAs before and after exposure to the interventional video. Questions were a combination of recall questions, primarily regarding terms and definitions, and application questions, which asked residents to place example students on the entrustment scale. Using paired T-tests, the scores of the pre- and post- surveys were compared.

Results: A total of 24 residents completed the pre-survey, watched the video, and completed the post-survey. The average scores of the surveys after the video intervention were 15% higher than the pre-intervention surveys (pre 65% vs post 80%, $p = 0.001$). In separating the questions between recall and application, the correct recall question average was 21% higher (pre 59% vs post 80%, $p = 0.01$) and the correct application question average was 7% higher (pre 73% vs post 80%, $p = 0.11$).

Conclusions: An educational video is an effective tool to provide residents with professional development regarding EPAs and can lead to a significant increase in understanding of these concepts. Limitations of the study include that participation was optional, which may have led to a self-selection bias, as well as a small sample size, which limits generalizability. While this intervention showed more significant gains in recall of information, a follow up qualitative study could further evaluate the effect on residents' application of the EPA framework after exposure to an educational video.

Katherine Penziner, MD

Katherine Gielissen, MD, MHS

Echocardiographic and Hemodynamic Markers of Venous Congestion are Associated with Diuretic Responsiveness

Maxwell Eder, M.D., Jeffrey Testani, M.D., MTR

Background: Recently a growing body of literature has shown that transthoracic echocardiogram (TTE) and pulmonary artery catheter (PAC) measures of venous congestion portend adverse cardiorenal interactions. Theoretically, these adverse cardiorenal interactions could lead to diuretic resistance by decreasing glomerular filtration. However, signs of severe volume overload also likely identify patients with a higher potential for diuresis.
Specific Aim: To examine the relationship between diuretic response, and echocardiographic and pulmonary artery catheter (PAC) measures of forward flow and venous congestion.
Hypothesis: Diuretic responsiveness will be associated with TTE and PAC measures of venous congestion but will have little to no association with cardiac index (CI) and ventricular function.
Methods: We analyzed a subset of patients from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) dataset. Diuretic efficiency (DE) was defined as daily urine output (UOP) per doubling of loop diuretic dose. For the PAC cohort (n=190), DE was compared with baseline, day of PAC removal and change in PAC variables. For the TTE cohort (n=324), DE was compared with TTE measures of the right atrium (RA), right ventricle (RV), left ventricle (LV) and inferior vena cava (IVC) at baseline and discharge.
Results: DE was positively correlated with baseline right atrial pressure (RAP) (r=0.16, p=0.03), RA area (RAA) (r=0.19, p=0.002), RV systolic area (r=0.15, p=0.046) and RV diastolic area (r=0.19, p=0.01). DE was negatively correlated with final RAP (r=-0.21, p=0.009), change in RAP (r=-0.27, p=0.001), change in RAA (r=-0.19, p=0.02) and change in IVC minimum (r=-0.19, p=0.04). There was no correlation between DE and CI (p=0.23), RV Fractional area change (FAC) (p=0.81) and LV ejection fraction (p=0.80). There were no significant differences in DE in subjects with CI >2.2 L/min/m2 vs. those with CI < 2.2 L/min/m2 at baseline (p=0.95) or time of final hemodynamic measurement p=0.91).
Conclusions: We were unable to identify a relationship between DE and ventricular function or cardiac output. However, baseline congestion predicted higher DE and end of therapy congestion was associated with worse DE. These data indicate indicating that the relationship between congestion and DE is complex and congestion likely serves more as a marker than mediator of diuretic resistance.

Max Eder

Resident's signature

Mentor's signature

Research Summary Abstract

Abnormal Liver Function Tests in COVID-19

Melanie A. Hundt, M.D., Joseph K. Lim, M.D.

Background: The coronavirus-19 disease (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 virus, is associated with significant morbidity and mortality attributable to pneumonia, acute respiratory distress syndrome, and multiorgan failure. Liver injury has been reported as a nonpulmonary manifestation of COVID-19. However, the early literature on liver injury in COVID-19 was limited and primarily performed in China.

Specific Aims: To characterize liver test abnormalities and their association with clinical outcomes in hospitalized patients with COVID-19 in a major United States hospital network.

Hypothesis: Liver test abnormalities will be seen in a significant proportion of patients hospitalized with COVID-19 in the United States and will correlate with illness severity.

Methods: We conducted a retrospective cohort study of 1,827 patients with confirmed COVID-19 who were hospitalized within the Yale-New Haven Health System between March 14, 2020 and April 23, 2020. Clinical characteristics, liver tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total bilirubin [TBIL], and albumin) at three time points (preinfection baseline, admission, and peak hospitalization), and hospitalization outcomes (severe COVID-19, intensive care unit [ICU] admission, mechanical ventilation, and death) were analyzed.

Results: Abnormal liver tests were commonly observed in hospitalized patients with COVID-19, both at admission (AST 66.9%, ALT 41.6%, ALP 13.5%, and TBIL 4.3%) and peak hospitalization (AST 83.4%, ALT 61.6%, ALP 22.7%, and TBIL 16.1%). Most patients with abnormal liver tests at admission had minimal elevations 1-2× the upper limit of normal (ULN; AST 63.7%, ALT 63.5%, ALP 80.0%, and TBIL 75.7%). A significant proportion of these patients had abnormal liver tests prehospitalization (AST 25.9%, ALT 38.0%, ALP 56.8%, and TBIL 44.4%). Multivariate analysis revealed an association between abnormal liver tests and severe COVID-19, including ICU admission, mechanical ventilation, and death; associations with age, male sex, body mass index, and diabetes mellitus were also observed. Medications used in COVID-19 treatment (lopinavir/ritonavir, hydroxychloroquine, remdesivir, and tocilizumab) were associated with peak hospitalization liver transaminase elevations >5× ULN.

Conclusions: Abnormal liver tests occurred in most patients with COVID-19 hospitalized within this U.S. healthcare system. Liver injury was primarily mild and demonstrated a hepatocellular pattern. Abnormal liver tests during hospitalization were associated with worse clinical outcomes, including intensive care unit admission and mortality. Further studies are needed to elucidate the mechanism of liver injury as well as understand its implications for both ambulatory and hospitalized patients with COVID-19.

Resident's signature

Mentor's signature

The Impact of Co-Localized Palliative Care in Liver Clinic for Advanced Care Planning

Melanie Pascal MD, Simona Jakab MD

Background: Several barriers limit the use of Palliative Care (PC) in patients with severe liver disease, including the assumption that PC means end-of-life care. We analyzed the rates of advance directive (AD) and code status completion/choice when patients received PC consult in liver clinic.

Specific Aim: The aim of this study is to assess the impact of integrating palliative care in liver clinic at the West Haven VA on several clinical outcomes including rates and timing of completion of advance care directive and code status.

Hypothesis: The hypothesis of this study is that integrating palliative care consultation in liver clinic offers more and earlier opportunities to discuss goals of care, facilitates a higher rate of completion of advance care directives, and increases the percentage of patients choosing Do Not Resuscitate (DNR) code status.

Methods: This is a retrospective study of patients with decompensated cirrhosis and/or advanced hepatocellular carcinoma (HCC) who agreed to have a PC consult when seen in liver clinic. We collected demographics, data on cirrhosis etiology/complications and AD/code status completion. Associations between categorical predictors and AD/code status completion were analyzed using Pearson's chi-square test or Fisher's exact test. Associations between quantitative predictors and AD/code status completion were analyzed using Student's t-test or the Wilcoxon rank sum test. Z-test was used to assess differences in AD/code status completion rate before/after PC consult.

Results: There were 61 patients seen by the PC team in liver clinic between March 2016 and December 2019. At one-year follow up from initial PC consult, there were 4.9 PC visits/patient, and 10 patients (16%) died. At the initial PC consult, 21% patients opted for DNR code status versus 6.5% DNR prior to PC consult ($p=0.02$), with 16% patients switching to a less aggressive code designation. There were no differences related to demographics, cirrhosis etiology/decompensation, MELDNa or HCC between patients who chose full code or DNR at initial PC visit. Patients with HCC were less likely to switch to a less aggressive code status. Subsequent changes in code status were noted in 14 patients (23%), last documentation indicating 70% full code, 20% DNR/DNI/DNT, 10% DNR but allow other treatments. Higher MELDNa was associated with DNR as last documented code status ($p=0.001$). Only 33% of patients had AD prior to PC consult versus 82% after PC consult ($p=0.0001$). Ascites was associated with AD completion, but HCC was inversely associated with AD completion.

Conclusions: At initial PC consult, 79% patients opted for full code and 16% patients chose a less aggressive code status. Among several variables studied, higher MELDNa was associated with DNR, and presence of ascites with AD completion. Patients with HCC had a lower rate of AD completion and were less likely to choose a less aggressive code status. Co-localized palliative care in liver clinic successfully increased the completion of advance directive and clarification of code status. Our patients welcomed the opportunity to plan their care when seeing the PC team in liver clinic, and only a minority opted for less aggressive care.

MPascal

Resident's Signature

Simona Jakab

Mentor's Signature

Research in Residency Abstract Summary

Title: Increased detection of *Mycobacterium tuberculosis* disease using a tissue-based laboratory-developed PCR Assay compared to standard diagnostics

Natalie Mackow, M.D., Marwan Azar, M.D.

Background: Early diagnosis and treatment are imperative for the control of *Mycobacterium tuberculosis* (MTB), yet standard diagnostics including acid-fast bacilli (AFB) smear and culture, and Xpert™ MTB/RIF real-time Polymerase Chain Reaction (RT-PCR; Xpert) have suboptimal sensitivity and/or long turnaround times, potentially leading to missed or delayed diagnoses. Even when standard diagnostics are deployed, MTB can be missed, especially in paucibacillary or extrapulmonary disease. Other methods including RT-PCR assays have shown high sensitivity for pulmonary and extrapulmonary MTB but their use has not been well evaluated for impact on clinical care and patient outcomes.

Specific Aim: To determine the sensitivity and specificity of an adapted laboratory developed tissue-based RT-PCR for pulmonary, pleural and lymph node (LN) MTB, and evaluate the use of such RT-PCRs in a clinical setting, which has not been well studied.

Hypothesis: We hypothesized that this PCR would be more sensitive than AFB culture alone, result significantly more rapidly, and impact clinical outcomes (diagnosis, treatment initiation).

Methods: The molecular pathology lab at Yale New Haven Hospital (YNHH) developed a laboratory assay combining a nested real-time PCR (MTB PCR) targeting the IS1160 transposon element with a method for DNA extraction from formalin-fixed paraffin-embedded tissue. We performed a retrospective, observational study of patients with suspected active MTB for whom MTB PCR was performed on pulmonary, pleural, and LN at YNHH in New Haven, Connecticut from 2011 to 2019. Chart review was performed to extract clinical, epidemiologic, radiographic, and laboratory data including AFB smear and culture, Xpert, and MTB PCR results. The sensitivity and specificity of MTB PCR and AFB cultures were calculated using a composite reference standard (CRS), composed of microbiology, pathology, radiographic and clinical parameters, as the reference standard definition of MTB.

Results: Over an 8-year period, 36 patients underwent testing with MTB PCR for diagnosis of pulmonary, pleural, and lymph node MTB. Of 36, 11 met the criteria for confirmed/probable MTB using CRS. MTB PCR was positive in 100% (11/11) while AFB cultures were positive in 73% (8/11) and Xpert in 0% (0/5). MTB PCR was negative in all 25 negative cases (100% specific). Mean time to MTB PCR result was significantly shorter than time to positive or negative AFB culture (4.2 vs. 47.1 days). Among 11 confirmed/probable MTB patients, positive MTB PCR results prompted treatment initiation in 7 patients and in 2 patients, MTB PCR results prompted readmission of discharged patients for treatment initiation.

Conclusions: Even when all standard methods are used, diagnosis of MTB can be delayed or missed. While it has transformed diagnostics, Xpert has low sensitivity for AFB smear-negative and extrapulmonary disease and is not validated for tissue specimens. Here, we demonstrated the utility of a MTB PCR assay in diagnosing culture and/or Xpert negative cases and in expediting diagnosis in culture positive cases. The study has limitations as a small, retrospective, a single center study with limited sample types. All cases required tissue biopsies on which the MTB PCR was performed because other means of testing were thus far negative or pending, suggesting selection bias for harder to diagnose cases. We conclude that use of a tissue-based MTB PCR showed high clinical sensitivity and rapid detection of MTB in cases with negative or pending standard testing and may be particularly useful for difficult to diagnose cases.

Natalie A Mackow

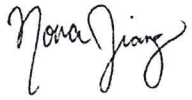
Natalie Mackow, MD

Marwan Azar, MD

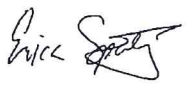
Determining Statin Eligibility and Cardiovascular Risk of Young Women Following an Acute Myocardial Infarction in VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients)

Nona Jiang, MD, Erica Spatz, MD, MHS

Background: Young women account for nearly 50,000 hospitalizations for acute myocardial infarction (AMI) in the U.S. annually, and they have greater risks of morbidity and mortality as compared with both young men and older women. Predicting risk in young women, however, remains challenging as most risk calculators underestimate cardiovascular risk in young adults, and especially in young women. The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study is a multi-center prospective cohort study of young adults ≤55 years with AMI, which consists of 2,009 women and 976 men. VIRGO presents a unique opportunity to further study statin eligibility and cardiovascular risk in young women with AMI.
Specific Aim: To determine how contemporary guidelines perform in identifying the need for statin therapy in young adults in VIRGO, with an emphasis on evaluating sex-differences
Hypothesis: The majority of young women with acute myocardial infarction (AMI) will not have met statin eligibility criteria prior to their AMI
Methods This was a retrospective cohort study using preexisting data from the VIRGO study. VIRGO is a multi-center prospective cohort study of young adults ≤55 years with AMI, which consists of 2,009 women and 976 men. Data on baseline characteristics, clinical characteristics, and biomarkers (hsCRP and lipoprotein-associated phospholipase A2) are available for analysis. Inclusion criteria were all patients enrolled in the VIRGO study who were not previously on a statin prior to their AMI. Exclusion criteria were patients who were on statin therapy prior their AMI, and those with missing values for lipid profiles or systolic blood pressure which is necessary for the pooled cohort equations (PCE) for estimation of cardiovascular risk and statin eligibility.
Results: Due to logistical matters of the VIRGO data set undergoing a merge with the GENESIS-PRAXY study (another prospective multicenter study of patients under 55 years of age admitted to the hospital with ACS), there were challenges in obtaining and analyzing data, which was further compounded by the downstream effects of the pandemic.
Conclusions: Despite the challenges faced in this project, it remains important to characterize statin eligibility and cardiovascular risk in young women. A more complete understanding of predicting cardiovascular risk in young women would allow for targeted primary prevention efforts in this population.



Nona Jiang, MD
Resident's signature



Erica Spatz MD, MHS
Mentor's signature

Impact of a multidisciplinary Diabetes Clinic on resident education

Janani Raveendran MD, MEd, Green Chung MD, Tamara Malm Pharm.D., MPH, BCPS, Stephen Huot MD, PhD, Tracy L. Rabin MD, SM

Background: Diabetes mellitus (DM) is one of the most prevalent chronic medical conditions in the U.S. The Centers for Disease Control and Prevention estimates that 26.8 million U.S. adults are living with diabetes, and that type 2 diabetes accounts for 90-95% of these cases. However, graduating internal medicine residents often feel underprepared to manage such chronic conditions, and experts in graduate medical education have called for curricular redesign to emphasize longitudinal patient-centered care. Since 2004, the resident-faculty practice of the Yale Primary Care Internal Medicine (YPC) Residency Program has employed a novel, targeted primary care-based approach to diabetes care. A multidisciplinary referral-based Diabetes Clinic is incorporated within the practice and provides an opportunity for patients with difficult-to-control diabetes to receive dedicated diabetes care. Under this model, residents have the opportunity to conduct longer patient visits with an exclusive focus on providing comprehensive diabetes care; partner in real-time with a pharmacist, dietitian, and social worker to enhance patient care; and receive mentorship from general medicine faculty with expertise in comprehensive diabetes care.

Specific Aim: To analyze the YPC Diabetes Clinic impact on the resident educational experience.

Hypothesis: The YPC Diabetes Clinic will have a positive impact on the resident educational experience via improvements in self-reported comfort with specific clinical skills and confidence in awareness of core aspects of comprehensive diabetes care.

Methods: We conducted an online survey of all residents in the YPC Residency Program in the 2019-2020 academic year, who completed at least one half-day session in the Diabetes Clinic. Each participant was recruited via mass e-mail sent out to the residency program listserv and to the list of 2020 program graduates. Participation was voluntary and anonymous. The survey included a combination of Likert scale and free-response questions that assessed resident perception of the Diabetes Clinic impact on their educational experience.

Results: Data included responses from 29 of 52 eligible participants. Greater than 85% of respondents indicated that participation in Diabetes Clinic "increased" or "slightly increased" their: comfort level with counselling patients on target glycemic range (92.9%), using non-insulin medications (85.7%) and insulin (89.3%) in the outpatient setting; awareness of the need to assess for ASCVD risk and to screen for complications of DM (92.9%); appreciation for psychosocial aspects of DM care (85.2%); understanding of roles of pharmacists, dietitians and social workers (88.9%); and likelihood of managing difficult-to-control DM as a future primary care physician instead of referring to a specialist (85.7%).

Conclusions: A multidisciplinary referral-based Diabetes Clinic within a resident primary care teaching clinic had a positive impact on the educational experience of internal medicine residents. Residents also indicated that the Diabetes Clinic experience could be strengthened via additional opportunities to apply practical medication counseling skills and work with clinical pharmacists and dietitians. The YPC Diabetes Clinic should serve as a model for resident-faculty practices to bolster trainee preparedness in managing chronic conditions.

Janani Raveendran, M.D.
Resident's signature

Mentor's signature

Utilization and safety of counterpulsation via intra-aortic balloon pump (IABP) for cardiogenic shock in patients with STEMI in the United States

Background. IABP is a commonly used mechanical circulatory support method in patients who present with cardiogenic shock. Limited data exists on utilization and safety of IABP in the United States.

Specific aim. To investigate the utilization and in-hospital outcomes of intra-aortic balloon pump (IABP) for cardiogenic shock in patients with ST-elevation Myocardial Infarction (STEMI) in the United States in 2016.

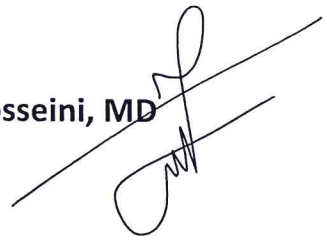
Hypothesis. We hypothesized that patients who received IABP post-STEMI have a better survival rate when compared to those with cardiogenic shock and STEMI who did not undergo IABP placement during their admission. Secondary endpoints were the rates of cerebrovascular events, bleeding diathesis, and overall characterization of patients who underwent this procedure versus those who did not.

Methods. This was a cross-sectional study using data from the National Inpatient Sample (NIS) database. NIS is the largest all-payer inpatient database in the United States. We queried all hospitalizations in calendar year 2016 to identify adults (>18 years old) who presented with STEMI (code: I21.x) AND in cardiogenic shock (R57.0). We further divided patients into two groups based on whether they underwent IABP placement (ICD-10-PCS code 5A02210). Weight files provided by AHRQ were used for inference of national estimates. In order to account for hospital-level clustering of discharges and the complex survey design of the database, we applied two-level mixed-effects multivariable logistic regression analysis to identify independent predictors in-hospital mortality. We used a propensity match score design for survey data to account for difference in baseline comorbidities and disease severity of those who received IABP from those who did not. For all aspect of the analyses, we used survey estimation (SVY) in Stata/SE 12.1 (College Station, TX: StataCorp LP.) to account for clustering, stratification, and weighting of the NIS database.

Results. We queried 649,704 weighted hospitalizations with ICD-10-CM codes I21.x for STEMI and R57.0 for cardiogenic shock. Due to the pandemic, all further analyses were postponed.

Conclusion. N/A

Reza Hosseini, MD



Robert R. Attaran, MBChB(Hons), F.A.C.C., F.A.S.E., F.S.C.A.I., R.P.V.I.,

The Impact of Pulmonary Subspecialty Referral from Primary Care on the Adherence to Vaccination Recommendations in COPD Patients

Solmaz Ehteshami-Afshar, MD, MSc, Kathleen M. Akgün, MD, MS

Background: Chronic obstructive pulmonary disease (COPD) is one of the most common causes of morbidity and mortality worldwide. Preventive treatments with successful vaccinations against lung infections are critical for improving COPD health.

Specific Aim: To evaluate the adherence to pulmonary infection-related vaccination recommendations in COPD patients, stratified by primary care management alone compared to those with pulmonary subspecialty referral.

Hypothesis: Despite the importance of providing guideline-based care, adherence to Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations regarding vaccination is sub-optimal and referral to pulmonary clinic can have an impact on the vaccination rate.

Methods: We performed a retrospective cross-sectional analysis on a random sample of COPD patients receiving primary care (PC) in a single clinical site from January 1, 2018 to December 31, 2019. Patients first diagnosed with COPD during that timeframe were identified by international classification of disease, tenth revision codes (ICD10=J40-44; n=3769). Our primary outcomes were vaccination for pneumococcal conjugate (PCV13), pneumococcal polysaccharide (PPSV23) and influenza (3 consecutive calendar years 2017-2019), based on guideline recommendations. Data was extracted from the electronic health record by chart review. Descriptive statistics were used to compare demographic and clinical variables by pulmonary subspecialty evaluation: the student's t-test to compare means for continuous variables and chi-square test for categorical variables. To assess the association between subspecialty pulmonary evaluation with vaccination adherence, multivariable-adjusted logistic regression was performed and odds ratio (OR) with 95% confidence interval (CI) were determined. The model was adjusted for age, gender and smoking status. Statistical significance was defined as $p<0.05$.

Results: Among 200 patients (mean age=70.5 ± 10.9), 78 patients had pulmonary subspecialty evaluation in the prior 3 years. Restricting to patients ≥65 years old, PCV13 and PPSV23 vaccination rates were significantly higher amongst patients referred to pulmonary (96.6% vs. 81.6%, P=0.009; 94.8% vs. 84.7%, P=0.03, respectively). Influenza vaccination rates were significantly higher for patients referred for pulmonary evaluation in all years studied compared to those only managed by PC providers. In multivariable models adjusting for age, gender and smoking status, pulmonary subspecialty evaluation was independently associated with increased likelihood of vaccination adherence for each of the three vaccines (PCV13 OR=3.55, [95% CI 1.47, 8.54]; PPSV23 OR=4.92, [1.51, 16.02]; influenza 2017 OR=2.89, [1.49, 5.62], influenza 2018 OR=1.79, [0.95, 3.39], influenza 2019 OR=1.97, [1.07, 3.65]).

Conclusion: While there remains ample opportunity to improve vaccination rates in patients with COPD, we showed patients who also received pulmonary subspecialty evaluations were more likely to receive guideline-concordant vaccinations. More studies are needed to better understand the modifiable contributors to poor adherence to vaccinations, especially in PC, and incorporating patient preferences, to improve the COPD management.

(Modified from Ehteshami-Afshar S, et al. Respiratory Research. 2021 Dec;22(1):1-4.)

Resident's signature

Mentor's signature

Kathleen Akgun

Incidence of Serious Infections and Associated Risk Factors in Patients on Ibrutinib

Thomas Holowka, M.D. Ph.D., Marwan Azar, M.D.

Background: Ibrutinib is a small molecule inhibitor of Bruton's Tyrosine Kinase that blocks the activity of B cells and other immune effectors and is used in a variety of hematologic malignancies including chronic lymphocytic leukemia (CLL) and non-Hodgkin Lymphoma (NHL) as well as in patients with graft-versus-host disease following hematopoietic stem cell transplant. Despite initial findings of reduced toxicity compared to standard chemotherapy, there have been numerous recent reports of increased frequency of serious infections including invasive fungal infections (IFI) in patients on ibrutinib.

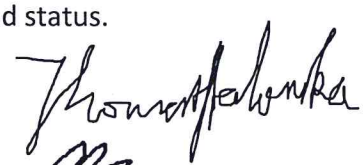
Specific Aim: To determine the rate of serious infection and IFI in all patients with hematologic malignancies on ibrutinib at a single medical center and characterize additional risk factors for infection in this population.

Hypothesis: There will be an increased rate of serious infections and IFI in patients on ibrutinib and infected patients will have an increased frequency of immunocompromising risk factors.

Methods: Demographic and clinical features of all patients receiving ibrutinib at a single tertiary care center were collected from electronic medical records. Univariate and multivariate statistical analyses were performed to compare features of patient who experienced serious infections (defined as an infection requiring hospitalization) to those who did not.

Results: A total of 254 patients received ibrutinib for hematologic malignancies, of which 46 (18.1%) experienced $\geq$ 1 serious infection including 41 (16.1%) with bacterial infections, 9 (3.5%) with viral infections and 5 (2%) with IFI (1 pulmonary cryptococcosis, 4 pulmonary aspergillosis). Eleven patients (4.3%) experienced multiple infections or co-infections while on ibrutinib and 10 (3.9%) expired or were transferred to hospice as a result of infection. Multivariate analysis demonstrated that risk factors associated with serious infection included advanced age (77 years vs. 72 years), Eastern Cooperative Oncologic Grade (ECOG) performance score ≥2 (30.4% vs. 6.7%), concurrent steroid use (30.4% vs. 10.0%) and neutropenia (19.6% vs. 5.3%).

Conclusions: There was a high rate of serious infection but relatively few IFI in patients receiving ibrutinib. Advanced age and frailty were among the factors associated with serious infection. Thus, ibrutinib is associated with an increased risk of serious infections, however this is usually in the presence of other risk factors including reduced functionality and immunocompromised status.

Resident Signature: 

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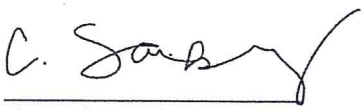
Assessing the Educational Impact of the Yale 20

Urs Weber, MD and Christopher Sankey, MD

Background: A recent survey of medical students and resident physicians revealed that 92% use online teaching videos to advance their medical education. The spectrum of online resources is wide and heterogenous, and their utility in medical education is not well understood. The bulk of the research on the use of video in teaching medical students and residents has been done in surgery. Two recent reviews each found nine such studies and both concluded that the use of videos generally led to gains in knowledge and skills. While there are many videos online that cover topics in internal medicine, studies of their educational impact are few and far between.
The Yale 20 are a series of videos produced by internal medicine residents at Yale-New Haven Hospital in conjunction with faculty mentors. The purpose of the videos is to cover basic pathophysiology, evaluation, and treatment of conditions commonly encountered in internal medicine. The videos are roughly 20 minutes long and can be accessed on the Yale 20 website (http://www.yale20.com/) and YouTube (www.youtube.com).
Specific Aim: The primary objective of this study was to determine whether viewing a Yale 20 video leads to significant knowledge acquisition in internal medicine clerkship students.
Hypothesis: We predicted a positive response to Yale 20 videos and a significantly improved mean performance on the knowledge portion of the post-test as compared to the pre-test.
Methods: We conducted a prospective quantitative survey-based pre-/post-intervention study. Internal medicine clerkship students were invited to participate during one of their scheduled didactic sessions. After consenting to participate, they were directed to an online session hosted on Panopto, a resource provided by Yale University. Participants were prompted to complete the pre-test. This included non-identifying demographic information (gender, age, internal medicine clerkship experience, career interest, frequency of educational video use), five knowledge-based questions (multiple choice) on the topic covered in the video, and two attitude questions (Likert scale) about the topic covered in the video. After completing the pre-test, the students then watched a 20-minute video on either cirrhosis or deep-venous thrombosis (DVT). Following the completion of the video, they were prompted to take the post-test, which included the same five knowledge-based questions (multiple choice) on the topic covered in the video, as well as the same two attitude questions (Likert scale) about the topic covered in the video and three new attitude questions about the video and the Yale 20. Once they completed the post-test, the students' participation in the study was over. Using the collected data, we calculated the mean scores on the pre- and post-tests (number correct out of five) for each of the two videos and overall. The pre- and post-intervention means were compared using a t-test. The pre- and post-intervention responses to the two attitude questions about the topics covered in the videos were compared using a 2x5 chi-square test.
Results: Due to difficulty accessing the study population (internal medicine clerkship students) during the COVID-19 pandemic, data collection and analysis is delayed. We anticipate that it will be completed by May 2021.
Conclusion: Due to difficulty accessing the study population (internal medicine clerkship students) during the COVID-19 pandemic, data collection and analysis is delayed. We anticipate that it will be completed by May 2021.

Urs Weber, MD



Christopher Sankey, MD

Research in Residency Project Summary Report

Resident: Yiduo I Hu, MD PhD **Mentors:** Dr Joseph W Kim, MD and Dr J Paul Eder, MD

Title: Circulating tumor DNA (ctDNA) as prognostic biomarker in advanced solid tumors treated with a PARP inhibitor-based therapy.

Background: Plasma tumor specific ctDNA in cancer patients has recently emerged as a new tool that could provide information to track tumors' response to treatment. However, there are considerable variations in such information derived from ctDNA depending on the types of tumor and classes of treatment involved. We previously showed a strong agreement between ctDNA change and radiographic response in non-small cell lung cancer (NSCLC) patients receiving a single agent immunotherapy. In the current study, we analyzed ctDNA data from a group of patients with advanced solid cancers (including PDAC - pancreatic duct adenocarcinoma, TNBC – triple negative breast cancer, SCLC – small cell lung cancer, and NSCLC) treated with the combination of a PARP inhibitor (olaparib) and a VGEFR inhibitor (cediranib) in a phase II trial (NCI9881). All patients had received multiple prior treatments.

Hypothesis: We hypothesized that ctDNA dynamics may provide early information regarding therapeutic response to treatment and can supplement radiographic assessment in patients with advanced solid tumor.

Specific aim: To study the correlation between the change of ctDNA over the course of treatment and radiographic best overall responses (BOR), as well as disease progression.

Methods: 122 patients received cediranib (C) 30mg once and olaparib (O) 200mg twice daily. CtDNA was measured longitudinally at baseline (T_0), after 3 to 7 days of C monotherapy (T_1), after 1 week of C+O combination (T_2), after 4 weeks of C+O (T_3), and every 4 weeks (T_{4+}) thereafter. Radiographic assessment by *RECIST v1.1* was done after 8 weeks of C+O, and every 8 to 12 weeks thereafter. Using a multi-gene NGS assay, ctDNA was quantified by determining the allele fraction of cancer-specific somatic mutations. Based on our and others' previous studies, we defined an early ctDNA response (e-ctDNA-R) as a >50% decrease in mutant allele fraction from T_0 to T_2, and an early ctDNA progression (e-ctDNA-P) as a > 50% increase; otherwise, it was stable ctDNA (e-ctDNA-S).

Results: 493 samples were analyzed from 94 patients, and 40 unique patients had both T_0 and T_2 ctDNA measurements, as well as corresponding radiographic assessments (including 10 NSCLC, 17 TNBC, 3 SCLC, and 10 PDAC). Among them, 4, 21, and 15 patients had radiographic partial response (PR), stable disease (SD), and progression of disease (PD) as best overall radiographic response, respectively. Ten (25%) patients had *e-ctDNA-R*, 8 of which had subsequent PR (2, 25%) or SD (6, 75%). Twenty (50%) had *e-ctDNA-S*, 12 of which had subsequent SD (60%). Ten (25%) had *e-ctDNA-P*, 5 of which had subsequent PD (50%). However, only a fair agreement was observed between *e-ctDNA-R* or *e-ctDNA-P* and radiographic PR/SD or PD with Cohen's k: 0.3 (65% agreement). All 25 patients with PR/SD eventually progressed. Of these, 18 (72%) had up-trending ctDNA level from the nadir prior to disease progression. Nine (36%) were noted to have >50% increase in ctDNA from the nadir. In this group, the time between ctDNA progression and ctDNA nadir was significantly shorter (median 28 days, 95%CI 25-28) than the time between radiographic/clinical progression and initial PR/SD (median 59 days, 95%CI 4-204, P=0.048).

Conclusions: Longitudinal ctDNA measurements could enable early assessment of treatment response, resistance, and disease progression in patients treated with PARP inhibitor-based therapy. However, in this study, tumor responses and ctDNA changes were generally not as robust as have been observed with other classes of therapy. Tumor heterogenicity and prior treatment may have contributed to the lack of strong correlation between ctDNA changes and radiographic/clinical outcomes.

Resident: Yiduo I Hu, MD PhD DocuSigned by: [signature] Date 3/10/2021

Co-mentor: Dr Joseph Paul Eder, MD Joseph Paul Eder, MD Digitally signed by Joseph Paul Eder, MD Date: 2021.03.10 08:56:41 -05'00' Date 3/10/21

Co-mentor: Dr Joseph W Kim, MD DocuSigned by: Joseph Kim Date 3/10/2021