The Burden of Forgone Medical Care in the United States Heart Failure Population

Resident: Alexander Thomas, MD
Mentor: Nihar R. Desai, MD, MPH

Background: Heart failure (HF) is a leading cause of morbidity and mortality with health care expenditures projected to increase 3-fold from 2012 to 2030. Available studies in the general and disabled populations have suggested forgoing or delaying medical care is associated with worse health outcomes and the usage of more costly care. Currently, the proportion of patients with HF who forgo and/or delay medical care, and the impact of forgone/delayed care on health care expenditures and utilization has been vastly understudied.

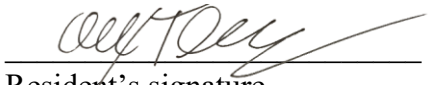
Specific Aims: To describe rates of forgone medical care in patients with HF in the United States. To assess the impact of forgone care on healthcare utilization and expenditures.

Hypothesis: More than 15% of patients with HF will report forgone medical care. Forgone care will be associated with higher medical costs as well as higher rates of healthcare utilization.

Methods: Data on patients with HF was obtained from the Medical Expenditure Panel Surveys (MEPS), between 2004-2015, to assess annual inflation-adjusted expenses and healthcare utilization (hospitalizations and ED visits). MEPS is a nationally representative database of cross-sectional surveys, which includes data on forgone/delayed care linked with health care utilization and expenditure data. Forgone medical care was defined as any inability to obtain, and/or delays in receiving, medical or prescription medication treatments. All adults ≥ 18 years of age with a diagnosis of heart failure, ascertained by ICD-9-CM code were included. The population was analyzed as a whole, as well as subsequently divided into two mutually exclusive categories based on age: non-elderly (≥ 18 & < 65 years) and elderly (≥ 65 years). Logistical regression and two-part econometric models were utilized to study healthcare utilization and expenditure data.

Results: Overall 16% of HF patients reported forgone care; with a prevalence of 10% among the elderly (≥65) and 27% among non-elderly (<65). After adjustment for confounders, adults with HF had 1.22 higher odds of reporting forgone care (OR 1.22 [95% CI 1.04, 1.44]). When comparing non-elderly to elderly HF patients, 60% and 46% respectively reported deferring care due to financial barriers. Among the total HF population, annual total healthcare expenditures for those who forwent medical care was higher than those who did not by $8,027 (95% CI $1,181-$14,872, p=0.02); no differences were found in inpatient, ED, prescription medication, or out-of-pocket (OOP) costs. When separated by age, elderly HF patients who reported forgone care had significantly higher inpatient and total expenditures; $7,548 (95% CI $1,109-$13,988, p<0.05) and $10,581 (95% CI, $1,754-$19,409, p<0.05) respectively. Among non-elderly HF patients, overall OOP expenditures were higher for those who forwent care (Difference: $867, p < 0.05). Elderly HF patients reporting forgone care had more ED visits (43% v. 58%, p < 0.05); this difference was not seen among non-elderly patients, or in the total HF population. No significant differences in hospitalizations were found.

Conclusion: Roughly 1 in 6 HF patients in the US report forgone medical care, with half owing it to financial reasons. Forgone medical care was associated with significantly higher health care spending, especially among the elderly) without significantly higher rates of healthcare utilization. Efforts to address the underlying drivers of delayed and forgone care, may help to improve patient outcomes while also reducing costs.



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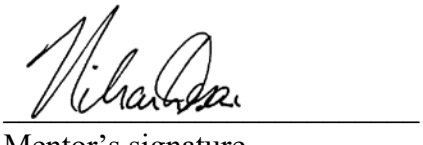

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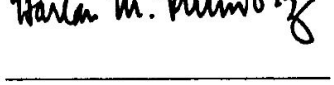
Between-Provider Differences in the Interpretation of Myocardial Perfusion Imaging

Aeron Small, MD MTR; Edward Miller, MD; Harlan Krumholz, MD

Background: Myocardial perfusion imaging (MPI) is widely used in the evaluation and management of patients with suspected coronary artery disease (CAD). The interpretation of MPI relies on nuclear cardiologist expert review to determine the probability of abnormal myocardial perfusion. The categorization of an MPI study as abnormal has downstream consequences for patient care including cardiac catheterization and percutaneous coronary intervention (PCI). To date, there are no studies systematically detailing between-provider variability in the number of abnormal MPI reads, or whether between-provider variability impacts downstream testing such as cardiac catheterization or PCI.
Specific Aim: To qualify between-provider variability in MPI interpretation at a large academic medical center, and to determine whether differences in the number of abnormal reads per provider impact downstream testing such as cardiac catheterization or PCI.
Hypothesis: nuclear cardiologist expert interpretation of MPI varies between provider.
Methods: data were collected from Yale New Haven Hospital (YNHH) for all MPI reads from January 2017 to March 2019 and all cardiac catheterization reads from January 2017 to August 2019. Analysis focused on the most commonly performed studies, specifically regadenoson PET, regadenoson SPECT, and exercise SPECT. Chest pain center studies were excluded. Patient characteristics, including age, sex, race/ethnicity, and Diamond-Forrester (DF) Classification were compared between providers to ensure random patient allocation. Study interpretation was limited to studies called as 'normal' or 'abnormal'. Between-provider differences in the number of abnormal MPI interpretations or cardiac catheterization events at 90 days following MPI were assessed by multiple logistic regression. Cardiac catheterization reports for individuals with an abnormal regadenoson PET MPI were manually adjudicated for the presence of PCI or obstructive CAD.
Results: there were a total of 2,256 regadenoson PET studies, 1,107 exercise SPECT studies, and 1,671 regadenoson SPECT studies after removing chest pain center studies, and non-diagnostic or equivocal interpretations. Regadenoson PET MPI demonstrated nominally significant between-provider differences for DF classification (chi-square $p = 0.01$). Regadenoson SPECT MPI demonstrated nominally significant between-provider for race (chi-square $p = 0.03$) and location (chi-square $p = 7.0 \times 10^{-3}$). There were no between provider differences for any clinical characteristic for exercise SPECT MPI. After adjustment for multiple testing and any differences in patient characteristics, only regadenoson PET MPI demonstrated significant between-provider differences in the number of abnormal studies. Specifically, a single reader called 62% of studies abnormal compared to an institutional average of 45%. There were no significant differences in the number of cardiac catheterizations at 90 days for regadenoson PET MPI. After manual adjudication of all cardiac catheterization events following regadenoson PET MPI, there were no significant differences in the number of cardiac catheterizations with obstructive disease, or in those requiring PCI.
Conclusions: we demonstrate significant between-provider differences in the number of abnormal interpretations for regadenoson PET MPI in a retrospective sample from a large academic hospital. In spite of variability in the number of abnormal reads between providers, there were no between-provider differences in the number of cardiac catheterization events at 90 days, or in the number of cardiac catheterization events demonstrating obstructive CAD or requiring PCI. Our results highlight the possibility for subjective interpretation of MPI to impact classifications of myocardial disease, and suggest that there may be human or other support structures in place ensuring appropriate downstream testing.

Resident Signature

Faculty Mentor Signature



RESEARCH IN RESIDENCY SUMMARY ABSTRACT

Exertional syncope in college varsity athletes

Chad Gier MD & Rachel Lampert MD

Background: Conventional wisdom describes syncope in athletes occurring during exertion as highly likely to be associated with underlying significant cardiac disease but is based on a small number of studies with limited sample sizes. We examined the underlying etiologies and diagnostic evaluation of syncope in athletes during or after exertion at a single Division 1 College over an eight-year period.
Specific Aims: To understand the underlying etiology and diagnostic evaluation of athletes presenting with syncopal events.
Hypothesis: Athletes who have syncopal events during exertion are more likely to have an underlying cardiac etiology than athletes who have syncopal events after physical exertion.
Methods: Patients were initially identified by a Joint Data Analytics Team (JDAT) request based on an encounter with a Yale University Sports Medicine physician at Yale Health and had any medical encounter with associated ICD-9 or ICD-10 code related to syncope from January 2011 to January 2019. Once identified, patients' charts were reviewed to determine if they met the inclusion or exclusion criteria. Patient were included if they met all three of the following criteria: age 17 to 26, identified as a varsity athlete based on an encounter with a Yale University Sports Medicine physician at Yale Health and had any medical encounter with associated ICD-9 or ICD-10 code related to syncope from January 2011 to January 2019. Patients were excluded if they were not an athlete or if they did not have an identifiable syncopal event based on medical record review. Data on demographics, presenting signs/symptoms, activities/sports played, diagnostic evaluation, final diagnosis was collected.
Results: Among the average 880 rostered athletes per year, syncope or presyncope occurred in 42 athletes, age 18 to 25, 16 male/26 female, over the 8-year period. Of these 42 athletes, 27 events (64.3%) were related to exertion: 12 with syncope, 6 during exertion and 6 post-exertion, and 15 with presyncope, 13 during exertion, and 2 post-exertion. No athlete with syncope or presyncope during or after exertion was found to have an underlying cardiac etiology. The most common causes of exertion-related syncope/presyncope were exercise-associated collapse (37%), and multifactorial causes such as viral or other illness and dehydration (25.9%). The most frequent activities related to syncope/presyncope were running (37%), erging (14.8%), and weight lifting (11.1%). Diagnostic evaluation included electrocardiography (85.2%), echocardiography (55.6%), stress echocardiography (48.1%), event monitors (implanted 11.1%, external 7.4%). Four athletes (14.8%) required hospital admission and 11 (40.7%) were seen in the emergency department or urgent care.
Conclusions: Underlying cardiac disease is not common in young athletes presenting with exercise-related syncope, whether during or after exertion. However, as syncope can be a harbinger of cardiac arrest, it remains important to exclude potentially life-threatening etiologies. Larger studies are needed to further define the incidence and optimal work-up of syncope in athletes.

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Research in Residency Summary Abstract

Title: Impact of HIV on T-Cell Lymphomas in the Veteran Population

Eric Chang, M.D. and Ellice Wong, M.D.

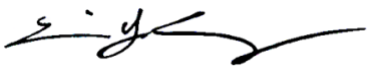
Background: T-cell lymphomas (TCLs) are a heterogenous group of rare, typically aggressive T-cell and natural killer cell neoplasms associated with poor outcomes but noted to be increasing in annual incidence. Peripheral TCLs, the most common subtype, do not respond well to traditional chemotherapy and there are no standardized treatment regimens. To date, attempts to better understand TCLs have been limited with a major challenge being its low overall incidence. Of particular interest is the increased incidence of TCLs described in the HIV-infected population. Examination of linked AIDS and cancer registry data has described up to a 15-fold increase in incidence of TCL in HIV-infected patients compared to the general population (Biggar, Engels, & Goedert, 2001). Subsequent studies have sought to better characterize HIV-infected patients with TCL, with the majority of studies containing only 10-100 patients given the relative rarity of the disease. Multi-center data is also limited.

Specific Aims: Our proposal aims to explore the biologic behavior and clinical outcomes of TCLs in HIV/AIDS-infected and HIV/AIDS-uninfected individuals using a national Veterans Health Administration (VA) database.

Hypothesis: We hypothesize that there will be differences in presentation and treatment outcome between veterans with HIV/AIDS and in those without HIV/AIDS, which may have important implications in prognosis and therapy selection.

Methods: We propose to conduct a retrospective, descriptive study of veterans with a documented history of TCL. National VA databases (VACS and/or the Birth Cohort) will be queried for patients with a diagnosis of TCL as well as HIV-infected and HIV-uninfected status. We plan to use ICD-O codes which will include both site and histology as well as unique medications used to treat TCLs (e.g. pralatrexate, romidepsin, cerdulatinib) to identify patients. After these patients have been identified, we plan to perform chart reviews as detailed below. Trends in demographics, clinical course, and treatment response will be reported along with a comparison of their HIV-infected and HIV-uninfected status.

Results & Conclusions: At this time, access to the VACS database has still not been established due to national staffing shortages and an unexpected hold on acceptance of new applications. Project is still in progress.



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Mentor

Differential platelet activity in coronary artery disease (CAD) versus peripheral artery disease (PAD); pathogenesis and therapeutic implications

Denizhan Ozdemir, MD, PhD; John Hwa, MD, PhD

Background: Atherosclerosis plays a crucial role in the pathogenesis of cardiovascular diseases including coronary artery disease (CAD), and peripheral artery disease (PAD). Despite this commonality, it is emerging that the disease processes in different vascular beds are likely very different. This is manifested in the poor response of PAD to antiplatelet therapy such as low dose aspirin, in comparison to CAD. Current guidelines suggest longer and more regimented antiplatelet therapy for coronary interventions than interventions for peripheral artery disease.

Specific aim: We sought to investigate whether there are differences in platelet activity in patients with CAD compared to PAD scheduled to undergo an intravascular intervention.

Hypothesis: We hypothesized differences in activity markers of platelets in CAD vs PAD.

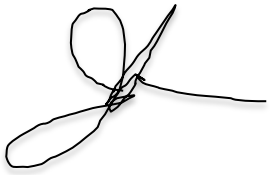
Methods: We collected arterial blood samples from three patients who underwent coronary angiography, and three patients who underwent peripheral angiography (HIC#1005006865). Medical history, medications, and laboratory results were collected. We isolated platelets from EDTA-stored tubes immediately after blood collection, and analyzed P-selectin, a platelet surface protein that can be released into the plasma. Plasma levels of P-selectin has been shown to correlate with platelet activity.

Results: Student t-test has been utilized for statistical analysis with standard error of the mean to assess variation. The average age in CAD cohort was 85.6 ± 5 (n=3) compared to 84.3 ± 7 in the PAD cohort (n=3) (p=NS). A third of patients in CAD cohort was male compared to two thirds in PAD cohort. For the effect of co-morbidities on our study, there was no statistical differences in the presence of diabetes mellitus, hyperlipidemia, and smoking between the groups. Hypertension was present in two third of the CAD cohort compared to all three patients in CAD cohort. As for medications, there was no difference in use of anticoagulation, statin and cilastozol in both groups. Aspirin was used in all three patients in CAD cohort compared to one third in PAD cohort. On the other hand, PY212 inhibitor was used in no patients with CAD cohort compared to two thirds in PAD cohort. We also assessed platelet count in both groups to ensure that the results were not impacted by the platelet counts. Average platelet count was $225{,}000 \pm 32{,}000$ /ml plasma in CAD cohort compared to $212{,}000 \pm 57{,}000$ /ml plasma in the PAD cohort (p=NS). P-selectin concentration was 0.104 ± 0.008 in the CAD cohort vs 0.063 ± 0.008 in the PAD cohort (p=0.002), 65% higher in the CAD cohort.

Conclusions: In this limited cohort study, we demonstrated potential differences in platelet activity in CAD compared to PAD. This could explain differential response of antiplatelet agents in PAD vs CAD. Further studies are needed to validate the differential platelet activation, and to explore platelet contributions to the pathophysiology of PAD vs CAD.

Denizhan Ozdemir

John Hwa



Utilization of Prone Positioning in Patients with ARDS

Gabriella Wilson, MD, Shyoko Honiden, MD, Margaret Pisani, MD

Background: Acute Respiratory Distress Syndrome (ARDS) has a high mortality rate. PROSEVA investigated prone positioning for patients with severe ARDS and found a significant mortality benefit. In May 2017 prone positioning was strongly recommended in practice guidelines from several societies including ATS.

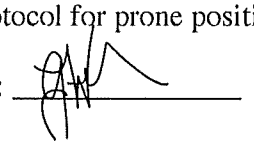
Specific Aim: To identify what proportion of patients with severe ARDS undergo prone positioning, understand reasons for deferring its use, and identify barriers that might impact the implementation of prone positioning.

Hypothesis: The prevalence of guideline-directed use of prone positioning in patients with severe ARDS in our Medical ICU at Yale New Haven Hospital is low despite data demonstrating mortality benefit with use of this procedure.

Methods: All patients admitted to Yale-New Haven Hospital MICU with a diagnosis of ARDS, Acute Respiratory Failure, or Sepsis with Mechanical Ventilation were identified using ICD-10 codes from July 2017 thru July 2018. Charts were reviewed to determine presence of ARDS based on the Berlin Criteria. Those with ARDS were subdivided by P_aO_2:F_IO_2 (P/F) ratios to characterize severity. Patients with P/F ratios <150 were considered candidates for prone positioning based on PROSEVA inclusion criteria. Charts were systematically reviewed to determine which patients underwent prone positioning, and the rationale for foregoing prone positioning when it was not provided. An anonymous survey was then distributed to attending physicians, nurses, and respiratory therapists to elicit opinions on the current process of prone positioning at YNHH and understand barriers to using this therapeutic maneuver.

Results: 114 encounters met diagnosis criteria and were reviewed. 52 patients met Berlin criteria for ARDS. Of those 52 patients, 28 met criteria for severe ARDS with P/F ratio less than 150, 6 with P/F ratios 100-150 and 22 with P/F ratio <100. Of the 6 patients with P/F ratio 100-150, none underwent prone positioning and the rationale for this decision was unclear in all cases. Of the 22 patients with P/F ratio <100, 6 underwent prone positioning. Of the remaining 16 that did not, the rationale for deferring prone positioning was unclear in about half of the cases. When a rational could be adjudicated, the reasons cited included hemodynamic instability, mechanical difficulty, and goals of care. The survey portion of this study revealed that there is inconsistent understanding of the physiologic rationale for prone positioning amongst providers, and most providers felt that the prone positioning process is not streamlined enough. Additionally, many survey respondents were unsure if a protocol exists to guide prone positioning, and the majority of respondents felt that simulation-based training would be helpful.

Conclusions: In this small study only 21% of patients who met PROSEVA criteria for severe ARDS underwent prone positioning. Reasons for underutilization include patient-specific goals of care and mechanical and hemodynamic limitations. However, the lack of clear rationale for deferment in a majority of cases reviewed in this study suggests that there are other unknown factors that may limit implementation. Our survey highlights a few possible factors that may limit implementation, including discrepancies in understanding the rationale for prone positioning, logistical difficulties with implementing prone positioning, and unfamiliarity with the process and protocol for prone positioning.

Resident Signature: 

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Research in Residency Summary

Evaluation of a Forced Titration Protocol for Optimal Guideline Directed Medical Therapy for Patients with Heart Failure With Reduced Ejection Fraction in Various Clinical Settings

Jadry Gruen, M.D., Richard Soucier, M.D.

Background: The American College of Cardiology (ACC) and the American Heart Association's (AHA) joint guidelines recommend that patients with heart failure with reduced ejection fraction (HFrEF) are on a certain set of medications, and that these medications are titrated to their maximally tolerated dose. There is an additive mortality benefit for each class of medications, and several studies have demonstrated that lower doses of medications do not provide maximal clinical benefit. Unfortunately, less than 2% of patients with HFrEF are on the appropriate medical regimen titrated to the target doses of each medication class. In response, we have developed a forced titration protocol (FTP) to aid in attainment of guideline-directed medical therapy (GDMT) in patients with HFrEF.

Specific Aim: We aim to evaluate the efficacy of our FTP in various clinical settings. Our primary endpoint will be the measurement of the proportion of patients on the following medications and proportion at target dose: Angiotensin Converting Enzyme Inhibitors (ACE-i), Angiotensin Receptor Blockers (ARB), Angiotensin Receptor Blockers/Neprilysin Inhibitors (ARB/ARNI), evidence-based Beta Blockers, and Aldosterone Antagonists. We will compare these results to recently published data as a control. Secondary endpoints will be clinical parameters including: change in renal function, hospital readmissions, shocks delivered from implantable cardioverter defibrillators, sodium and chloride levels, and death.

Hypothesis: Our hypothesis is that our patients who completed the FTP will be more likely to be on GDMT than the general population of patients with HFrEF.

Methods: We are conducting a retrospective chart review of patients enrolled in our clinics for GDMT optimization using our FTP. The electronic medical record was queried for patients enrolled in our clinic between March 2018 to August 2019 in accordance to the YNHH International Review Board. Clinic sites involved in the study include: YNHH, University of Connecticut, and St. Francis Hospital. A standardized protocol for data collection was created, and there is ongoing data collection by approved investigators from all involved clinic sites. Once completed, an appointed statistician will have access to the raw data and conduct statistical analyses.

Results: 172 patients at YNHH sites and 120 patients at University of Connecticut and St. Francis Hospital were enrolled in our FTP protocol. Due to expansion of the project to include other clinic sites, there was significant delay in the role-out of study protocol and initiation of data gathering. There is ongoing data collection with approximately 50% completion.

Conclusions: As data collection continues, our conclusions are yet to be determined.

Applicant Signature:  **Mentor Signature:** 

Mechanical ventilation is associated with increased risk of permanent and long term cognitive decline in a large scale observational cohort

Authors: Abbas Shojaee [1], Hiam Naiditch, Naftali Kaminski [1], Yunqing Liu [2], Jonathan M. Siner [1], Margaret A. Pisani [1]*

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Rationale: Adverse cognitive outcomes have been previously described in ICU survivors. To further understand the association of intensity of care with cognitive outcomes we examined the effect of mechanical ventilation (MV) on subsequent neurological diagnosis.

Methods: We conducted a two-step population-based study using claims data from the Healthcare Utilization Project California State datasets 2005-2011. Causal Inference Using Composition of Transaction (CICT) was used to identify potential effects of MV. CICT, uses features of the stochastic process of patients' healthcare encounters to predict potential causal associations between clinical conditions and MV. To further explore CICT-suggested relationships, we defined two retrospective cohort studies. In each cohort, several statistical methods were used to measure the effect size. Additional studies conducted on balanced cohorts matched by Coarsened Exact Matching (CEM) procedure on age, gender and race. ICD-9-CM was used to identify MV and neurological diagnosis.

Results: A total of 10,293,354 patients, age >18 years with two or more visits were included in our analyses. CICT identified multiple associations between invasive procedures in intensive care and consequent transient and permanent neurological diagnoses. mechanical ventilation for > 96 hours (OR:2.24 to 3.48, HR:1.27 to 1.47) had the strongest association with subsequent diagnosis of a neurological disorder followed by mechanical ventilation for < 96 hours. These findings held true for both transient and permanent disorders.

Conclusion: Our large-scale population-based study affirms prior findings that invasive procedures associated with ICU could contribute to subsequent delirium. We also demonstrated that these exposures are associated with increased rate of dementia.

Hiam Naiditch, M.D.

Margaret Pisani, M.D.

Non-Invasive Ventilation Initiation Optimization at a Tertiary Care Center

Peter A. Kahn MD MPH, Jonathan M. Siner, M.D.

Background: Non invasive ventilation (NIV) with bi-level positive airway pressure (Bi-PAP) has been extensively studied in various forms of acute respiratory failure as a destination therapy for certain patients and as a bridge to intubation in others. Prior research has identified that specific sub-groups of patients such as those with heart failure or COPD tend to benefit from NIV as they experience less mortality, fewer intubations and shorter MICU length of stay. Minimal information is available regarding process metrics to ensure that those in whom NIV is initiated receive optimal therapy. Current practice guides recommend post procedure monitoring for approximately 8 hours, based on a small randomized prospective trial which did not use monitoring as a primary outcome. There is no further guidance provided about the setting in which NIV should be initiated, the sorts of testing which are appropriate after initiation or the suggested associated care which should be provided to patients after NIV initiation. The goal of this investigation is to elucidate practice patterns and associated process associated with NIV initiation episodes.

Specific Aim: To examine process metrics for new (NIV) initiations across the Yale New Haven Hospital York Street Campus as an attempt to understand clinical practice uses of NIV in large academic settings.

Hypothesis: Structural factors related to delivery of care will impact the time to the following interventions related to the initiation of BiPAP: presence or absence of arterial blood gas, timing the arterial blood gas, timing of chest x-ray, and/or presence or absence of primary team responsible for care members present at the bedside.

Methods: IRB approval was obtained. Our study included all patients with newly initiated BiPAP in the inpatient or Emergency Department (ED) setting presenting for care between January 2015 and September 2018. Patients were identified by the presence of non-sleep BiPAP settings being charted by a respiratory therapist in pre-specified locations. Demographic data, location of care, dates and times of admissions and transfer to the medical ICU were obtained in addition to arterial blood gas and chest x-ray data, if available. Presence of rapid response medical team (RRT) activations was identified in the EMR for each NIV initiation. CPAP NIV excluded due to infrequency of use. Data was tabulated in both Excel and Tableau 2018.1.

Results: 1,250 NIV events for 999 distinct patients were recorded. BiPAP was started in the ED 72% of the time and in a non-ICU setting 24% of the time. Individuals in whom the RRT team was activated with non-ICU and non-ED BiPAP initiations had shorter hospital and MICU length of stay and lower costs associated with their hospital stay. 72% (n=905) of patients had an arterial blood gas performed within 3 hours of NIV initiation and 52% of these patients had PaCo2 values greater than 50. 21% of all patients were intubated and 14% of all patients expired prior to discharge. Of those patients who were intubated in the setting of a non-ICU BiPAP start (n=69), 48% of those patients ultimately expired while of those patients who were not intubated (n=198) 18% expired.

Conclusions: Structural elements in the delivery of care impact process metrics and potentially outcomes in patients with newly initiated NIV. The development of reliable metrics are helpful for improving and measuring the process of care. A substantial proportion of BiPAP/NIV initiation was reported in patients with normocarbia on the first measured ABG.

Peter Kahn

Resident's signature

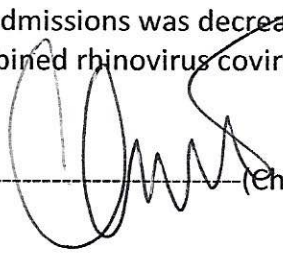
Mentor's signature

Title: Characteristics and outcomes of adults with multiple co-occurring respiratory viral infections

S. Kalra; A. Rebaza; S. Bermejo; J. Gomez; C. Dela Cruz
Yale University School of Medicine, New Haven, CT, United States

Rationale: Respiratory viral infections are common with adults developing 2-3 viral respiratory infections yearly. The prevalence of patients presenting with more than one viral infection, termed a co-viral infection varies widely. Patient characteristics and significance of co-viral infections on severity of illness are unclear, with few adult studies demonstrating increased hospitalizations and severity of illness, while others showing no significant differences. Furthermore, the specific viruses involved in co-viral infection may modify the severity of illness.
Specific Aim: we sought to determine the characteristics and outcomes of adult patients diagnosed with co-viral infections, and subgroup the most common co-viral infections and determine severity of illness.
Hypothesis: Patients with co-viral infections would be more likely to have underlying lung disease and have worse outcomes than patients with single viral infections
Methods: We conducted an IRB-approved retrospective cross-sectional single center study of adults 18 or older, with positive respiratory viral testing, in the ED and hospitalized setting from January 2013 to March 2018. Predictor variables were single virus or co-viral infection. Demographic data, comorbidities, and severity of illness, were then obtained from the electronic medical record. Severity of illness was a composite outcome determined by length of stay, ICU admission, and in-hospital mortality.
Results: 8730 patients were included accounting for 10,173 unique encounters. 188 of those encounters had co-viral infections (1.8 % of encounters). At baseline, patients with co-viral infections were not significantly different from single viral infections with regard to age, gender, race, smoking status, or Charlson comorbidity score. Patients with co-viral infections demonstrated statistically significant longer lengths of stay (19.1 vs 7.0 days; $p = 0.01$), increased rate of ICU admissions (36.6 vs 20.3 %; $p < 0.0001$), and a greater in-hospital mortality rate (7.8 vs 2.9%; $p < 0.0001$). The most prevalent single viral infection was Influenza A (31%, n = 3175). Rhinovirus was most prevalent in patients with co-viral infections, with the most common co-viral infections pairings being rhinovirus-human metapneumovirus (12%, n = 24) or rhinovirus-adenovirus (11%, n = 23). Patients with rhinovirus-influenza A subtype were less likely to be admitted to the ICU compared to other rhinovirus co-viral infections. (7% vs 32%, $p = 0.043$).
Conclusions: In this single center study of adult ED and hospitalized patients with positive respiratory viral infections, patients with co-viral infections had longer lengths of stay, higher rates of ICU admissions and in-hospital mortality compared to single viral infections. When subgrouped by coviral infection, the prevalence of ICU admissions was decreased in the rhinovirus-influenza A group compared to all other combined rhinovirus coviral infections.


----------(Sean Kalra)


----------(Charles Dela Cruz)

The Impact of Structured Reporting of Incidental (Category S) Findings Identified on Lung Cancer Screening LDCTs on Management by Primary Care Providers

Yukiko Kunitomo, M.D., Lynn Tanoue, M.D.

Background: Lung cancer is the leading cause of cancer-related death globally and in the United States. The National Lung Screening Trial demonstrated reduction in mortality from lung cancer and all-cause mortality in patients screened with low dose chest CT (LDCT) compared to screening with chest radiography. The USPSTF now recommends annual screening with LDCT for high-risk individuals. Incidental findings (IFs) are commonly identified on CT studies, including in lung cancer screening. The American College of Radiology Lung CT Screening Reporting and Data System (Lung-RADS) defined a category S modifier for clinically significant non-lung cancer findings. However, the lack of a formalized structure for LDCT IFs results in a lack of guidance for primary care providers (PCPs). It is unclear how variations in report structure affect management decisions by PCPs. The Yale Lung Screening and Nodule Program developed a structured reporting template for Category S findings using available evidence- or consensus-based guidelines.

Specific Aim: To understand how the reporting structure of IFs identified on lung cancer LDCT influences PCPs' decision-making for evaluation of those findings.

Hypothesis: Structured reporting of IFs on LDCT will improve guideline adherence for evaluation and management of IFs by PCPs.

Methods: Study subjects included 30 PCPs in hospital-based, VA primary care, or community settings. Information was collected about subjects' clinical experience and approaches to decision-making for screening LDCTs. Subjects were asked to read 10 LDCT reports. 5 reports had been read by chest radiologists using LungRADS without the structured Category S reporting template; the other 5 reports were the same LDCTs re-read by the study chest radiologist using the structured template. Subjects were asked to indicate their management of the findings via interview. Data analysis was performed using the Wilcoxon Signed Rank Test to assess for significance in difference in management with and without structured reporting.

Results: The study group was 43% male and 57% female. Average years of practice was 17±12 years. 73% of providers reported they never or almost never review LDCTs with a radiologist and 80% never or almost never personally view CT images. 73% indicated the radiology recommendations for IF in the report informs management decisions. The management of each IF with and without the structured reporting was matched by physician, resulting in 270 pairs. Overall, the probability of PCPs ordering guideline-adherent management for incidental findings was significantly higher with structured template reporting compared to without (83.33% vs 51.67%, $p<.001$). The probability of a correct management with the structured template given incorrect management without the template was 68.97%. The odds ratio for a physician ordering guideline-adherent management with compared to without structured reporting was 4.677 (95%CI: 3.396,6.443). Broken down by IF type, the effect was present for thoracic aortic aneurysms, renal cystic lesions and thyroid nodules (although not statistically significant), but not for adrenal adenomas.

Conclusions: Structured reporting of Category S findings on screening LDCTs is associated with significant improvement in guideline-adherent management of IFs by PCPs.

Resident Signature

Mentor Signature

Assessing Payment Model Education During Residency

Mary Clare Higgins-Chen, M.D. M.P.H., Bradley Richards, M.D. M.B.A.

Background: The U.S. has the most costly biomedical health system in the world, at 17.7% of the GDP. Much of the blame for these costs has been placed on fee-for-service (FFS), which reimburses providers for each test and procedure, regardless of care quality. Alternative payment models (APMs) shift the focus from the volume of care provided to care value and are increasingly becoming adopted in the U.S. As APMs become more widespread, residency graduates will need to understand payment models (PMs) both to make informed choices about their career and understand the effect of PMs on their practice. This will be an area of challenge for many residency programs because (1) PMs are diverse and (2) little time has historically been devoted during residency to teaching the economics of medicine.

Specific Aim: To perform a needs assessment survey of internal medicine graduates' knowledge of and desire for more residency-based education on payment models (PMs).

Hypothesis: Survey respondents will report inadequate residency education on PMs, poor understanding of the principles of PMs, and payment structure will affect job choice.

Methods: An educational needs assessment survey was compiled from several sources including the 2004-2005 Community Tracking Study Physician Survey, Deloitte 2016 Survey of US Physicians, and by the authors through a think-aloud process. The survey included questions about demographics, basic knowledge of PMs, current exposure to APMs, and effect of payment on job choice. The survey consisted of 40 multiple choice, Likert, and free-response items. All graduates of the Yale Internal Medicine Primary Care Program, starting with the inaugural graduating class in 1992, were emailed a link to an online survey from August-October 2019 with 2 reminder emails. Associations between variables were explored using Kruskal-Wallis tests, and for multi-level predictor variables a post-hoc Dunn's test was performed using a Benjamini-Hochberg multiple testing correction to determine which levels were different.

Results: A total of 427 graduates were emailed a Qualtrics link to the survey. 174 completed the survey, greater than the 126 needed for 80% power. Graduates from all years replied, with a mean of 6 respondents per year. While the majority (57%) of respondents stated they understood how the care they provided was reimbursed, only 14% felt prepared by residency to understand healthcare payments and 11.5% answered all payment knowledge questions correctly. Participants who received <10% or 10-20% of their income from meeting performance goals were less likely than those who were ineligible to agree they were prepared in residency to understand healthcare payments. Payment structure was the primary reason 24% of participants had changed jobs.

Conclusions: Most graduates felt inadequately prepared to understand healthcare payments by their residency training. This is likely not only a perception of inadequate preparation, but a true need for more education because graduates with more exposure to APMs in their current job reported feeling less prepared than those with limited exposure. Most respondents are practicing outside of a purely FFS or salaried system with a limited conception of PMs. The effect of payment structure is not abstract, causing a substantial portion of graduates to change jobs. This study supports the need for further education on healthcare PMs in residency.

Resident's signature

Mentor's signature

Research Summary Abstract

Title: Relationship Between Upper Esophageal Sphincter Pressures and Cough Severity

Mona Lalehzari, MD and Mayra Sanchez, MD

Background: It is known that gastroesophageal reflux is a common etiology of cough, which can significantly impact patient quality of life. However, it is unclear if differences in upper esophageal sphincter (UES) pressure—which functions to prevent reflux of esophageal contents into the pharynx and protect against aspiration—can contribute to cough. UES pressure rises during cough, likely as a protective mechanism to prevent further reflux and aspiration of gastric contents. However, given that this increase in pressure is a reaction to the cough rather than pre-cough, it is possible that a low UES pressure may be associated with the cough trigger.

Specific Aim: To compare UES pressures in patients with varying degrees of cough severity.

Hypothesis: We hypothesized that patients with lower UES pressures, as measured on manometry, will experience more severe cough, as reported on patient questionnaire.

Methods: A retrospective chart review was completed on all patients referred to our tertiary care hospital for esophageal manometry with impedance in 2016. UES pressure, cough severity, age, and sex were recorded for each patient in an Excel spreadsheet. Only patients who reported both cough symptoms and specified its severity were included in the final analyses. Mean UES pressures were compared between cough severities using t-tests and p-values were calculated for all pairwise comparisons.

Results: Of 357 patients referred for testing, 156 (21% Males, Mean Age 56.3 and 79% Females, Mean Age 57.4) endorsed symptoms of cough, as reported on pre-manometry patient questionnaire. The remainder of the patients were excluded either because they did not endorse cough or did not further specify their cough severity. Of the 156 patients with cough, 47 (30.1%) endorsed mild cough, 55 (35.3%) moderate cough, 37 (23.7%) severe cough, and 17 (10.9%) very severe cough. Basal UES pressure was 62.5 mmHg for the mild cough group, 58.4 for moderate cough, 53.6 for severe cough, and 51.8 for very severe cough. As expected, the most notable difference in UES pressures was between those with mild and very severe cough ($p=0.28$). There was a trend towards lower UES pressures among patients with more severe cough, although this was not statistically significant.

Conclusions: Overall, patients with increasing cough severity were noted to have lower UES pressures, although this did not achieve statistical significance. The lack of significance may be related to our low sample size, subjectivity of patient reporting, or the inherently invasive nature of manometry testing, requiring esophageal intubation and inhibiting swallows that may lead to a partial increase in the UES pressure. It would be valuable for future studies to look at actual measured acid exposure in patients with various cough severities paired with UES pressures. To summarize, the trends towards lower UES pressures in more severe cough that we observed may point towards a key relationship between esophageal-laryngopharyngeal interactions.

Mona Lalehzari
Resident's signature

Mayra Sanchez
Mentor's signature

Abstract Title: Racial and Ethnic Disparities in Medical Student Research Thesis Awards

Abstract Author(s): Ria Roberts, MD; Amy Justice, MD, PHD; Joseph King, Jr, MD, MSCE

Introduction: Studies have shown that race permeates the experiences of Underrepresented In Medicine (URIM) students. The Liaison Committee on Medical Education mandates instruction in the conduct of research and many U.S. medical schools, Yale School of Medicine (YSM) included, require students to complete a research project. Each year, all Yale graduating medical students submit a research thesis with ~5% awarded highest honors. However, few URIMs are recipients of such recognition. We explore whether factors typically associated with receiving research honors can explain the observed racial and ethnic disparities.

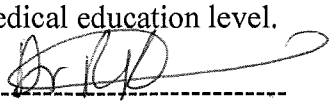
Specific Aim: Investigate whether underrepresented in medicine (URIM) disparities exist in research recognition at the medical student level.

Hypothesis: Yale medical student research thesis awards are subject to racial/ethnic related disparities.

Method: Retrospective review of 1,372 theses submitted by graduating medical students from YSM from 2003 to 2018. PhD candidates or recipients were excluded. Data on race, ethnicity, gender, age, year of graduation, additional year of study/5th year of medical school, accessory degree programs, research type and funding, mentors and sponsoring department were analyzed using multivariate regressions.

Results: Over the 16-year study period, only 5 of 250 (2.0%) URIM students versus 62 of 1,122 (5.5%) non-URIM students were awarded highest honors for their research. After adjustments, URIMs were equally likely to work with a successful mentor and perform laboratory research (for all, $P>0.133$). URIM students were however less likely to extend medical school to a 5th year, obtain research funding, or earn an additional degree (for all, $P<0.003$). They were also less likely to be nominated by their mentors and sponsoring departments (OR=0.51; 95% CI: 0.36, 0.74; $p <0.001$), less likely to receive honors (OR 0.42; 95% CI: 0.26, 0.67; $p <0.001$), and less likely to win highest honors (OR 0.25; 95% CI: 0.09, 0.72, $p =0.010$).

Conclusion(s): None of the identified factors associated with receipt of thesis honors explains the observed racial disparities. The selection process for research thesis awards at YSM may be vulnerable to racial bias given that URIMs were significantly less likely to be nominated for or win recognition for their medical school research. Racial and ethnic disparities in postgraduate biomedical research accomplishments may start at the medical education level.



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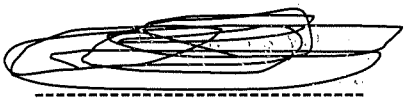

Mentor's Signature

Association Between Cumulative Mobility Achieved and Hospital-acquired and Ventilator-associated Pneumonias among Critically Ill Patients

Wei Maggie Qi, M.D., Lauren Ferrante, M.D., M.H.S.

Background: Prolonged immobilization is a known risk factor for developing neuromuscular weakness, which can lead to complications such as pneumonia. Early mobilization is associated with improved physical function and likelihood of discharge to home, but its association with hospital-acquired and ventilator-associated pneumonias (HAP and VAP) is unknown.
Specific Aim: To study the association between average cumulative level of maximum mobility achieved and incidence of HAP and VAP among critically ill patients.
Hypothesis: Higher cumulative mobility achieved is associated with lower incidence of HAP and VAP among critically ill patients.
Methods: We conducted a retrospective chart review of medical ICU patients at the Yale-New Haven Hospital who participated in an early mobilization program during the first quarter of 2015 and 2016. We used a validated method to abstract new diagnoses of HAP and VAP, as well as clinician diagnosed HAP and VAP. We captured detailed information about physical therapy during the hospital stay, demographics, baseline ambulatory status, and mechanical ventilation (MV) status. Patients who were transferred from an outside facility or had a diagnosis of pneumonia prior to hospital day 3 were excluded. We used a Bayesian, discrete time-to-event model to evaluate the association between cumulative level of maximum mobility achieved and the time to first occurrence of HAP or VAP, where statistical significance was defined as a credible interval (CI) exclusive of a hazard ratio (HR) of 1. Covariates included the previous day's MV status and baseline ambulatory status, and follow-up was censored by death, discharge, or 30 days. Cumulative level of maximum mobility was operationalized as a time varying exposure, in which the maximum level of mobility achieved each day (on a scale of 0 to 6) was averaged across hospital length of stay (LOS) through the day preceding evaluation for the outcome. This exposure can be interpreted as the average sustained maximum mobility achieved over the entire LOS. Given the daily variation in covariates and exposure, logistic regression with the complementary log-log link was used to calculate the hazard ratios. The coefficients from this model can be interpreted like Cox-model coefficients.
Results: Among the 146 person-admissions (1145 person-days) in the analysis, 32 events were observed, of which 56.3% met both clinician and chart review definitions, while 34.4% were from clinician diagnosis only and 9.4% only met chart review criteria. The median age was 68.0 (IQR 54.0-77.0) in the HAP/VAP group and 61.5 (IQR 51.5-79.0) in the group without HAP/VAP. Approximately 50% of patients ambulated at baseline in both groups. In bivariate analysis, the cumulative average dose of maximum mobility exhibited a protective association with occurrence of HAP or VAP (HR 0.54, 95% CI 0.35, 0.81), an association that was retained after adjustment for baseline ambulatory status and previous day's MV status (HR 0.56; 95% CI 0.36, 0.84).
Conclusions: Among critically ill patients in an early mobilization program, each incremental increase in cumulative maximum mobility achieved was associated with a 50% decrease in the risk of HAP or VAP. Larger studies are needed to confirm these findings.

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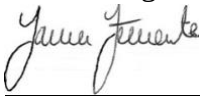

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Yale Internal Medicine Research in Residency Day

An Assessment of Smartphone Use Habits and Attitudes Towards Health Apps of Patients at a Resident Primary Care Clinic

Trevor Parker MD, David Rosenthal MD

BACKGROUND: Smartphone use has skyrocketed in recent years. There are currently over four-billion smartphones in use worldwide, and they have become nearly ubiquitous in the hands of US citizens. People are now interfacing with technology constantly, and this has created a new path by which people can obtain information with an ease never before known. A recent development in the smartphone world are health apps— programs on smartphones with the intention of tracking or improving user health in some way. This study aimed to assess smartphone use habits of patients at a resident primary care clinic, with specific emphasis on health app usage, attitudes, and barriers to utilization of this new and promising technology.

SPECIFIC AIM: To assess smartphone use habits of patients at a resident primary clinic with the eventual goal of creating a smartphone app that aligns with patient use habits.

METHODS: A 10-question survey was offered to all patients checking in for primary care and urgent care visits at the Saint Raphael Adult Primary Care Center. The survey was optional and collected de-identified demographic data of each respondent. The completed surveys were then analyzed and stratified by demographic data.

RESULTS: There were 61 survey respondents, with most reporting demographic data. Over 75% of survey responds reported that they owned a smartphone and felt comfortable using it. Over 80% of respondents used apps for messaging, email and internet— while only around 36% had used a health app. Of those who have used a health app, only about a third of users actually use the app daily or weekly (~15% of all respondents). When respondents who don't have any health apps we asked why they did not have any health apps, the most common response was that they do not know any health apps. Roughly 79% of respondents stated that they would be willing to use a health app every day if it could improve their health in some way. Questions were also asked to assess important qualities in designing a health app, and respondents reported the most important factors in app design would be credibility and ease of use. Over 88% of respondents reported that they believed knowledge about their disease was important to management, and 55% reported that it didn't matter if they read their health information on paper or on an app.

CONCLUSIONS: A large majority of patients today own a smartphone and feel comfortable using apps. Although patients have a desire to use health apps if they can be shown to improve health, a majority currently do not utilize health apps, most commonly because they don't know of any health apps. Further health app design should focus of credibility of the app and ease of use.

Resident's Signature

Mentor's Signature

Mindfulness Based Interventions in the Treatment of Fatigue in Patients with Primary Biliary Cholangitis: A Pilot Study

Shivani K. Shah, M.D., Laura Cusack, Marina G. Silveira, M.D

Background: Primary biliary cholangitis (PBC) is a chronic, progressive cholestatic liver disease. Fatigue is present up to 80% of patients with PBC, which has been associated with increased mortality and can be associated with poor quality of life (QOL). The pathogenesis of fatigue is unclear and may persist despite biochemical response to treatment. Mindfulness-based interventions (MBI) consist of a combination of yoga therapy and meditative techniques and may help improve QOL in chronic diseases and may be of benefit in treatment of fatigue in PBC.
Specific Aim: To assess the efficacy of MBI on fatigue, emotional and physical health, and pain in patients with moderate to severe fatigue and PBC, as well as the effect of MBI on biomarkers of fatigue and stress (AMA titers, alkaline phosphatase (ALP) dehydroepiandrosterone (DHEA), leptin, c-reactive protein (CRP), IL-1β, IL-6, brain-derived neurotrophic factor (BDNF), and macrophage inhibitory factor (MIF)).
Hypothesis: An 8-week MBI program would lead to an improvement in the subjective symptoms of fatigue (as quantified by the PBC-40 fatigue domain) and serum biomarkers of fatigue and stress.
Methods: 20 patients with moderate-severe fatigue and PBC (defined as a PBC-40 fatigue score >33) will be recruited. The protocol consists of an 8-week control phase, followed by an 8-week intervention phase and 12-week follow up period. The intervention phase consists of weekly 2.5-hour group-based MBI with a 7.5-hour retreat during the intervention. Blood tests and the following pre-and post-test surveys during the control phase, pre-MBI, post-MBI and at follow up: PBC-40, Epworth Sleepiness Scale (ESS), SF36 scales, orthostatic grading scale (OGS), Hospital Anxiety and Depression Scale (HADS), Patient-Reported Outcomes Measurement Information System (PROMIS) scales. Physical activity is measured through the BodyGuard 2 (BG2) wearable sensor, measuring highly accurate heart rate (HR), HR variability, VO2 and energy expenditure. The participants will wear the tracker at baseline, end of control phase, immediately after the MBI intervention and 12 weeks after the end of the MBI intervention.
Results: To date, 6 female participants, with an average age of 64.7, completed the protocol. The average change in PBC-40 Fatigue score from pre- to post-MBI was -0.80 points (SEM of ± 6.83); assuming a control average of 33, the overall change from control to post-MBI was a decrease in 5 points (SEM ± 4.94). Pre-and post-MBI physical health and pain domains of the SF36 showed average improvement of +5 points (SEM ± 31.62) and +8.67 points (SEM ± 23.95), respectively. Average change from control to post-MBI tests were as follows: decrease in ALP -10.17 U/L (SEM ± 51.16) and CRP -10.0 mg/L (SEM ± 21.31); increase in AMA +5.43 units (SEM ± 50.51) and leptin +3.42 ng/mL (SEM ± 9.32). Average change in DHEA from control phase to post-MBI increased: +12.8 ng/d (SEM± 49.76); pre-MBI to post-MBI change decreased: -52.83 ng/dL (SEM± 104.24). There was no significant change (<5-point change) in OGS, HADS-D, ESS, PROMIS, SF-36 emotional well-being, fatigue or general health subdomains from pre-MBI to post-MBI. IL-1β, IL-6, MIF, BDNF, BG2 tracker data are pending.
Conclusions: An 8 week in-person MBI program may help treat fatigue in PBC, as evidenced by improvement in the PBC-40 Fatigue domain scores and serologic measures of stress, such as CRP and DHEA. The improvement in ALP may have implications in management of disease activity. Despite great interest, recruitment was challenging presumably secondary to the need for in-person sessions. Future adaptations for the trial include limiting the number of in-person sessions.

Shivani K Shah, MD
Yale Traditional Internal Medicine, PGY 3

Marina G. Silveira, MD
Associate Professor of Medicine (Yale Digestive Diseases)

Return to play for athletes with cardiac disease: Routes and barriers to return and experience after

Kayle Shapero MD PhD, and Rachel Lampert MD

Background: Recommendations for return to play for athletes with cardiovascular disease have evolved from an initially conservative approach to more flexible decision making, but the implications for patient-athletes is unknown.

Specific Aims: This study was designed to examine routes and barriers that athletes and their families face as they return to play, and to explore the development of emergency action plans (EAP)s to ensure safety upon their return to the field.

Hypothesis: Despite changes in guidelines, many barriers exist for athletes returning to play. EAPs are not universally in place for these athletes.

Methods: A mixed methods telephone survey combining quantitative and qualitative components was administered to 30 patients and 23 parents from the Yale ICD Sports registry and Mayo Clinic's Inherited Disease clinic. Qualitative data was analyzed with a coding scheme to identify common themes.

Results: Demographic and clinical variables: Most common diagnoses were long QT syndrome(n=12), hypertrophic cardiomyopathy (n=5), CPVT (N=4). Twenty-one had an ICD, 11 a history of arrest. The most prevalent sports included soccer (n=8), basketball (n=6), and football (n=4). The highest level of participation was semi-professional (n=3), college varsity (n=10), college club (n=4), and high school (n=13).

Results: Process of return to play: Patients saw an average of 2.6 MDs, maximum 7 MDs. 23 patients encountered barrier(s): 17 could not participate per their first cardiologist; 6 met with school administrators, 2 met with social workers/counselors, 4 signed waivers, and 3 hired lawyers. Two patients changed schools and 4 were unable to participate at their intended level and/or had scholarships revoked. Both patients and their families noted that areas for improvement include communication with physicians and increased support/resources for patients and their families. Themes that were commonly expressed by the patients included a minimization of their diagnosis, lack of disclosure, and a sense of special treatment because of their diagnosis. Two common themes expressed by athletes but even more commonly in parents is frustration with lack of physician knowledge of their diagnosis and cynicism that physicians and schools had more concerns for liability than for patients well-being. Parents noted additional emotional challenges including the emotional/mental health toll it took on the child.

Results: EAPs: 26 of the 30 athletes had some form of EAP, with 25 of the 30 having an AED with them at all times, 4 were required to wear protective gear and 2 were required to wear heart rate monitors. These EAPs were largely recommended by the patient's cardiologist (9/26). Only one EAP was enacted when the patient's ICD fired during a game. When these athletes returned to the field, half (15/30) felt that their experience had taken a toll on their sports participation, whether in the form of lost fitness, physical effects of medications, having to quit a sport, or having lost collegiate scholarships. Even several years out from their diagnosis, 28/30 patients have continued to participate in athletics, whether it be through coaching, semiprofessional sports, or recreational sports team.

Conclusions: Many barriers exist for athletes with cardiac disease who wish to return to play after their diagnoses, and their families. Challenges in the lack of physician familiarity and concern by physician and schools around liability has delayed their participation. While recommendations regarding competitive sports participation for such athletes have changed, adoption has lagged. Shared decision-making with patients and their families is critical for return to play for athletes with cardiovascular disease.

Resident Signature: _____ Mentor Signature: emailed to L Gambardella

Characterizing a novel variant in the thrombomodulin gene in a patient with VTE

Lauren Shevell, MD and Alfred Lee, MD, PhD

Background: Thrombomodulin is a membrane protein that modulates hemostasis and thrombosis through the activation of protein C and downstream degradation of factors Va and VIIIa. Thrombomodulin also plays a key role in inflammation, and has been shown to decrease inflammatory cytokines. Recent studies suggest that variants in the thrombomodulin gene, THBD, are significantly more common in African Americans compared to other ethnic groups and single nucleotide polymorphisms in this population may double their risk for VTE. Using whole exome sequencing (WES), we identified a novel variant in THBD A184T.
Specific Aim: Further characterize the pathogenicity of THBD A184T using in silico protein modeling and extensive biochemical analysis.
Hypothesis: Variant THBD A184T causes pathologic changes to the thrombomodulin protein, and increases risk for thrombosis.
Methods: A 33-year-old African American woman with a history of left lower extremity DVT underwent whole exome sequencing with a focused analysis on a 55-gene thrombosis panel. A novel variant was identified in THBD A184T. This variant was further analyzed using in silico protein modeling, sequence homology comparisons and extended biochemical analysis including thromboelastography (TEG), thrombin-antithrombin (TAT) complex, heparin cofactor II, PT/PTT, d-dimer, plasminogen activator inhibitor-1 (PAI-1), fibrinogen, PFA-100, tissue plasminogen activator, vWF, Factor II, V, VII, VIII, IX, XI, and a cytokine panel including TNF-alpha, interferon gamma, soluble interleukin-2 receptor, and interleukins 1 beta, 2, 4, 5, 6, 8, 12, 13 and 17.
Results: In silico protein modeling for variant THBD A184T showed a substitution of nonpolar alanine to a more polar threonine, likely affecting a linker region and disrupting protein function. The variant is located in a hydrophobic region of the lectin-like domain, a part of the protein that manages anti-inflammation signaling, but does not have a known role in hemostasis and thrombosis. The variant is exceedingly rare, with an allele frequency of 0% in the gnomAD database; homology comparison revealed it to be well-conserved. Extensive biochemical analysis revealed a shortened R time on TEG (4.6 min, reference range 5-10), an increased TAT complex (5.3 mcg/L, reference range < 4), elevated D-Dimer (1.23 mg/L, reference range ≤ 0.5) and elevated PAI-1(59 ng/mL, reference range 4-43). Other values were within normal limits.
Conclusion: This patient may be at higher risk to develop VTE by two separate mechanisms. The shortened R time, elevated D-Dimer and increased TAT complex may indicate that the patient is prone to thromboses due to an overall increase in coagulation factors in general, and thrombin specifically. Secondly, an elevated PAI-1 suggests an increased inhibition of plasminogen activation, thus decreasing fibrin break down. Interestingly, in silico protein modeling revealed the variant to be in the domain of thrombomodulin related to inflammation, rather than thrombosis. Several studies have demonstrated PAI-1 to be upregulated during inflammation, and the elevated PAI-1 in this patient may reveal PAI-1 mediated connection between inflammation and thrombosis that has not been previously reported. Further studies are needed to understand the clinical implications of this variant including WES of family members and in vitro studies to evaluate the function of THBD A184T on coagulation activation.

Lauren Shevell

Alfred Lee

Research in Residency Summary Abstract

Project Title: Longitudinal Measurement of Post-Liver Transplant Cognitive Impairment
Principal Investigator: Jennifer Batisti, MD
Co-investigator: Sloane Heller, PGY3

Background:
Cognitive impairment following adult liver transplant is a known entity, which is associated with worse clinical outcomes and poorer quality of life. Cognitive testing of post-transplant adult patients who were transplanted as adults has shown that a significant number of patients experience some degree of cognitive impairment within the first year of transplant; additional research has revealed the presence of cognitive impairment in patients up to 10 and 20 years post-transplant.
To date, there has been no exploration of whether the degree of post-transplant cognitive impairment might change in an individual patient over time. This information will be helpful both in terms of a more full understanding of post liver transplant cognitive impairment and also in terms of judging the effects of any interventions.

Specific Aim:
We aim to discover if there is any change in the degree of cognitive impairment over time after liver transplant.

Hypothesis:
Our hypothesis is that subjects who are the longest out from transplant will have the least degree of cognitive impairment.

Methods:
The original study design called for administering the Montreal Cognitive Assessment (MOCA) to all adult patients who received a liver transplant as an adult and who receive care at the Yale New Haven Hospital Transplantation Center who consented to participate in the study. However, in consultation with a cognitive and behavioral neurologist, it was decided that the MOCA was not a sensitive enough instrument to use for this purpose. Another instrument, the Cambridge Neuropsychological Test Automated Battery (CANTAB) – which has proven more sensitive to detect mild cognitive impairment and has been used in the liver disease population – was selected for use. This substitution required a project redesign, reapplication to the IRB, and applications for funding, which are currently pending. Therefore, data collection has not yet started.

Results:
No results have been collected yet.

Conclusions:
No conclusions have yet been reached.

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Resident Signature Mentor Signature

RESEARCH SUMMARY ABSTRACT

Impact of Anatomic Site of Metastasis on Clinical Outcomes in Patients with Metastatic Melanoma Treated with Immune Checkpoint Inhibitors

Thejal Srikumar MD, Sarah Weiss MD

Background: Melanoma is estimated to be the 6th most common malignancy in the United States and is increasing in incidence. While melanoma remains the deadliest of all skin cancers, the advent of immunotherapy and targeted therapy has revolutionized the treatment of advanced melanoma. Immune checkpoint inhibitors (ICIs) including anti-programmed cell death protein-1 (PD-1) (nivolumab and pembrolizumab) and anti-cytotoxic T-lymphocyte associated protein-4 (CTLA-4) (ipilimumab) alone or in combination are front-line standard therapies for advanced melanoma. Multiple prognostic factors exist for melanoma, but known factors to predict response to systemic therapies are limited. Preliminary studies have suggested that site of metastases may affect response to ICI, though this has not been thoroughly studied.
Specific Aims: To determine whether anatomic site or number of anatomic sites of metastasis in patients with advanced melanoma is associated with response to standard of care immune checkpoint inhibitors and survival outcomes.
Hypothesis: Anatomic sites of metastasis in patients with melanoma may affect response to immunotherapy.
Methods: We are conducting a single-center retrospective cohort analysis to determine whether response to ICI is influenced by anatomic site(s) of metastases in patients with advanced melanoma. The patient population was derived from the Joint Data Analytics Team (JDAT) at Yale New Haven Hospital, with IRB-approved data extraction from the Epic electronic medical record. Inclusion criteria consisted of patients who received treatment with ICIs (either ipilimumab, nivolumab, pembrolizumab, or ipilimumab/nivolumab) for diagnosis of AJCC unresectable stage III or stage IV melanoma at the Smilow Cancer Center from 2013, and have undergone at least one restaging assessment after ICI treatment began. Data currently undergoing collection include patient demographics (sex, BMI, race, age); vital status; dates of birth, primary melanoma diagnosis, and death (if applicable); age of diagnosis; date of metastatic melanoma diagnosis; features of primary melanoma; sites of metastatic melanoma and number at each site; molecular status; type of immunotherapy used; dates of initiation and change in therapy; reason for change in therapy; response to therapy. Statistical analysis is ongoing.
Results: 1864 patients were initially identified by the JDAT data query as meeting inclusion criteria, with 48.3% males and 51.7% females. Data collection for remainder of variables are ongoing.
Conclusions: This project aims to study how site(s) of melanoma metastasis may impact response to ICIs. We will accomplish this aim with the single-center retrospective cohort analysis described. Database building and subsequent analysis is ongoing.

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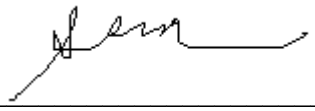

Mentor's signature

Title: Analysis of effectiveness of EMR Best Practice Alert (BPA) for birth cohort HCV screening in an underserved academic primary care setting

Authors: Jessica Su, M.D., Joseph Lim, M.D.

Background: With the advent of direct-acting antiviral therapies in the treatment of chronic hepatitis C virus (HCV) infection, it is possible to cure HCV safely and effectively with high rates of sustained virologic response. However, barriers to eradicating HCV include challenges in screening, diagnosis, and access to care and initiation of treatment. Guidelines previously recommended one-time screening in the cohort of patients born between 1945 and 1964, and current guidelines have expanded to recommend one-time screening in all patients age 18 to 79.

Specific Aim: This study aims to assess the effectiveness of an automated reminder system built into a local EMR in promoting appropriate HCV screening and subsequent referral to care and treatment as necessary through an underserved primary care center at a large academic institution.

Hypothesis: BPAs may have a small impact in promoting HCV screening during the initial encounter but may have a more longitudinal impact in eventual screening and linkage to care.

Methods: In October 2014, Yale New Haven Health System's commercial EMR (EpicCare, Epic Systems Corp., Madison, Wisconsin) rolled out an automated HCV best practice alert (BPA) that would remind providers during an encounter to perform guideline-based HCV screening in identified patients. In this study EpicCare was queried for BPA alerts generated during patient encounters at the Yale Primary Care Center (PCC) Adult Continuity Clinic, one of Yale's primary care clinics for underserved populations in the community. From the total number unique patient charts that generated an HCV BPA, the number of patients that received screening and the number of tests that were abnormal were queried. From the patients who were found to have HCV infection, the number that had a subsequent encounter with a gastroenterologist or hepatologist and the number that ultimately had an HCV treatment regimen listed as an active medication within the analysis period were queried. Time to completion of each step was also analyzed to assess completion within the same year versus within the analysis period.

Results: Between October 2014 and February 2020, a total of 6839 unique patient charts prompted an HCV BPA alert during a Yale PCC Adult Continuity Clinic encounter. Out of those 6839 patients, 4166 (60.9%) had received screening by the end of the study period. Of those that received screening, 287 results (6.9%) were abnormal. Of the patients found to have HCV infection, 177 (61.7%) had a subsequent encounter in a gastroenterology or hepatology clinic within the health system. Only 63 patients (21.9%) with HCV infection had an HCV treatment regimen listed as an active medication at any point within the study period. The majority of patients did not have screening, subspecialist encounter, or treatment completed within the same year of the initial BPA alert, with most actions completed later during the analysis period.

Conclusions: An EMR-based automated reminder system has the potential to improve screening rates for chronic HCV infection. Between 2014-2020, 4166/6839 (60.9%) of patients for whom an electronic BPA alert was activated within the Yale PCC Adult Continuity Clinic successfully underwent a HCV screening test. The majority of screening tests were not completed at the time of the initial encounter but at later dates during the analysis period, suggesting the role of additional factors to completion of HCV tests. Despite screening, only a minority were successfully linked to care and received HCV DAA therapy. Within an academic primary care clinic caring for underserved populations, an EMR-based reminder was associated with high rates of HCV testing, but longitudinal, integrative, systems-based strategies are likely needed to meaningfully improve HCV screening, linkage to care, and treatment.

Resident:  Mentor: 

Outcomes in Primary Refractory Multiple Myeloma Patients in the Era of Novel Treatments

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Background: Multiple myeloma (MM) is an incurable plasma cell neoplasm with a great deal of heterogeneity. Achieving a deep response with a very good partial response or complete response is the goal of induction therapy. Whereas patients with partial response or less is suboptimal and has been associated with poorer outcomes. With the advent of novel therapies, such as monoclonal antibody, Daratumumab, little is known of its effect on primary refractory and suboptimal responding disease.

Specific Aims: Evaluate the overall survival and characterize the prevalence of induction treatments of MM who were primary refractory versus very good partial response and better.

Hypothesis: Primary refractory sub optimally responding MM patients will have shorter overall survival compared to patients who achieve VGPR or better. Survival rates of primary refractory patients will be unfavorable even with novel antibody regimens, including daratumumab.

Methods: Multiple myeloma patients treated at Yale New Haven Hospital and Smilow from 2011-2019 were identified via JDAT. Smoldering myeloma were excluded. A retrospective cohort analysis was performed on 136 patients 3-months following induction therapy. Patients with partial response, stable disease, or progressive disease were defined as primary refractory (PR). Patients who achieved very good partial response or complete response were defined as ≥VGPR. Statistical analysis was performed with 2-tailed contingency χ^2-tests, t-tests, and log-rank tests using GraphPad Prism 8.0.

Results: Out of 136 patients identified, 71 (52%) patients were PR and 65 (48%) were ≥VGPR. Median age of PR patients was 66 and 61 in ≥VGPR (p=0.04). 52.05% of men and 52.38% of women were PR at 3 months. High risk cytogenetics (del17, t4;14, t14;16, t14;20, and 1q gain) were seen in 26.5% of PR patients and 30% of ≥VGPR (p=0.8). Median overall survival was 8.95 years among primary refractory patients and 11.83 years in patients with VGPR or better (p=0.27). No patients in either cohort received Daratumumab as part of induction therapy. There was no significant difference in the usage of common induction therapies, such as VRD[1](PR 42.2%, ≥VGPR 33.8%, p 0.6), RD[2] (PR 25.3%, ≥VGPR 12.3%, p 0.07), and CyBorD[3] (PR 8.45%, ≥VGPR 15.4%, p 0.5). In the 2nd line of treatment, novel monoclonal antibody drugs consisted of 15.5% of the regimens used in PR patients compared to 8.8% of ≥VGPR (p 0.5).

Conclusions: Our analysis demonstrates that primary refractory multiple myeloma patients 3 months following induction therapy had a lower median OS. The median OS in our cohorts consistent with other studies' average OS of 10-11 years with the use of modern therapies. However, the difference was not statistically significant, which may be due to a small sample size or the possibility of effective subsequent lines of therapies used to treat PR patients. Because daratumumab was only recently approved in the first line setting, there is limited data on the full impact of this monoclonal antibody in induction therapy in primary refractory patients. Further analysis of the Yale's MM cohort is ongoing with additional plans to examine patterns of use of monoclonal antibodies in first and second line setting.

[1] Velcade, revlimd, dexamethasone
[2] Revlimid, Dexamethasone
[3] Cyclophosphamide, Velcade, dexamethason

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