# Filipino Seafarers and their Impact on Family Wellness

Queenie A. Abad, M.D., Rafael Y. Lefkowitz, M.D., M.P.H.

**Background:** Seafarers, in choosing their profession, balance the risks and benefits of going to sea. The potential to earn is high, but it comes at a cost to the seafarer and their families. At sea, the seafarer may risk life, limb, mental health, and family relationships. Few published studies have explored the impact of seafaring on the families of seafarers globally, and studies of the impact on Filipino families and their communities in particular are more limited.

**Specific Aim:**

To understand the psychosocial impact of seafaring on families in the Philippines, the study aims to assess well-being of seafaring families and to investigate challenges they face with the long periods of separation. The study also aims to identify protective factors for family well-being.
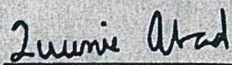
**Hypothesis:** The long periods of separation between seafarers and their families is inherent to seafaring as an occupation and leads to decreased wellness and increased stress to families of seafarers. The left-behind parent assumes an expanded role in household duties, an increased responsibility in childcare, and may sacrifice career opportunities. Protective factors are freqent communication between seafarers and their families, shorter duration deployments, and increased support from extended family and the community.

**Methods:** Seafaring families in Borongan, Cebu, and Tacloban were identified with the assistance of a Sailors' Society Family Outreach Officer based in the Philippines.
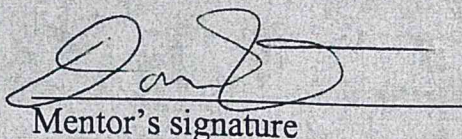A questionnaire was administered to participants to evaluate psychosocial well-being, marital satisfaction, and child and adolescent well-being. Semi-structured interviews were conducted to identify patterns and themes regarding psychosocial well-being and to explore perceptions, attitudes, and thoughts on family and community changes as a result of seafaring.

**Results:** 32 interviews were conducted. 15 were spouses of seafarers, 7 were active or retired seafarers, 5 were children of seafarers, and 5 were other family members of seafarers. 16 interviews were conducted in Tacloban, 9 in Cebu, and 7 in Borongan. Common themes were feelings of loneliness, anxiety, and worries of marital fidelity when the seafarer is away at sea. Many women discussed having to sacrifice their careers because of the absence of the seafaring spouse and the need to tend to household duties and children. Financially, sources of stress included managing debt from mandatory seafaring training in between deployments, managing savings and finding alternate sources of income when the seafarer spouse is not at sea, and finding work and sources of income after the seafarer retires, which is often at the age of 50. Many families described cases of unjust compensation in the event of work-ending occupational related injuries or deaths. Factors associated with improved wellness were access to email, social media, and cellphones to communicate with family, decreased duration of deployments of 6 months or less, and the seafarer's ranking as an officer.

**Conclusions:** There is a need for mental health services and family support for dependents of seafarers when the seafarer is at sea. Family separation is a source of great stress which can be improved via shorter term deployments and improved access to communication. Although the earning potential of seafarers is higher compared to their land-based counterparts, income is only earned during deployment and seafarers are often not re-hired past 50 years of age. There is a need for financial counseling to budget income when the seafarer is not at sea and to plan for life after seafaring. Given the current and continued predicted shortage of seafarers involved in global shipping, focus on the retention of seafarers by meeting the needs of seafarers and their families is in the best interest of shipping companies.

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# Left Ventricular Systolic Dysfunction following Acute Neurological Events: Beyond Takotsubo Cardiomyopathy

Jason A Bonomo, MD PhD, Ben Lin, MD PhD

**Background:** The development of Takotsubo cardiomyopathy (CM) in the setting of acute cerebrovascular events (ACE), such as stroke and intracerebral hemorrhage, is a well-documented phenomenon reportedly occurring in approximately 1% of patients. Neurogenic stunned myocardium in ACE has been described as a similar phenomenon with different patterns of myocardial involvement compared with Takotsubo CM variants. However, the frequencies of neurogenic stunned myocardium and Takotsubo CM remain poorly defined.

**Specific Aim:** In this study, we evaluated the frequency of left ventricular (LV) systolic dysfunction in the setting of ACE.

**Methods:** Transthoracic echocardiograms (TTE) performed between May to October 2017 as part of a workup for stroke or intracerebral hemorrhage were retrospectively reviewed. Patients without CT or MRI evidence of an ACE, i.e. those with transient ischemic attacks, were excluded. Inclusion criteria were CT or MRI evidence of ACE and TTE performed during admission. The follow-up period extended between four to nine months from ACE. In total, 120 patients met inclusion criteria.

**Results:** 48% of patients were female. 18 patients (15%) had echocardiographic evidence of LV systolic dysfunction. Of these, eight patients (7%) developed transient LV systolic dysfunction followed by documentation of complete resolution. Of these, two had apical ballooning syndrome, one had mid-ventricular CM, one had global hypokinesis, and four had regional wall motion abnormalities (WMA) not matching common Takotsubo CM variants. For these eight patients, mean EF at time of ACE was 48±14% which improved to 57±4% on repeat TTE. None of them developed acute heart failure. All were discharged with a beta blocker, but only three were started on an angiotensin converting enzyme inhibitor. The 10 additional patients (8%) identified as having echocardiographic evidence of LV systolic dysfunction lacked follow-up TTE after discharge.

**Conclusions:** The observed frequency of LV systolic dysfunction in the setting of ACE is much higher than what has previously been reported. Importantly, a large proportion of these patients did not have close echocardiographic monitoring after hospital discharge and may not have received optimal cardioprotective therapy.

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<u>Tidal volume trends and current practices: a retrospective review and survey study</u>

Research in Residency: Catherine A. Gao MD, Lauren E. Ferrante MD, MHS

**Background**: It is widely known that low tidal volume ventilation (LTVV ≤6 cc/kg ideal body weight (IBW)) is beneficial in Acute Respiratory Distress Syndrome (ARDS). There is also a strong body of evidence demonstrating the benefits of lung-protective ventilation (LPV ≤8 cc/kg IBW) in patients without ARDS. Past surveys of critical care providers have revealed positive attitudes towards LTVV, with few barriers perceived, however adherence in practice is low.

**Aim**: To evaluate tidal volumes (TV) trends over time by ICU and gather information on current approaches to TV calculation and practice.

**Hypothesis**: TV will decrease over time as evidence of the benefits of LPV accumulates. MICU providers will use lower TV than providers in other ICUs.

**Methods**: We reviewed adult ventilation episodes from February 2013 through December 2018. Patients on ECMO were excluded. 18,890 episodes were identified; after excluding data with incomplete information, we analyzed 17,819 encounters. We converted recorded TV in cc to cc/kg IBW based on patient height and gender from the selected encounter and categorized this information by type of ICU. We also evaluated the number of TV order changes and the initial and final TV per encounter. We surveyed MICU and NICU rotators from 1/17/19-2/6/19. We collected demographics and presented hypothetical cases and asked respondents to choose TV. We asked respondents to rate the benefit of LTVV in ARDS, LTVV in non-ARDS, and LPV in non-ARDS situations on a 5-pt Likert scale. We asked their current approaches to calculating TV (ARDSnet table, manually, online calculators) and how difficult they found it with the current EMR setup on a 5-pt Likert scale. Survey data were compiled in Qualtrics and data were analyzed in Excel using Visual Basic and GraphPad PRISM with unpaired t-tests.

**Results**: From 2013 to 2018, the avg initial set TV (in cc/kg IBW) decreased from 8.99 ± 2.19 to 7.45±1.34 (p<0.001). The CTICU had the largest change in avg initial TV from 11.09±1.96 in 2013 to 7.97±1.03 in 2018 (p<0.001). The MICU had the lowest avg initial TV with a mean of 7.05±1.63 in 2018 (range for other ICUs 7.20-7.97). The MICU and Cardiac ICU had a higher number of ventilator TV order changes per encounter (in 2018, 2.34 ± 0.063 and 2.62 ± 0.069, respectively; range in other ICUs 1.76-1.84). The MICU also had the lowest avg final TV: in 2018, 6.70±1.46 (range for other ICUs 6.93-8.33). While the majority of TV across all ICUs were between 6.58-8.01 (interquartile range) in 2018, 25% of patients were still being ventilated at volumes greater than 8cc/kg IBW. We received 104 surveys from 118 distributed, a response rate of 88%. We had 64 Medicine, 26 Neurology, 14 Other; there were 8 attendings, 11 fellows, 47 residents, 15 nurses, and 12 APPs, and 11 RTs. Medicine favored lower TVs than Neurology in both non-ARDS cases (cc (cc/kg IBW) - 337 (6.74) vs 358 (7.16), p=0.054) and ARDS cases (300 (6) vs 342 (6.48), p<0.001). Attendings favored lower TV than residents in both non-ARDS cases (287 (5.74) vs 352 (7.04), p<0.001) and ARDS cases (281 (5.62) vs 311 (6.22), p=0.054). Compared with Neurology, Medicine felt more strongly that patients with ARDS benefitted from LTVV (1.2 vs 2 on Likert scale, lower score = more benefit, p<0.001).

**Conclusions**: We found that TV trended down significantly across all ICUs, even with exclusion of ECMO. The MICU had the lowest avg set TV and the CTICU had the highest. In 2018, 25% of ventilator encounters still had a set TV>8cc/kg IBW. We found that attendings chose lower avg TV than residents, and that Medicine preferred lower avg TV than Neurology. More than half of respondents found it difficult to calculate optimal TV with the current EMR. Targeted education may help regulate appropriate TV choices across roles and departments. A calculator embedded in the EMR may improve standardization and adherence to LPV.

# Piloting an Interdisciplinary Clinic with Primary Care Physicians and Health Psychologists to Improve Quality of Life among Patients with End-Stage Heart Failure

Leila Haghighat, MD; Eugenia Betz, MD; Jonathan Pumilia, MD; Janet Ku, APRN; Benjamin Lu, MD; Clinesha Johnson, PsyD; Noel Quinn, PhD; Susan Langerman, APRN; Graham Taylor, MD; Rebecca Brienza, MD, MPH

**Background:**
In the past year, there has been increasing interest in improving the quality of life (QOL) of patients with end-stage heart failure (HF). However, the lack of physicians who are board certified in palliative care limits how many patients receive their services. One of the major contributions of palliative care specialists is symptom relief, which we posit can be addressed in the primary care setting by providers collaborating with health psychologists. The Center of Excellence (COE) within the West Haven VA Hospital in Connecticut is an interdisciplinary primary care clinic in which health psychologists are available for co-visits during appointments scheduled with medical providers. The goal of this study is to identify patients with end-stage HF within the COE panel and demonstrate the acceptability of co-visits between health psychologists and primary care providers for these patients, to improve their QOL.
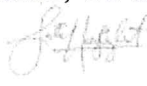
**Methods:**
Patients in the COE will be screened using the Primary Care Almanac tool. From this list, individual patient charts will be reviewed to identify those patients with New York Heart Association (NYHA) Classes III-IV. Demographics of these patients will be reported as the primary outcome. These patients will then be mailed a letter explaining the purpose of the co-visit, followed by a telephone call inviting them to schedule their co-visit. Secondary outcomes will include the proportion of patients screened in for this study who agree to attend a co-visit, with acceptability being defined as at least half of patients agreeing to a co-visit. Additionally, a chi-square comparison test will be performed to compare those patients who did and did not agree to co-visits, with significance defined as p-value of 0.05 or lower.
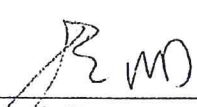
**Results:**
From among the 1,974 patients that comprise the COE clinic, 20 patients were identified with NYHA Stage III-IV heart failure and included in this study. All were male with an average age of 77 and ejection fraction of 46%. Co-morbidities of anxiety, depression, and obstructive sleep apnea were diagnosed by chart review in 25%, 35%, and 40% of patients, respectively. Palliative care specialists actively followed a single patient for reasons unrelated to HF. Further results pertaining to secondary outcomes will be reported at the time of abstract presentation.

**Conclusions:**
Within the COE, few patients with end-stage HF receive palliative care services, suggesting there is a role for focusing on improved QOL in the primary care setting. By piloting co-visits between primary care physicians and health psychologists for patients with end-stage heart failure, we show the acceptability of such an approach that can be used in clinics elsewhere.

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# Research in Residency Summary Abstract

**Title**: Septic Arthritis of Native Joints: Are Outcomes Better with Medical or Surgical Management?

Kaoru Harada, MD and Shaili Gupta, MD

**Background**: Septic arthritis (SA) of native joints has an incidence rate of 4-12 per 100,000 person-years with mortality of 4-13%. Standard of care is antibiotics and early joint drainage, but no guidelines exist for choosing the joint drainage method. Drainage can be performed either medically via serial closed-needle aspiration at the bedside or surgically via arthrotomy or arthroscopy. More data is necessary to formulate guidelines for native joint SA management.
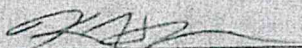
**Aim**: To determine whether there are differences in the outcomes of native joint SA in adults based on medical versus surgical management.

**Hypothesis**: There will be no significant difference in outcome between medical and surgical management groups.
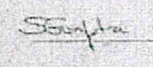
**Methods:** We conducted a 10-year retrospective single-center study at the West Haven, VA of patients admitted between January 1, 2006 and December 31, 2015 with a diagnosis of SA. We excluded cases of SA associated with Lyme disease, gonococcus infection, prosthetic joint infections, and SA with hardware overlying the infected joint because these conditions already have established clinical guidelines. Evaluated outcomes included joint recovery, time to recovery, length of stay, disposition to home versus rehabilitation unit, recurrence of SA in same joint, and mortality. Management-based outcomes were stratified based on organism isolated, joint involved, duration of antibiotics, number of days to OR, and patient demographic criteria; the outcomes were analyzed using simple descriptive statistics. All of the statistical analyses were conducted using SAS version 9.4. Categorical variables are reported as frequency and percentage, and continuous variables are reported as either mean with standard deviation or median with interquartile ranges. For comparison between the management groups, all of the tests were two-sided with a designated significance threshold of $P < 0.05$. For categorical variables, we used the $\chi2$ or Fisher exact test when appropriate to compare the groups. For continuous variables, the Student t test or the Mann-Whitney U test was used.
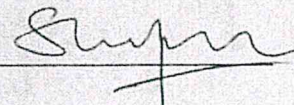
**Results**: There was no statistically significant difference in long-term outcomes between medically and surgically managed native joint infections. Medically managed patients had a statistically higher percentage of joint function recovery within 3 months; there was no difference at 12 months after diagnosis. Medically managed patients had a statistically higher likelihood of disposition to home instead of rehabilitation unit.

**Conclusion:** Medical management with serial aspiration may be an adequate course of therapy for native joint infection. Medical management is likely more cost-effective compared to surgery because less staffing and equipment are needed, and patients have a shorter course of recovery.

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# Primary Cardiac Hospitalizations in Pulmonary Arterial Hypertension: Trends and Outcomes from 2001 to 2014

Eileen Harder, MD; Wassim Fares, MD, MSc

**Background:** Pulmonary arterial hypertension (PAH) is characterized by progressive right ventricular dysfunction, which in turn promotes cardiac disease and mortality. Despite the high frequency of hospitalizations in PAH, data on inpatient outcomes is limited.

**Specific Aim:** 1) To characterize hospitalizations in PAH for primary cardiac diagnoses, 2) to study the temporal trends of these admissions, and 3) to study inpatient mortality of primary cardiac hospitalizations in PAH.

**Hypothesis:** Primary cardiac hospitalizations in PAH will have decreased in frequency from 2001 to 2014 and will be associated with decreased mortality.
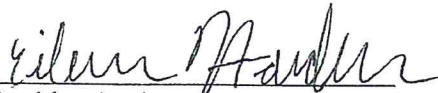
**Methods:** From the 2001 to 2014 National (Nationwide) Inpatient Sample (NIS), all adult hospitalizations with any discharge diagnosis of PAH were identified. Primary cardiac disease was defined as a primary diagnosis of congestive heart failure (CHF), heart valve disorder, acute myocardial infarction, coronary atherosclerosis, pulmonary heart disease, conduction disorder, dysrhythmia, cardiac arrest, and cardiomyopathy or carditis. Analysis was performed with survey procedures in SAS 9.3.

**Results:** From 2001 to 2014, there were 207,095 hospitalizations in PAH, of which 100,509 (48.5%) carried a primary cardiac diagnosis. CHF was the most common primary cardiac diagnosis (19.7% of all PAH admissions). Primary cardiac hospitalizations were associated with fewer comorbidities and a mean shorter length of stay. Over the study period, primary cardiac hospitalizations in PAH fell from 52.9% to 41.4% (from 21,622 to 2,405; p<0.001).

On univariable analysis, the inpatient mortality in primary cardiac hospitalizations was significantly lower than that in primary non-cardiac diagnoses (5.3% vs. 6.9%, p<0.001). In multivariable analysis, a primary cardiac diagnosis remained significantly associated with decreased inpatient death risk (odds ratio 0.85, p=0.010) in PAH.

Notably, primary CHF was associated with the highest number of deaths (1,865); however, the associated mortality rate in primary CHF admission was 4.6%. In contrast, sepsis, the most common primary non-cardiac cause of death (1,226), had a mortality rate of 24.9%.

**Conclusions:** Within a large national database, primary cardiac diagnoses were responsible for almost 50% of the all PAH hospitalizations from 2001 to 2014. Over this period, the rate of these admissions declined significantly, likely reflecting advances in PAH therapy. The overall mortality of primary cardiac PAH hospitalizations was 5.3%. While primary cardiac diagnoses significantly contributed to death in terms of absolute numbers, they were actually associated with a decreased risk of inpatient mortality in PAH. Given the negative long-term impact of admission in PAH, primary cardiac hospitalizations are likely important in portending future decline; however, PAH cohorts with certain primary non-cardiac conditions, such as sepsis, may be at higher risk of death.

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**Title:** Skilled Nursing Facility Use for Patients with Cirrhosis and Impact on Hospital Readmission

**Eric Jordan, MD, Sofia Simona Jakab, MD**

**Background:** Patients with decompensated cirrhosis have a high rate of hospitalization, with 30-day readmission rates reported between 25-50%. While several predictive factors for hospital readmissions in patients with cirrhosis have been studied, data is lacking in regard to use of Skilled Nursing Facility (SNF) in these patients. For similar chronic conditions such as congestive heart failure (CHF), discharge to SNF was necessary in 24% of patients, with higher readmission rate for SNF versus home discharge (27.0% versus 23.5%). Understanding the risk factors for hospital readmission after SNF discharge in patients with cirrhosis can be used to establish strategies to optimize post-discharge care and collaboration with SNF.
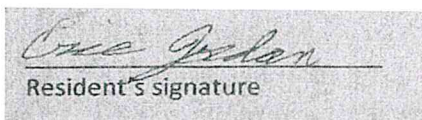
**Specific Aims:** To analyze use of SNF in hospitalized patients with cirrhosis, and explore impact of SNF for 30-day readmissions in these patients.

**Hypothesis:** Discharge to SNF is an independent predictor for 30-day readmission in patients with cirrhosis.

**Methods:** A retrospective observational study was conducted in patients with a primary diagnosis of cirrhosis admitted to a single academic medical center from the time period of 3/26/2015 to 12/31/2017. Data collected included demographics, ICD-10 codes for cirrhosis etiology, complications of cirrhosis, discharge diagnoses and comorbidities, laboratory results, length of stay, medications on discharge, discharge disposition (home or SNF), dates of readmissions. Chi-square calculator was used to compare rates of SNF use, also rates of readmissions after discharge to home vs SNF. Regression analysis was used to identify predictors for discharge to SNF, and predictors for 30-day readmissions.

**Results:** There were a total of 696 individual patients which comprised 1361 encounters. Of these patients, 552 (79%) were discharged home and 98 (14%) were discharged to SNF. The 30-day readmission rate was 11.2% for patients initially discharged to SNF and 19.5% for patients initially discharged home, which was borderline statistically significant (p=0.049). After their index discharge to SNF, 37 patients were readmitted, with 19 patients discharged again to SNF (SNF/SNF), and only 14 discharged home (SNF/H). After their index discharge home, 237 patients were readmitted, with 193 discharged home again (H/H), and only 22 discharged to SNF (H/SNF). Use of SNF on second discharge after a prior SNF discharge was significantly higher than for index discharge (51.3% vs 14%, p=0.00001) or if prior home discharge (51.3% vs 9.2%, p=0.00001). After the second hospital discharge, 63 of 274 patients were readmitted within 30 days, but the 30-day readmission rate was not statistically significant between patients discharged home and patients discharged to SNF (26% vs 22%, p=0.57). Final data analysis on predictors for discharge to SNF and 30-day readmissions is pending.

**Conclusions:** The SNF use for this cohort of patient with cirrhosis was 14% for the index discharge, lower than reported in patients with CHF. After a prior SNF discharge, use of SNF was significantly higher (51.3%). SNF discharge does not seem to impact the 30-day readmission rate, either for index discharge or second discharge. We are exploring the impact of several variables to predict discharge to SNF and 30-day readmissions – final data pending.

_Eric Jordan_

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_Simona Jakab_

Sofia Simona Jakab, MD

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**Effect of Institutional Trans-catheter Aortic Valve Replacement (TAVR) Volume on Patient Outcomes- a Systematic review and Meta-analysis**

Devika Kir MD, Nihar R. Desai MD, MPH

**Background and Aim:** TAVR was introduced to treat patients with severe aortic stenosis and high surgical risk and given the excellent results from TAVR, there has been an exponential increase in the number of TAVR centers since its introduction in 2011. Multiple studies have been conducted to evaluate if there is any relationship between institutional TAVR volume and patient outcomes. We aim to systematically review all available literature on TAVR institutional volume and patient outcomes and then perform a meta-analysis to assess if there is any relationship between institutional volume and patient outcomes, mainly all-cause mortality.
**Hypothesis:** We hypothesized that patient outcomes would improve with increase in annual TAVR volumes at TAVR centers.
**Methods:** We performed a systematic literature search for relevant articles in Ovid Medline ®All, Ovid Embase, the Cochrane Library, Google Scholar, PubMed, and Web of Science. Databases were searched using a combination of controlled vocabulary and free text terms in the title/abstract related to *volume (volume, number, experience)*, *TAVR (trans-catheter, percutaneous, trans-apical, trans-arterial, trans-femoral)* and *patient outcomes (treatment outcome, complications, survival, mortality)*. Two reviewers independently screened all titles/abstracts for eligibility based on pre-specified inclusion and exclusion criteria. Data was extracted from the eligible studies using a standardized format. We pooled the all-cause mortality data from all the eligible studies and centers were categorized as low, intermediate and high volume based on their annual TAVR volumes. We performed a network meta-analysis with random effect models, each analysis was based on vague priors for effect sizes.
**Results:** Our systematic search yielded an initial list of 9,515 citations. From the 9515 abstracts, 117 studies were selected for full text review after the initial screening. After careful review of these full text-articles, only 6 studies met all inclusion and exclusion criteria and these studies yielded a total of 97,242 patients undergoing TAVR across the world, categorized according to the center's annual TAVR volume; 18,235 TAVRs were categorized as performed in low volume centers, 40,541 in intermediate volume centers and 38,466 in high volume centers. Network meta-analysis revealed an inverse relationship between hospital TAVR volume and all-cause mortality; high volume group ranking one (SUCRA 99.98%) followed by intermediate volume group (SUCRA 49.93%) and low volume group ranking last (SUCRA 0.08%).
**Conclusions:** Meta-analysis of existing research clearly shows an inverse relationship between annual procedural volume and all-cause mortality for TAVR. Raising the volume threshold for establishing and maintaining a TAVR center would likely improve outcomes, lower costs, and promote value. However, there are real concerns regarding the impact of raising the procedural volume threshold on access to TAVR for rural and disadvantaged populations. We need more research on access-to-care and outcome disparities in TAVR to better understand the impact of more stringent procedural volume thresholds.

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**Title:** Early detection of DLBCL in HIV by measurement of circulating tumor DNA using an optimized targeted oncogene panel. Gillian Kupakuwana-Suk, M.D. and Brinda Emu, M.D.

**Background:** Circulating tumor DNA (ctDNA) is derived from apoptotic and necrotic tumor cells shed into circulation. The utility of ctDNA detection continues to expand since the advent of massive parallel sequencing that led to the success of whole exome sequencing of circulating cell-free DNA, and has been used to identify minimal residual disease, assess treatment response, and identify druggable targets. Early detection efforts, however, have been slowed by detection limit of circulating DNA molecules in pre-cancer samples, as well as optimization to ensure minimization of potential allelic bias in the capture process as well as polymerase and sequencing errors. Here, we describe an effort using ctDNA technology for early detection of DLBCL using a unique cohort of longitudinally archived pre-cancer patient samples.

**Specific Aim:** Use cryopreserved plasma to measure ctDNA both at the time of and prior to clinical cancer diagnosis (DLBCL) to evaluate its potential use in early detection of DLBCL.

**Hypothesis:** Individuals who get diagnosed with DLBCL in the setting of HIV will have evidence of circulating tumor-derived DNA prior to clinical diagnosis of cancer.

**Methods:** _Study cohort and samples:_ The U.S. Military HIV Natural History Study (NHS) is a longitudinal, prospective multicenter observational study cohort with >5,000 participants with archived PBMC, plasma, and serum. Query identified 101 plasma samples from 47 patients, at timepoints 12 months prior, 6 months prior, and peri-cancer diagnosis. Cases included DLBCL diagnosed after diagnosis of HIV and controls include HIV+ individuals with no cancer diagnosis. _Capture Library Design:_ We identified 197 DLBCL hotspot driver mutations by whole-exome tumor sequence data analysis of 37 tumors from the TCGA, 41 tumors from the Yale-Gilead collaboration and 39 additional tumors with publicly available data. 200 individual 120-base biotinylated capture probes were synthesized (Yale Oligo-synthesis Keck facility) covering hotspot mutations identified across all 82 oncogenes, and combined to generate the capture library. _ctDNA extraction:_ Plasma samples were thawed and ctDNA was purified using a QIAamp Circulating Nucleic Acid Kit (Qiagen). Quantity of DNA was verified using qPCR, and extracted DNA was stored at −20°C until use. _ctDNA prep and targeted capture:_ Extracted ctDNA had unique molecular tags ligated to flank each sequence and subsequently PCR amplified. Following ligation and amplification, the tagged ctDNA amplicons were purified using a AmPure XP magnetic beads (Beckman Coulter) and subsequently incubated with the biotinylated targeted hotspot oncogene panel for capture. Bound ctDNA sequences were recovered via magnetic streptavidin beads and prepared as previously described for Illumina sequencing. Sequencing was done at the Yale Center for Genomic Analysis on the Illumina HiSeq 2500 platform. _Sequencing and data analysis:_ The sequencing data was processed using duplex sequencing bioinformatic pipeline. Using the unique molecular tag ligated during the library preparation, each dsDNA molecule was reconstructed, with annotation of any variation from the human genome.

**Results:** Sequencing data has not allowed for determination of conclusive variant calls on targeted hotspot regions, which may be due to the nature of early-stage samples where tumor burden and tumor allele fraction may be low (<1%) requiring increased efficiency of capture and greater sampling of the pool of ctDNA. Efforts are ongoing to optimize library preparation, and increase ligation efficiency.

**Conclusions:** This work represents a unique dataset to apply ct-DNA technology to probe for the presence of hotspot mutations associated with DLBCL in patients prior to cancer diagnosis. The systematic synthesis of the most abundant driver mutations using available sequencing data represents the most comprehensive approach to probe rare events in this disease to date.

_Gillian Kupakuwana-Suk_

# DIFFERENTIAL EXPRESSION AND FUNCTIONAL PROFILE OF IMMUNE MARKERS IN LUNG CANCER-ASSOCIATED BRAIN METASTASES

**Trainee:** Benjamin Y. Lu, MD
**Mentor:** Sarah B. Goldberg, MD, MPH

**Background:** Lung cancer brain metastases (BrM) are associated with significant morbidity and mortality. Immune checkpoint inhibitors (ICIs) have emerged as safe and clinically active therapeutic agents in lung cancer BrM; however, they are only effective in a subset of patients. While programmed death-ligand 1 (PD-L1) expression in extracranial sites has been associated with increased tumor infiltrating lymphocytes (TILs) and sensitivity to ICIs targeting the PD-1/PD-L1 axis in extracranial tumors, the immune composition and functional characteristics of adaptive immune markers in BrM remain poorly characterized.

**Specific Aim:** To evaluate the differential expression and prognostic value of PD-L1 and major T-cell subsets among primary tumors, BrM, and extracranial metastases (ECM) from lung cancers.

**Hypothesis:** BrM will overall demonstrate lower PD-L1 and adaptive immune markers relative to extracranial sites.
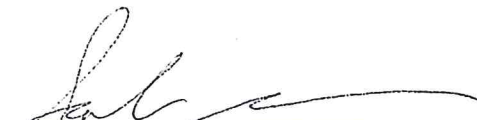
**Methods:** A tissue microarray was constructed from formalin-fixed, paraffin-embedded tumor samples of 94 lung cancer patients treated at Yale Cancer Center between 2002-2013. Multiplexed QIF was used to evaluate the cases with a panel containing phenotype markers for PD-L1, major T-cell subsets (CD3, CD4, CD8 and FOXP3), cell-localized activation and proliferation (granzyme-B and Ki-67), and T-cell exhaustion markers (TIM3, LAG3, PD1). Signal for each marker was measured in marker-selected tissue compartments using the Automated Quantitative Analysis (AQUA) platform. Associations between markers and major clinicopathologic variables were studied.

**Results:** In total, 40 primary lung tumors, 63 BrM, and 15 ECM were analyzed, including paired samples from 22 patients. Lung cancer histology included adenocarcinoma 62.5%, squamous cell carcinoma 11.5%, small cell 9.4%, and other non-small cell 16.7%. There were no significant differences between PD-L1 expression across tissues despite lower levels of CD3+ T-cells ($p<0.0001$), CD4+ T-cells ($p=0.0416$), CD8+ T-cells ($p=0.0003$), T-cell granzyme B ($p=0.0188$), and CD20+ B-lymphocytes ($p=0.0058$) in BrM compared to primary lesions. No significant differences were observed in T-cell Ki-67 levels across tissues. FOXP3 measured in CD4+ T-cells were significantly lower in BrM compared with primary malignancies ($p=0.0002$) and ECM ($p=0.0404$). TIM3, LAG3, and PD1 measured in CD3 were all lower in BrM compared with primary cancers ($p=0.0166$; $p=0.0039$; $p=0.0042$). Among patients with BrM, higher levels of CD3+ T-cells in BrM were associated with longer overall survival.

**Conclusions:** Despite lower T-cell infiltration, cytolytic function, regulatory T-cells, and exhausted T-cells in BrM compared with primary lesions, PD-L1 expression remained comparable across tissues. These results indicate differences in the adaptive immune modulation of PD-L1, lower adaptive anti-tumor responses, and the presence of a tolerogenic microenvironment in the brain. Overcoming this could be used to design optimal treatment strategies.

Resident's signature

Mentor's signature

**Examining How Individuals Understand Uncertainty in the Healthcare Setting**
Veronica Azmy, M.D., Liana Fraenkel, M.D., M.P.H.

**Background:** Shared decision-making relies on the premise that individuals are well-informed regarding the benefits and harms of all available treatment options before coming to a decision regarding their healthcare. There is often significant aleatory and epistemic uncertainty associated with proposed risks and benefits, but prior studies have demonstrated that uncertainty is rarely communicated in provider-patient interactions. Additionally, there has been conflicting evidence regarding the use of visual aids as a method to improve understanding of uncertainty. In the healthcare setting, patients are often confronted with the uncertainty of medication risks and benefits, but little has been done to analyze how individuals think about these uncertainties.

**Specific Aim:** To better understand how individuals conceptualize uncertainty as it pertains to the risks and benefits of medications so that we may ultimately improve shared decision-making.

**Hypothesis:** We hypothesize that there are several different sources of uncertainty that may influence individuals' decisions in the healthcare setting and that these sources may be elucidated in order to better communicate with the individual. We also hypothesize that the way uncertainty is communicated, including using verbal or visual modalities, will influence an individual's perception or understanding of the uncertainty involved.

**Methods:** We conducted a qualitative, think-aloud study using a semi-structured interview guide. Participants were recruited from the inpatient wards of Yale-New Haven Hospital. Inclusion criteria included English-speaking adult inpatients who were not mentally altered through the use of sedating medications or by their illness and able to answer questions out loud. The participants were presented with two hypothetical medications. The first scenario involved a medication with a 20% risk of adverse effect and the second involved a medication with a 20% chance of benefit. Using block randomization, participants were randomized to receiving either the risk scenario or benefit scenario first. They were also randomized to receiving either no additional information, an icon array, or a spinner. We conducted individual in-depth interviews following a semi-structured interview guide. Transcripts were analyzed separately by both authors using the constant comparative method of grounded theory, first outlined by Glaser & Strauss (1967). Data analysis included three phases: open coding, axial coding, and selective coding (Strauss & Corbin, 2008). Coding ended with thematic saturation, or when both authors were unable to identify additional core themes within the data.

**Results:** We reached thematic saturation after interviewing twenty patients. The participants' mean (SD) age was 64.6 (18); 60% male, 84% were non-Hispanic Whites, 10% Blacks, and 60% had a college education or higher. Participants were recruited from both medical and surgical medical units. Several themes regarding difficulties understanding uncertainty of risks and benefits emerged: 1) rejection of uncertainty, 2) failure to distinguish between aleatory and epistemic uncertainty, 3) difficulty distinguishing between different magnitudes of probabilities, and 4) reduction of uncertainty by manipulation of the scenario in order to eliminate choices. The utility of visual aids did not appear to facilitate understanding of uncertainty in most cases.

**Conclusions:** Individuals interpret uncertainty surrounding medication risks and benefits in several different ways. There is reason to believe that visual aids are less useful for those at the extremes of high and low numeracy, and that there may be a group of individuals of moderate numeracy for whom visual aids may be helpful. Given the great discrepancy among individuals in the understanding of probabilities and the uncertainty surrounding risks and benefits, providers should use features such as "talk-back" to ensure reasonable understanding during shared decision-making encounters. Further research is needed to identity potential successful ways of communicating different types of uncertainties in the healthcare setting.

Resident's Signature: _[signature]_     Mentor's Signature: _[signature]_

**Title:** Comparison of Patients with High-grade Hepatotoxicity from Checkpoint Inhibitors

**Resident:** Nilofar Najafian   **Mentor:** David Assis

**Background**: Checkpoint inhibitors (CPI) have revolutionized the field of oncology by utilizing the host immune system to combat tumors. Blockage of inhibitory signals enables unrestrained cytotoxic T-cells to exert anti-tumor activity; however, notable immune related toxicities have been observed. Although CPI-related hepatotoxicity has been described in the literature, there is limited data exploring risk factors in patients with high grade hepatotoxicity (grade ≥3). In addition, the utility of the standard scoring system (Roussel Uclaf Causality Assessment Method, RUCAM) used to assign the likelihood of causality for drug induced liver injury (DILI) has not been examined in this population.
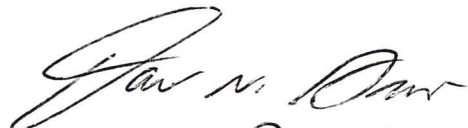
**Hypothesis & Aim:** We hypothesize that patients with RUCAM scores >8 (indicating highly probable DILI) will exhibit more extra-hepatic immune related adverse events (IRAE), a higher ALT serum level, and more CTLA-4 inhibitor use compared to patients with RUCAM scores <8. Our aim was to stratify patients with CPI-induced hepatotoxicity grade ≥3 according to RUCAM scores, describing clinically relevant risk factors, markers of disease, and outcomes.

**Methods:** A retrospective chart review was conducted examining 1,838 patients treated with CPIs between February 2013 and May 2018. Cases of grade ≥3 hepatotoxicity (ALT >5x baseline) were analyzed. Patients were excluded if they were <18 years old, had hemodynamic shock at the time of ALT elevation, or unclear documentation of CPIs used. Patient demographics, clinical data, comorbidity, IRAE, checkpoint inhibitor use, and outcomes including use of immunosuppressive medications and death were assessed. The RUCAM was used to calculate a drug causality score for each case. RUCAM scores were defined as: >8 highly probable, 6-8 probable, 3-5 possible, 1-2 unlikely, and ≤ 0 excluded. Group comparisons were made between patients with RUCAM >8, RUCAM 6-8, RUCAM <6.

**Results**: A total of 291 patients had grade ≥3 hepatotoxicity; median age was 63 (24-91) years, 155 (53%) were male, and 249 (85%) were Caucasian. This represented 15.8% of patients exposed to CPIs. Drug causality was assigned with RUCAM scores >8 in 36 patients (12%), 6-8 in 108 (37%), and <6 in 147 (51%). Patients with RUCAM >8 compared to those with RUCAM <6 had a higher frequency of combination treatment with CTLA-4 and PD-1 inhibitors (58% vs 21%, p <0.0001), had more IRAE (83% vs 53%, p = 0.001), were more likely to receive corticosteroids (82% vs 53.7%, p=0.004), and had a higher rise in ALT with median of 12x (range 5-156x) vs 8x (range 5-70x) baseline, p = 0.005. Furthermore, preliminary analysis suggests a lower risk of death in patients with RUCAM >8 compared to those with RUCAM <6 (38% vs. 75%). There were no significant differences between the group with RUCAM > 8 (highly probable) vs 6-8 (probable DILI). Among patients with pre-existing autoimmune disease 5 (19%) had flares of their underlying disease and 20 (77%) experienced IRAE. Of 186 patients who received corticosteroids, 124 (67%) had no evaluation with diagnostic liver imaging, 147 (79%) did not receive viral hepatitis screening, and 104 patients (56%) were missing both.

**Conclusion**: Among patients receiving CPIs who developed grade ≥3 hepatotoxicity, those with a high probability of DILI (RUCAM >8) had more IRAE, were more likely to receive corticosteroids, and had a higher degree of ALT elevation compared to patients with lower RUCAM scores (<6). Despite this, fewer patients with RUCAM >8 died compared to those patients with lower RUCAM scores. Many patients with elevated ALT were not screened for hepatitis nor received diagnostic imaging. The RUCAM scoring system for DILI assessment may have a role in the care of patients with grade ≥3 hepatotoxicity to guide management and is potentially informative as a prognostic marker.

Nilofar Najafian 3/12/19

David N. Assis 3/12/19

**The Role of Biopsy to Assess for Primary Biliary Cholangitis in Anti-Mitochondrial Antibody Positive Patients with Normal Alkaline Phosphatase Levels**

Phillip Nickerson, MD                                    Marina Silveira, MD

**Background:** Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease. Early identification of those affected is important because early treatment with ursodeoxycholic acid (UDCA) has been shown to improve liver biochemistries and survival, and patients with early histologic stage respond best to UDCA treatment. A previous study showed that in patients with positive AMA serology and serum alkaline phosphatase level (AP) >1.5 times the upper limit of normal liver biopsy is not necessary due to the high positive predictive value of those features.  Hence, current guidelines recommend the diagnosis of PBC when at least 2 of the following three criteria are positive: 1. Positive AMA serology, 2. AP >1.5 times the upper limit of normal, and/or 3. Histologic evidence of PBC on liver biopsy. Additionally, some have proposed that patients with positive AMA but normal serum alkaline phosphatase may not need biopsy to effectively "rule out" PBC but there is not high quality data to validate this.
**Specific Aim:** To clarify the role of liver biopsy to rule out PBC in patients with positive AMA but normal serum AP level by developing a negative predictive value for this set of characteristics
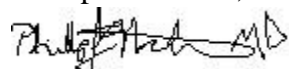**Hypothesis:** Patients with positive laboratory testing for anti-mitochondrial antibody but with alkaline phosphatase within normal limits have a low incidence of findings consistent with primary biliary cholangitis on biopsy and therefore liver biopsy is not necessary in these patients.
**Methods:** This was a single center, retrospective chart review study.  We submitted a JDAT request for records for all patients with positive AMA serology in the EPIC EMR (2012-2018) at Yale-New Haven Hospital and Yale School of Medicine affiliated outpatient clinics.  A total of 186 patients were identified.  94 patients had biopsies on file.  The serum AP level most recently preceding the date of biopsy was used for purposes of further classification, with a total of 30 patients having AP within normal limits as defined by the laboratory. The biopsy results for these patients were closely reviewed for any histologic evidence of PBC.
**Results:**  Of the patients with positive anti-mitochondrial antibody serology and normal alkaline phosphatase serum levels, 8/30 (26.7%) had histologic evidence of primary biliary cholangitis on liver biopsy. 22/30 (73.3%) did not have histologic evidence of primary biliary cholangitis.  Interestingly, in the subcategory of 10 male patients, 9/10 had biopsies negative for PBC. In female patients, meanwhile, 13/20 (65.0%) had biopsies negative for PBC.
**Conclusions:** In our study population a fairly significant proportion of patients (26.7%) with positive AMA serology but serum alkaline phosphatase levels within normal limits had histologic evidence of PBC on biopsy, meaning they met diagnostic criteria for PBC and might benefit from initiation of treatment with UDCA.  There may be patient characteristics (for example sex, as indicated in our sample) which could help guide clinical decision-making.  Overall, these findings indicate that biopsy may still be important in this population to determine who would benefit from closer monitoring and earlier treatment.  More data (particularly from larger cohorts) is needed to better understand this issue.

Phillip Nickerson, MD                                    Marina Silveira, MD

**Duodenal Bulb Biopsy for Diagnosis of Celiac Disease**

Corey O'Brien, MD, Thomas R. McCarty, MD, Tarun Rustagi, MD

**Background:** Although duodenal biopsy is considered the gold standard for diagnosis of celiac disease, location of biopsy within the small bowel for accurate diagnosis remains unclear. When compared to distal duodenal biopsies, duodenal bulb biopsies may increase the diagnostic yield, however studies to date have shown varied results.

**Specific Aim:** To evaluate the diagnostic utility of endoscopic duodenal bulb biopsy for celiac disease via structured systematic review and meta-analysis.

**Hypothesis:** Duodenal bulb biopsy will have increased diagnostic yield compared to distal duodenal biopsy for the diagnosis of celiac disease.

**Methods:** A comprehensive and systematic search of PubMed, EMBASE, Web of Science and Cochrane Library data through December 2017 was performed. A full review of potentially relevant studies with data abstraction was performed. Outcomes of adult and pediatric patients were measured, included location of biopsy, mean number of biopsies performed, and diagnosis of celiac disease as defined by the modified Marsh-Oberhuber classification. The meta-analysis was performed by calculating pooled proportions. After appropriate studies were identified through systematic review the individual study proportion was transformed into a quantity using the Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion was calculated as the back transform of the weighted mean of the transformed proportions using inverse arcsine variance weights for the fixed effects model and DerSimonian-Laird weights for the random effects model.

**Results:** A total of 17 studies (n 4050) were included. Seven studies evaluated adults and eleven studies assessed pediatric populations. Mean age of adult and pediatric patients was 46.70+/-3.69 and 6.33+/-1.26 years respectively. The diagnosis of celiac disease was histologically confirmed in 97% (95% CI: 91 to 100; $p<0.001$) of biopsy samples obtained from the duodenal bulb. From the distal duodenum histologic confirmation of celiac disease was reported in 89% (95% CI: 81 to 94; $p<0.001$) of biopsy samples. Sampling from the duodenal bulb demonstrated a 5% (95% CI: 3 to 9; $p<0.001$) increase in the diagnostic yield of celiac disease. When stratified by pediatric and adult populations duodenal bulb biopsy demonstrated a 4% (95% CI: 1 to 9; $p<0.001$) and 8% (95% CI: 6 to 10; $p<0.001$) increase in the diagnostic yield of celiac disease. Non-celiac Brunner gland hyperplasia was more common in the duodenal bulb as compared to the distal duodenum with an increase in diagnostic yield of 4% (95% CI: 3 to 5; $p<0.001$).

**Conclusions:** Our results indicate that biopsy and histologic examination of the duodenal bulb during routine upper endoscopy increases the diagnostic yield of celiac disease. Sampling of the duodenal bulb in addition to the distal duodenum is recommended to improve the histologic diagnosis of celiac disease.

**Corey R. O'Brien**
Resident's signature

Mentor's signature

**Macrophage Migration Inhibitory Factor Expression in Disseminated Coccidioidomycosis**

Camila Odio, MD, L. Leng, PhD, E. Siu, MS, Marta Piecychna and Richard Bucala, MD, PhD

**Background:** While inhalation of *Coccidioides* spores usually produces little illness, 25 – 30% of infections result in self-limited pneumonia, and <1% of cases are complicated by dissemination. The determinants of *Coccidioides* control are unclear, but dissemination rates of 30-50% in immunocompromised individuals emphasize the importance of host factors. Genetic polymorphisms may account for some of the variability in infection severity. Macrophage migration inhibitory factor (*MIF*) is an inflammatory cytokine, and two common promoter polymorphisms are linked to variability in *MIF* expression. High expression *MIF* polymorphisms have been associated with granulomatosis with polyangitis (GPA) and with tuberculosis. Despite the overlap between *MIF* and *Coccidioides* immunity, *MIF* has never been studied in coccidioidomycosis.

**Specific Aims:** (1) To test whether *Coccidioides* spherules stimulate *MIF* transcription. (2) To compare the frequency of high expression *MIF* alleles (-173C and -794 $CATT_7$ containing genotypes) in patients with disseminated coccidioidomycosis versus healthy controls. (3) To measure plasma MIF levels in patients with disseminated coccidioidomycosis

**Hypotheses:** Cell stimulation with *Coccidioides* spherules will increase *MIF* transcription. Patients with disseminated coccidioidomycosis will have enrichment of the high expression *MIF* alleles and elevated *MIF* plasma levels compared to healthy controls.

**Methods:** A549 human pulmonary epithelial cells transfected with *MIF* promoter/luciferase plasmids of 0 or 8 CATT repeats were stimulated with 50 µg/mL of inactivated *Coccidioides posadasii* spherule lysate for 24 hours, and luciferase expression was measured as relative units (RU) of luminescence. Steven Holland, MD (NIH) provided 48 DNA and serum samples from patients with disseminated coccidioidomycosis. Genomic DNA was analyzed for two *MIF* promoter polymorphisms: -794 $CATT_{5-8}$ microsatellite and -173 G/C SNP. Because *MIF* alleles are stratified by race, cohorts were divided into self-identified African-Americans and Caucasians. All other races were excluded due to small sample size. Allele frequencies were compared using Fisher's exact test. Plasma MIF levels were analyzed by enzyme-linked immunosorbant assay using specific antibodies. Differences in plasma MIF levels were compared by T-test.

**Results:** Human lung epithelial cells exposed to *Coccidioides* spherules had significantly higher *MIF* expression than unexposed cells (3.02 ± 0.24 vs. 3.94 ± 0.44 RU, $p = 0.0162$). Among Caucasians (n = 26), the high *MIF* expression -173C containing genotype was present in 50% of the coccidioidomycosis patients vs. 40% of healthy controls ($p = 0.396$). The -794 $CATT_7$ containing genotype was present in 40% of patients vs. 27% of controls ($p = 0.240$). In African Americans (n = 11), 70% of cases had the -173C containing genotype vs. 64% of controls ($p > 0.999$) and 0% of cases had the -794 $CATT_7$ containing genotype vs. 20% of controls ($p = 0.222$). Plasma MIF levels were higher in coccidoidomycosis patients with high- versus low-expression alleles ($p = 0.008$), but lower in patients vs. controls ($p < 0.0001$).

**Conclusions:** *Coccidioides* spherules stimulated *MIF* expression in human lung epithelial cells supporting the hypothesis that *MIF* is involved in immunity against this pathogen. Among Caucasian subjects, the higher *MIF* expression genotypes appeared more commonly in patients with disseminated coccidioidomycosis as compared to healthy controls, although significance was limited by sample size. This is consistent with high expression *MIF* alleles associated with other granulomatous diseases. Plasma MIF levels were higher in patients with high- versus low-expression alleles, and lower in patients versus controls.

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Resident's Signature

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Mentor's Signature

Patients Receiving Multiple Types of Intravenous Fluids (IVFs) During Treatment (Tx) of Colonic Ischemia (CI) Have More Severe Disease, Higher Rates of Antimicrobial Usage and Worse Outcomes

O'Donnell M, Bhutta AQ, Brandt LJ, Aroniadis O, Mansoor MS, Fenster M, Silverman M, Feuerstadt P

**Introduction:** CI is frequently Tx with IVFs. Little is known about IVF Tx patterns and their respective outcomes. We hypothesized that pts Txd with Normal Saline (NS) were more likely to have better outcomes than those receiving other IVFs and those receiving multiple types of IVFs (mIVFs) during Tx are at risk for even worse outcomes.

**Methods:** A retrospective multi-center cohort study of consecutive pts admitted to Montefiore Medical Center and Yale-New Haven Hospital between 1/05 and 12/16 with bx-proven CI. Clinical factors and outcomes for those Txd with NS were compared with those receiving only one other type of IVF (Dextrose 5[D5], ½Normal Saline[NS], D5NS, Lactated Ringer[LR] and Dextrose[D]). We performed a sub-group analysis comparing pts receiving NS with those receiving mIVFs. Pts who received 2 or more types of IVF (2+IVF) were compared with those that received only 2 IVF (2IVF). Data were analyzed (SPSS 25.0).

**Results:** Of 829 pts with bx-proven CI, 585 had documentation of their IVF. There were no accessible records for those excluded. Of those receiving only 1 IVF (n=448), the majority received NS (65.0%); D5½NS (22.1%), D5 NS (7.6%), LR (3.3%) and D (2.0%) were also given; 137 pts received mIVFs. When comparing pts given a single IVF, there were no differences in Charlson co-morbidity scores, but ACG guideline risk score ($4.94 \pm 4.27$, $3.68 \pm 2.75$, $p<0.05$) and initial IVF rate ($p<0.01$) were higher in NS compared with D5NS. Long-term recurrence was lower in NS compared with D5½ NS ($p<0.01$). For those receiving a single IVF, there were no other differences in outcome. When comparing NS with mIVFs, ACG guideline risk score was higher in mIVFs ($3.68 \pm 2.75$, $6.98 \pm 5.78$, $p<0.001$). There were no differences in water deficit, rate of initial IVF, or peak IVF rate at 72 hrs, however, mIVFs had a higher rate of concomitant antimicrobial usage ($p<0.001$), 30-day colectomy (6.9%, 19.7%, $p<0.001$) and a trend for higher mortality (3.5%, 7.3%, $p =0.08$) compared with NS. When comparing 2+IVF with 2IVF, 2+IVF were associated with higher 30-day colectomy (57.9%, 14.1%, $p<0.001$) and 30-day mortality (26.3%, 4.7%, $p<0.001$).

**Conclusion:** There is no widely accepted IVF to Tx CI and this was reflected in our Tx patterns. NS is most common, but does not seem to be associated with better outcomes. Further study is needed to identify optimal IVF under various clinical circumstances. Pts requiring mIVFs should be treated more aggressively with consideration for earlier vascular or surgical intervention.

**Enhanced EHR Ambulatory Training for Internal Medicine Interns**

Shawn Y. Ong, MD; Julie R. Rosenbaum, MD

**Background**: Recent research shows that physicians spend significant time with electronic health records (EHR). Successful management of patient care demands proficiency in a clinic's EHR system, which requires a unique workflow and skillset separate from inpatient processes. Incoming interns receive basic or unorganized training in how to efficiently perform ambulatory tasks. Prior studies have evaluated pilot training programs during intern orientation and demonstrated positive results.

**Specific Aim**: To standardize clinic workflow processes and assess the impact of an EHR ambulatory training course on intern preparedness and confidence.

**Hypothesis**: A resident-led course teaching incoming interns how to effectively utilize EHR outpatient functionality will be a valuable experience and increase participants' confidence with ambulatory workflow processes.

**Methods**: Internal Medicine (IM) interns from the Yale Primary Care (YPC) and Traditional (YIM) programs at the end of the 2016-2017 academic year were found to have no significant difference in confidence levels of eight ambulatory workflow processes. Therefore, incoming IM interns from both programs for the 2017-2018 year were deemed acceptable for comparison, with YPC interns in the intervention group and YIM interns as controls. YPC interns took a four-hour EHR training course led by two residents and one faculty member covering 18 topics related to Epic EHR use in the ambulatory setting. Course participants took an eight-question confidence survey with ratings from 0 (no confidence) to 10 (full confidence) immediately before and after the course. They also completed a five-question survey rating the course itself. YPC interns repeated the confidence survey at six and 12 months into intern year. YIM interns received standard hospital-provided EHR training and took the same confidence survey at one, six, and 12 months. We used the Student's t-test for analysis between the control and intervention groups.

**Results**: In the intervention group, all 15 course participants agreed that they learned useful information and their confidence increased in navigating clinic workflow processes. A large majority (93%, 14/15) agreed that the course will allow them to provide better care for their patients and agreed that the course content was best delivered by physicians. Most (80%, 12/15) agreed that the course should be a required part of internship. Respondents ranked their confidence in using the EHR to perform outpatient tasks as follows with YPC intern ratings listed first and YIM interns second: patient preparation (7.93 post-course, 7.75 at six months, 8.22 at 12 months versus 6.44, 8.09, 8.60), keep within visit time (6.43, 6.50, 7.22 versus 5.41, 6.36, 7.00), electronically prescribe medications (7.57, 6.92, 8.22 versus 5.59, 7.00, 7.60), enter lab orders (7.64, 7.92, 8.56 versus 6.11, 6.82, 7.80), order referrals (7.43, 6.17, 7.56 versus 4.41, 5.82, 7.40), document clinic procedures (6.57, 5.08, 7.44 versus 4.11, 5.55, 6.60), compile data for paper forms (7.21, 7.08, 7.67 versus 5.63, 6.91, 7.60), and manage the electronic inbox (7.57, 8.08, 8.44 versus 5.89, 7.55, 8.60). All p-values $<0.05$ at one month and all p-values $>0.05$ at six and 12 months.

**Conclusions**: A four-hour resident-led EHR ambulatory training course was highly rated and significantly elevated incoming intern confidence levels. Gains were realized for the first six months of intern year. Additional studies with residents from other specialties can help determine if this effect is generalizable.

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# Circulating Mitochondrial DNA is Associated with Acute Exacerbations of Cystic Fibrosis
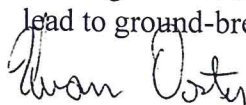
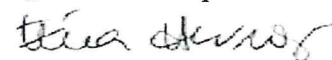Vivian Ortiz, Changwan Ryu, Clemente Britto, Jonathan Koff, Erica L. Herzog

**RATIONALE:** Cystic fibrosis (CF) is an autosomal recessive disease related to mutations in the cystic fibrosis transmembrane conductance regulator gene. Despite similarities in disease genotype, significant phenotypic variability results in a broad range of clinical severity, including frequent hospitalizations from acute CF exacerbations. Biomarkers identifying those at risk for CF exacerbations remain elusive. Extracellular mitochondrial DNA (mtDNA), which is released by pulmonary epithelial cells in response to various stressors has emerged as a biomarker in multiple diseases; however, its relevance to CF has yet to be determined. Through our state-of-the-art translational platform, we assayed for the presence of extracellular mtDNA in mouse and human samples to test the *hypothesis that elevated concentrations of extracellular mtDNA are associated with CF exacerbations and provide insight into clinically relevant outcomes.*

**METHODS:** Supernatant from mouse tracheal epithelial cells (MTEC) were harvested from $\Delta$DF508 homozygous and heterozygous mice as well as wild-type (WT) mice that were exposed to normal saline (NS) or pseudomonas derived lipopolysaccharide (PSA-LPS) for 6 hours. Extracellular mtDNA concentrations were measured using qPCR for the murine COX1 gene. For human studies, mtDNA concentrations were measured using qPCR for the human MT-ATP6 gene on 29 sputum samples and 33 plasma samples from CF subjects and from demographically matched sputum (n=7) and plasma (n=25) samples. Subjects were followed for 55 months for a hospitalization related to a CF exacerbation.

**RESULTS:** MTEC supernatant from $\Delta$DF508 homozygous mice have higher concentrations of mtDNA when compared to MTEC supernatant from WT mice (p<0.0001). MTEC supernatant from $\Delta$DF508 homozygous mice exposed to PSA-LPS showed higher mtDNA copy numbers than that of WT supernatant (p=0.001). MTEC supernatant from $\Delta$DF508 homozygous exposed to PSA-LPS lead to higher extracellular mtDNA release than those exposed to NS (p=0.034). Relative to sputum from healthy controls, sputum obtained from CF subjects exhibited elevated mtDNA concentrations (p=0.007). Sputum samples between stable and exacerbated subjects did not reveal any significant changes in mtDNA concentrations. When examining the plasma, compared to healthy controls, CF plasma was enriched in mtDNA copy numbers (p=0.007), particularly in the plasma of subjects with $\Delta$F508 homozygous mutations (p=0.025). When those with stable disease were compared to those with an acute exacerbation, plasma mtDNA concentrations were profoundly elevated (p=0.009). Receiver Operator Curve and Kaplan-Meier analyses revealed that a plasma mtDNA copy number > 4.35 log10 copies/$\mu$l was predictive of a hospitalization related to a CF exacerbation (HR: 5.89, 95% CI: 2.05 to 16.95, p=0.04).

**CONCLUSIONS:** We found that elevated concentrations of extracellular mtDNA are present in the MTEC supernatant, particularly those derived from $\Delta$F508 homozygous mutations, suggesting a strong genotypic contribution towards the pathogenic release of mtDNA. In a clinical translation of these findings, we found that mtDNA concentrations are increased in the lungs and blood of CF subjects. The latter compartment was robustly predictive of a CF-related hospitalization. Further understanding of the CF airway epithelium are needed to characterize the contribution of the genotypic versus inflammatory mediators of mtDNA release. Our findings demonstrate an unrecognized connection between extracellular mtDNA and clinical outcomes in CF that could lead to ground-breaking pathophysiologic insights and therapeutic avenues.

Vivian Ortiz, MD

Erica Herzog, MD, PhD

# Population-Based Standing Orders: A Novel Approach to Hepatitis C Screening

Jesse O'Shea MD, MSc, I-Hsin Lin PhD, MPH, Bradley Richards, MD, MBA

**Background:** An estimated 4 million people in the United States have been infected with Hepatitis C Virus (HCV). Up to 75% of patients infected are born between 1945-1965, many unaware of their infection. Therefore, the CDC and USPSTF recommends a universal one-time HCV screening for this birth cohort. Despite previous attempts to increase screening such as electronic health record alerts, screening rates remain low. Meanwhile, the US is migrating from fee-for-service reimbursement models to payments linked to value, which means payment based on quality data such as HCV screening.

**Specific Aim:** To investigate the feasibility of population-based standing orders and its impact on HCV screening and linkage to care, without risking increased provider workload.

**Hypothesis:** Implementing a novel initiative of population-based bulk standing orders will increase HCV screening rates.

**Methods:** Yale New Haven Hospital St. Raphael's Adult Primary Care Clinic (SRC) was the primary experiment group and uses Epic-based electronic health record (EHR) system. A second similar clinic, the Yale New Haven Hospital Primary Care Clinic (PCC), was used as a control group without intervention. After partnering with the SRC laboratory on creation of a HCV antibody testing with reflex testing to RNA, a database of eligible patients was created. Patients were eligible for inclusion if they: 1) were born between 1945-1965; 2) lacked a prior diagnosis of HCV infection; 3) lacked prior documented anti-HCV testing; and 4) were active with our clinic in the last 2 years. Using the EHR, bulk standing labs were ordered for all eligible patients, independent of a patient-provider interaction, and to be performed with their next blood draw. Providers were notified of the screening via EHR messaging and note documentation. Patients were notified of the test order via mail and EHR messaging (opt-out in nature). Patients were notified of results and positive cases were linked to care. Data were abstracted from the EMR for 3 periods: December 2016-November 2017 (pre-intervention), December 2017-March 2018 (3-month trial period) and March 2018-May 2018 (post-intervention). The primary outcome was the rate of HCV antibody testing. Summary statistics for demographic characteristics (gender, race, and insurance payor) were calculated between the two sites using the Chi-square test. An interrupted time-series analysis was performed to examine change in HCV screening rates.

**Results:** Prior to the intervention the HCV screening rate was 3.08% at SRC and 3.53% at the PCC site (p<0.001). Before the intervention, there was no significant month-to-month change in the difference of screening rates between the two sites (p-=0.66). Immediately following the intervention, the SRC screening rate significantly increased to 8.35% (p<0.001), with significant month-to–month trend following intervention (p<0.05), while the change remained insignificant at the PCC site. Compared to the year prior, there was over a 3.75-fold increase in monthly screening rates for the first 30 days. Viral PCR seroprevalence in the intervention group during trial period was 6.67%, slightly higher than prior studies.

**Conclusions:** We demonstrated that implementation of a population-based standing order for HCV screening among baby boomers in the primary care setting is not only feasible but resulted in a significant increase in screening rates. This type of EHR-based intervention presents a low cost, efficient means to improve HCV screening. The intervention could be further scaled-up to larger health systems and can be applied to many other diseases. Obtaining laboratory testing for entire patient populations without the need for a provider-patient encounter moves patient panel management to a new frontier.

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Resident's signature                                      Mentor's Signature

# Influence of Gender on Initiation and Recovery from Acute Kidney Injury

Dipal Patel, MD, PhD; *Advisor*: Chirag Parikh, MD, PhD, FACP

**Background:** Acute kidney injury (AKI) occurs frequently and has a broad scope of mechanisms for its development. In addition to various etiologies of AKI, certain populations of patients are considered to be more or less at risk for AKI development. The female gender has been described as being protective against the need for renal replacement therapy and against the development of renal ischemia after perfusion injury. However, the extent to which the female gender may be protective, and the question of whether or not this protection is lost after menopause, is unclear.

**Specific Aim:** To perform a systematic review of case reports and clinical trials, studying gender differences in incidence of AKI in human patients. Within this analysis, to study differences in AKI between pre- and post- menopausal women.

**Hypothesis:** We hypothesize that the female gender will be associated with a relative protection from the initiation of AKI, in addition to a more rapid recovery from AKI. Given that we expect this benefit to stem from differences in hormonal expression (namely, estrogens), we hypothesize that this protection will be neutralized after menopause.
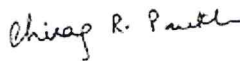
**Methods:** A preliminary literature review was conducted using PubMed. A query for "gender differences in acute kidney injury" resulted in 257 papers which were reviewed for inclusion criteria, namely that the primary data was a study or case series of human adult patients.

**Results:** From this preliminary literature review, 50 studies were fit for inclusion in this analysis. While the female gender was reported to confer protection against the development of AKI in general studies of hospitalized patients (including critically ill patients), the influence of gender in certain subsets of patients was less clear. The female gender was associated with a greater risk of AKI in patients receiving contrast load for angiography, and in patients who had received prior kidney transplants. The female gender was protective in a number of studies of post-surgical patients. There was no clear trend in the role of gender in influencing outcomes after incidence of AKI. Finally, studies did not clearly stratify results by age or hormonal status of female patients, and therefore there was no clear data to determine if differences in AKI incidence or progression were related to the hormonal status of female patients.

**Conclusions:** While the female gender seems to confer protection against development of AKI, it may actually be associated with more harm in certain subsets of patients. Careful identification of these patient subsets, in addition to stratification by hormonal status of female patients, is needed before defining the role of gender in AKI.

Dipal Patel, MD, PhD

Chirag Parikh, MD, PhD, FACP

# Factors Associated with Health-Related Quality of Life (HRQoL) in Patients with Decompensated Cirrhosis

Anahita Rabiee, MD, Guadalupe Garcia-Tsao, MD

**Background**: HRQoL is a multi-dimensional concept that encompasses physical, mental, emotional, and social function domains. While compensated cirrhosis is mostly an asymptomatic stage, patients with decompensated cirrhosis, in addition to a limited life expectancy, have a poor HRQoL. Knowledge of the underlying factors that affect HRQoL in patients with decompensated cirrhosis is key when planning treatments for these patients.

**Aim**: Our aim was to systematically review the literature to identify factors commonly associated with a poor HRQoL in adult patients with decompensated cirrhosis.

**Hypothesis**: Multiple factors including severity of cirrhosis and complications arising from cirrhosis are associated with a poor HRQoL in adult patients with decompensated cirrhosis.
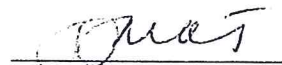
**Methods**: Four literature databases (MEDLINE, EMBASE, CENTRAL and PsycINFO) were searched from inception to August 2017, using terms related to patient-reported outcomes plus cirrhosis. Fully published studies in English were included if $\geq 70\%$ of patients had decompensated cirrhosis (on transplant list, Child-Pugh class B/C and/or any decompensating event, namely ascites, variceal hemorrhage, hepatic encephalopathy [HE]) and if the study analyzed an association between specific factor(s) and HRQoL. Studies were excluded if they evaluated specific interventions or if they used a single-item questionnaire to assess HRQoL. Abstract and full-text screening was performed by two reviewers. Data were collected on factors evaluated in each study and the significance of the association with each HRQoL domain.

**Results**: From 8,132 abstracts, 49 studies met the inclusion/exclusion criteria. Short Form 36 (SF-36) (67%), and Chronic Liver Disease Questionnaire (CLDQ) (29%) were the most commonly used generic and disease-specific HRQoL instruments, respectively. We identified 33 factors that were evaluated in more than two studies. Some of the results are shown in the table. Demographic factors such as age, gender, and ethnicity were not generally associated with HRQoL. Depression and muscle cramps affected HRQoL, but they were evaluated in only a small number of studies. The factor that most consistently affected HRQoL in a larger number of studies was overt HE (9 of 12 studies, 75%). Ascites was associated with poor HRQoL in 5 of 12 studies (42%).

**Conclusion**: Among cirrhosis decompensating events, HE was the complication most commonly associated with a poor HRQoL. Child-Pugh classification appears to be more commonly associated with a poor HRQoL compared to MELD which could be due to inclusion of HE in Child-Pugh classification.

Anahita Rabiee

Guadalupe Garcia-Tsao

# PHENOTYPIC EXPRESSION OF *CDH1* GERMLINE MUTATIONS UNSELECTED FOR HEREDITARY DIFFUSE GASTRIC CANCER

**Resident: Nicolette Juliana Rodriguez**
**Mentor: Dr. Xavier Llor**

Background: *CDH1* mutations cause hereditary diffuse gastric cancer (HDGC), a syndrome associated with very high risks of stomach and lobular breast cancer (LBC). However, HDGC penetrance estimates have been derived from the analysis of a limited number of families with several members affected with gastric cancer, and some at a very young age.

Aim: This study aimed to assess cancer phenotype and cancer risk estimation among a group of *CDH1* mutation carriers, independent of the indication for testing, thus not previously selected by HDGC criteria
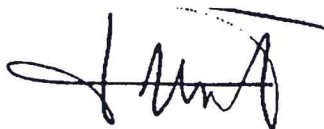
Hypothesis: Disease penetrance may be less than initially thought and the clinical approach and recommendations for these patients may need to change.

Methods: A retrospective study was conducted analyzing all *CDH1* mutation carriers identified at a major commercial genetics laboratory and a large academic center. Clinical phenotypes including cancer phenotype, demographic information, mean age at diagnosis, and genotype-phenotype correlations were analyzed among *CDH1* mutation carriers (n=113) and family members (n=476). Age-specific cumulative cancer risks (penetrance) were calculated based on 38 families with available pedigrees.

Results: Among the 113 *CDH1* mutation probands and 476 relatives, 113 had gastric cancer, 177 had breast cancer and 196 had other cancers. The mean age at diagnosis was 47 years for gastric cancer and 54 years for breast cancer. Thirty-six percent of probands fulfilled criteria of HDGC. While 36% of families had both gastric and breast cancers, 36% had breast but no gastric cancers and 16% had gastric but no breast cancers. The cumulative risk of cancer by age 79 was 37.2% for gastric cancer and 42.9% for breast cancer.

Conclusions:
In unselected *CDH1* mutation carrier families, cancer risks were lower and age at diagnosis higher than previously reported in families that were pre-selected for HDGC criteria. A substantial proportion of families did not present with any gastric cancers and instead their cancers were limited to breast. Thus, clinical criteria for *CDH1* testing should be expanded, including breast cancer families only, and a consideration for delayed prophylactic gastrectomy/surveillance should also be evaluated and considered.

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Xavier Llor, MD, PhD

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Nicolette Juliana Rodriguez, MD, MPH

# Improving Deep Venous Thrombosis Prophylaxis Rates in the Veteran Population: A Single- Center Study

Dushyanth Srinivasan MD[1], Victor Bilan MD[1,2], Benjamin Rodwin MD[1,2], and Naseema Merchant MD[1,2]

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**Introduction:** Efforts are underway to improve appropriate deep venous thrombosis (DVT) prophylaxis rates across health systems. Current guidelines recommend risk stratification into high and low risk groups using the Padua scoring system. Prophylaxis is recommended for high risk groups while no prophylaxis is recommended for low risk groups. Despite guideline-based recommendations, appropriate DVT prophylaxis rates remain variable throughout healthcare systems.

**Aim:** In this single center study, we sought to improve the appropriateness of DVT prophylaxis amongst medical inpatients through specific system wide interventions at the West Haven Veteran's Affairs (VA) hospital.
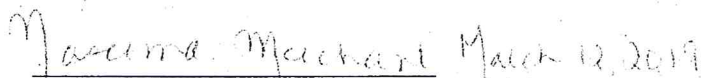
**Hypothesis:** Resident education and system wide force function interventions will improve appropriate DVT prophylaxis rates across medical admission as the West Haven VA.

**Methods:** Adult patients admitted to the Internal Medicine service at the West Haven VA hospital were eligible for inclusion. 269 patient charts were reviewed between January 2018 to February 2018 to establish baseline DVT prophylaxis rates. Our first intervention included resident education with distribution of Padua Scoring pocket cards with subsequent analysis of 349 medical admissions between October 2018 to November 2018. Our second intervention included modifying the medical admission "History and Physical" templates in the hospital's electronic health system to include the Padua scoring system, with subsequent analysis of 286 admissions between December 2018 to January 2019. Statistical comparison between groups was performed using ANOVA analysis.

**Results:** 904 medical admission were reviewed, of which 587 patients were eligible for risk stratification into high and low risk groups. Mean age and Padua score in this cohort were $69.6 \pm 12.9$ and $3.69 \pm 1.7$ respectively. Mean baseline inappropriate DVT prophylaxis rates pre-intervention was $26.0\% \pm 6.6$. Mean inappropriate DVT prophylaxis rates decreased to $21.6\% \pm 4.4$ and $12.8\% \pm 4.2$ ($p=.17$) post-intervention one and post-intervention two respectively.

**Conclusion:** There was no statistical difference in the reduction of inappropriate DVT prophylaxis following two separate interventions: resident education and modification of electronic health system. However, there was a trend towards significant improvement following our second intervention targeting patient records to include Padua scoring system documentation for all medical history and physical notes. Further prospective analysis is needed to determine sustained improvements in appropriateness of DVT prophylaxis following these interventions.

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Dushyanth Srinivasan MD

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Naseema Merchant MD     March 12, 2019

# Characterizing hospitalizations among older adults receiving palliative chemotherapy for hematologic malignancies

Natalie Uy, MD, Rupak Datta, MD PhD, Noffar Bar, MD, Manisha Juthani-Mehta, MD

**Background:** As treatment and supportive care for cancer improves, the population of older adults with incurable cancers will rise. This will impact health care systems as these patients seek care for management of infection, comorbid conditions, and worsening pain. Although older adults with hematologic malignancies often carry poor prognoses and require acute care, hospitalizations among older adults receiving palliative chemotherapy for hematologic malignancies are not well characterized. Moreover, older adults with hematologic malignancies may receive less palliative referrals than older adults with solid tumors.
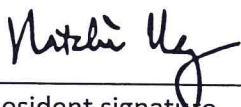
**Specific Aim:** This study aims to (1) characterize the outcomes of older patients following receipt of palliative chemotherapy for hematologic malignances and (2) evaluate the involvement of palliative care among older adults receiving palliative chemotherapy for hematologic malignancies.

**Hypothesis:** We hypothesize that the majority (≥50%) of older adults will have received chemotherapy prior to receiving palliative chemotherapy for hematologic malignancies, the majority will have received palliative chemotherapy within 2 months of death, and the majority will not have had palliative medicine consultation.

**Methods:** We conducted a retrospective study of patients aged ≥ 65 years who received palliative chemotherapy between January 1, 2016 and September 30, 2017. Palliative chemotherapy was defined as treatment administered for non-curative intent based on the treatment intent (curative versus palliate symptoms) designated on order entry in EPIC. Specific chemotherapy regimens were reviewed with a hematologist (NB) to confirm that the intent was palliative. Medical record review of all hospitalizations through January 28, 2018 was performed among the subset of patients with at least one hospitalization following initiation of palliative chemotherapy. Patients with hematologic malignancies were identified using ICD 10 codes and verified with medical record review. Data was stored in REDCap and analyzed using MS Excel.

**Results:** A total of 290 older adults receiving palliative chemotherapy for hematologic malignancies were identified and confirmed. Median age was 79 years (range 65-96 years), and 50% (n=146) were male. Hematologic malignancies included plasma cell dyscrasia (n=108), non-Hodgkin's lymphoma B-cell type (n=54), chronic lymphocytic leukemia (n=42), acute myeloid leukemia (n=33), myelodysplastic syndrome (n=23), chronic myeloid leukemia (n=9), non-Hodgkin's lymphoma T-cell type (n=8), myeloproliferative disease (n=5), acute lymphocytic leukemia (n=5), chronic myelomonocytic leukemia (n=2), and Hodgkin's lymphoma (n=1). One hundred forty-two (49%) had prior lines of treatment while 148 patients had palliative chemotherapy as their first treatment. During the first admission following receipt of palliative chemotherapy, median length of stay was 7 days (range 1-41 days). Out of 658 admissions among 290 patients, 193 (29%) admissions among 100 unique patients were followed by readmission within 30 days, and 37 (13%) out of 290 patients were discharged to outpatient hospice. One hundred sixty (55%) patients were still alive as of March 11, 2019; 43 (23%) died in the hospital, 13 (4%) died out of hospital, 73 (25%) died in inpatient or outpatient hospice, and 10 deaths (3%) were at an unknown location. Forty (14%) deaths were within 30 days of a hospitalization discharge. Palliative chemotherapy was common prior to death: 10% (n=29) received palliative chemotherapy within 2 weeks of death, 8% (n=24) within 1 month of death, 9% (n=26) within 2 months of death, and 13% (n=39) >2 months prior to death, 4% (n=12) had unknown timing. Fifty-one patients (18%) were seen by palliative care either outpatient prior to the first admission following receipt of palliative chemotherapy or during any inpatient hospitalization through January 28, 2018.

**Conclusion:** Chemotherapy regimens and clinical outcomes vary among older adults receiving palliative chemotherapy for hematology malignancies. Notably, formal palliative care consultations occurred in a minority of older adults. Future studies should identify the subset of patients at high risk for recurrent admission who would benefit from earlier palliative care involvement.

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# Brachytherapy and Non-Cancer Mortality in Patients with Oral Cavity and Oropharynx SCCs

Jovian Yu, MD, Barbara Burtness, MD

**Background:** Oral cavity and oropharyngeal squamous cell cancers (OC-OPSCC) display high cancer mortality. Aspiration, infection, other complications or treatment, and age- and tobacco-related comorbidities contribute to non-cancer mortality. This single-institution study examines cause of death in patients treated for OC-OPSCC with brachytherapy, chemotherapy, external beam radiation, surgery, or combination of modalities.

**Hypothesis:** We hypothesize that brachytherapy results in lower non-cancer mortality.

**Methods:** IRB approval was obtained. Our institution's Tumor Registry and electronic medical record were used to create a database of patients with first OC-OPSCC diagnosis between 2000-2010. Patients with a second primary cancer at diagnosis were excluded. The primary outcome was association between treatment modality and non-cancer mortality. Secondary outcomes were effects of comorbidities on death, specific causes of non-cancer mortality, and cancer-specific mortality. Statistical analyses were conducted in Python with the pandas and lifelines libraries.
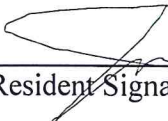
**Results:** Of 693 eligible patients, 460 (66%) were deceased. 84 died of the primary malignancy. Non-primary cancer cause of death was determined in 96 patients; 24 died from a second primary (16 second head and neck and 5 lung cancers). Cox proportional hazards regression was performed on treatment regimen and exposures, stratified by AJCC stage, race, and sex (Table 1). Non-smoking OPC patients had a 76% 5-year overall survival (OS), suggesting these were largely HPV-driven cancers. In smokers with OPC, OS was 33% at 5 years, with a HR for non-cancer mortality of 0.35 for brachytherapy-treated patients.

## Table 1: Non-Cancer Survival Analysis

| Covariate | Coefficient | HR [CI] | p-value |
|---|---|---|---|
| Age at Diagnosis | 0.05 | 1.05 [1.04-1.06] | <0.005 |
| History of Tobacco Use | 0.31 | 1.36 [1.17-1.55] | 0.11 |
| History of Alcohol Use | 0.80 | 2.23 [2.07-2.39] | <0.005 |
| Brachytherapy | -0.65 | 0.52 [0.33-0.71] | <0.005 |
| External Beam Radiation | -0.04 | 0.96 [0.78-1.14] | 0.80 |
| Surgery | -0.30 | 0.74 [0.55-0.93] | 0.11 |
| Chemotherapy/Targeted Therapy | -0.23 | 0.80 [0.61-0.99] | 0.23 |

## Conclusions

We report non-cancer mortality from an extensively annotated cohort of curatively treated OC-OPSCC. We show a significant correlation between receipt of brachytherapy and non-cancer survival, independent of remission status. Potential explanations include improved disease control, patient selection for brachytherapy, and reduced exposure to external beam radiation later in their course. Although HPV status was not available, OPC in non-smokers displayed OS characteristic for HPV-associated cancer. The impact of brachytherapy in OPC was strongest in smokers.

Resident Signature

Mentor Signature