2. SPECIFIC AIMS

Patients with cirrhosis suffer from catastrophic complications of portal hypertension, such as acute variceal hemorrhage or spontaneous bacterial peritonitis. Liver transplantation offers hope for a durable cure. But cirrhosis also leads to more insidious – but equally lethal – "extra-hepatic" effects like muscle wasting and malnutrition that severely impair functional status. In contrast to the liver-specific cirrhotic hallmarks (e.g., jaundice, ascites) that normalize soon after receiving a new liver, these extra-hepatic manifestations may take months to reverse, if at all, compromising global functional health and potentially even survival after transplant.[3-7]

Liver transplant clinicians have long recognized the potential impact of pre-transplant functional impairment on post-transplant outcomes, removing 1 in 10 transplant candidates from the waitlist for becoming "too sick for transplant".[8] Yet, despite the implications of functional status to this decision, there are no data on the actual impact of functional status on post-transplant outcomes and, as a result, no objective criteria exist to guide this critical decision of who is "too sick" for transplant. Rather, assessment of functional status in transplant is subjective and applied to decision-making *ad hoc*, resulting in unequal transplant access among centers and among clinicians within a center. Furthermore, assessments of "too frail" may be inaccurate, denying transplant to an otherwise suitable candidate. A precise understanding of how pre-transplant functional status impacts post-transplant outcomes is needed to inform prediction of who will do poorly *after* transplant (i.e., "too frail") and therefore is in greatest need of pre-habilitation to optimize post-transplant outcomes.

We are uniquely poised to address this knowledge gap. In an effort to operationalize what transplant clinicians consider "frail", we established the Functional Assessment in Liver Transplantation (FrAILT) Study and demonstrated that pre-transplant physical function, as measured by instruments originally developed in the geriatrics field, strongly predicts mortality that occurs *before* liver transplantation.[9-12] Next, in preparation for this proposal, we developed a Liver Frailty Index that is better suited for longitudinal study in the transplant setting than the traditional composite "geriatric" tools as it is entirely performance-based (i.e., objective) and scored on a continuous scale that can detect changes in functional status pre- and post-liver transplantation.[1]

Building logically upon our prior work on *pre-transplant* outcomes, we now propose to investigate *post-transplant* outcomes, including mortality and global functional health (i.e., functional status, disability, and health-related quality of life). We will leverage our existing FrAILT Study infrastructure in which liver transplant candidates undergo serial pre-transplant functional testing [to capture an outpatient assessment prior to their (unpredictable) transplant date and dynamic changes in function]. To ensure adequate power for the outcome of post-transplant mortality, we have expanded to 4 centers that will collect data on at least 1,493 liver transplant recipients with pre- and post-transplant functional status assessments. Using these data, we aim to:

Aim 1: Determine the extent to which pre-transplant functional status – at a single time point – is associated with 1-year post-transplant mortality and global functional health. We will investigate the value of a single assessment closest to the time of transplant to identify those who may be "too frail" for transplant and/or are in need of pre-habilitation. This time point is clinically useful – not only because it is easier to measure in clinical practice (rather than multiple measurements), but because decisions regarding transplant candidacy are often made after a single visit (e.g., at the initial liver transplant evaluation).

Aim 2: Determine the extent to which trajectories of pre-transplant functional status – while on the waitlist – are associated with 1-year post-transplant mortality and global functional health. Variability in functional status may indicate "recoverability" post-transplant that is important beyond a single assessment alone. We will use a mixed-model approach to isolate the slope, intercept, and variability for this analysis. We will also compare the prognostic value of the one-time measurement (Aim 1) versus the trajectory (Aim 2) of pre-transplant functional status on outcomes.

Aim 3: Develop and validate a clinical prediction rule that incorporates both pre-transplant functional status, patient, and donor characteristics to predict 1-year post-transplant mortality and global functional health. We will develop the model using data on liver transplant recipients (>900) from Years 1 and 2 and validate the model using data on liver transplant recipients from Years 3 and 4 (>480). This rule will fill a critical need for prognostic models that incorporate information that transplant patients care about in an objective manner to facilitate shared decision-making between patients, caregivers, and clinicians.

Potential impact: This project will positively impact the field by concretely expanding our ability to measure the benefit of transplant both by how *long* a recipient will live and by how *well* a recipient will live after transplant. Furthermore, given that functional impairment is modifiable in cirrhotic patients,[13] our data will simultaneously support future investigations to develop effective strategies to improve pre-transplant functional status with the goal of reducing mortality and optimizing post-transplant functional health.

SPECIFIC AIMS

Liver transplantation is a well-established therapy for patients with end-stage liver disease; 16,000 individuals are on the U.S. liver transplant wait-list[38]. Paralleling the aging demographics in the U.S., the total proportion of patients ≥60 years old undergoing liver transplant has increased annually, reaching 40% in 2012[37,38]. This rapid escalation will continue with the emerging epidemic of cirrhosis in older patients with hepatitis C[39] and non-alcoholic fatty liver disease[40]. While older age is associated with poorer survival before and after transplant[38,41-44], small single center studies have suggested that acceptable outcomes can be achieved in *select* older patients[42,45,46]. Yet, little is known of what constitutes "select". Currently, the few metrics that exist in the field of hepatology to objectively assess mortality risk in cirrhotics only quantify liver disease severity[47,48], independent of age. As a result, selection of "older" cirrhotics for transplant is often based solely on clinical intuition of who will do well with surgery and recover to their expected functional baseline. The age cut-off for "older" generally begins around 60 years, as patients <60 years have few co-morbidities and low peri-operative risk, and they are perceived as able to rapidly regain function after transplant. What is lacking in the field are tools to *objectively* measure non-liver related factors that may identify patients ≥60 years who will achieve acceptable survival rates and functional recovery after transplant[37].

Currently, the most widely used metric to assess prognosis in cirrhotics is the Model for End-Stage Liver Disease (MELD) score, a simple metric calculated from 3 common blood tests[47]. But older cirrhotics may experience increased vulnerability to adverse health outcomes due to the combined, and likely synergistic, effects of chronic liver failure *and* aging[38,41,42,44]. In geriatrics, vulnerability to adverse health outcomes in older adults has been operationalized using validated measures of the distinct, but interrelated, concepts of frailty, functional status, and disability that can be performed repeatedly in the clinical setting[49]. In non-cirrhotic elderly and other surgical populations, these measures (herein referred to as "frailty and functional status") predict clinically important outcomes often better than laboratory tests alone[32,33,50-52]. In my preliminary study of 127 cirrhotics ≥60 years, 20% exhibited the "frail" phenotype[53] – rates commensurate with those seen among community-dwelling adults >80 years[53]. Importantly, measures of frailty and functional status predicted death on the wait-list independent of liver disease severity[18]. Whether the same measures can be used to identify cirrhotics ≥60 years who are at high risk for poor outcomes *after transplant* remains unknown. Perhaps even more significantly, milder degrees of frailty (i.e., "pre-frail") defined by these measures can identify those at risk who would not otherwise have been recognized as vulnerable by clinical intuition alone. This research provides the hepatology community with tools needed for routine clinical assessments of older cirrhotics and has the potential to be incorporated as a required assessment within the national transplant data registry.

My long-term research goal is to integrate the geriatric constructs of frailty and functional status to the field of hepatology. Using a foundation career development award and an NIA GEMSSTAR, I have initiated the single-center Functional Assessment in Liver Transplant Candidates (FrAI-LT) Study to evaluate the association between measures of frailty and functional status with outcomes *before* transplant in cirrhotics ≥60 years. Building directly on this early work, I propose to expand this study through the following 3 aims:

Aim 1: To evaluate the association between pre-transplant frailty and functional status and post-transplant outcomes, including number of days hospitalized within 3 months of transplant and mortality. *Hypothesis 1: Pre-transplant frailty and functional status will predict post-transplant outcomes independent of liver disease severity (as assessed by the MELD score).*

Aim 2: To characterize frailty and functional status 3-, 6-, and 12-months after liver transplant and evaluate the association between pre- with post-transplant frailty and functional status. *Hypothesis 2: Pre-transplant frailty and functional status will be associated with post-transplant frailty and functional status.*

Aim 3: To test the feasibility of measuring frailty and functional status in a pilot multi-center cohort. I will utilize an existing transplant consortium to perform geriatric assessments of frailty and functional status in a pilot cohort of 120 liver transplant candidates ≥60 years at 3 centers. This will lay the groundwork for my goal of making these measures part of the standardized dataset for all U.S. liver transplant candidates.

The K23 Beeson award will support my career development through coursework and didactic training in aging and advanced biostatistics, integration into the UCSF and national aging research communities, and structured mentorship with national leaders in aging, hepatology, and transplant surgery. I believe that the core geriatric principles of frailty and functional status can transform the care and transplant evaluation of older patients with end-stage liver disease – and I will use the protected training and research development period of the Beeson to pioneer these concepts into my specialty. Ultimately, a greater understanding of frailty and functional status on outcomes in this population is critical to accurately identify those who will and will not benefit from transplant and to improve the care of all older adults with chronic liver disease.

PROJECT DESCRIPTION & SPECIFIC AIMS

Chronic liver disease and cirrhosis is the 12th leading cause of death in the US population,[1] and is a common cause of hospital admission. A 2002 study estimated that cirrhosis accounts for 150,000 hospitalizations at a cost of $4 billion each year.[2] Patients with cirrhosis, and particularly those this decompensated cirrhosis, are often readmitted soon after hospital discharge, with studies estimating 30-day readmission rates of 20-50% in patients with decompensated cirrhosis.[3-5] Studies have shown that early readmissions are associated with increased mortality even when controlling for liver disease severity.[5]

In an environment focusing on value-based care, early hospital readmissions for patients with chronic medical conditions have become an important quality metrics with significant financial implications. In 2012, the Center for Medicare and Medicaid Services (CMS) began reducing Medicare payments for hospitals with excess 30-day readmissions for certain medical conditions through the Hospital Readmissions Reduction Program (HRRP). These conditions include acute myocardial infarction, congestive heart failure (CHF), pneumonia, COPD, hip/knee replacements, and coronary artery bypass graft surgery.[6] While liver disease is not currently one of the medical conditions that results in Medicare penalties for readmissions, the rising incidence of cirrhosis in the US population is likely to lead to increased focus on liver disease readmissions in the future. A recent study comparing cirrhosis to CHF admissions at the Department of Veterans Affairs found that cirrhosis patients have higher 30-day readmission rates than CHF patients, and that annual mortality of hospitalized cirrhosis patients is >30%, compared to 20% among patients with hospitalized CHF patients.[7]

In order to reduce readmissions for cirrhosis, it is essential to understand the patient, provider, hospital, and health system-level factors that increase risk of readmission in this population. To date, there are relatively few studies on readmissions in cirrhosis (see Table 1).[3,5,8-13] Moreover, most of these studies are derived from single-center or consortium data which are limited in size and generalizability. Two larger studies have been published using administrative claims data, but are limited in the clinical detail that can be provided and are state-based, not national samples.[5,11] With my T32, I hope to characterize variation in readmission rates in cirrhosis on a national level, using data from the Vizient Clinical Database Research Manager (CDB/RM), a consortium of academic medical centers across the United States.

Vizient (formerly known as the University HealthSystem Consortium) is a consortium of more than 117 academic medical centers and more than 300 affiliate hospitals across the United States, representing 95% of the nation's non-profit academic medical centers. Most of these hospitals participate in the CBD/RM, which is comprised of clinical, discharge, procedure, and outcome data for each hospital encounter among member institutions. Vizient allows participating institutions to use the consortium data to accelerate organizational clinical performance. The Vizient CDB/RM includes information about patient readmissions to participating institutions.

Aim 1: Evaluate hospital-level variation in risk-adjusted readmission rates for patients admitted with a primary diagnosis of cirrhosis using a large United States-based administrative data set. We will first identify all patients admitted to a Vizient member institution in 2016 with a primary hospital diagnosis of cirrhosis. In order to do this, we will utilize the ICD-10 Clinical Classification System, which groups ICD-10 diagnosis codes into 260 clinically meaningful categories. We will next determine proportion of patients readmitted within 30 days by participating institution. We will then adjust for patient, provider, and system-level factors that are available in the database (see Table 2), to develop an adjusted estimate of readmission risk by hospital. We will also evaluate which of these factors are independently associated with risk of readmission. Hypothesis 1: We hypothesize that there will be wide variation in readmission rates across academic medical centers in the US.

Aim 2: Define additional patient factors (e.g. etiology of cirrhosis, comorbidities associated with cirrhosis, complications of cirrhosis) using secondary diagnosis codes that are associated with risk of readmission in patients admitted with cirrhosis. Using our fully-adjusted model of readmission risk created in Aim 1, we will test influence of secondary diagnosis codes relating to etiology of cirrhosis and complications of cirrhosis on risk of readmission in cirrhosis by identifying interactions between primary and secondary diagnosis codes. Hypothesis 2: We hypothesize that readmission risk will vary based on underlying etiology of cirrhosis and complications of cirrhosis.

Aim 3: Investigate whether inpatient consultation by a hepatologist or gastroenterologist is associated with lower risk of readmission among patients admitted with cirrhosis. Given that the likelihood of consultation by hospital is not a random occurrence, we will build a propensity score model to determine how hepatology or gastroenterology consult is associated with readmission, and apply this to our fully-adjusted model created in Aim 1. Hypothesis 3: We hypothesize that, after accounting for likelihood of consultation, readmission risk will be lower in patients who have inpatient gastroenterology or hepatology consult.