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Frailty and Outcomes in Liver Transplantation: A Dissertation

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FRAILTY AND OUTCOMES IN LIVER TRANSPLANTATION

A Dissertation Presented

By

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ABSTRACT

In recent years, the transplant community has explored and adopted tools for quantifying clinical insight into illness severity and frailty. This dissertation work explores the interplay between objective and subjective assessments of physical health status and the implications for liver transplant candidate and recipient outcomes. The first aim characterizes national epidemiologic trends and the impact of Centers for Medicare and Medicaid quality improvement policies on likelihood of waitlist removal based on the patient being too frail to benefit from liver transplant ("too sick to transplant"). This aim includes more than a decade (2002–2012) of comprehensive national transplant waitlist data (Scientific Registry of Transplant Recipients (SRTR)). The second aim will assess and define objective parameters of liver transplant patient frailty by measuring decline in lean core muscle mass ("sarcopenia") using abdominal CT scans collected retrospectively at a single U.S. transplant center between 2006 and 2015. The relationship between these objective sarcopenia measures and subjective functional status assessed using the Karnofsky Functional Performance (KPS) scale are described and quantified. The third aim quantifies the extent to which poor functional status (KPS) pre-transplant is associated with worse post-transplant survival and includes national data on liver transplantations conducted between 2005 and 2014 (SRTR). The results of this dissertation will help providers in the assessment of frailty and subsequent risk of adverse outcomes and has implications for strategic clinical management in anticipation of surgery. This research will also to serve to inform national policy on the design of transplant center performance measures.

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
BMI	body mass index
CI	confidence interval
CMS	Centers for Medicare and Medicaid
COP	Conditions of Participation
CT	computed tomography scan
hgt	height
HR	hazard ratio
Hu	Houndsfield units
IQR	interquartile range
kg	kilograms
KPS	Karnofsky Performance Status scale
LPA	lean psoas area
MELD	Model for End-Stage Liver Disease
m	meters
mm	millimeters
N	number of transplant centers (for chapter II only)
n	number in group
N	total sample size
n/a	not applicable
OPTN	Organ Procurement and Transplant Network
OR	odds ratio
p	probability
q	quarter
r	correlation coefficient
r_s	Spearman's rho
SD	standard deviation
SRTR	Scientific Registry of Transplant Recipients
TPA	total psoas area
UMMHC	UMass Memorial Healthcare Center
UNOS	United Network for Organ Sharing

PREFACE

Work presented in this dissertation was published; will be published; is currently under review; or has been submitted for peer-reviewed publication.

Chapter II

Dolgin N, Movahedi B, Martins PNA, Goldberg R, Lapane KL, Anderson FA, Bozorgzadeh A. Decade-Long Trends in Liver Transplant Waitlist Removal Due to Illness Severity: The Impact of Centers for Medicare and Medicaid Policy. *Journal of the American College of Surgeons* 2016 (in press).

Dolgin N, Movahedi B, Martins PN, Bozorgzadeh A. Trends in Waitlist Removal Due to Illness Severity: The Impact of CMS Policy [abstract]. *Am J Transplant.* 2016; 16 Suppl 1.

Dolgin N, Martins PN, Bozorgzadeh A. Trends in Waitlist Removal Due to Illness Severity: The Impact of Policy Changes [abstract]. *Transplantation.* 2015; 99 Supplement 7S: pp.83–320.

Chapter III

Dolgin N, Smith A, Harrington S, Martins PNA, Movahedi B, Anderson FA, Bozorgzadeh A. Functional Status and its association with Sarcopenia in Liver Transplant Recipients. (preparing for submission).

Chapter IV

Dolgin N, Martins PNA, Movahedi B, Lapane KL, Anderson FA, Bozorgzadeh A. Functional status predicts postoperative mortality after liver transplantation. *Clinical Transplantation* 2016 (in press).

Dolgin N, Martins PNA, Movahedi B, Anderson FA, Bozorgzadeh A. Impact of Recipient Functional Status on Liver Transplant Outcomes. (prepared for submission).

Dolgin N, Martins PN, Bozorgzadeh A. Functional Status Predicts Postoperative Mortality after Liver Transplantation [abstract]. *Hepatology*. 2016; 62: 807A–842A.

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Dolgin N, Martins P, Anderson F, Bozorgzadeh A. Functional Status Predicts Mortality After Liver Transplant [abstract]. *Am J Transplant.* 2015; 15 Suppl 3.

Dolgin N, Martins P, Lapane K, Bozorgzadeh A. Functional Status As A Predictor Of 30-Day Mortality Among Liver Transplant Recipients [abstract]. *Am J Transplant.* 2015 Jan;15 Suppl 1:39–114.

Third Party Copyrighted Material

Table 1.1: Karnofsky Performance Status scale, Karnofsky *et al,* 1948 (1)

Disclaimer

The data reported here have been supplied by the Minneapolis Medical Research Foundation (MMRF) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

CHAPTER I

INTRODUCTION

Liver Disease and Transplantation

Liver disease is the 4th leading cause of death among Americans aged 45–54 years old and the 12th leading cause of death overall (2–4). The mortality rate among patients with advanced liver disease is approximately 26% per 2-year interval (3). Liver disease results in over 1.2 million hospitalizations per year (5), with direct and indirect costs estimated at upwards of $13.1 billion annually (6,7). In 2012, over 3 million U.S. adults were estimated to be affected with liver disease, and the incidence has been on the rise (8). While there are more than 100 types of liver disease, over half of all cases are due to viral hepatitis, predominantly hepatitis C, followed by alcohol and non-alcoholic steatohepatitis, a component of metabolic syndrome (3).

The liver is the largest organ in the human body and serves over 2000 metabolic functions, including regulation of metabolism and nutrients, detoxification, and synthesis of bile and proteins such as albumin and coagulation factors. In order to serve these functions, virtually all venous drainage from the stomach, intestines, pancreas, and spleen pass through the liver. Thus, chronic liver damage can lead to consequences for many of these and other organ systems as well. Clinical manifestations of liver disease are heterogeneous, systemic, and often unpredictable. Largely attributable to the diversity and complexity of liver disease, transplant is the mainstay of treatment for end-stage liver disease; there is no equivalent to hemodialysis as for end-stage kidney disease (9).

The field of liver transplantation faces dramatic and worsening shortages in organ availability. Although 5,921 adult liver transplants were performed in the U.S. in 2013, 15,027 candidates remained on the waiting list on December 31 of that year (10). In

2002, in response to increasing shortages and waitlist mortality, the liver allocation system was reorganized to prioritize patients according to urgency. The conceptual definition of "urgency" was operationalized as calculated risk of 3-month mortality according to the Model for End-Stage Liver Disease (MELD) score, which is based on 3 objective laboratory parameters. However, MELD was originally designed for a different purpose - to predict the risk of procedure-related mortality for placement of Transjugular Intrahepatic Portosystemic Shunt - and the new system has required multiple adaptations to correct for subpopulations for which MELD score underestimates mortality (11–14). In the context of a disease with such a broad range of causes and manifestations, accurately defining "urgency" using only 3 objective parameters, and at only one time point, comes with inherent challenges (15). The current allocation system has continuously evolved and will likely continue to mature with each subsequent modification for many years to come (16–29).

It has been shown that MELD score underestimates the risk of both waitlist and post-transplant mortality among patients who are frail (25,30,31). It is hypothesized that progressive malnutrition, muscle wasting ("sarcopenia"), and subsequent functional decline, all hallmark sequelae of liver disease, result in a frailty phenotype wherein patients are more vulnerable to stressors such as surgery and infection due to limited physiologic reserve (Figure 1.1) (30,32–39).

In recent years, the transplant community has explored and adopted tools for better quantifying clinical insight into illness severity and frailty. Recent research has

shown that clinician assessment of illness severity (commonly referred to as the "eye-ball test") is predictive of waitlist mortality independent of MELD score (31).

Research on quantifying risk of post-transplant mortality, for which there is no equivalent to MELD score for pre-transplant mortality in terms of both predictive ability and generalizability, is very active and much needed in the field today. Several components of frailty syndrome, including sarcopenia as well as functional status, have been associated with poor morbidity and mortality outcomes *after* many different types of surgeries, including after liver transplantation (34,35,38,40–67).

Muscle wasting is one of many pathognomonic consequences of end-stage liver disease. Sarcopenia describes a combination of decrease in muscle mass and quality due to decrease in muscle fiber number and size, strength, and subsequently, functional performance (68–71). It is a key component of frailty syndrome (Figure 1.1) and may be key to quantifying and understanding frailty syndrome in a liver transplant population. One biologic mechanism that has been proposed to explain the discrepancy between MELD-based mortality estimates and actual risk among frail patients for whom MELD score underestimated mortality risk, is that creatinine concentration, the primary driver of MELD score, is proportional to muscle mass, and with muscle wasting being a major component of both frailty and liver disease, MELD may be disproportionate to extent of liver disease in these patients (Figure 1.2).

Clinical manifestations of frailty and impaired functional status in liver transplantation may not be as directly related to each other in liver transplant patients as

is illustrated in the context of a geriatric population in Figure 1.1; there may be many additional consequences of end-stage liver disease that may result in disability and not previously illustrated in other populations, and this tool must still be refined for this population.

Translation of "Frailty Syndrome" for an End-Stage Liver Disease Population

The concept of "frailty syndrome" originated from a geriatric framework. Diagnostic criteria and definitions of "frailty" are heterogeneous across geriatric, nutritional sciences, nursing/rehabilitation, and surgical bodies of literature (32,34,40,41,43–50,54,56,59,61,65,68–136). It describes a dynamic and potentially modifiable phenomenon of decreasing strength, function, and overall health status as a result of advanced age, chronic malnutrition, comorbidities and other systemic dysfunctions (Figure 1.1) (85,86,104,108,136).

Although many of the definitions and objective measures of frailty that were developed in non-transplant populations have been widely validated (125), there are important differences in these populations that limit their direct translation. For example, whereas age was originally conceptualized as the primary driver of frailty among geriatric populations, and cachexia, an irreversible progressive inflammation-based is the driver of frailty in oncology populations, it is actually "secondary sarcopenia," due to chronic disease and malnutrition (79), that drives frailty in end-stage liver disease.

Disease courses and prognoses in these populations also differ dramatically. In the original populations where frailty is described, frailty is conceptualized as progressive and mostly irreversible. This is in contrast to a liver disease population, which may have some, or potentially all, of these processes reversed after replacing the non-functioning organ with a new, non-diseased organ.

Recommendations regarding frailty cut-points or thresholds, as well as treatment strategies and implications for prognoses, are dependent on the relative potential benefit of a particular treatment such as surgery compared to the risk of undergoing the surgery (also referred to as "futility" of transplant). Interventions that may slow frailty and sarcopenia progression, such as nutritional supplementation and strength/resistance muscle training have been hypothesized across many populations (54–57,60–62,137–139). However, as the underlying etiologies are hypothesized to differ greatly, interventions may also need to target different deficits or approach the deficits differently.

This dissertation addresses an important gap in the literature by working toward an updated framework and approach to measuring and defining "frailty syndrome" that is specific to a liver transplant population.

Specific Aims

This dissertation examines the interplay between frailty, functional status, transplant outcomes. The first aim characterizes national epidemiologic trends in incidence of waitlist removal on account of the patient being too frail to benefit from transplant ("too sick to transplant"), using more than a decade of national data (Scientific Registry of Transplant Recipients (SRTR)) from 2002 to 2012. The second aim explores objective parameters of liver transplant patient frailty by measuring decline in lean core muscle mass ("sarcopenia") using abdominal CT scans collected retrospectively at a single U.S. transplant center between 2006 and 2015 (42,43,47). The relationship between these objective sarcopenia measures and subjective functional status, assessed by transplant providers using the Karnofsky Functional Performance scale (Table 1.1), is then described and quantified. The third and final aim seeks to quantify the extent to which poor pre-transplant functional status (KPS) is associated with worse post-liver transplant outcomes using national data from 2005 to 2014 (SRTR).

The specific aims of this dissertation were as follows.

Aim 1. To evaluate the impact of transplant policy on incidence of candidate delisting due to "too sick to transplant."

> **Hypothesis 1.1:** Incidence has been increasing since implementation of CMS Conditions of Participation (2007).

Aim 2. To describe the relationship between objective (sarcopenia) and subjective (functional status, KPS) measures of pre-transplant frailty among liver transplant recipients using single center data.

Hypothesis 2.1: Sample distribution of muscle mass and sarcopenia would vary by gender, time on the waiting list, MELD, and medical condition.

Hypothesis 2.2: Poorer functional status at transplant will be correlated with greater extent of sarcopenia.

Aim 3. To quantify the extent to which patients that are of poor functional status pre-transplant are at increased risk of 1-year post-transplant mortality and graft failure.

Hypothesis 3.1: Both Low and Moderate functional status would be associated with worse survival 1 year after liver transplantation.

Table 1.1: Karnofsky Performance Status scale and variable handling

KARNOFSKY PERFORMANCE STATUS SCALE		
Condition*	**%**	**Rating Criteria**
A ("None/Normal") Able to carry on normal activity and to work; no special care needed.	**100**	Normal, no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
B ("Moderate") Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
C ("Severe") Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

*Author-assigned variable labels in parentheses

Figure 1.1: Cycle of frailty hypothesized as consistent with demonstrated pairwise associations and clinical signs and symptoms of frailty (Fried *et al* 2001).

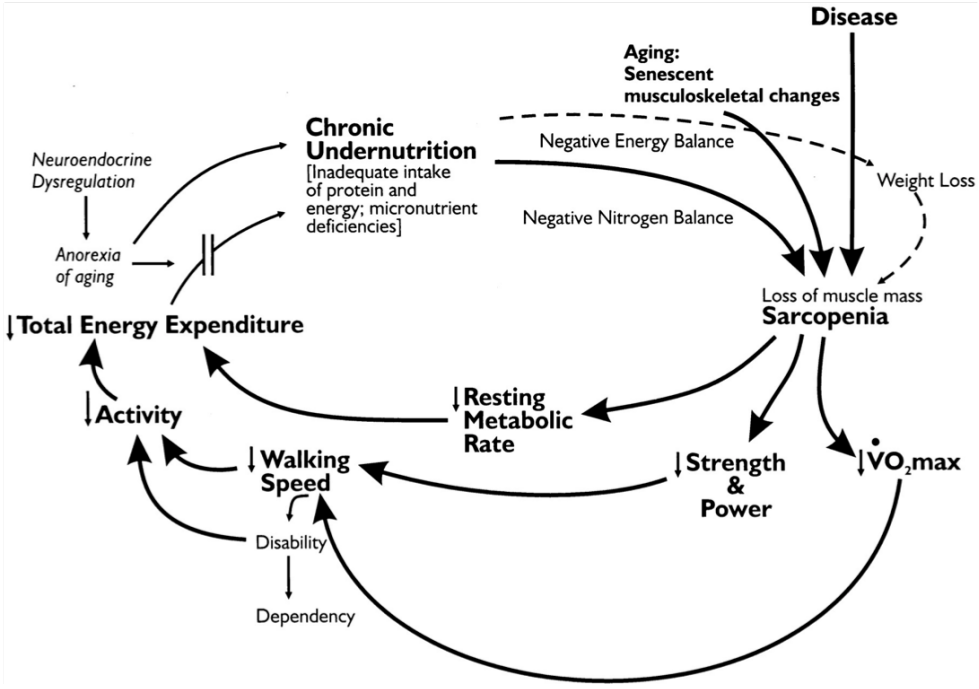
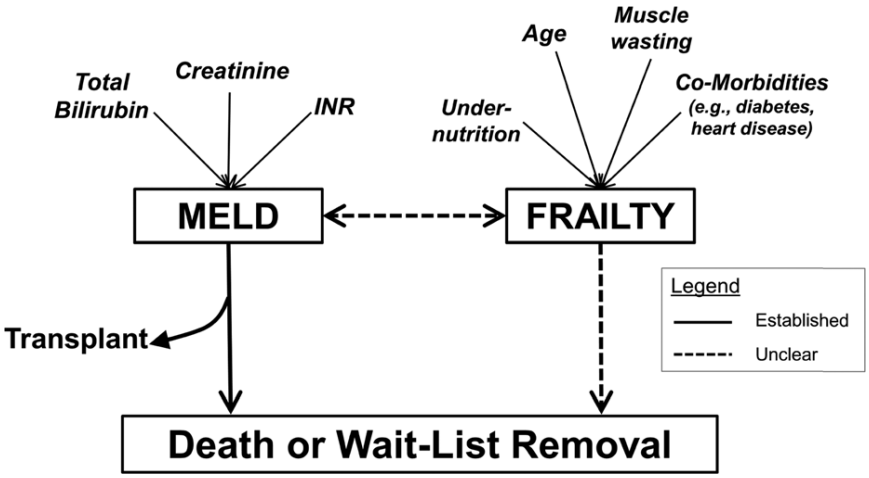


Figure 1.2: Conceptual model of the relationship between frailty, Model for End-Stage Liver Disease (MELD) and adverse outcomes as pertaining to liver transplantation (Lai *et al* 2014).



CHAPTER II

DECADE-LONG TRENDS IN LIVER TRANSPLANT WAITLIST REMOVAL DUE TO ILLNESS SEVERITY: THE IMPACT OF CENTERS FOR MEDICARE AND MEDICAID POLICY

ABSTRACT

Background: The central tenant of liver transplant allocation is to prioritize the sickest first. However, a 2007 Centers for Medicare and Medicaid (CMS) regulatory policy, "Conditions of Participation (COP)," which mandates publically reported transplant center performance assessment and outcomes-based auditing, critically altered waitlist management and clinical decision-making. We examine the extent to which COP implementation is associated with increased removal of the "sickest" patients from the liver transplant waitlist.

Study Design: This study included 90,765 adult (≥ 18 years old) deceased donor liver transplant candidates listed at 102 transplant centers from April 2002 to December 2012 (Scientific Registry of Transplant Recipients). We quantified the effect of COP implementation on trends in waitlist removal due to "illness severity," and one-year post-transplant mortality using interrupted time series segmented Poisson regression analysis.

Results: We observed increasing trends in delisting due to "illness severity" in the setting of comparable demographic and clinical characteristics. Delisting abruptly increased by 16% at the time of COP implementation, and the likelihood of being delisted continued to increase by 3% per quarter thereafter, without attenuation ($p < 0.001$). Results remained consistent after stratifying on key variables (MELD, age). COP did not significantly affect 1-year post-transplant mortality ($p = 0.38$).

Conclusions: Although the CMS Conditions of Participation policy (2007) was a quality initiative designed to improve patient outcomes, in reality, it failed to show beneficial

effects in the liver transplant population. Patients who could potentially benefit from transplant are increasingly being denied this life-saving procedure while transplant mortality rates remain unaffected. Policy makers and clinicians should strive to balance candidate and recipient needs from a population-benefit perspective when designing performance metrics and during clinical decision-making for patients on the waitlist.

INTRODUCTION

The current Model for End-Stage for Liver Disease (MELD)-based liver allocation system was introduced in 2002 in response to rising waitlist mortality in the setting of increasingly limited resources (organs) relative to rising demand. MELD is based on the fundamental principle that scarce resources should be allocated to those most in need ("sickest first"). Though waitlist mortality has stabilized since the introduction of the MELD system, removal of patients "*too* sick to transplant" has been on the rise (53,63,140–145). This clinical decision invariably results in patient death without a transplant; an estimated 80% will die within 2 weeks of waitlist removal (145).

The MELD score, calculated using 3 laboratory values (creatinine, international normalized ratio, bilirubin), is used to rank candidates *within* transplant centers' waiting lists. It allows the local or regional organ bank to easily and objectively sort potential recipients of a new organ offer. However, the *composition* of waiting lists and decisions on whether to accept or reject an organ once offered are made at the level of the transplant center. These decisions take into account not only the risk status of the patient and organ, but are also affected by institution-level financial pressures and potential regulatory consequences of high-risk transplantation (146–148).

In 2007, the Centers for Medicaid and Medicare Services (CMS) implemented the policy, Conditions of Participation (COP) (149,150). This regulatory policy uses Scientific Registry of Transplant Recipient (SRTR)-generated transplant program-specific performance reports to audit and publically report "underperforming" transplant

centers. This puts centers at risk for losing contracts with CMS and exclusion from private insurance "Centers of Excellence" networks, among other consequences (151,152). However, the policy only evaluates post-transplant survival. Without the consideration of waitlist outcomes, COP has led to unintended consequences for patients. Centers that have been flagged as "underperforming" have been shown to exhibit risk aversion with respect to candidate and donor selection (146,147,151,153–161), decreased waitlist and transplant volume (157,162), and prolonged waiting times (163,164). These changes ultimately result in reduced access to essential resources for patients, changing definitions of transplant "futility" toward conservatism, and conflict with the central tenet of modern transplant allocation: to prioritize the sickest patients first.

The purpose of this study was to evaluate whether known effects of COP flagging at the *transplant center* level translate to meaningful changes in waitlist dynamics at the *national* level. Specifically, we use more than a decade of comprehensive national data to describe and quantify the extent to which trends in candidate waitlist removal for being "too sick to transplant" were altered in the short- and long-term after the introduction of the COP policy. Further, we will examine whether COP implementation resulted in worse overall (waitlist and post-transplant) population survival.

METHODS

Study Population

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

This quasi-experimental (retrospective) study includes adults (≥ 18 years old) on U.S. deceased donor liver transplant waitlists for first liver transplant between April 1, 2002 and December 31, 2012, inclusive (Figure 1). Patients listed with hepatocellular carcinoma were excluded because, for this indication, waitlist removal due to condition deterioration is primarily based on objective measures of tumor progression (Milan criteria) and these patients are removed by mandate rather than clinical judgment. Furthermore, allocation policies have changed multiple times over the course of the study period for these patients (165,166).

Subjects listed at transplant centers with very small or fluctuating waitlist volumes, as defined in earlier literature (167), where each quarter that a candidate was on the waiting list was counted as a unique observation, were excluded (Figure 1). For patients listed at multiple centers, one record was chosen at random using a computer-generated randomization schema.

Comparison Groups

The key intervention of interest was implementation of Centers for Medicare and Medicaid (CMS) "Conditions of Participation (COP)" on June 28, 2007 (153). Our intervention group consisted of observations occurring after COP implementation (July 1, 2007–December 31, 2012). Pre-intervention observations (April 1, 2002–June 30, 2007) were categorized as the referent group (168).

Study Outcomes

The primary outcome of interest was the proportion of candidates removed from the waiting list due to "illness severity" per thousand candidates on the waitlist at any time during the respective quarter. Transplant centers are required to report reason for waitlist removal (including reasons such as transplant or death); we used the codes "13: Candidate Condition Deteriorated, Too Sick for Transplant," and "5: Medically Unsuitable" to define removal due to "illness severity." Because "Medically Unsuitable" represented < 0.2% of events in our population, we use the terms "illness severity" and "too sick" interchangeably to refer to the primary outcome.

The secondary outcome of interest was 1-year post-liver transplant mortality, defined as the proportion of patients transplanted per quarter that did not survive to postoperative day 365 (Social Security Death Master File, Organ Procurement and Transplant Network).

Potential confounders were selected through review of the published literature and *a priori* clinical knowledge (63,141,169). Patient characteristics known at the time of waitlist registration that, 1) are potential risk factors for waitlist removal due to illness severity, *and* 2) may have different prevalence estimates pre- versus post-COP implementation, were considered potential confounders. All MELD scores reported represent laboratory-calculated MELD scores.

Statistical Analysis

We explored key study variables both graphically (time series plots) and using contingency table analyses to compare changes in patient characteristics pre- and post-COP policy implementation. We then used interrupted time series analysis to explore trends in candidate delisting and 1-year post-transplant mortality. Quantitative evaluation of immediate and long-term policy impacts was conducted using segmented Poisson regression adjusted for pre-intervention trends, which serve as a historical control (referent group) against which the post-intervention trends are compared (168,170). Models were fit using Newey-West standard errors to account for potential correlation in the outcomes at adjacent time points (171). To evaluate potential time-varying confounding, the primary model was stratified on each variable observed to have meaningfully different prevalence estimates pre-post COP (Table 1).

To facilitate comparison of waitlist removal model results to transplant survival model results, we restricted the modeling period to April 1, 2003–December 31, 2011

only. This start date was selected based on observed instability in waitlist trends during the first year after MELD implementation (n = 6,953 waitlist candidates and n = 3,546 transplants excluded, Figures 2 and 3). This end date was selected in order to allow for complete ascertainment of 1-year post-transplant survival (n = 7,079 candidates and n = 3,555 transplants excluded). The final regression models included 76,733 candidates (44,085 pre-COP, 45,892 post-COP) and 34,603 transplants (17,630 pre-COP, 16,973 post-COP), respectively.

After confirming comparability (e.g. age, sex, race, transplant center) among delisted patients with versus without death data available (144), we qualitatively compared 1-year survival after waitlist removal to 1-year survival after transplant to explore whether there was a net change in outcomes at the population-level, pre-post COP.

Results are reported as population-level incidence rate ratios (95% confidence intervals (CI); p-value ≤ 0.05 was considered statistically significant). All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX). This study was deemed exempt by the University of Massachusetts Medical School Institutional Review Board.

RESULTS

The final study sample included 90,765 liver transplant candidates on waitlists at 102 unique transplant centers between 2002 and 2012. The mean waitlist volume by

center ranged from 1 to 742 candidates per quarter. The median age of candidates at listing was 53 years, 38.3% were women, and 14.2% were Hispanic/Latino and 8.3% African American. The median MELD score at listing was 15. The median time on the waitlist was 6.6 months, and the median time to transplant was 2.5 months.

Table 1 describes the waitlist population pre-post Conditions of Participation (COP) implementation using information known at the time of waitlist registration. Although all pre-post comparisons were statistically significant due to the large sample size, baseline characteristics were relatively similar pre-post COP. The greatest changes in patients' characteristics over time were observed as proportion of patients aged 55 years and older (10.2% absolute increase) and MELD score of less than 15 at listing (7.6% decrease).

Table 2 compares the characteristics of waitlist candidates removed due to illness severity and characteristics of transplant recipients, pre-post COP. Of the 90,765 candidates on the liver transplant waitlist between 2002 and 2012, 7.3% were removed due to illness severity ("too sick," n = 6,972; "medically unsuitable," n = 12).

Almost twice as many patients were removed after COP implementation (n = 4,340) than before (n = 2,311). By the end of 2012, incidence increased from 8.6 in the quarter immediately following COP implementation (2007, Quarter 3) to 19.7 at the end of 2012. The ratio of patients delisted-to-transplanted increased from 1 delisting for every 9 transplants to 1 delisting per every 5 transplants, on average.

Compared to before COP implementation, patients who were delisted post-COP were older (the proportion of patients 55 years or older increased by an absolute 12.4%) and more often without private insurance (4.6% absolute increase, compared with 2.5% increase among transplanted patients) (Table 2). End-MELD scores of ≥ 35 represented a greater proportion of delisted patients pre-post COP (6.6% increase) while MELD < 15 decreased by 5.8% (absolute changes). The proportion of delisted patients who underwent dialysis in the week prior to transplant versus waitlist delisting increased by 5.8% pre-post versus 9.3%, respectively.

Figure 2 is a time-series plot of the incidence of delisting due to illness severity over time. We observed increasing trends in the incidence of candidate delisting due to illness severity throughout the study period. While there was a baseline trend of increasing incidence, a marked change can be observed at time of COP implementation. In the first quarter immediately after COP went into effect, the number of patients delisted (per 1,000 candidates) abruptly increased by 16% ($p < 0.001$) (Table 3). The incidence rate continued to increase at a rate of 3% ($p < 0.001$) per quarter thereafter, with no sign of attenuation.

Upon stratification of delisting trends by key sociodemographic and illness factors, COP was observed to have a greater impact for patients with higher MELD scores at delisting (Figure 3B) and older patients (Figure 3D), despite modest, secular increases in the variable means over the study period (Figures A and C, respectively).

Estimates for each stratified model remained consistent (< 10% change) with whole-population delisting trends described in Table 3.

Figure 4 is a time-series plot of the incidence of transplants resulting in recipient death within 1 year of transplant. The implementation of COP did not have a statistically significant impact on the trends ($p = 0.38$) or level ($p = 0.62$) of post-transplant mortality rates (Table 3).

Death after "too sick" waitlist removal versus after transplant, pre-post COP

Eighty-nine percent of transplant candidates removed due to illness severity died within 1 year (87.2% pre-COP, 90.0% post-COP), and 52% died within 1 week (missing n = 735). Based on these estimates (calculated 1-year mortality among patients not missing death data), approximately 1,423 additional candidates died within one-year post-waitlist removal after COP implementation than before. In contrast, 87.5% of transplant recipients survived to 1-year post-transplant (86.6% pre-COP, 88.5% post-COP); there were 396 fewer 1-year post-transplant deaths after COP implementation than before (Table 3). The result is a net increase of 1,027 one-year deaths (1,423 - 396) post-COP implementation.

DISCUSSION

The COP policy adopted by CMS in 2007 has had a significant nation-wide impact on the likelihood that an adult liver transplant candidate will be removed from the waiting list due to "illness severity." The impact was evident immediately after implementation, when the national incidence of delisting "too sick" patients increased abruptly. The likelihood of candidate delisting continued to increase over the subsequent 5-year post-COP observation period and failed to show signs of attenuation. COP did not significantly impact 1-year post-transplant survival.

Our findings are supported by earlier literature that has shown the direct effects of CMS oversight at the transplant center level. Centers audited for low or near-low performance have been shown to reactively accept fewer high-risk candidates for transplantation, and reduce procedure and waitlist volumes overall (146,147,151,153–162). Our findings provide potential answers to questions raised as to whether changes that occur after auditing at individual centers (e.g. volume) are adequately compensated for by other centers in the region (167). In contrast, we show continuously increasing national rates of candidate delisting after COP. One explanation may be that altered risk tolerance persists over time, resulting in national incidence rates that accumulate over time as additional centers are flagged in subsequent evaluation waves. Another explanation may be that definitions of "too sick to transplant," or, transplant futility, are shifting nation-wide, and protocols or risk tolerance are generally changing regardless of audit history.

This study reveals limited improvement in liver transplant survival despite increased rates of waitlist removal among patients considered too high risk ("too sick") for transplant. The lack of significant improvement in post-transplant survival may be explained by the inherent complexity of post-liver transplant outcome prediction given the multitude of patient, donor, center, and surgical factors that contribute to transplant outcomes. Though waitlist mortality can be relatively accurately predicted using the MELD score, the added complexity when considering donor and surgical factors, in addition to patient factors, has stunted the development of accurate post-transplant mortality prediction for many years (20,100,172–181). The current SRTR-generated Program Specific Reports, which are used by CMS for assessment of center performance, rely on imperfect approaches for determining "expected survival," against which transplant centers' outcomes are compared, as well as imperfect risk-adjustment of center-specific outcomes (151,158,161,182–184). The models suffer from inadequate adjustment and the methodology is continuously under study (185) and changing (151). Thus, the disconnect between increased delisting of the sickest patients and no change in post-transplant outcomes may be partially attributable to heterogeneity in definitions of "high risk" in the absence of reliable objective criteria.

Implications of Results

The central tenant of liver transplant allocation is to prioritize the sickest first. In 1999, Institute of Medicine recommendations to temper aggressive urgency-based

allocation through the "avoidance of futile transplants or wastage of organs" were incorporated into the "Final Rule" (186). Today, external regulatory pressure from CMS has overpowered the primarily urgency-based allocation system; increasing numbers of potentially viable transplant candidates are being turned away since the implementation of COP policy.

Merion and Schaubel propose "population benefit" models that balance urgency (pre-transplant mortality) and utility (post-transplant mortality) to prioritize *relative* transplant benefit that maximizes net population life-years (21,169,176,187). Our results illustrate that the current system is increasingly moving away from a net benefit approach in favor of maximizing transplant outcomes only. For example, although higher MELD scores are associated with greater transplant benefit, patients in higher MELD categories were being delisted at increasingly higher rates after COP policy went into effect (169). As delisting due to illness severity invariably results in death without transplant, COP resulted not only in a shift of mortality burden from post-transplant to the waiting list but an overall net loss in benefit.

In an effort to rebalance the scale, the Organ Procurement and Transplant Network recently (2014) proposed a new performance assessment tool specifically for waitlist outcomes, the "Composite Pre-transplant Metric" (188). The tool evaluates outcomes as a function of centers' decision-making (i.e. transplant/delisting/waitlist mortality ratios) in addition to known patient and other factors (i.e. geography) relating to waitlist mortality (189–195). However, the tool's intended use as a stand-alone (waitlist

only) center performance measure, and the plan not to report the results publicly or to incorporate results into reimbursement policies as with the current post-transplant Program Specific Reports, may limit its effectiveness at decreasing risk aversion. The extent to which implementation of Share 35 policy may have reversed the trends we observed is another important question to address in future research.

Strengths & Limitations

A major strength of the present study is the use of interrupted time series segmented regression analysis, a powerful tool and method of choice for policy evaluation (196). A limitation of this method, however, is the inability to adjust for potential time-varying confounding that may have affected the observed trends. However, exploration of the data revealed secular (gradual) changes in variable means over time, which would not explain the sudden jump observed in waitlist removal incidence at time of COP implementation. Furthermore, model estimates remained consistent after stratification on key variables. As information on center-level quality metrics is unavailable in the UNOS/SRTR database, we were unable to evaluate the role of poor performance.

The UNOS/SRTR database used in this study has strengths and limitations common to administrative databases. Similar to other surgical datasets, data on patients evaluated but ultimately not considered surgical candidates (i.e. patients not waitlisted and follow-up data on patients removed from the waiting list) were either unavailable or

underreported. We would anticipate attenuation of our delisting trend estimates in the setting of such potential survivor bias (167), and we analyze mortality after waitlist removal conservatively. Accurate coding of "Reason for Removal" was reviewed using medical records at 4 tertiary care centers from 2002 to 2010, and underreporting of "too sick to transplant" and "medically unsuitable" by < 10% was shown (145). Such random misclassification would have attenuated our estimates of effect. Overall, the benefits of using this large, comprehensive, transplant-specific national database that includes over 2 decades of data outweigh the potential limitations for this study.

CONCLUSIONS

We illustrate that implementation of CMS's Conditions of Participation regulatory policy in 2007 was associated with an immediate, sharp increase in the likelihood of liver transplant candidate waitlist removal; this trend did not attenuate over the duration of the 5-year period after COP. Patients who could potentially benefit from liver transplantation are increasingly denied this life-saving procedure while post-transplant survival did not significantly improve pre-post COP, resulting in a net population-level loss.

Although the CMS Conditions of Participation policy (2007) was a quality initiative designed to improve patient outcomes, in reality, it failed to show beneficial effects for the liver transplant population overall. The National Organ Transplant Act, the Institute of Medicine, and the Final Rule consistently supported 3 goals: to increase

transplantation, to decrease waitlist mortality, and to maximize transplant benefit. However, this study illustrates that population benefit has declined since the implementation of COP.

Future studies on understanding these trends and efforts to rebalance the waitlist-transplant outcome scale are warranted, and this balance should be considered during development of future national policies and in clinical decision-making in order to better serve this patient population.

Table 2.1: Baseline* Characteristics of Patients on the Liver Transplant Waitlist, Scientific Registry of Transplant Recipients 2002–2012 (n = 90,765†)

Characteristic	Pre-COP April 2002–June 2007, % (n = 51,038)	Post-COP July 2007–December 2012, % (n = 52,971)
Age in years		
< 45	20.1	16.7
45–54	41.6	34.8
55–64	30.0	38.4
≥ 65	8.3	10.1
Gender		
Men	61.8	61.1
Women	38.2	38.9
Race/ethnicity		
White	73.9	72.1
Hispanic	13.9	14.8
African American	7.8	8.3
Insurance Status		
Private	63.4	60.8
Medicare	16.1	19.1
Medicaid	15.6	16.1
Diabetes‡	21.9	24.4
Primary diagnosis		
Hepatitis C§	37.4	35.9
Alcoholic§	16.9	18.5
Cholestatic	8.8	8.2
Acute hepatic necrosis	6.4	4.8
Listing MELD		
< 15	56.2	48.6
15–24	30.0	34.3
25–34	8.3	10.5
≥ 35	5.5	6.7
Medical condition		
Home	85.7	82.4
Hospitalized	8.5	11.3
ICU	5.8	6.3

*Baseline: Measured at time of initial waitlist registration.

†13,244 patients present on the waiting list both pre- and post- COP; when randomly assigned to either category, all variables were significant at $p < 0.001$ except gender, which was significant at $p < 0.05$, after 5 repeat randomizations

‡Types 1, 2, or unspecified

§Primary diagnosis of "alcoholic cirrhosis with hepatitis C" were categorized under "Hepatitis C"

COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 28, 2007); MELD, Model for End-Stage Liver Disease

Table 2.2: Characteristics of Patients Removed from the Liver Transplant Waitlist Based on "Illness Severity"*, Scientific Registry of Transplant Recipients 2002–2012 (n = 90,765)

	"Too Sick to Transplant"*			Transplanted		
Characteristic	**Pre-COP (n = 2,311)**	**Post-COP (n = 4,340)**	**p-value**	**Pre-COP (n = 21,176)**	**Post-COP (n = 20,528)**	**p-value**
	Percentage			*Percentage*		
Age in years†						
< 45	12.5	8.6		18.2	15.5	
45–54	33.9	25.4		40.4	31.4	
55–64	35.8	45.8		32.0	41.6	
≥ 65	17.8	20.2	< 0.001	9.4	11.5	< 0.001
Women	40.8	41.9	0.38	34.0	36.0	< 0.001
Race/ethnicity						
White	73.2	70.0		74.7	72.5	
Hispanic	15.0	16.8		12.3	12.9	
African American	7.8	8.6	0.05	9.0	10.2	< 0.001
Insurance status						
Private	59.2	54.6		64.0	61.5	
Medicare	20.0	23.9		16.0	18.6	
Medicaid	15.6	17.3	< 0.001	14.8	15.6	
Diabetes (any type)	26.8	28.8	0.08	21.0	24.4	< 0.001
Prior abdominal surgery	36.2	34.3	< 0.001	32.7	33.3	< 0.001
Primary diagnosis						
Hepatitis C	36.1	37.0		36.7	35.2	
Alcoholic	16.0	17.0		15.6	16.6	
Cholestatic	8.2	7.3		9.5	8.4	
Acute hepatic necrosis	8.8	5.1	< 0.001	6.9	5.7	< 0.001
Final MELD†						
< 15	26.3	20.5		23.5	16.7	
15–24	31.1	28.7		44.1	38.8	
25–34	18.6	20.2		20.0	26.5	
≥ 35	24.1	30.7	< 0.001	12.3	17.9	< 0.001
Dialysis in prior week†	14.3	23.6	< 0.001	8.6	14.4	< 0.001
Ascites†						
Slight	50.7	46.3		54.8	47.6	
Moderate	35.8	39.1	< 0.005	29.6	34.4	< 0.001
Encephalopathy†						
Slight (1–2)	52.4	46.8		61.5	56.6	
Moderate (3–4)	30.9	33.1	< 0.001	13.0	13.9	< 0.001

*Delisted for removal reasons "too sick" or "medically unsuitable".
†At time of waitlist removal

COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 28, 2007); MELD, Model for End-Stage Liver Disease

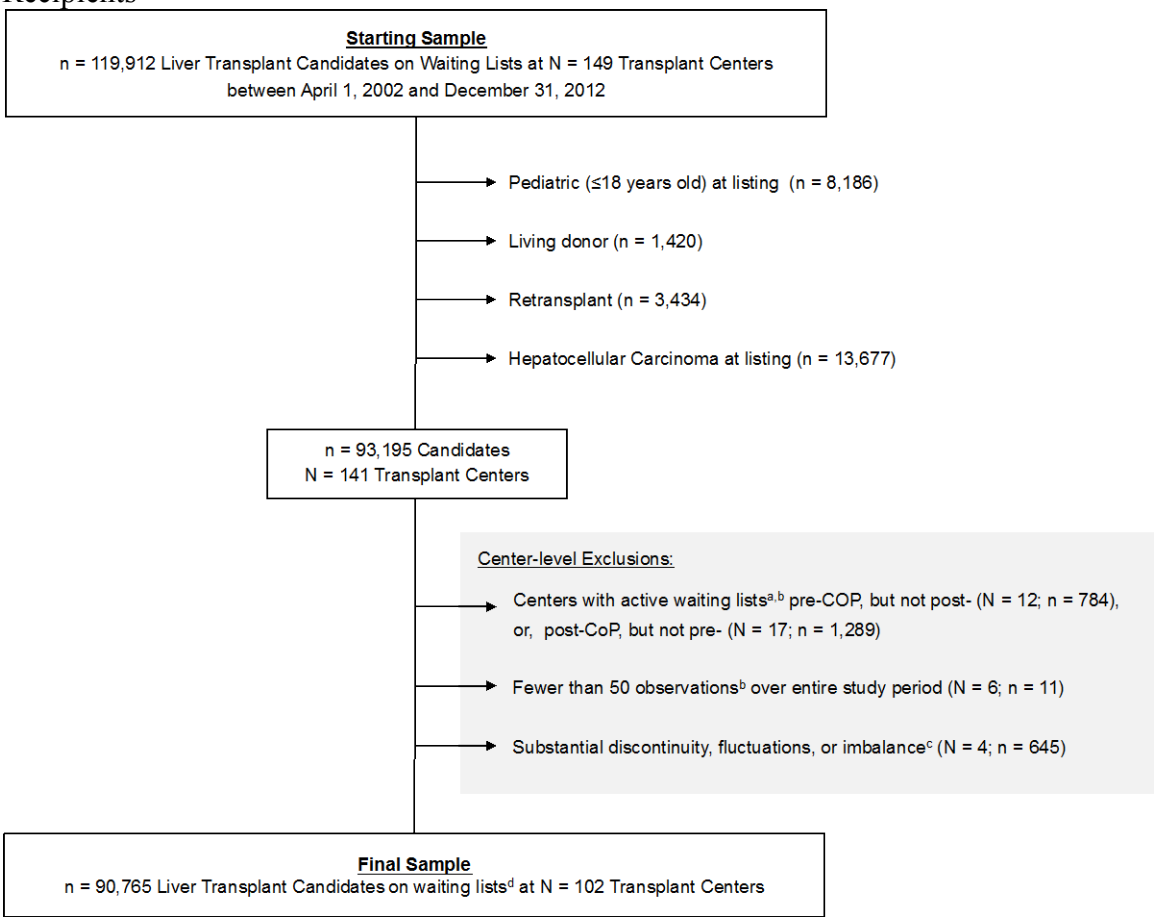
Table 2.3: Effect of Centers for Medicare and Medicaid Conditions of Participation Policy Implementation on Rate of Waitlist Delisting Based on "Illness Severity"[*] and 1-year Post-Transplant Mortality, Scientific Registry of Transplant Recipients 2002–2012 (n = 76,733 candidates[†]; 34,603 transplants)

			Incidence Rate		
Outcome	**Pre-COP**	**Post-COP**	**Ratio**	**95% CI**	**p-value**
"Too Sick" Waitlist Removal[*]					
Event, n removed	1,829	3,353			
Observation, person-quarters	256,148	263,162			
Level Change[‖]			1.16	1.12–1.20	< 0.001
Trend Change[‖]			1.01	1.00–1.01	< 0.001
Death < 1 Year After Transplant					
Event, n deaths	2,356	1,960			
Observation, liver transplants	17,630	16,973			
Level Change[‖]			0.99	0.94–1.04	0.62
Trend Change[‖]			1.00	1.00–1.01	0.38

[*]Delisted for removal reasons "too sick" or "medically unsuitable".
[†]Pre-COP, April 2003–June 2007 (n = 44,085 candidates); Post: July 2007–December 2011 (n = 45,892 candidates).
[‡]Observations (person-quarters), Model 1: number of candidates present on the waiting list, times number of quarters they were on the waiting list during each respective period; Model 2: number of transplants at any time during respective period.
[‖]*Level change* represents change in the level of the quarterly incidence of the respective model outcome immediately after COP implementation (akin to a change in y-intercept). *Trend change* represents change in the slope, comparing post-COP slope to the projected pre-COP (historical) slope. Incidence rate ratio and 95% CI derived from exponentiated poisson model parameters.

COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 28, 2007)

Figure 2.1: Study inclusion/exclusion flow chart. Scientific Registry of Transplant Recipients



[a]Inactive if had fewer than 10 observations (# observations = sum of #candidates on waiting list in each quarter) per period or < 50 over entirety of study period

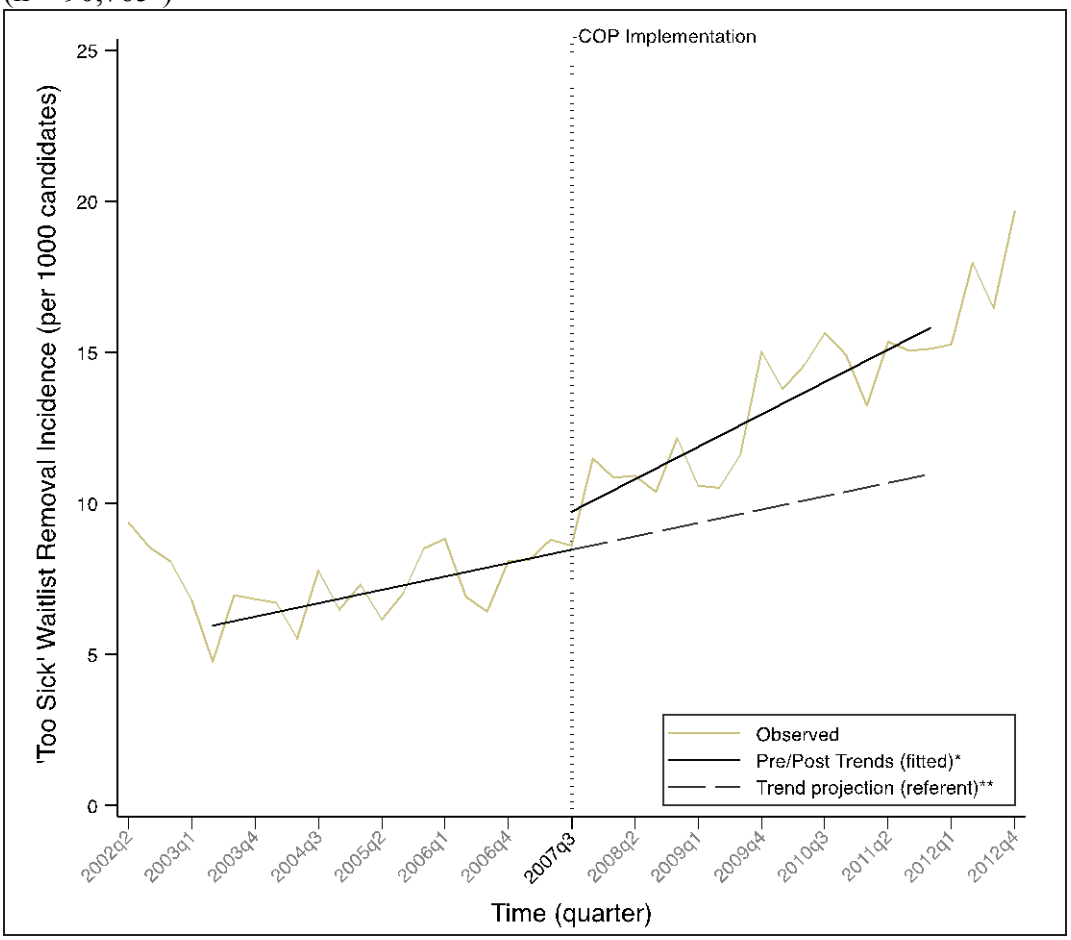
[b]Imbalance if < 6 quarters of data available immediately pre- or post-COP

[c]Dropped observations for one center with early gap in data (n = 45)

[d]Randomly selected waitlist record for multi-listed patients at this point

n, people; N, facilities; COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 28, 2007)

Figure 2.2: Change in the rate of liver transplant waitlist removal based on "illness severity" pre-post Centers for Medicare and Medicaid Conditions of Participation policy implementation, Scientific Registry of Transplant Recipients April 2002–December 2012 (n = 90,765[§])

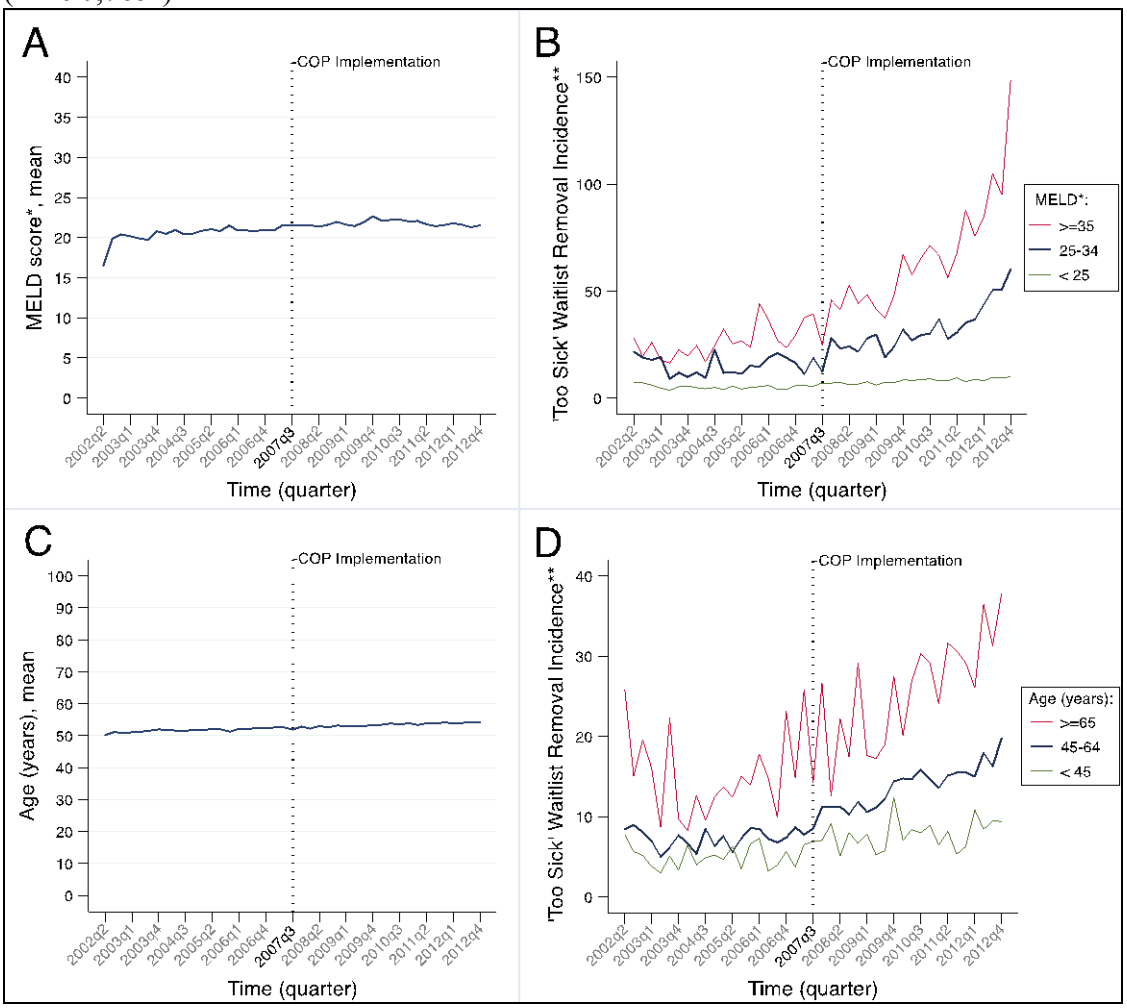


[§]Trends fitted[*] for study period used for regression modeling. Pre-COP trend line: April 1, 2003–June 30, 2007(n = 44,085); Post-COP trend line: July 1, 2007–December 31, 2011 (n = 45,892).
[*]Pre/post trends, fitted
[**]Projected pre-COP trend (referent)

Results of regression model, comparing post-COP trend[*] to the referent pre-COP trend[**], expressed as Incidence Rate Ratios: Difference in y-intercepts at the time of COP implementation: 1.16, 95%CI: 1.12–1.20 ($p < 0.001$); Difference in slopes: 1.01, 95%CI: 1.00–1.01 ($p < 0.001$).

COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 30, 2007)

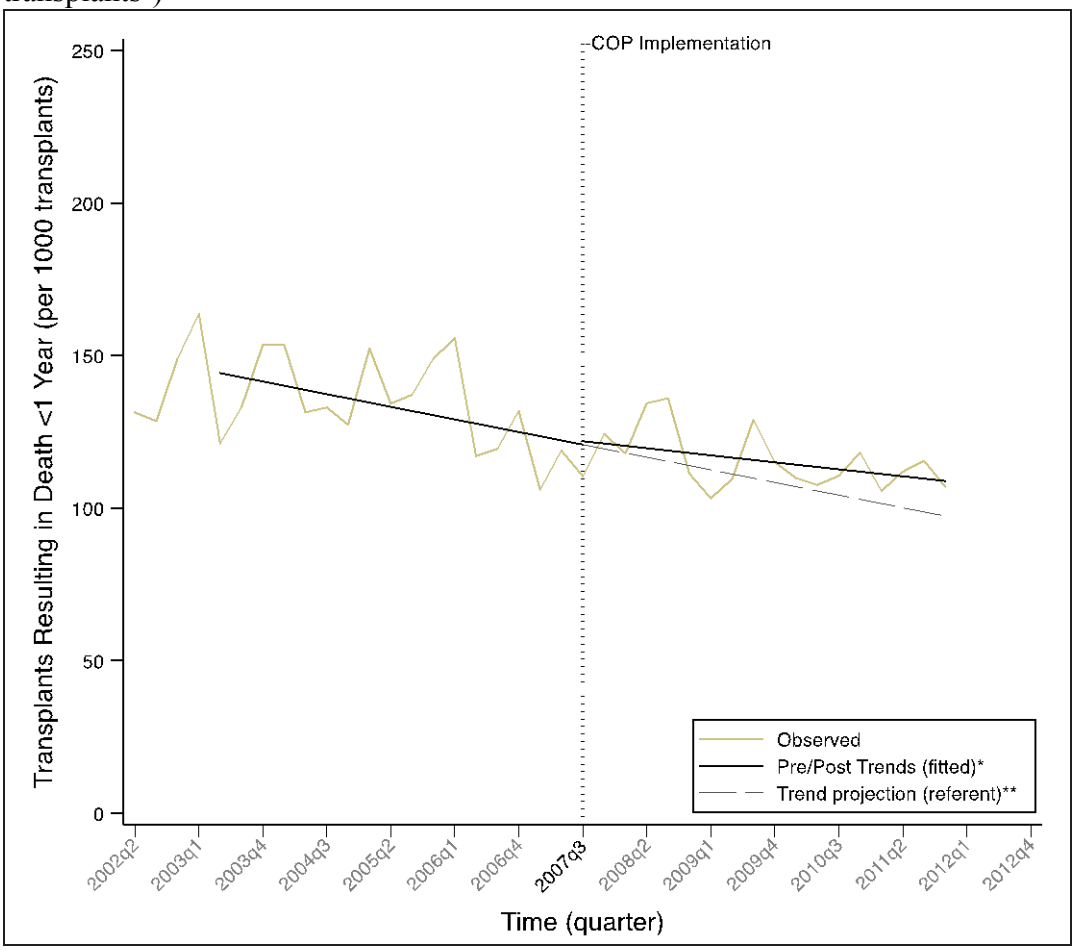
Figure 2.3: Trends in (A) mean Model for End-Stage Liver Disease (MELD), (C) age and (B) rate of patient removal from the liver transplant waitlist based on "illness severity," stratified by MELD and (D) age, pre-post Conditions of Participation policy implementation, Scientific Registry of Transplant Recipients April 2002–December 2012 (n = 90,765[§])



[§]718 people were missing data on final MELD score.
*Final laboratory-based MELD score. Initial MELD mean versus time ran parallel to final MELD score.
**Waitlist removals for reason "too sick" or "medically unsuitable" per 1000 waitlist candidates per quarter.

COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 30, 2007); MELD, Model for End-Stage Liver Disease

Figure 2.4: Change in the incidence of death within 1-year of liver transplant, pre/post Centers for Medicare and Medicaid Conditions of Participation policy implementation, Scientific Registry of Transplant Recipients April 2002–December 2011 (n = 38,149 transplants[§])



[§]Trends fitted[*] for study period used for regression modeling. Pre-COP, April 1, 2003–June 30, 2007 (n = 17,630 transplants); post-COP: July 1, 2007 – December 31, 2011 (n = 16,973 transplants).
[*]Pre/post trends, fitted
[**]Projected pre-COP trend (referent)
Results of regression model, comparing post-COP trend* to the referent pre-COP trend[**], expressed as Incidence Rate Ratios: Difference in y-intercepts at the time of COP implementation: 0.99, 95%CI: 0.94–1.04 (p = 0.62); Difference in slopes: 1.00, 95%CI: 1.00–1.01 (p = 0.38)

COP, Centers for Medicare and Medicaid Conditions of Participation policy implementation (June 30, 2007)

CHAPTER III

ASSOCIATION BETWEEN FUNCTIONAL STATUS AND SARCOPENIA IN LIVER TRANSPLANT PATIENTS

ABSTRACT

Background: There is a growing body of evidence that frailty and functional performance independently predict liver transplant outcomes. The Karnofsky Performance Status (KPS) scale is the United Network of Organ Sharing assessment tool of choice for measuring transplant center case-mix. Its utility for liver transplant patients is unknown. The purpose of this study is to explore the relationship between provider-assessed KPS and objective, validated markers of frailty (sarcopenia).

Methods: This observational study includes 136 adult, first-time liver transplant recipients at UMass Memorial (2006–2015) that had two abdominal CTs available: (1) ≤ 90 days pre-transplant, and (2) ≥ 7 days before (1). We used psoas muscle size and quality measures to explore sarcopenia pre-transplant, as a relative change and as a rate of muscle wasting. We used correlation and logistic regression to examine the relationship between sarcopenia and KPS.

Results: The mean age was 55 years and last laboratory-calculated MELD was 22; 34% were women. Half was sarcopenic pre-transplant, and 71.3% declined in lean psoas area (LPA) at an average rate of 11% per month. Functional impairment was present in 86%. Compared to subjects with minimal or no evidence of sarcopenia on CT scan, subjects who experienced muscle wasting at a rate of ≥ 1% per month had 2.83 times the risk (95% confidence interval (CI): 1.18–6.80) of being severely impaired, disabled and/or moribund pre-transplant (adjusted for age, gender and race). This risk increased by 2.32 (CI: 1.44–3.75) times for every standard deviation decrease in pre-transplant LPA.

Conclusions: Provider-assessed physical health status is moderately correlated with objective measures of frailty. More research on the utility of using either or both measures in prognostication and management of high-risk liver transplant patients is warranted.

INTRODUCTION

The growing shortage in liver donation in the U.S. has transformed practice patterns in liver transplantation over the last decade (197). To minimize mortality on the waiting list, the current system of liver allocation was designed to prioritize the "sickest first." Patients are ranked according to the Model for End-Stage Liver Disease (MELD) score, which is calculated using 3 objective laboratory values (creatinine, bilirubin, and international normalized ratio). Although MELD is a reliable predictor of 3-month waitlist mortality at the population level, it is a poor predictor of post-transplant mortality (19,25,26,198). Recent studies have shown that MELD score underestimates the risk of waitlist and post-operative mortality among liver transplant patients who are considered to be "frail" (25,30,31). It is hypothesized that frailty may make patients more vulnerable to stressors such as surgery due to limited physiologic reserve, leading to worse outcomes when faced with a stressor such as major abdominal surgery (30,32).

Frailty syndrome describes a dynamic and potentially modifiable phenomenon of decreasing strength, function, and overall health status as a result of advanced age, chronic disease and malnutrition, comorbidities and other systemic dysfunctions (85,86,104,108,136). Muscle wasting, or sarcopenia, is a hallmark of end-stage liver disease and has been used as an objective measure of frailty and predictor of morbidity and mortality in this population (34,35,38,40–67). However, assessment of sarcopenia or other objective measures of frailty proposed have limited clinical utility since they are often not practical to assess in the perioperative setting. Moreover, this measure may be

too narrow to describe global physical health status (42) compared with a phenotypic, clinician-assigned, score on a validated scale of frailty (34).

Decrease in muscle mass due to reductions in muscle fiber number and size as well as strength lead to declines in functional performance (68–71). Functional status has also been shown to independently predict liver transplant outcomes (32,129,199–201). In accordance with a UNOS/OPTN mandate, functional status data have been collected from all U.S. transplant centers using the Karnofsky Performance Status (KPS) scale for more than a decade. These data are then used to risk-adjust for center case-mix in the creation of Program Specific Reports on outcomes. Though the KPS is a widely validated tool for assessment of global physical function across many disease indications and has been used clinically and in clinical trials for over 60 years (51,64,66,67,101,114,131,201–218), its validity in a liver transplant population remains unknown. While analytic morphomics research has been used to identify a strong correlation between objective measures of sarcopenia and global assessments of physical health status, the study was conducted in a population of older (> 70 years) general surgical patients and not liver transplant patients (219). There remains a gap in the literature on defining and understanding the mechanisms underlying the frailty phenotype for liver transplant patients. This will be the first study to describe the relationship between phenotypic and physiologic signs and symptoms of frailty syndrome in a liver transplant population.

The aim of this study is to describe the relationship between provider-assessed functional status (KPS) and objective measures of sarcopenia, collected using validated analytic morphomics methodology.

MATERIALS & METHODS

Study Design and Population

This retrospective cohort study includes adults who underwent first-time liver transplantation at UMass Memorial Healthcare Center (UMMHC) between January 1, 2006, and October 31, 2015. UMMHC is a 781-bed, tertiary care medical center located in Worcester, Massachusetts, U.S. The UMMHC transplant program includes adult and pediatric liver, kidney, and pancreas transplants. In 2012, this center transplanted more livers than any other program in New England (220). Patients without both a "pre-transplant" (≤ 90 days before transplant) abdominal computed tomography (CT) scan (n = 228) and a referent ("baseline") CT scan at least 7 days prior to pre-transplant CT (n = 28), or patients that were missing data on functional status at transplant (n = 3) were excluded (Figure 3.1).

Data Collection and Variable Definitions

Muscle Measures

Muscle measurements were collected from CT scans performed as part of routine clinical care. Patients on the UMMHC liver transplant waitlist undergo routine abdominal imaging at the time of candidacy evaluation and every 6–12 months until transplant, depending on their primary diagnosis. Baseline and pre-transplant psoas muscle size (cross-sectional area, mm^2) and quality (density, Hounsfield units (Hu)) for both left and right psoas muscles were measured at the L4 vertebral level superior plate according to Analytic Morphomics methodology (43). All measures were collected by a UMass radiology attending physician with fellowship training in abdominal radiology (AS) using tools built into the radiology management system (General Electric (GE) Centricity^{TM} Radiology Information System /Picture Archiving and Communication System (PACS)). Intra-rater reliability was confirmed using Test-Retest methodology prior to initiation of study data collection (see Appendix 3A for details) (221).

Individual psoas muscle measurements were combined to create the following variables: Total Psoas Area (LPA) (left + right cross-sectional area, mm^2), mean density ((left + right density)/2, Hu), Lean Psoas Area (LPA) (TPA x (mean density+85/) 170), mm^2) and stature-normalized(49) LPA (LPA/height^2, mm^2/m^2) for each time point. These measures were explored in the following ways: 1) Sarcopenia pre-transplant: pre-transplant LPA relative to "normal," 2) Relative Sarcopenia, or, extent of muscle wasting: relative LPA change from baseline, and 3) Muscle wasting rate: rate of relative change per month. Normal in (1) was defined using gender-specific LPA averages

reported in a sample of over 1,200 elective surgery patients (222) and assessed at a single time point (pre-transplant) sarcopenia (Sarcopenic/Not Sarcopenic: > 1 standard deviation below average/≤ 1 standard deviation above average; cut points: 1,488.4 mm^2 for men, 974.8 mm^2 for women). Cut-points were used to facilitate comparability with other studies. Relative sarcopenia uses patients' own "baseline" (psoas measures from earliest available abdominal CT scan) as the referent: $Pap_{er\text{-}transplant}$-$LPA_{baseline}$ /$LPA_{baseline}$ (%). Because this was a retrospective study, time between scans was not uniform among subjects. We therefore standardized relative change in LPA per the number of months between CT scans (%/month). Relative change variables are explored as both continuous variables and grouped into tertiles.

Functional Status

Functional status was defined using the Karnofsky Performance Status scale, which is described in Table 1.1. The KPS scale was designed to be assessed by providers and has been widely used and validated in many different populations, including patients with end-stage renal disease (51,64,66,67,101,114,131,201–218). The original KPS is an 11-tiered scale, decreasing from a maximum of "100%: normal, no complaints, no evidence of disease" to "0%: Dead," in 10% increments. A collapsed, 3-tiered version is also available and has high inter-rater reliability (201,202,210). We assigned labels to summarize extent of functional impairment/disability in each respective category as follows: None/Normal function (A: 80–100%), Moderate limitations (B: 50–70%),

Severely impaired disabled (C: ≤ 40%). We explore the KPS as a continuous, categorical, and as a binary variable.

Covariates of Interest

Potential confounders of interest were selected based on literature review and *a priori* knowledge. Characteristics of interest included sociodemographics, body habitus, comorbidities, liver diagnoses, and illness severity (laboratory-based MELD scores, Child-Pugh scores, sequelae of liver disease, medical condition). As previous studies have shown substantial differences in degree and mechanism of muscle wasting in men versus women, gender was a key characteristic that we explore in the most depth.

These data were collected from the UMMHC transplant registry, which includes variables collected and submitted by mandate to UNOS/SRTR database and other clinical and laboratory variables from patients' electronic medical records that are auto-imported into the registry in real-time.

Data analysis

Univariate and bivariate distributions of muscle measures, functional status, and key characteristics at baseline and pre-transplant were explored graphically and with contingency table analyses. Descriptive statistics for the study sample are presented as follows: Continuous variables are described as mean (standard deviation (SD)) if

normally distributed and median (interquartile (IQR)) range if skewed; categorical variables are described as proportions (%).

The relationship between sarcopenia and functional status was assessed using correlation and logistic regression analyses. Correlation between continuous KPS and LPA rate of change was compared using Spearman's rho (r_s) rank correlation coefficient for ordinal data (223). Testing correlation assumptions revealed a parabolic relationship between variables, with an inflection point at 20% increase in LPA per month; therefore, we report correlations for subjects with values of less than +20%, excluding 5 people (see Appendix 3B for details). Power calculations for minimum detectable effect size are described in Appendix 3C.

We evaluated unadjusted and adjusted odds of severe functional impairment (KPS 10–40% versus referent, 50–100%) for 3 working definitions of muscle wasting: 1) rate of muscle wasting, 2) pre-transplant sarcopenia (yes/no), and 3) pre-transplant LPA (per SD decrease), using logistic regression and adjusting for age (≥ 55/< 55 years), gender (women/men), and race (white/non-white ethnicity). Results are presented as odds ratios (OR) with accompanying 95% confidence intervals (CI).

Tests of statistical significance were selected as appropriate based on normality of the dependent variable (please see Appendix 3D for details); p-values ≤ 0.050 were considered significant. All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX). This study was approved by the UMass Medical School Institutional Review Board.

RESULTS

The final study sample included 136 patients who underwent first-time liver transplantation between 2006 and 2015. Descriptive statistics for the overall study sample are listed in Supplemental Table 3.1 and summarized here. The mean age was 55.4 years, 33.8% were women, and the most common ethnic minority was Hispanic/Latino (14.7%); 77.2% of the sample was white. The most prevalent primary etiology of liver disease was hepatitis C/viral hepatitis (47.1%), and hepatocellular carcinoma was present in 36.0% of the sample. The mean laboratory-calculated MELD score pre-transplant was 22.3, and the majority (68.4%) of the sample was in the worst Child-Pugh class (C) for cirrhosis severity. The median (interquartile range (IQR)) waitlist time was 3.2 (0.8–12.4) months.

Muscle wasting and recipient characteristics

Table 3.1 includes descriptive statistics of the sample according to the presence or absence of sarcopenia on pre-transplant CT (in relation to gender-specific thresholds of "normal" lean psoas area (LPA)). Patients with sarcopenia were 5 years older on average, and weighed an average of 20 pounds less, and were twice as likely to have been previously diagnosed with diabetes than patients who did not have sarcopenia. Alcoholic hepatitis was a more common primary etiology (29.9% versus 18.8%) and hepatocellular carcinoma was less likely among patients with sarcopenia. Sarcopenic patients' disease was more severe according to pre-transplant MELD score, labs, and hospitalization status

(31.3% vs. 11.6% ICU); three-quarters of the patients with sarcopenia were classified in Child-Pugh class C.

Table 3.2 summarizes changes in psoas muscle measures by gender and Supplemental Table 3.2 displays more detail. The majority of the sample declined in either muscle size or density (86.8%). Approximately three-quarters of the sample lost total psoas area (TPA) and slightly over half declined in muscle quality (55.2%); 71.3% declined in lean psoas area (LPA) from baseline to pre-transplant CT overall (average time between scans: 12 (IQR: 3.6–36.5) months). The mean (SD) relative change in LPA was -10.7 (19.9) % and the average rate of relative change was -0.5% per month (-1.5 to -0.04% per month).

While total psoas area (TPA) and density changed significantly from baseline to pre-transplant in the overall sample, women only lost a median of 2.9% of baseline TPA compared with 12.6% among men. In contrast, women significantly declined in muscle quality (-10.0%, $p = 0.03$) while men did not (-1.5%, $p = 0.20$). A significant difference persisted even after accounting for density in LPA. However, normalizing relative LPA change for time (months) between CT scans equalized differences by muscle wasting by gender ($p = 0.07$).

Table 3.3 shows recipient characteristics by tertiles of rate of LPA loss (% LPA lost per month between CT scans) and Supplemental Table 3.3 shows characteristics by tertiles of relative LPA loss (%). By tertile of LPA loss rate, in order of increasing severity, the median (IQR) change in LPA was 7% (2 to 13%), -14% (-26 to -6%), and -

22% (-32 to -12%). Characteristics associated with more rapid rates of LPA loss included higher rate of weight loss per month on the waitlist, higher MELD score at registration and pre-transplant, with worse bilirubin and coagulation labs, and more critical medical condition (Table 3.3). Patients with higher rates of muscle wasting were less likely to have hepatocellular carcinoma.

Sarcopenia and Functional Status

Functional impairment (moderate or severe physical limitations per KPS) was present in 86.0% (n = 117) of the sample at transplant. The mean KPS score was 47.3% and one-third (31.6%) of the sample had a KPS of 20%. KPS distributions did not vary by gender ($p = 0.92$).

Figure 3.2 illustrates the relationship between continuous functional status and rate of LPA loss. A moderate correlation was identified ($r_s = 0.31$; $p < 0.001$). Supplemental Table 3.5 shows the correlations stratified by recipient characteristics of interest, with average LPA rates displayed for each category of functional status.

Table 3.4 shows the results of logistic regression models for severe functional impairment/disability by 3 different measures of muscle wasting. Severe impairment/disability was more common among subjects with higher rates of muscle wasting, and among those who were sarcopenic pre-transplant. Mean LPA among severely impaired subjects was 1,215.4 mm^2 compared with 1,473.9 mm^2 for subjects who were of Moderate or Normal functional status ($p = 0.001$).

Compared to subjects with minimal or no evidence of sarcopenia on CT scan, subjects who experienced muscle wasting at a rate of ≥ 1% per month had 2.83 times the risk (95% confidence interval (CI): 1.18–6.80) of being severely impaired, disabled and/or moribund pre-transplant (adjusted for age, gender and race). The adjusted odds ratio observed for subjects with pre-transplant sarcopenia compared with those without was similar (2.67; CI: 1.29–5.52). The odds of severe functional impairment/disability more than doubles for each standard deviation decrease in lean muscle size on pre-transplant CT (2.32; CI: 1.44–3.75).

DISCUSSION

We present results from the first study to evaluate the relationship between Karnofsky Performance Status scale and objective measures of frailty (sarcopenia) in a liver transplant population. The mean age of the sample was 55 years, last laboratory-calculated MELD was 22.3, and hepatitis C was the most prevalent etiology of liver disease. Prevalence of muscle wasting (loss in psoas area or density compared to "baseline" CT) and prevalence of functional impairment (KPS ≤ 70%) pre-transplant were almost identical (86.8 versus 86.0%, respectively). Pre-transplant sarcopenia, defined relative to average in a general surgery population, was present in about half of the sample.

The prevalence of sarcopenia we report is consistent with that reported in other studies of liver transplant patients (41% (65), 45%(49)). We observed differences

between men and women in terms of the type of muscle wasting subjects experienced (size (total area) for men versus quality (density) for women) and these findings are supported in earlier literature (43,47,49,65,222). We also report a new finding: after accounting for changes in density, relative change from baseline as a percent, and months over which the changes occurred, degree of muscle wasting was no longer statistically different for men and women ($p = 0.07$).

Compared with a study that examined change in psoas muscle perioperatively (90 days pre or post) in a cohort of general and major vascular surgery patients, we showed a similar but smaller proportion of patients who declined TPA in our study (73%) compared to theirs (83%) (224). This minor difference could be explained by the period of observation: the body goes through a rollercoaster of physiologic changes in recovering from major surgery, and trunk muscle size may substantially decline for bedbound patients with postoperative complications from not only misuse but physiologic stress (e.g. infection). Perioperative change in psoas muscle has been shown to independently predict mortality among cirrhotics undergoing transjugular intrahepatic portosystemic shunt procedures (139). For these reasons, we did not include CT scans performed within 90 days post-transplant, as the aforementioned postoperative setting is generally very intensive but also variable for liver transplant patients.

We found that functional status was associated with sarcopenia on pre-transplant CT as well as with change in muscle mass and/or quality (loss of lean psoas area). Our findings are supported by results of studies of sarcopenia in general surgery patients at

University of Michigan (219,222). In one study of patients aged 70 and over who were admitted for general surgery procedures, 42% exhibited functional impairment on in-clinic assessment of physical function (e.g. walk test) and only 22% reported difficulty with activities of daily living (219). The prevalence of functional impairment in this population was substantially lower than in our sample of 136 liver transplant recipients (86.0%). Despite these differences, the estimates of effect that the authors found for total psoas area in relation to difficulties performing instrumental activities of daily living (ADLs) were almost identical to findings in our study (OR 0.53 per SD of TPA versus OR 0.55 per SD increase in LPA (or TPA) pre-transplant (note that these results are currently presented in Table 3.4 as the inverse: OR 1.83 per SD *decrease*). We also showed that muscle wasting of as little as 1% per month is associated with an almost three-fold higher risk of severe functional impairment, compared to patients with no sign of muscle wasting and after adjusting for age, gender, and race (OR 2.83 CI: 1.18–6.80).

Implications of Results

UNOS/SRTR replaced the previously collected activities of daily living (ADL) as the primary measure of functional status with the Karnofsky Performance Status (KPS) around 2005. However, the Liver and Intestinal Transplant Committee of OPTN recently asked that research on using KPS nationally be pursued, as there is concern in the transplant community about whether it is appropriate to risk-adjust centers' outcomes for case-mix using a variable that has not been validated in a liver transplant population

specifically (218). This study found moderate correlations between provider-assessed KPS and objective markers of frailty but more research is warranted.

Interventions that may slow frailty and sarcopenia progression, such as nutritional supplementation and strength/resistance muscle training, have been hypothesized across many populations (54–57,60–62,137–139,225). The concept of "frailty syndrome" originates from a geriatric framework and describes a dynamic and potentially modifiable phenomenon of decreasing strength, function, and overall health status as a result of advanced age, chronic disease and malnutrition, comorbidities and other systemic dysfunctions (85,86,104,108,136). Although many of the definitions and objective measures of frailty that were developed in non-transplant populations have been widely validated (125), there are important differences in these populations that limit their direct translation to liver transplant patients.

Whereas age was originally conceptualized as the primary driver of frailty among geriatric populations, and cachexia, an irreversible progressive inflammation-based is the driver of frailty in oncology populations, it is actually "secondary sarcopenia," due to chronic disease, malnutrition, and endocrine abnormalities (79), that drives frailty in end-stage liver disease. This has important implications for both designing potential interventions and for prognostic indications of sarcopenia in liver transplant patients compared to other populations.

As the underlying etiologies of frailty are hypothesized to vary across the different groups in which sarcopenia has been recognized as a strong predictive variable

for outcomes, interventions may also need to target different deficits or approach the deficits from different angles. Nutritional supplementation has been studied in liver disease and it has been shown that meal-induced albumin synthesis is impaired even in compensated cirrhotic patients (226) and may be insufficient to overcome underlying endocrine abnormalities.

Furthermore, disease courses and prognoses in aged versus cirrhosis populations differ dramatically. In the original populations where frailty is described, frailty is conceptualized as progressive and mostly irreversible. This is in contrast to a liver disease population, which may have some, or potentially all, of these processes reversed after replacing the non-functioning organ with a new, non-diseased organ. We call for further research on understanding whether and which preventive measures, or, "prehabilitation" interventions, some thus far shown to be effective in other types of major surgeries such as cardiac surgery, may be needed in a liver transplant population. Although the literature has shown that sarcopenia predicts mortality, functional status predicts mortality, and now we add that functional status maps onto objective measures of sarcopenia adequately, none of these associations are necessarily linked directly to outcomes as causal. In other words, sarcopenia may simply be a proxy for describing global health status of the patient. Intervening to improve muscle mass directly through physical training and protein supplementation may not bear meaningful effects on improving outcomes as for cardiac surgery patients, who do not suddenly recover muscle satellite cell generation after surgery the way that transplant patients recover protein metabolism

with a new organ, but recover slowly through cardiac rehabilitation therapy involving exercise.

Strengths & Limitations

This work must be considered in the context of its limitations. The primary limitation of this study is the relatively small sample size. This limited the number and types of analyses we were sufficiently powered to conduct. A potential limitation of using single-center data is generalizability of findings. To address generalizability of measures, we evaluated sarcopenia variable definitions using a referent from previously published averages in a general surgery population and used percent of loss for within-patient changes. A limitation to the averages we used as "normal," however, is that although elective general surgery patients may be healthier than the average liver transplant patient overall, they are likely sicker than a general healthy population such as from trauma patients and may too be suffering from sarcopenia, perhaps due to other etiologies (cancer, advanced age). This limitation is inherent to the literature available thus far, and we call for further research describing general population prevalence and definition of "normal" for analytic morphomics methods, which measure psoas at the L4 level specifically and for which no referent values are published. However, the use of single-center data is also a strength for this retrospective study, as KPS assessment protocols and patient population norms are likely to be more consistent and more homogenous within a single transplant center than between centers.

A major but unavoidable limitation to the study is the retrospective design of the study, which introduced potential selection bias. There was potential for survivor bias by including only transplant recipients rather than all waitlist candidates. In contrast, the sample may have been biased toward sicker patients if sicker patients are likely to undergo more frequent abdominal CT scans. We compared characteristics among patients excluded versus included and found some indication that excluded patients were less sick. However, the primary outcome variable, functional status, was not significantly different between groups. As sarcopenia and muscle wasting were associated with cirrhosis severity, it is possible that our results are exaggerated by focusing on a subset of sicker patients. The retrospective design also meant we were also likely unable to capture true "baseline" psoas muscle measures.

This study was innovative in its approach by focusing on clinical translation of our process and results: we worked with an MD Radiologist with fellowship training in abdominal imaging to collect data in real-time. In contrast, most research studies on sarcopenia rely on expensive and technically sophisticated Matlab engineering/image processing software to collect and interpret data. While having a single rater for psoas muscle measures could be a limitation, the very high level of technical expertise and high agreement between measures (97%) on assessment of intra-rater reliability virtually eliminate this potential threat to validity. We defined the primary variables, specifically "sarcopenia" and functional status, using universally available cut-points or relative to the patient's own baseline rather than only reporting tertiles within our unique population,

which may not necessarily translate to another center or for assessing an individual patient.

CONCLUSIONS

The results of this study show a moderate correlation between clinically evident functional impairment/disability, assessed by providers, using the Karnofsky Performance Status scale, and sarcopenia, an objective marker of frailty syndrome that can be measured on abdominal CT scan. Both the extent and rate of muscle wasting were significantly associated with pre-transplant functional status on regression modeling, increasing risks of severe functional impairment/disability by 2–3-fold after adjustment for age, gender and race. However, if sarcopenia were a direct objective representation of clinical functional status, the correlation coefficients and odds ratios would be many times greater than we observed. We hypothesize that sarcopenia and functional status likely measure different aspects of liver failure and that global health status in liver transplant patients may be affected by an array of heterogeneous disease manifestations that we were unable to dissect due to limited sample size. More research on the utility of using either or both measures in prognostication and management of high-risk liver transplant patients is warranted. Better understanding and characterization of frailty syndrome in liver transplant patients holds great potential for improving clinical care and informing decision-making for patients on the transplant waitlist.

Table 3.1: Pre-transplant characteristics of subjects that underwent liver transplantation at UMass Memorial 2006–2015, by category of sarcopenic versus not sarcopenic on pre-transplant CT (n = 136)

	Sarcopenia, pre-transplant†	
Characteristic*	**> 1 SD below normal (n = 67)**	**Within normal limits (n = 69)**
Age ≥ 55 years	70.2	46.4
Women	34.3	33.3
Ethnic minority	25.4	20.3
Primary insurance		
Private	43.3	34.8
Public-Medicaid[a]	26.9	42.0
Public-Medicare	29.9	23.2
Body Mass Index, kg/m^2	27.0 (5.5)	29.3 (5.6)
Weight, kg	77.6 (19.3)	86.2 (19.1)
Height, m	1.69 (0.1)	1.71 (0.1)
Diabetes[b]	34.3	14.5
Primary Cause of Liver Disease		
Hepatitis C and similar infections	38.8	55.1
Alcoholic Hepatitis	29.9	18.8
Other liver diseases	31.3	26.1
Hepatocellular Carcinoma	29.9	42.0
Child-Pugh class		
A (mild)	4.5	10.1
B (moderate)	19.4	29.0
C (severe)	76.1	60.9
Waitlist time, months	2.2 (0.6–11.1)	3.6 (1.0–13.0)
MELD score (laboratory)	24 (16–34)	17 (12–27)
< 15	19.4	43.5
15–29	44.8	34.8
≥ 30	35.8	21.7
Creatinine	2.1 (1.8)	1.5 (1.4)
Total bilirubin	9.4 (10.9)	8.5 (11.5)
International Normalized Ratio	2.0 (1.4)	2.0 (2.0)
Albumin	3.0 (0.7)	3.0 (1.0)
Medical Condition		
Hospitalized	25.4	27.5
ICU	31.3	11.6
Life support	17.9	5.8
Psoas muscle density, Hu	36.1 (7.6)	43.4 (8.9)
Total psoas area, mm^2	1,442 (376.9)	2,212.3 (491.1)

*Column percent, mean (standard deviation), or median (interquartile range)

†Lean psoas area on pre-transplant (≤ 90 days) abdominal CT that is > 1 standard deviation below gender-specific averages (cut-points: men: 1,488.4 mm^2; women: 974.8 mm^2) reported in a study of 1,279 patients admitted for elective general surgery procedures from 2006–2011 at University of Michigan (Kirk PS, *et al* 2015).

[a]Includes 1 person with insurance type - other

[b]Diabetes types 1, 2, or unspecified

Kg: kilograms; **KPS:** Karnofsky Performance Status; **m**: meters**; MELD:** Model for End-Stage Liver Disease; **n**: number

Table 3.2: Changes in psoas muscle measures from baseline to pre-transplant CT, by gender, UMass liver transplant recipients 2006–2015 (n = 136)

Relative Change, %*	Men (n = 90)	Women (n = 46)
Δ **Total Psoas Area**[a]	-11.3 (-21.1 to -0.7)	-2.9 (-16.7 to 8.9)
Δ **Density**[b]	-1.5 (-20.2 to 12.0)	-10.0 (-24.5 to 16.6)
Δ **Lean Psoas Area**[c]	-10.9 (-25.3 to -1.0)	-3.4 (-20.3 to 6.4)
Δ **Lean Psoas Area/month**[d]	-0.5 (-1.4 to -0.1)	-0.1 (-1.6 to 0.8)

*% = (Pre-transplant – baseline) / baseline, median (interquartile range)
[a]Total psoas area = left + right psoas, mm^2
[b]Density = Mean density of left and right psoas, Hounsfield units
[c]Total psoas area x Density adjustment factor
[d]Per month between CT scans; median (interquartile range) values for men: 11.6 (4.7–41.4) months, women: 13.0 (1.4–33.7) months (p = 0.30).

CT: Computed tomography scan; **n:** number in group; **p:** probability.

Table 3.3: Characteristics in relation to rate of change of lean psoas area (tertiles), UMass liver transplant recipients 2006–2015 (n = 136)

	Tertiles of Rates of Change in Lean Psoas Area over Baseline[†]		
	Highest	**Moderate**	**Minimal/No loss**
Median (range), %/month:	-2.75 (-57.92 to -1.02)	-0.45 (-0.95 to -0.09)	1.13 (-0.06 to 79.08)
Time between CT scans, months:	6.8 (2.7–13.0)	37.6 (16.6–64.8)	8.7 (1.8–35.2)
Characteristic*			
Age ≥ 55 years	56.5	62.2	55.6
Women	30.4	20.0	51.1
Ethnic minority	17.4	26.7	24.4
Public health insurance	56.5	66.7	60.0
Body Mass Index, kg/m^2	24.5 (4.9)	29.0 (5.1)	28.1 (6.8)
Weight, kg	81.2 (19.1)	85.4 (16.7)	79.3 (22.5)
Height, m	1.71 (0.1)	1.71 (0.1)	1.67 (0.1)
Diabetes[a]	21.7	35.6	15.6
Primary Cause of Liver Disease			
Hepatitis C/viral-other	45.7	53.3	42.2
Alcoholic Hepatitis	23.9	24.4	24.4
Other liver diseases	30.4	22.2	33.3
Hepatocellular Carcinoma	21.7	44.4	42.2
Time on waiting list, months	1.7 (0.5–6.1)	6.4 (1.5–15.5)	3.0 (0.8–13.9)
Weight loss per month on waitlist			
< 0–≤ 5%	28.3	57.8	45.5
> 5%	26.1	8.9	25.0
MELD at registration[b]	22 (12–29)	14 (10–20)	15 (10–20)
MELD pre-transplant[b]	29 (20–38)	19 (12–24)	16 (12–25)
Creatinine	1.4 (0.9–2.4)	1.0 (0.8–1.6)	1.1 (0.8–2.1)
Total bilirubin	11.1 (3.5–19)	3.0 (1.5–6.1)	3.1 (1.4–6.3)
International Normalized Ratio	2.0 (1.4–2.6)	1.5 (1.2–1.9)	1.4 (1.2–1.8)
Albumin	2.9 (2.7–3.3)	2.8 (2.5–3.5)	3.0 (2.4–3.4)
Child Pugh			
B	17.4	24.4	31.1
C	80.4	62.2	62.2
Portal Vein Thrombosis	17.4	15.6	13.3
Medical condition			
Not Hospitalized	32.6	57.8	66.7
Hospitalized, not ICU	32.6	26.7	20.0
ICU	34.8	15.6	13.3
Life support	21.7	6.7	6.7

*Column percent, mean (standard deviation), or median (interquartile range)
†Tertile categories, %/month; Severe/Moderate/None: n = 46/45/45
[a]Diabetes types 1, 2, or unspecified
[b]Laboratory calculated MELD score

Kg: kilograms; **m:** meters**; MELD:** Model for End-Stage Liver Disease; **n:** number

Table 3.4: Unadjusted and adjusted odds ratios (95% CIs) for severe functional impairment/disability by rate of muscle wasting, pre-transplant sarcopenia, and decrease in lean psoas area, UMass liver transplant recipients 2006–2015 (n = 136)

		Severe impairment/disability[†]	
	% Impaired	**Unadjusted**	**Adjusted[a]**
Rate of muscle wasting[b]			
High	56.5	2.60 (1.11–6.09)	2.83 (1.18–6.80)
Moderate	46.7	1.75 (0.75–4.11)	1.84 (0.75–4.51)
Minimal/None	33.3	*Referent*	*Referent*
Sarcopenic pre-transplant[c]			
> 1 SD below normal	56.7	2.46 (1.23–4.91)	2.67 (1.29–5.52)
Within normal limits	34.8	*Referent*	*Referent*
Lean Psoas Area pre-transplant[d]			
Per standard deviation unit decrease		1.83 (1.24–2.69)	2.32 (1.44–3.75)

[†]Karnofsky Performance Status, 10–40% versus 50–100% (referent)

[a]Adjusted for age (≥ 55/< 55 years), gender and race (white/non-white).

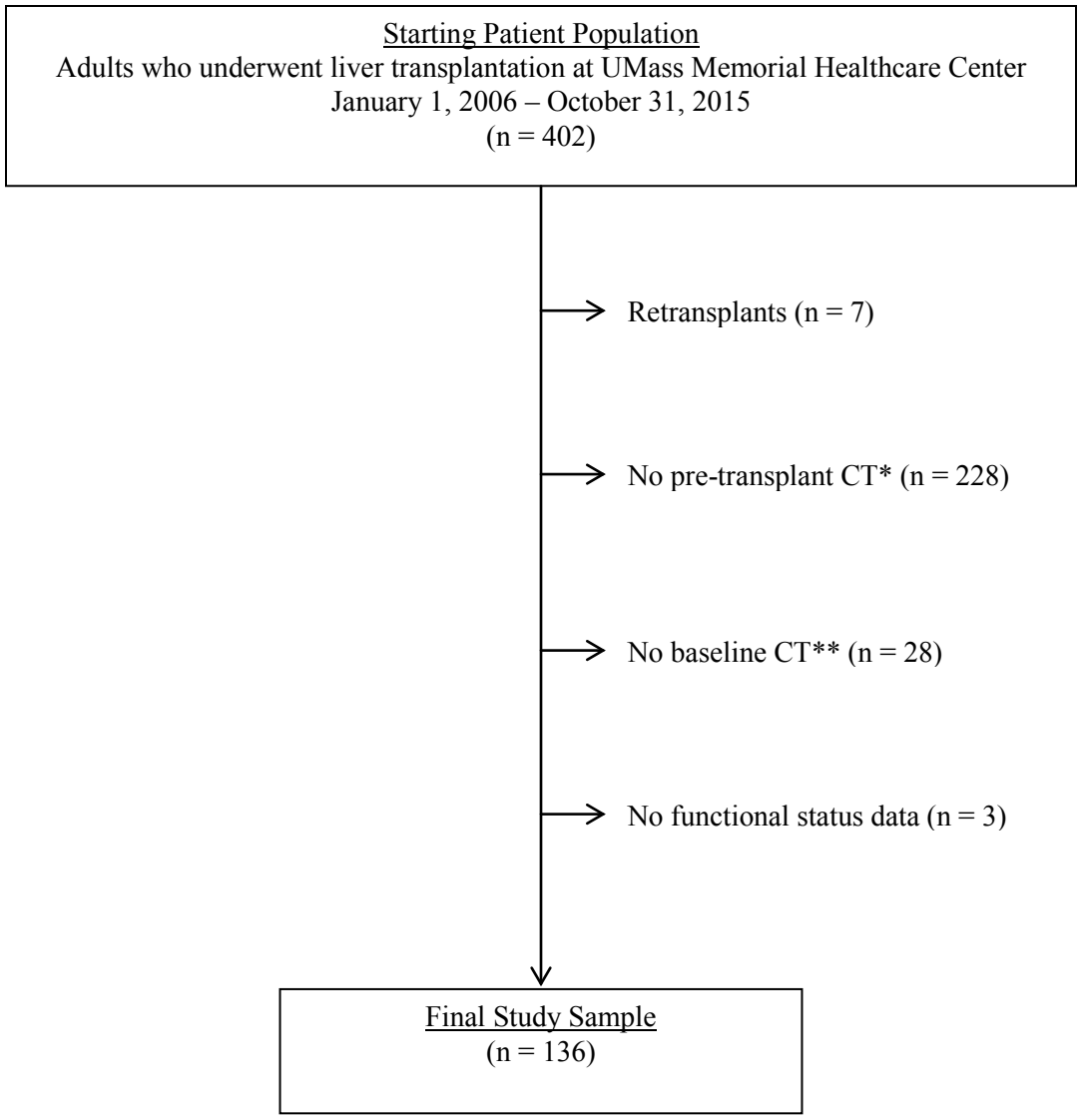
[b]Tertiles of relative loss in lean psoas area per month, High: ≥ 1% loss/month; Moderate: < 1%–0.1% loss/month; Minimal/None: < 0.1% or increase in lean psoas area

[c]Lean psoas area on pre-transplant (≤ 90 days) abdominal CT that is > 1 standard deviation below gender-specific averages (cut-points: men: 1,488.4 mm^2; women: 974.8 mm^2) reported in a study of 1,279 patients admitted for elective general surgery procedures from 2006–2011 at University of Michigan (Kirk PS, *et al* 2015).

[d]Decrease relative to sample distribution at single pre-transplant time point

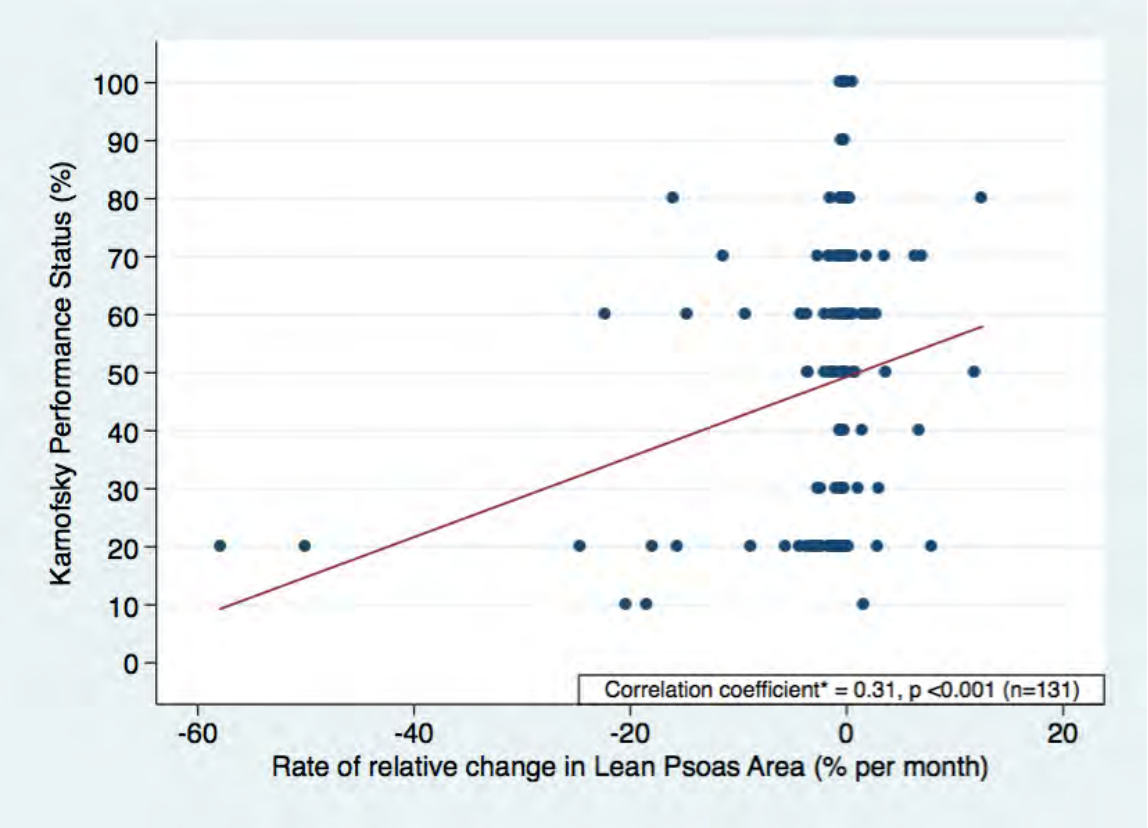
CI: confidence interval. **n:** number in group.

Figure 3.1: Study inclusion/exclusion flow chart



*Abdominal CT ≤ 90 days before transplant
**Abdominal CT at least 7 days before pre-transplant CT

Figure 3.2: Correlation between pre-transplant functional status and rate of change in Lean Psoas Area from baseline to pre-transplant, UMass liver transplant recipients 2006–2015 (n = 131)



*Correlations were assessed using spearman's rho for rank-order correlation between 10-point Karnofsky Performance Status scale and continuous sarcopenia and restricted to the range of lean psoas area values for which test assumptions were not violated: below (+) 20% increase in the rate of relative Lean Psoas Area change/month (see appendix 3B for further detail on this determination).

CHAPTER IV

IMPACT OF RECIPIENT FUNCTIONAL STATUS ON LIVER TRANSPLANT OUTCOMES

ABSTRACT

Background: Program Specific Reports attempt to risk-adjust outcomes for transplant centers' unique case-mix by including a global measure of physical health status in their liver transplant survival models, the Karnofsky Performance Status (KPS) scale. Although the KPS scale has been widely validated and used in clinical practice and research for over 60 years, there is a paucity of evidence on its utility in patients undergoing liver transplantation. We examined the extent to which pre-transplant functional status is associated with increased risk of mortality and/or graft failure at 1-year post-transplant.

Methods: This retrospective cohort study included 38,278 U.S. adults (≥ 18 years) who underwent first, non-urgent, liver-only transplantation from 2005 to 2014 (Scientific Registry of Transplant Recipients). We used the KPS to categorize patients as having functional impairment/disability that is Severe (10–40%), Moderate (50–70%), or None/Normal (80–100%) and examined the risk of patient and graft survival using multivariable-adjusted Cox survival regression models.

Results: The median age of this population was 56 years, 31% were women, and median laboratory-calculated pre-transplant MELD was 18. Functional impairment/disability was present in 70%; approximately one-quarter was severely impaired. After controlling for key recipient and donor factors, severely and moderately impaired/disabled patients had a 1-year mortality rate that was 1.73 (95% confidence interval (CI): 1.56–1.91) and 1.32 (CI: 1.21–1.44) times higher than patients with normal functional status, respectively. Subjects with severe and moderate disability also had multivariable-adjusted 1-year graft

failure rates that were 1.16 (CI: 1.02–1.31) and 1.13 (CI: 1.02–1.24) times higher than patients with normal function, respectively.

Conclusions: Pre-transplant functional status is an important prognostic indicator for 1-year post-transplant patient and graft survival for liver transplant recipients.

INTRODUCTION

Due to increasing organ shortages in the U.S., patients on the liver transplant waiting list are older and sicker than ever before and wait time continues to climb (10,197). Among the 15,000 patients with End-Stage Liver Disease on the transplant waiting list in 2013, 20% were over 65 years old, 20% had been waiting for at least 5 years already, 20% died while awaiting transplant, and fewer than 6,000 patients received an organ in 2013 (10). In 2002, in response to increasing shortages and waitlist mortality, the liver allocation system was reorganized to prioritize patients according to urgency (196). "Urgency" was defined according to risk of 3-month mortality, calculated using 3 objective laboratory parameters (creatinine, bilirubin, international normalized ratio) to create individualized Model for End-Stage for Liver Disease (MELD) scores used to rank patients. Although this system successfully lowered population-level waitlist mortality rates, it is an insufficient summary measure for describing global health status (19,25,26,198), and has recently been shown to underestimate mortality risk among subgroups of "frail" patients (25,30,31).

Frailty syndrome is defined by a cluster of subtle signs and symptoms that were originally observed in a geriatric population, but also hallmark sequelae of liver disease: malnutrition, sarcopenia, functional impairment/disability, and ultimately, increased vulnerability to stressors due to depleted physiologic reserve (86). Frailty is increasingly recognized as an important predictor of outcomes after many different major surgical procedures, including liver transplantation (34–39,50,199,200,227,228). However, there is no gold standard measure of frailty (229). At present, U.S. liver and lung transplant

centers are mandated to submit Karnofsky Performance Status (KPS) functional status data on all patients, with other clinical data, to the Organ Procurement and Transplantation Network (OPTN) each quarter. The KPS scale has been widely validated across many disease groups, including End-Stage Renal Disease, and has been widely used in clinical practice and research for over 60 years (51,64,66,67,101,114,131,201–218). Several studies have used KPS as a predictor of liver transplant outcomes, but the studies were limited in generalizability as they were single-center studies (32,201), outside of the U.S. (199,200), limited to the early post-transplant period (199,200), and/or took place before MELD implementation at which point the transplant recipient population shifted dramatically (201,230). In 2013, the Liver and Intestinal Transplant Committee of OPTN publically asked for researchers to fill the gap in the literature on the utility of the KPS scale in a national liver transplant population (218).

To our knowledge, this will be the first study to evaluate a standardized, validated measure of functional status as a predictor of transplant survival in a national U.S. liver transplant population. Using data from the only comprehensive nationwide transplant database, the United Network for Organ Sharing (UNOS) Scientific Registry of Transplant Recipients, we assessed the clinical utility of the Karnofsky Performance Status (KPS) scale for the prediction of 1-year post-liver transplant patient and graft survival.

METHODS

Study Design and Sample

This retrospective cohort study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR is contracted to UNOS by the U.S. Department of Health and Human Services to manage data collected via government-mandated reporting by all U.S. transplant centers (195).

The study population included patients that underwent a first liver transplant between January 1, 2005 and October 1, 2014 (Figure 1). Exclusion criteria consisted of the following: 1) pediatric transplant (< 18 years), 2) multi-organ transplant, 3) UNOS Status 1 or acute liver failure (231,232), 4) Intensive Care Unit (ICU) pre-transplant, or 4) subjects with missing data in any of the key variables of interest (variables with ≥ 5% missing values were not used in this study). We excluded urgent (Status 1 or acute hepatic necrosis) and ICU-admitted patients. This was done because these are often patients who rapidly decline due to an inciting event (e.g., infection) and may, therefore, be categorized as being of poor functional status due to the event as opposed to being truly "frail," which is conceptualized as a chronic process leading to depletion of physiologic reserve.

Data Collection

Exposure Variable

The primary exposure of interest was provider assessment of preoperative ("pre-transplant") functional status using the Karnofsky Performance Status (KPS) scale (Table 1.1). The KPS defines functional status on an 11-point scale from 100% (normal, no complaints, no evidence of disease) to 0% (dead) in 10% increments, with 3 corresponding tiers. We used the 3-tiered version of the scale based on higher inter-rater reliability scores (201,202,210). We assigned labels to the categories with respect to level of functional impairment/disability as follows: subjects with minimal or no symptoms of disease (80–100%) were labeled "(A) None/Normal [function]"; subjects needing varying levels of assistance in daily activities (50–70%) were labeled "(B) Moderate [impairment in function]"; and subjects who were disabled and/or hospitalization indicated and/or moribund (10–40%) were labeled "(C) Severe [functional impairment/disability]."

Study End Points

The primary outcome of interest was 1-year all-cause mortality (Social Security Death Master File/Organ Procurement and Transplant Network). We also examined death rates during the 1-month postoperative period (day 0–30) as compared to residual risk during the remaining 11 months of the year (day 31–365). Since mortality after transplantation is highest in the early postoperative period and likely related to operative risks and complications that may become less relevant for long-term outcomes, the importance of functional status may change with time and context (233). The secondary outcome of interest was 1-year graft failure.

Lastly, among patients who did not experience either adverse outcome (death or graft failure), we describe the proportion that was able to return to "Normal" functional status during the first year post-transplant. Transplant centers must report follow-up data on transplant recipients at 6-months post-transplant, 1-year, and annually thereafter; follow-up records from day 0 to 395 (365+30 days) with functional status data available (< 5% of recipients were missing follow-up functional status) were analyzed (but counted once per patient).

Potential Confounding Variables

Potential confounders were identified from *a priori* clinical knowledge, literature review, and variables included in the SRTR risk-adjustment models, available at srtr.org (234). Potential confounders included recipient sociodemographic and medical/surgical history factors (i.e. information known at least 2 weeks before transplant, e.g. primary liver diagnosis; Table 4.1), pre-transplant illness severity markers (e.g. last-calculated laboratory MELD (233); Table 4.2), and all Donor Risk Index (235) factors (e.g. cause of death; Table 4.3) as potential confounding variables. Every variable evaluated for potential confounding was categorized and described in Tables 4.1–4.3 (exceptions: baseline functional status, time on the waitlist, and MELD component labs are listed for descriptive purposes only).

Statistical Analysis

We explored bivariate relationships between the primary exposure (functional status) and potential confounders of interest using contingency table analyses (chi-squared (χ^2) tests for categorical variables, ANOVA for continuous variables, and Spearman's rho (r_s) for ordered-variable correlations, using expanded KPS, continuous MELD). Relationships between variables and post-transplant time were explored graphically. One-year cumulative failure rates were estimated using the Kaplan Meier method.

To quantify the extent to which impaired functional status was associated with increased risk of 1-year all-cause mortality and 1-year graft failure, we developed separate Cox survival regression models for each outcome. We applied a manual forward approach, sequentially adding conceptually meaningful groups of variables to the model. With the exception of recipient age, sex, race/ethnicity, and MELD, variables (and variable interactions) with p-values of > 0.05 were excluded from the final model. Goodness-of-fit and proportionality of hazards were tested using the omnibus Gronnesby and Borgan test and martingale residuals and confirmed non-significant (no evidence of poor fit) for all models reported (236).

Results are reported as hazard ratios (HR) and accompanying 95% confidence intervals (CI); p-values ≤ 0.05 were considered statistically significant. All analyses were conducted using Stata version 13 (StataCorp LP, College Station, TX). This study was deemed exempt by the University of Massachusetts Medical School Institutional Review Board.

RESULTS

Sample Characteristics

The final study sample included 38,278 liver transplant recipients (Figure 4.1). The median (interquartile range [IQR]) age was 56 (51–61) years and MELD was 18 (12–25). Women represented 31% of the sample and the largest ethnic minority was Hispanic/Latino (12.7%). Median follow-up time was 3.3 (1.5–6.0) years after transplant.

At pre-transplant assessment, approximately 70% of the sample had some degree of functional impairment or disability. Approximately one-quarter (23.7%) had "Severe" functional impairment/disability (≤ 40% function), 45.8% were "Moderately" impaired, and the remaining 30.5% had no functional impairments (≥ 80% function). The median (IQR) pre-transplant functional performance status score was 60% (50–80%) and the mean (standard deviation) was 61% (21%).

Baseline Characteristics and Changes over Waitlist Course

Table 4.1 describes baseline characteristics of the sample by category of pre-transplant functional status. Subjects who were of worse functional status pre-transplant were more likely to be female, of Hispanic/Latino race/ethnicity, and/or have Medicaid insurance. Primary diagnosis of hepatic malignancy was associated with better physical function. Baseline and pre-transplant functional status were moderately correlated (r_s =

0.42, $p < 0.001$). Sixty-percent of recipients maintained the same level of function over their waitlist course while 30% declined from a higher level of function at baseline.

Table 4.2 describes recipient clinical characteristics pre-transplant by category of pre-transplant functional status. Significant weight loss (≥ 5% of baseline weight) over the waitlist period was more common among transplant recipients who were impaired/disabled pre-transplant, and the weight loss occurred more rapidly; more disabled patients had shorter average wait times compared to patients of Normal functional status. Poor functional status was moderately correlated with worse (higher) MELD scores ($r_s = -0.49$; $p < 0.001$). However, only 64% of subjects with MELD scores ≥ 30 were "Severely" impaired/disabled, and less than half (44%) of patients with MELD scores < 15 were of "Normal" functional status. Cirrhosis severity according to Child-Pugh class was associated with severity of functional status. However, twice as many subjects were classified as Child C (severe) than were considered to have severe functional impairment/disability (20,937 versus 9,074). Around 10% of severely impaired subjects were on dialysis pre-transplant, compared to < 1% of Normal functional status subjects.

Table 4.3 describes donor characteristics by categories of pre-transplant functional status. Donor characteristics were mostly comparable across functional status categories. Only 8.3% of living donor liver transplant recipients was Severely impaired/disabled (n = 729). Functionally impaired patients were slightly less likely to receive higher risk organs (e.g. donor ≥ 70 years, nationally allocated or with prolonged cold ischemia time).

All-Cause Mortality

Death within one year was observed in 3,595 (9.4%) transplant recipients. The mortality rate was directly related to functional status. Among patients that were severely impaired/disabled, 12.8% died compared with 9.3% of those with moderate functional limitations and 6.9% of those with normal functional status at the time of transplant.

Table 4.4 describes the results of unadjusted and adjusted Cox regression models for 1-year mortality. Subjects with severe or moderate functional impairment pre-transplant were at significantly increased risk of dying within one year post-transplant. After multivariable adjustment, severely and moderately impaired patients had 1-year mortality rates that were 1.73 (CI: 1.56–1.91) and 1.32 (CI: 1.21–1.44) times greater than the hazard for subjects without any functional impairment, respectively.

Mortality risks were greatest in the immediate postoperative period (day 0–30) when 881 (2.3%) deaths were observed in a single month. The adjusted 30-day mortality risk for Severely impaired/disabled patients was more than double (HR: 2.10; CI: 1.71–2.59) that of patients of "Normal" functional status, after adjusting for all variables controlled for in the full 1-year survival model (Table 4.4). Approximately three-quarters (n = 2,714) of all one-year deaths occurred during the remaining 11 months of the postoperative year (day 31–365); HRs were comparable to estimates for overall one-year mortality (< 10% relative difference).

Graft Failure

Graft failure was observed in 2,214 of the study population within one year of transplant. The estimated failure rate on day 365 was 6.2% (cumulative failure *or* death rate on day 365: 12.7%). Approximately half (53.8%) received a second transplant within the first post-transplant year, of which 75.9% (n = 905) survived the year; 98.6% (n = 1,008) of those who did not undergo retransplantation within the first postoperative year did not survive to 1-year post-transplant.

Table 4.5 describes the results of unadjusted and adjusted Cox regression models for 1-year graft failure. Subjects with severe and moderate impairment/disability had multivariable-adjusted 1-year graft failure rates that were 1.16 (CI: 1.02–1.31) and 1.13 (CI: 1.02–1.24) times higher than patients with normal function, respectively.

Functional Status Post-Liver Transplant

Among the 33,764 (88.2%) transplant recipients who experienced neither outcome (death or graft failure within a year), 95% (n = 32,004) had at least 1 follow-up functional status assessment within a year. The majority (86.3%) recovered from transplant and reached "Normal" functional status within 1 year. Of the 7,258 recipients in this subsample that were severely impaired/disabled pre-transplant, 81% (n = 5,861) recovered full physical function ("Normal" functional status) within 1 year of transplant.

DISCUSSION

Almost 1 in 4 patients included in this national study of 38,278 U.S. adults that underwent non-urgent liver transplantation between 2005 and 2014 had severe functional impairment/disability at the time of transplant. This group of patients was found to have a markedly increased hazard of dying and/or having graft failure at 1 year compared to Normal functional status patients. This increased hazard was observed in both unadjusted and multivariable-adjusted regression analyses controlling for a variety of potentially confounding factors of prognostic importance. Approximately 86% of recipients who did not experience 1-year death or graft failure (and had follow-up data available) recovered from transplant and reached "Normal" functional status within 1-year.

We present data from the first national study illustrating the role of pre-transplant functional status as a predictor of one-year survival among liver transplant recipients. Our results are in agreement with the findings from earlier studies that evaluated Poor functional status as a predictor of adverse transplant outcomes (32,199–201). Two such studies, each with approximately 4,000 U.K. recipients of a liver transplant, reported a near 2-fold increased risk of post-transplant mortality at 90 days for the worst functioning group relative to the highest functioning group (199,200). Studies have also shown that objective measures of physical function, such as walking distance or speed and grip strength, are also strong predictors of adverse liver transplant outcomes regardless of recipient age, size, or cause/severity of liver disease (32).

Implications

Insight into a transplant patient's global health status guides day-to-day clinical management, as well as transplant decisions, particularly in the face of contradictory laboratory or otherwise objective measures of pathological disease progression (e.g. MELD score). Capturing such insight through the use of a quantitative physical health scale may help transplant teams to strategize and communicate complex medical and surgical management decisions with patients, families, and the many other members of multidisciplinary transplant teams that provide longitudinal care for liver transplant patients.

Knowledge of a patient's functional status before transplant may practically assist transplant teams to anticipate, communicate, and coordinate resources for postoperative critical care, rehabilitation after discharge, and potentially longer-term occupational therapy to help patients recover physical health and quality of life (237). Many well-established risk factors for adverse outcomes among patients undergoing liver transplant may be unpredictable or sudden (spontaneous bacterial peritonitis), unavoidable (older age), and/or untreatable (portal vein thrombosis). Furthermore, many of the strongest predictors of adverse outcomes are present in a relatively small percentage of the liver transplant population. Many risk factors are unknown until very close to transplant time (e.g. life support, cold ischemia time), whereas functional impairment can present very early and progress insidiously in end-stage liver disease patients over the course of waiting for an organ. All patients can also be assigned a value for functional status at baseline, which can be used as a reference point to assess change over time. While this

scale is an all-encompassing global physical function measure and a patient can fall anywhere on the continuous scale, many risk factors considered in transplant decisions are individual dichotomous variables, which are usually assessed in combination with other risk factors that can take time to accumulate. Thus, as functional status is a harbinger of adverse outcomes and may present early, it may be a useful clinical tracking tool that can be used for strategic care management.

Promising interventional studies have also shown that "prehabilitation," physical therapy (e.g. strength training) and nutritional support, designed to improve functional status (or slow decline) in anticipation of a physiologic stressor such as surgery (137,138), is effective at improving postoperative recovery and outcomes after major abdominal surgery (54,55,60–62). Although none of these studies focused on liver transplant patients, several included cohorts that similarly have a high likelihood of becoming frail due malnutrition, inflammation, and sarcopenia (e.g. cancer patients (55,61) and older populations (60,62)). Prehabilitation has the potential for providing clinicians with a way to not only recognize, but also slow or prevent decline to the point of "Severe" impairment/disability. However, more research on prehabilitation specific to a liver disease population is warranted. Frailty due to liver failure may not respond to the same interventions that have successfully slowed progression of frailty due to aging as there may be fundamental differences in etiology and pathogenesis between these populations that may limit their effectiveness (226).

Strengths and Limitations

Strengths of this study include its use of the SRTR with complete capture of every solid organ transplant in the U.S. since 1987, including waitlist, donor, follow-up, and external data file linkages (e.g. Social Security Death Master File). Mandated reporting of KPS providing more than a decade of nationally representative data on functional status is also a major strength of our investigation.

This study relies on the Karnofsky Performance Status scale as the only available measure of functional status in the SRTR. Limitations to using KPS to represent functional status on a national scale include: 1) lack of adequate validation in the liver transplant population, 2) subjectivity of the scale (relative to direct measures of frailty such as grip strength) which may result in heterogeneity across transplant centers depending on how, when, and by whom the variable is measured, and 3) vulnerability to transplant center "gaming" due to its inclusion as a risk-adjustment factor for SRTR-generated outcomes reports serving as the basis for federal regulatory action when outcomes are below-expected (218).

The KPS has been included in validation studies in transplant populations, where it has been compared with the Short Form survey and other physical function scales in liver, as an outcome (207), and has also been extensively validated in end-stage renal disease as a predictor (101,114). Results of validation studies across disease groups have shown excellent interrater reliability when the Karnofsky is used as a 3-tiered scale, regardless of provider type (201,202,210). Furthermore, an online SRTR analysis of measure variability across transplant centers and relationship with regulatory decisions on flagging centers found that inter-center variation had an impact on only a few centers'

outcomes enough to affect CMS auditing decisions. Lastly, we expect suspected "gaming" could result in some centers exaggerating their patients' functional status scores; this would mean that the risk estimates we report in this study have been artificially diluted by such behavior, and that "truly" impaired patients have even higher hazard ratios than we were able to show.

Finally, this study was limited to evaluating the KPS scale though there may be other, more appropriate scales to use in this population. Several different measures of physical function and composite frailty scores have been used in the literature and were effective predictors of waitlist and transplant outcomes. However, direct measures of frailty would demand more resources (time, training, materials) from transplant centers than the KPS alone, and should be compared with KPS for predictive value (area under the curve) before changing current practices. Future research may show that a liver transplant-specific functional status scale, incorporating additional objective parameters, may better suit this population's needs.

A better understanding of this phenomenon could help transplant centers to dynamically monitor patients on ever-growing waiting lists from a more comprehensive standpoint than MELD rank alone.

CONCLUSIONS

In summary, we have demonstrated the importance of a simple 3-point functional status scale for predicting one-year liver transplant outcomes. We highlight areas where future research may further the validity, and ultimately, the clinical utility of the

Karnofsky Functional Performance scale in a liver transplant population. It is important to continue to develop objective measures for describing global health status and illness severity to help in the allocation of organs and waitlist management, patient health improvement, and accurate adjustment for transplant center case-mix for transplant reimbursement.

Table 4.1: Baseline characteristics[†] by pre-transplant functional status, Scientific Registry of Transplant Recipients 2005–2014 (n = 38,278)

	Functional impairment/disability		
Characteristic[*]	**A None (n = 11,674)**	**B Moderate (n = 17,530)**	**C Severe (n = 9,074)**
Sociodemographics			
Age in years			
18–44	11.6	10.3	12.7
45–54	28.9	30.2	32.1
55–64	44.9	45.3	43.2
≥ 65	14.5	14.3	12.0
Women	26.8	32.1	33.4
Race/ethnicity			
White	73.1	74.3	70.4
Hispanic/Latino	10.6	12.5	15.9
Black	8.9	8.4	9.1
Health Insurance			
Private	68.1	55.3	54.2
Medicare	18.5	26.5	24.6
Medicaid	8.8	14.0	17.0
Medical/Surgical History			
Functional impairment at registration			
None	74.6	33.4	22.4
Moderate	19.9	57.0	35.4
Severe	2.5	6.6	37.0
Primary cause of liver disease			
Non-Cholestatic	56.2	64.7	75.8
Cholestatic	9.5	8.1	7.8
Malignancy	30.1	23.0	12.5
Hepatitis C	44.4	45.5	42.1
Diabetes[a]	23.2	25.8	25.3
Previous Abdominal Surgery	46.2	51.6	50.3

All distributions varied significantly across categories of functional status ($p<0.001$)
[†]Characteristics known at least 2 weeks prior to transplant
[*]Column percentage
[a]Diabetes types 1, 2, or unspecified

n: number in group; **p**: probability

Table 4.2: Pre-transplant clinical characteristics by pre-transplant functional status, Scientific Registry of Transplant Recipients 2005–2014 (n = 38,278)

	Functional impairment/disability		
Characteristic*	**A None (n = 11,674)**	**B Moderate (n = 17,530)**	**C Severe (n = 9,074)**
Waitlist time, months	4.0 (1.3–10.2)	3.7 (1.1–10.3)	2.1 (0.4–8.4)
Weight loss ≥ 5%[a]	19.7	24.2	27.0
BMI, kg/m^2			
Underweight (<18.5)	1.6	1.6	2.4
Normal (18.5–< 25)	28.3	27.5	27.1
Overweight (25–< 30)	37.0	36.0	34.0
Obese (≥ 30)	33.2	35.0	36.5
MELD			
< 15	49.9	34.9	14.3
15–29	45.9	56.5	45.9
≥ 30	4.2	8.6	39.8
Total bilirubin	2.3 (1.2–4.4)	3.0 (1.6–6.1)	6.6 (2.9–17.2)
International normalized ratio	1.4 (1.2–1.7)	1.5 (1.3–1.9)	2.0 (1.5–2.6)
Serum creatinine	0.9 (0.7–1.2)	1.0 (0.8–1.3)	1.4 (0.9–2.3)
Serum sodium	137 (134–140)	136 (133–139)	135 (132–139)
Child Pugh score			
A (Good)	23.8	11.8	4.1
B (Fair)	38.7	33.8	18.5
C (Poor)	37.5	54.4	77.4
Ascites[b]			
None	36.9	23.0	14.0
Mild/Moderate	48.4	52.4	43.5
Severe	14.8	24.6	42.6
Encephalopathy[c]			
None	52.7	36.6	26.0
Grade 1–2	44.4	57.5	61.4
Grade 3–4	2.9	5.9	12.6
Albumin			
> 3.5	26.7	19.3	22.8
2.8–3.5	41.7	41.2	39.0
< 2.8	31.6	39.6	38.2
Dialysis[d]	0.9	1.6	10.9
Portal Vein Thrombosis	6.5	9.7	12.4

All distributions varied significantly across categories of functional status ($p < 0.001$)
*Column percentage or median (interquartile range)
[a]Relative to weight at time of waitlist registration
[b]Mild/Moderate ascites: diuretic-responsive; Severe ascites: diuretic-refractory
[c]Encephalopathy grade 1–2 (or precipitant-induced); Grade 3–4 (or chronic)
[d]Dialyzed at least twice in prior week

BMI: body mass index; **kg:** kilograms; **m**: meters**; MELD:** Model for End-Stage Liver Disease; **n**: number in group; **p**: probability

Table 4.3: Donor characteristics by pre-transplant functional status, Scientific Registry of Transplant Recipients 2005–2014 (n = 38,278)

	Functional impairment/disability			
Characteristic*	**A None (n = 11,674)**	**B Moderate (n = 17,530)**	**C Severe (n = 9,074)**	**p-value**
Transplant type: Living donor	5.5	5.0	2.3	< 0.001
Donor Risk Index[a]	1.6 (1.3–1.9)	1.6 (1.3–1.9)	1.5 (1.2–1.9)	< 0.001
Age in years				
18–39	37.3	37.1	39.9	
40–49	19.7	19.7	19.7	
50–59	19.8	20.4	20.7	
60–69	11.7	12.7	10.8	
≥ 70	5.5	4.9	3.9	< 0.001
Women	40.5	41.4	40.9	0.35
Race/ethnicity				
White	68.2	68.1	65.6	
Black	17.2	17.9	17.5	
Other	14.6	14.0	16.9	< 0.001
BMI, kg/m^2				
Underweight (< 18.5)	2.9	2.9	2.6	
Normal (18.5–< 25)	36.5	35.9	36.2	
Overweight (25–< 30)	33.5	34.2	33.4	
Obese (≥ 30)	27.1	27.0	27.9	0.43
Cause of death				
Trauma	34.3	34.1	34.1	
Anoxia	21.5	22.5	24	
Cardiovascular accident	41.4	40.9	39.4	< 0.01
Donation after cardiac death	12.6	13.2	12.1	0.04
Split/Partial liver	1.5	1.4	1.3	0.38
Allocation type				
Regional	17.8	19.9	23.3	
National	6.6	5.0	3.8	< 0.001
Cold ischemia time ≥ 8 hours	30.9	28.9	27.9	< 0.001

*Column percentage or median (interquartile range)
[a]Donor risk index as described by Feng *et al* 2006

BMI: body mass index; **kg:** kilograms; **m**: meters; **n**: number in group; **p**: probability

Table 4.4: Association between pre-transplant functional status and 1-year (all-cause) post-transplant mortality, Scientific Registry of Transplant Recipients 2005–2014 (n = 38,278[†])

Functional impairment /disability	**Hazard Ratio (95% CI)**	
	1-Year	
	Unadjusted	Adjusted[a]
Severe	1.94 (1.77–2.13)	1.73 (1.56–1.91)
Moderate	1.38 (1.27–1.51)	1.32 (1.21–1.44)
None	*Referent*	*Referent*

	Day 0–30[b]		**Day 31–365[c]**	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Severe	2.40 (1.99–2.89)	2.10 (1.71–2.59)	1.82 (1.64–2.02)	1.62 (1.45–1.82)
Moderate	1.60 (1.34–1.92)	1.53 (1.27–1.83)	1.33 (1.20–1.46)	1.26 (1.15–1.40)
None	*Referent*		*Referent*	

[†]Adjusted model n = 38,0762 (missing albumin (n = 1) or donor body mass index (n = 200))
[a]Adjusted for recipient age, sex, race, insurance, BMI, diabetes, previous abdominal surgery, liver disease, MELD, albumin, portal vein thrombosis, dialysis; donor age, race, BMI, donor type (living or deceased) and cause of death, donation after cardiac death, allocation type, cold ischemia time ≥ 8 hours; interactions: recipient BMI and diabetes, recipient hepatitis C and portal vein thrombosis, recipient hepatitis C and donor age.
[b]Postoperative day 0–30: n = 38,278; 881 deaths
[c]Postoperative day 31–365: n = 37,352; 2,714 deaths

BMI: body mass index; **CI:** confidence interval; **MELD:** Model for End-Stage Liver Disease; **n**: number in group

Table 4.5: Association between pre-transplant functional status and 1-year graft failure, Scientific Registry of Transplant Recipients 2005–2014 (n = 38,278)

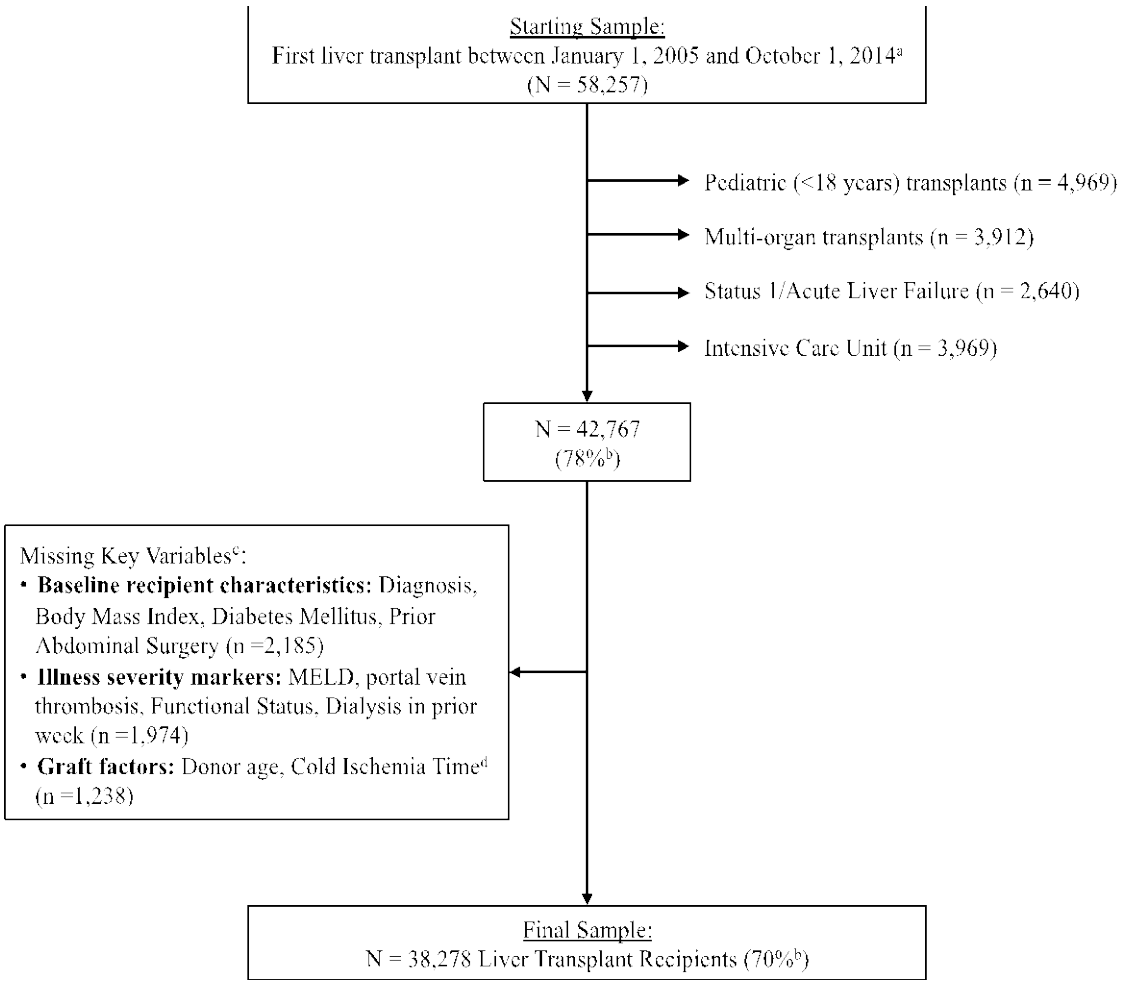
Functional impairment /disability	Events, n*	**Hazard Ratio (95% CI)** Unadjusted	Adjusted[a]
Severe	527	1.10 (0.98–1.23)	1.16 (1.02–1.31)
Moderate	1,051	1.12 (1.01–1.23)	1.13 (1.02–1.24)
None	636	*Referent*	*Referent*

*Number of graft failures within 1 year of liver transplantation

[a]Adjusted for recipient age, sex, race, BMI, primary diagnosis of liver disease, MELD, portal vein thrombosis; donor age, race, BMI, donor type (living or deceased) and cause of death, donation after cardiac death, cold ischemia time ≥ 8 hours; interactions: recipient hepatitis C and portal vein thrombosis, recipient hepatitis C and donor age.

BMI: body mass index; **CI:** confidence interval; **MELD:** Model for End-Stage Liver Disease; **n**: number in group

Figure 4.1: Study inclusion/exclusion criteria flow chart. Scientific Registry of Transplant Recipients



[a]Re-transplants were not included in analyses
[b]Percent = $N_{\text{remaining}} / N_{\text{starting sample}}$
[c]Only variables with < 5% missing values were considered
[d]Deceased donor cold ischemia time (living donor values corrected to median)

N: number in study population; **n:** number in group

CHAPTER V

FINAL SUMMARY & CONCLUSIONS

In this dissertation, we 1) evaluated the impact of transplant policy on incidence of candidate delisting due to “too sick to transplant” (Chapter II); 2) described the relationship between objective (sarcopenia) and subjective (functional status, KPS) measures of pre-transplant frailty (Chapter III); and 3) quantified the extent to which patients that are of poor functional status pre-transplant are at increased risk of 1-year post-transplant mortality and graft failure (Chapter IV).

CMS Policy and Trends in “Too Sick to Transplant” Delisting

In Chapter II, we examined national epidemiologic trends in incidence of waitlist removal on account of the patient being too frail to benefit from transplant (“too sick to transplant”), using more than a decade of national data (Scientific Registry of Transplant Recipients (SRTR)) from 2002 to 2012. Given the adverse effects that CMS Conditions of Participation policy has been shown to have on risk aversion among centers “flagged” for poor performance, we hypothesized that there would be a significant impact of COP implementation on trends in candidate removal from the liver transplant waitlist due to "illness severity" at the national level.

We observed increasing trends in delisting due to "illness severity" in the setting of comparable demographic and clinical characteristics. Delisting abruptly increased at the time of COP implementation and likelihood of being delisted continued to increase without attenuation over the duration of the study period. In contrast, COP

implementation had no significant impact on 1-year post-transplant mortality trends or incidence.

The implications of these findings are that patients who could potentially benefit from transplant are increasingly being denied this life-saving procedure while transplant mortality rates remain unaffected. The National Organ Transplant Act, the Institute of Medicine, and the Final Rule consistently supported 3 goals: to increase transplantation, to decrease waitlist mortality, and to maximize transplant benefit. However, we conclude that although the COP policy was a CMS quality initiative designed to improve patient outcomes, in reality, it failed to show beneficial effects for the liver transplant population overall.

Future studies on understanding these trends and efforts to rebalance the waitlist-transplant outcome scale are warranted, and this balance should be considered during future development of national policies and in clinical decision-making in order to better serve this patient population.

Association between Functional Status and Sarcopenia

In Chapter III, we explored the relationship between objective and subjective parameters of liver transplant patient frailty. We measured decline in lean core muscle mass ("sarcopenia") on abdominal CT scans collected retrospectively at a single U.S. transplant center between 2006 and 2015. The relationship between objective sarcopenia measures and subjective functional status, as assessed by transplant providers using the Karnofsky Functional Performance scale, was described and quantified.

The majority of the sample exhibited signs (70% with muscle wasting) and/or symptoms (86% with functional impairment) of frailty syndrome. Measures of sarcopenia including rate of muscle wasting and size of LPA pre-transplant were associated with elevated risks of functional impairment, disability, and/or being moribund pre-transplant. Our findings were in agreement with a recent study that asked a similar question in a different study population of aged (> 70 years) patients admitted for general surgery procedures at University of Michigan.

We concluded that the overall correlation between provider-assessed physical health status and sarcopenia in our sample was moderate. More research on the relationship between these variables is warranted. Understanding the clinical utility of using either or both measures for prognostication and management of high-risk liver transplant patients would further understanding of frailty and advance the field in refining and improving upon existing tools for assessing and describing illness severity in this population.

Association between Functional Status and Outcomes after Liver Transplantation

In Chapter IV, we quantify the extent to which pre-transplant functional impairment/disability (KPS) is associated with worse patient and/or graft survival within 1-year post-liver transplant using a decade of national data from 2005 to 2014 (SRTR). The majority of the sample (70%) was functionally impaired pre-transplant. Severely impaired patients had markedly increased hazards for both death and graft failure within 1-year of transplant compared to Normal functional status patients. These increased risks

were observed in both unadjusted and multivariable-adjusted survival regression analyses controlling for a variety of potentially confounding factors of prognostic importance. Among subjects who experienced neither outcome and had follow-up data on postoperative functional status available, the majority (86%) recovered from transplant and reached "Normal" functional status within the first post-transplant year. We conclude that pre-transplant functional status is an important prognostic indicator of 1-year post-transplant outcomes.

It is important to continue to develop objective measures for describing global health status and illness severity to help in the allocation of organs, waitlist management, patient health improvement, and accurate adjustment for transplant center case-mix for transplant reimbursement.

APPENDICES

SUPPLEMENTAL TABLES FOR CHAPTER III

Supplemental Table 3.1: Characteristics of the overall study cohort of UMass liver transplant recipients by inclusion/exclusion status, 2006–2015 (n = 402)

Characteristic*	Included (n = 136)	Excluded (n = 266)	p-value
Age in years	55.4 ± 9.5	55.6 ± 9.5	0.81
Women	33.8 (46)	39.1 (104)	0.30
Ethnicity			
White	77.2 (105)	84.4 (221)	
Hispanic/Latino	14.7 (20)	11.8 (31)	
Primary insurance			
Private	39.0 (53)	41.4 (110)	
Public-Medicaid[a]	34.6 (47)	28.2 (75)	
Public-Medicare	26.5 (36)	27.4 (73)	0.14
Body Mass Index, kg/m^2	28.2 ± 5.6	28.8 ± 6.8	0.60
Weight, kg	81.9 ± 19.6	83.1 ± 21.5	0.60
Height, m	1.70 ± 0.1	1.70 ± 0.1	0.69
Diabetes[b]	24.3 (33)	27.8 (74)	0.45
Primary Cause of Liver Disease			
Hepatitis C and similar infections	47.1 (64)	34.2 (91)	
Alcoholic Hepatitis	24.3 (33)	38.4 (102)	
Other liver diseases	28.7 (39)	25.9 (69)	< 0.01
Hepatocellular Carcinoma	36.0 (49)	16.9 (45)	< 0.001
MELD score, pre-transplant	22.3 ± 10.5	18.7 ± 11.0	< 0.01
Creatinine	1.8 ± 1.6	1.5 ± 1.1	0.02
Total bilirubin	9.0 ± 11.1	8.3 ± 11.6	0.62
International Normalized Ratio	2.0 ± 1.7	1.7 ± 0.8	< 0.01
Albumin	3.0 ± 0.8	2.9 ± 0.8	0.37
Child-Pugh class, pre-transplant			
A (mild)	7.4 (10)	6.0 (16)	
B (moderate)	24.3 (33)	30.5 (81)	
C (severe)	68.4 (93)	61.7 (164)	0.20
Waitlist time, months	3.2 (0.8–12.4)	3.4 (0.9–10.1)	0.96
Portal Vein Thrombosis	15.4 (21)	13.9 (37)	0.12
Medical condition			
Home	52.2 (71)	63.2 (168)	
Hospital	26.5 (36)	18.8 (50)	
ICU	21.3 (29)	15.0 (40)	0.02
Life Support	11.8 (16)	10.2 (27)	0.12
Functional Status[c]	47.3 ± 24.8	49.3 ± 23.2	0.42
Muscle wasting			
Lean psoas area	71.3 (97)	n/a	
Size, total psoas area	72.8 (99)		
Quality, mean density	55.2 (75)		

*% (n), mean ± standard deviation, or median (interquartile range)
[a]Includes 1 person with "public insurance-other"
[b]Diabetes type 1, 2, or unspecified
[c] Provider-assessed using the Karnofsky Performance Status scale pre-transplant
CT: Computed Tomography; **kg:** kilograms; **m:** meters; **MELD:** Model for End-Stage Liver Disease; **n:** number; **n/a:** not applicable

Supplemental Table 3.2: Frailty measures: Sarcopenia and functional status by gender, UMass liver transplant recipients 2006–2015 (n = 136)

Psoas Measures*	Men (n = 90)	Women (n = 46)	p-value[d]	All (n = 136)
BASELINE[a]				
Time between CTs, months	11.6 (4.7–41.4)	13.0 (1.4–33.7)	0.30	12.0 (3.6–36.5)
TPA	2,344.3 (551.0	1,518.0 (437.8)	**< 0.001**	2,064.8 (646.5)
Density[b]	42.7 (8.8)	41.4 (10.3)	0.45	42.3 (9.3)
LPA	1,771.1 (474.4)	1,131.1 (349.1)	**< 0.001**	1,554.7 (530.4)
LPA/hgt^2	582.7 (157.1)	435.4 (134.1)	**< 0.001**	532.9 (164.8)
PRE-TRANSPLANT				
Time from last CT to transplant, days	27 (11–47)	26 (11–60)	0.89	27 (11–50.5)
TPA	2,028.9 (547.7)	1,449.5 (447.7)	**< 0.001**	1,832.9 **(**583.3)
Density[b]	41.0 (8.3)	37.3 (9.9)	**0.023**	39.8 (9.0)
LPA	1,513.2 (451.9)	1,048.6 (354.4)	**< 0.001**	1,356.1 **(**474.5)
LPA/hgt^2	499.2 (158.2)	403.8 (133.7)	**< 0.001**	466.9 (156.6)
CHANGE (Δ[c])				
ΔTPA	-266.5 (-496.8 to -13.6)	-49.6 (-232.4 to 121.4)	**0.001**	-167.6 (-415.3 to 11.6)
%Δ TPA	-12.6 (16.4)	-3.2 (19.0)	**0.003**	-9.5 (17.8)
ΔDensity[b]	-0.6 (-9.9 to 5.4)	-4.2 (-11.4 to 4.0)	0.25	-1.6 (-10.6 to 5.2)
%ΔDensity[b]	-1.5 (-20.2 to 12.0)	-10.0 (-24.5 to 16.6)	0.26	-4.5 (-21.1 to 12.3)
ΔLPA	-175.7 (-445.2 to -17.7)	-26.0 (-272.3 to 67.4)	**0.003**	-148.2 (-377.4 to 19.1)
%Δ LPA	-13.3 (18.6)	-5.7 (21.5)	**0.034**	-10.7 (19.9)
ΔLPA/hgt^2	-51.6 (-145.7 to -6.1)	-10.6 (-101.4 to 28.1)	**0.008**	-48.0 (-130.2 to 6.4)
RATE OF CHANGE				
ΔLPA/hgt^2/month	-3.2 (-8.8 to -0.6)	-0.5 (-7.0 to 2.8)	**0.031**	-2.65 (-8.5 to 0.2)
%Δ LPA/month	-0.5 (-1.4 to -0.1)	-0.1 (-1.6 to 0.8)	0.07	-0.5 (-1.5 to 0.04)

*Mean (standard deviation) or median (interquartile range)
[a]Baseline defined as earliest available abdominal CT scan before pre-transplant CT (with at least 7 days between scans)
[b]Mean of left and right psoas muscle densities, Houndsfield units
[c]Δ = Change from baseline CT to pre-transplant CT, % Δ = (pre-transplant LPA–baseline LPA)/baseline LPA (note: height in the denominator cancels out)
[d]Women versus Men

CT: computed tomography abdominal scan; **hgt:** height, meters; **LPA:** lean psoas area (TPA x density adjustment factor), mm^2; **p:** probability; **TPA:** total psoas area (sum of left and right psoas muscles as separate measures for pre-transplant and baseline CTs), mm^2

Supplemental Table 3.3: Characteristics of liver transplant recipients in relation to change in lean psoas area relative to baseline (tertiles), UMass 2006–2015 (n = 136)

	Tertiles of Relative Change in Lean Psoas Area†		
	Severe loss of LPA	**Moderate loss of LPA**	**Minimal or no loss of LPA**
Median ΔLPA (Range):	-30.1 (-64.5to -19.0)	-9.1 (-18.8 to -1.3)	7.4 (-1.0 to 46.1)
Months between CTs, median (IQR):	19.7 (8.7–54.9)	9.8 (4.0–31.7)	8.1 (1.8–31.9)
Characteristic*			
Age ≥ 55 years	65.2	53.3	55.6
Women	26.1	26.7	48.9
Ethnic minority	10.9	33.3	24.4
Public health insurance	54.4	71.1	57.8
Body mass index, kg/m^2	27.4 (4.8)	29.1 (5.3)	28.1 (6.7)
Weight, kg	82.6 (18.6)	83.4 (18.2)	79.8 (22.0)
Height, m	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Diabetes[a]	30.4	26.7	15.6
Primary Cause of Liver Disease			
Hepatitis C/viral-other	50.0	46.7	44.4
Alcoholic Hepatitis	21.7	26.7	24.4
Other liver diseases	28.3	26.7	31.1
Hepatocellular Carcinoma	32.6	31.1	44.4
Time on waiting list, months	2.2 (0.7–11.1)	4.6 (1.5–13.0)	3.0 (0.8–9.1)
Weight loss per month on waitlist			
< 0–≤ 5%	41.3	44.4	45.5
> 5%	21.7	13.3	25.0
MELD at registration[b]	20.5 (11–26)	15 (10–22)	15 (10–20)
MELD pre-transplant[b]	25.5 (16–36)	22 (12–30)	16 (12–24)
Creatinine	1.3 (0.9–2.5)	1.0 (0.8–1.6)	1.1 (0.8–1.8)
Total bilirubin	6.4 (2.8–19)	5.0 (1.7–12.5)	2.9 (1.4–6.1)
International Normalized Ratio	1.7 (1.3–2.2)	1.7 (1.3–2.3)	1.4 (1.1–1.8)
Albumin	3.0 (2.5–3.4)	2.8 (2.5–3.5)	3.0 (2.4–3.3)
Child Pugh			
B	19.6	22.2	31.1
C	78.3	66.7	60.0
Portal Vein Thrombosis	15.2	17.8	13.3
Medical condition			
Not Hospitalized	41.3	46.7	68.9
Hospitalized, not ICU	26.1	35.6	17.8
ICU	32.6	17.8	13.3
Life support	19.6	8.9	6.7

*%, mean (standard deviation), or median (interquartile range (IQR))
†Tertile categories, Severe/Moderate/Minimal: n = 46/45/45
[a]Diabetes type 1, 2, or unspecified
[b]Laboratory calculated MELD score

IQR: interquartile range; **kg:** kilograms; **m:** meters; **MELD:** Model for End-Stage Liver Disease; **n:** number

Supplemental Table 3.4: Characteristics of liver transplant recipients in relation to functional status, UMass 2006–2015 (n = 136)

	Functional impairment/disability		
	Severe (n = 62)	**Moderate (n = 55)**	**None/Normal (n = 19)**
Median %Δ LPA (Range):	-13.1 (-33.3 to -1.3)	-9.5 (-20.9 to 4.0)	-2.2 (-8.2 to 0.95)
Months on the waitlist, median (IQR):	1.7 (0.39–8.7)	4.3 (1.3–13.0)	3.8 (1.2–13.9)
Months between CT scans, median (IQR):	10.4 (2.7–43.0)	15.0 (4.8–35.4)	16.9 (6.1–35.2)
Characteristic*			
Age ≥ 55 years	56.5	60.0	57.9
Women	33.9	33.2	21.1
Ethnic minority	27.4	18.2	21.1
Public health insurance	66.1	61.8	42.1
Body mass index, kg/m^2	27.9 (5.6)	29.4 (5.8)	25.6 (4.2)
Weight, kg	80.8 (20.0)	85.9 (20.0)	74.2 (14.4)
Height, m	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Diabetes[a]	27.4	23.6	15.8
Primary Cause of Liver Disease			
Hepatitis C/viral-other	43.6	49.1	52.6
Alcoholic Hepatitis	29.0	25.5	5.3
Other liver diseases	27.4	25.5	42.1
Hepatocellular Carcinoma	13.4	40.0	79.0
Weight loss per month on waitlist			
< 0–≤ 5%	26.2	16.4	10.5
> 5%	37.7	43.6	63.2
MELD at registration[b]	21.5 (16–31)	13 (9–17)	10 (7–14)
MELD pre-transplant[b]	29.5 (22–37)	15 (11–24)	12 (9–13)
Creatinine	1.5 (1.0–3.0)	0.9 (0.7–1.5)	0.9 (0.8–1.1)
Total bilirubin	8.6 (3.8–18.8)	2.8 (1.4–6.4)	1.5 (0.9–3.4)
International Normalized Ratio	2.0 (1.7–2.6)	1.3 (1.1–1.7)	1.2 (1.1–1.4)
Albumin	3.1 (2.5–3.4)	2.9 (2.4–3.3)	2.8 (2.6–3.5)
Child Pugh			
B	4.8	38.2	47.4
C	95.2	52.7	26.3
Portal Vein Thrombosis	17.7	14.6	10.5
Medical condition			
Not Hospitalized	9.7	85.5	94.7
Hospitalized, not ICU	46.8	10.9	5.3
ICU	43.6	3.6	0
Life support	22.6	3.6	0

*%, mean (standard deviation), or median (interquartile range)

[a]Diabetes type 1, 2, or unspecified

[b]Laboratory-calculated MELD score

IQR: interquartile range; **kg**: kilograms; **m:** meters; **MELD:** Model for End-Stage Liver Disease; **n**: number

Supplemental Table 3.5: Rate of muscle wasting versus functional status pre-transplant: stratified distributions and correlations, UMass liver transplant recipients 2006–2015 (n = 136)

		Functional impairment/disability			
Sarcopenia, ***Rate of change****	n[a]	**Severe (n = 62)**	**Moderate (n = 55)**	**None (n = 19)**	**Correlation[b]** ***(p-value)***
All	131	-0.66 (-2.62 to -0.12)	-0.29 (-1.43 to 0.56)	-0.20 (-0.53 to 0.02)	0.31 (< 0.001)
Age in years					
< 55	55	-0.83 (-3.71 to -0.12)	-0.23 (-1.43 to 1.82)	-0.08 (-0.31 to 0.25)	0.36 (< 0.01)
≥ 55	76	-0.63 (-2.62 to -0.00)	-0.39 (-1.39 to 0.26)	-0.33 (-0.65 to -0.09)	0.25 (0.03)
Gender					
Women	42	-0.52 (-2.62 to 2.91)	-0.06 (-0.95 to 0.56)	0.45 (-0.57 to 6.54)	n/a[c]
Men	89	-0.72 (-2.5 to -0.33)	-0.50 (-1.43 to 0.52)	-0.21 (-0.53 to -0.09)	0.30 (< 0.01)
Primary Liver Disease					
Hepatitis C/viral	63	-0.72 (-2.44 to -0.13)	-0.25 (-1.51 to 0.26)	-0.20 (-0.36 to -0.09)	0.34 (< 0.01)
Alcohol, Other	68	-0.65 (-5.55 to 1.50)	-0.37 (-1.30 to 0.66)	-0.18 (-0.63 to 0.13)	n/a[c]
Hepatocellular carcinoma					
None	82	-0.90 (-2.80 to -0.20)	-0.25 (-1.95 to 0.26)	-0.20 (-0.28 to 6.18)	0.37 (< 0.01)
Present	42	-0.21 (-0.56 to -0.05)	-0.35 (-1.02 to 0.67)	-0.20 (-0.63 to 0.02)	n/a[c]
Child-Pugh					
A or B	43	-0.33 (-0.65 to -0.18)	-0.18 (-1.21 to -0.75)	-0.20 (-0.53 to 0.02)	n/a[c]
C	88	-0.72 (-2.69 to -0.03)	-0.39 (-1.51 to 0.04)	-0.20 (-0.36 to -0.18)	0.28 (< 0.01)

*Sarcopenia: Relative change in Lean Psoas Area (LPA) per month = [(LPA within 90 days before transplant–Baseline LPA)/ Baseline LPA/ months between CT scans], median (interquartile range)

[a]Samples included in stratified analyses; correlations not reported for groups with not sufficiently powered (< 80%; see appendix 3C for details).

[b]Correlations were assessed using Spearman's rho for rank-order correlation between 10-point Karnofsky Performance Status scale and continuous sarcopenia and restricted to the range of lean psoas area values for which test assumptions were not violated: below (+) 20% increase in the rate of relative Lean Psoas Area change/month (see appendix 3B for further detail on this determination).

n: number; **n/a:** not applicable; **p:** probability

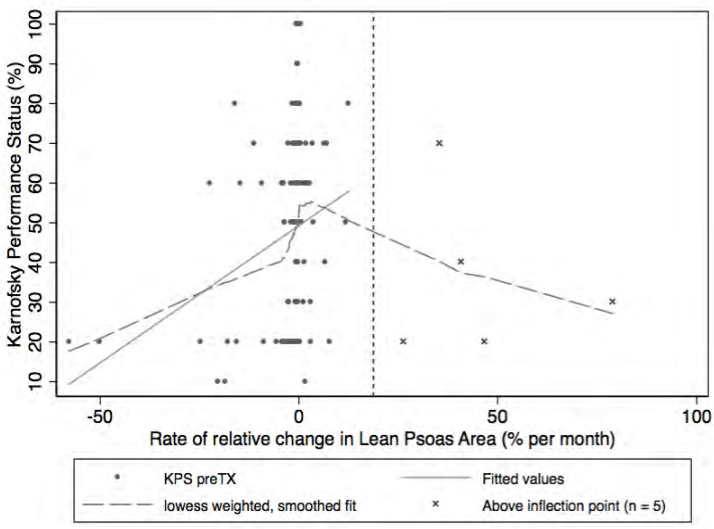
APPENDICES FOR CHAPTER III

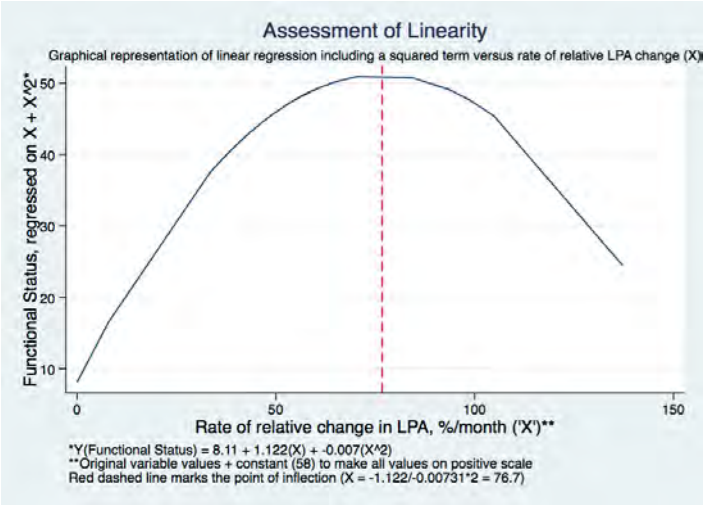
Appendix 3A. Assessing Intra-Rater Reliability of psoas muscle measurement

Intra-observer reliability for measures of muscle mass (cross-sectional area, density) were assessed using Test-Retest methodology and confirmed before initiating primary study data collection. This approach involves re-ascertainment of the same subjects, using the same tools, and administered by the same research staff, ideally 2 weeks apart to prevent recall bias (221). We used images from patients who did not otherwise meet study inclusion criteria. Power calculations determined a sample that was 5% of the target study sample (n = 125), which included 4 images per patient, would be sufficient to determine good reliability, defined as ≥ 90% correlation using Pearson's Correlation Coefficient. Correlation between the identical images measured 2 weeks apart was found to be 97%.

Appendix 3B. Assessing correlation assumptions

We assessed linear and monotonic assumptions of correlation (for Pearson's and Spearman correlation, respectively) by exploring scatter plots and LOWESS-weighted curves for 10-point Karnofsky Performance Status scale versus rate of muscle wasting (% change in lean psoas area (LPA)/month). Based on the LOWESS results in the first graph below, which shows that the association reverses direction past a certain (extreme) point and potentially parabolic relationship between the 2 variables, we explored a squared transformation of LPA rate. A linear regression model was run with functional status as the dependent variable and LPA rate plus a squared (positive value) transformation of the LPA rate to test whether this was the case (yes if p-value of squared variable was significant), and in order to quantify point of inflection





where the effect reverses (-B1(LPA rate)/[-2*B2(LPA rate^2)]). Transformation of the primary independent variable was decided against in order to simply the primary variable of interest and allow for ease of interpretation from a clinician perspective. Instead, correlations were assessed in the subset of the sample for which the monotonic form in the relationship between variables held (uniform direction of effect – no reversal). After exploring potential explanations for the 5 unlikely values of increasing LPA at a rate of > 20%/month, we were unable to determine a definite explanation that would have otherwise been considered a conceptually important exclusion criteria.

Appendix 3C. Power calculations for minimum correlation detectable

Assuming normal distributions of both sarcopenia and functional status variables, a sample size of 131 subjects (after applying exclusions described in Appendix B), an alpha of 0.05 and power (1-beta) of 0.80, with a null correlation of 0: the smallest correlation detectible is 0.24 for a two-tailed test (weak correlation). A correlation weaker than 0.24 may not be detected in our analyses given these parameter restrictions.

Appendix 3D. Tests of significance for descriptive statistics

Appropriate tests were selected based on normality of the dependent variable, as follows:

- For normally distributed continuous variables: t-tests, paired t-tests for baseline versus pre-transplant comparisons, ANOVA
- For skewed continuous variables: Wilcoxon rank-sum for unmatched pairs or signed-rank for pairs (baseline versus pre-transplant psoas measures)
- For categorical variables: chi-squared (χ^2) or Fischer's exact for cell sizes < 5

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