LIVER TRANSPLANTATION AND OLDER ADULTS

by
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ABSTRACT

As the population of older adults in the United States grows, not only will there be an increased number of potential older adult organ donors, but the number of older adults with end-stage liver disease who need liver transplantation will also increase. As a transplant community, it is imperative to know how to utilize these older donors and care for older liver transplant recipients.

First, the underutilization of older liver donors (age≥70) represents a possible expansion of the donor pool. However, older donor grafts have been historically associated with poor outcomes and higher discard rates, but clinical protocols, organ allocation, and the donor pool have changed in the last 15 years. Using national registry data from 2003-2016, we estimated the odds of discard of older liver donors was two-fold higher every year compared to younger liver donors and that discard of older liver donors increased over this time period. Yet, outcomes in older liver donor recipients improved over time (40% lower risk of graft loss and 41% lower risk of mortality), and these were more marked improvements than seen in younger liver donor recipients (Chapter 2).

Secondly, given the increased burden of end-stage liver disease in older adults, we focused on temporal trends in the incidence of transplantation and outcomes for older liver transplant recipients (Chapter 3). Using national registry data, we found that liver transplantation in older recipients increased five-fold from 2003 to 2016 and that length of stay, acute rejection, graft loss, and mortality improved over time.

Finally, as the average age of waitlisted liver candidates and liver transplant recipients continues to increase, we sought to quantify the association of waitlist mortality and frailty, a state of decreased physiologic reserve by candidate age. We found that older candidates experienced higher rates of frailty than younger candidates. However, regardless of age, frailty was associated with nearly two-fold increased risk of waitlist mortality.

Overall, this dissertation quantifies the utilization of older liver donors, outcomes for recipients of older liver donors, outcomes of older liver transplant recipients, and delves into the relationship between age and frailty in liver transplant candidates.

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LIST OF ABBREVIATIONS

aHR, adjusted hazard ratio

aOR, adjusted odds ratio

aRR, adjusted relative risk

aSHR, adjusted subhazard ratio

BMI, body mass index

ESLD, end-stage liver disease

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

LFI, Liver Frailty Index

LOS, length of stay

LT, liver transplantation

MELD, model for end-stage liver disease

OLD, older liver donor

OPO, organ procurement organization

OPTN, Organ Procurement and Transplantation Network

SD, standard deviation

SRTR, Scientific Registry of Transplant Recipients

YLD, younger liver donor

Chapter 1. Introduction

Over 14,000 patients are currently on the U.S. liver transplant waitlist, yet only 8,082 liver transplants were performed in 2017.[2] Each year more than 10% of liver waitlist candidates die awaiting transplantation,[3] making the donor shortage a significant public health problem.[4,5] The disparity between the number of available liver donors and the demand of the liver transplant waitlist has motivated novel ways to expand the donor pool. Donor characteristics such as Hepatitis C virus positive donors, older age, high body mass index, and donation after cardiac death are examples of higher risk donors that are used cautiously in the transplant community. Specifically, one controversial approach that has been used over the past 3 decades is utilization of older liver donors (age≥70).[6-8] However, this potential donor pool is becoming increasingly more relevant and timely, as nearly 15% of the U.S. population is projected to be older than age 70 by 2030.[9] With continued attention to the use of older liver donor grafts and the donor shortage, utilization of older liver donor grafts has likely evolved.

Older liver donor grafts have historically been associated with recipient graft loss and mortality, which has led to reluctance to transplant these organs.[10-14] For this reason, older liver donor grafts only accounted for 4.3% of all liver donors from 2007-2011[15] with substantial center-level variation in older liver donor graft transplantation, ranging from 0-33% of all transplanted grafts.[16] While several single-center studies reported more routine use of older liver donors and showed similar graft and patient survival regardless of donor age, but these studies were limited by small sample size.[17-20] Yet, older liver donors offer a survival benefit for recipients across all model for end-stage live disease scores compared to remaining on the waitlist.[21] Furthermore, a more up-to-date exploration of national changes in older liver donor grafts is necessary, as

temporal changes in older liver donor graft utilization and recipient outcomes have likely changed with evolving donor and recipient demographic trends (increasing age of liver transplant recipients[22] and donors,[23,24] indication for liver transplantation[22,25]), treatment for Hepatitis C virus with direct-acting antivirals, and changes in liver allocation policy (e.g. Share 35, hepatocellular carcinoma exception points).

As the proportion of older adults in the United States population grows, not only are there more potential older organ donors, but the number of older adults with end-stage liver disease is also increasing. The burden of end-stage liver disease in older adults (aged ≥65) in the United States is increasing,[22,26-28] and older adults comprise 23.8% of the current liver transplant waitlist, up from 8% in 2002.[22,29] The increase in older adults with end-stage liver disease is driven by the aging population with hepatitis C virus cirrhosis along with the increase in nonalcoholic steatohepatitis and hepatocellular carcinoma, which typically affect older adults.[27,28,30,31] Historically, older adults were denied access to liver transplantation because of poor posttransplant survival,[32-34] but there are more recent reports of liver transplantation in older adults, including small reports of liver transplantation in octogenarians.[35,36]

It is possible that advances in immunosuppression regimens and surgical techniques [37-40] may be leading to improved liver transplant outcomes in older adults. However, older adults are uniquely susceptible after liver transplant given increased comorbidity, higher prevalence of frailty, and physical impairment.[41-43] Among older liver transplant candidates and recipients, physical impairment, frailty, and older age are associated with an increased risk of mortality.[22,42,44-46] Additionally, older adults have immunosenescence, leading to lower tolerance of posttransplant immunosuppression.[47-49] Therefore, improvements in modern immunosuppression may not translate to improved posttransplant outcomes over time in older recipients. Further, poor

outcomes in older liver transplant recipients are typically due to cardiac complications, malignancy, and infection,[32,33,50] so surgical and immunosuppression changes do not necessarily translate into improved outcomes for older recipients. A better understanding of the trends over time in outcomes for older liver transplant recipients is warranted for appropriate referral, evaluation, and counseling prior to transplantation.

As a transplant community, we are obligated to identify the best transplant candidates to undergo transplantation, not only because of the national organ shortage, but also to do what is in the best interest for our patients. Thus, identification of appropriate transplant candidates is imperative and improvement of suboptimal transplant candidates in preparation for transplantation is important. One way to identify appropriate transplant candidates is through frailty assessments. Frailty, a measure of physiologic reserve and increased vulnerability to stressors, was initially described by gerontologists in older community dwelling adults.[51] Frailty was subsequently examined in older general surgery patients,[52] kidney transplant candidates and recipients,[41,49,53-59] and recently in liver transplant candidates and recipients, [44,60-64] where it was found to be associated with adverse outcomes in these populations. The Liver Frailty Index, comprised solely of performance-based measures (grip strength, balance testing, and chair stands), was developed and validated in patients with cirrhosis evaluated for transplantation[44,60] and improves risk prediction for waitlist mortality over the Model for End-Stage Liver Disease (c-statistic: 0.80 vs. 0.76). Up to 25% of liver transplant candidates are frail;[44,60] beyond waitlist mortality,[44,65] frailty is associated with increased hospitalizations[64] and depression[61] in liver transplant candidates and longer length of stay and hospitalized days in liver transplant recipients.[62]

While there is a higher prevalence of frailty in older adults, there is also a greater burden of comorbidities[41-43] and an increased prevalence of functional impairment in older adults.[42] Older candidates may therefore, because of comorbidity burden and underlying functional impairment, have a more marked association between frailty and waitlist mortality as compared to younger candidates. Yet, studies of frailty in liver transplant candidates have not examined whether there is effect modification by candidate age on the association between frailty and waitlist mortality: in other words, whether frailty has the same impact on younger patients as it does on older patients.[44,60] As the average age of waitlisted liver candidates and liver transplant recipients continues to increase,[22,66] it is even more important to understand this effect.

The population of older adults in the United States has increased substantially within the past few decades; however, the impact of age on outcomes for liver transplant recipients of older donors and separately on older recipients is not well characterized. This dissertation seeks to improve the understanding of liver transplantation with older donors and in older recipients. Chapter 2 quantifies the temporal trends in discard and utilization of older liver donor grafts, quantifies the organ procurement organization level variation in older liver donor graft discard, and characterizes the changing landscape of older liver donor grafts and their recipients. Additionally, Chapter 2 describes the trends over the last 15 years in graft loss and mortality for older liver donor recipients and compares posttransplant outcomes between recipients of older donors and younger donors. Chapter 3 details the temporal trends in liver transplantation and posttransplant outcomes, such as length of stay, acute rejection, graft loss, and mortality, for older recipients. Chapter 4 describes the prevalence of frailty in older liver transplant candidates and quantifies the interaction of candidate age and frailty on waitlist mortality.

Chapter 2. Trends in Liver Transplantation with Older Liver Donors in the United States

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ABSTRACT

Importance: In light of the growing population of older adults in the U.S., older liver donors (age≥70) represent an expansion of the donor pool, yet are underutilized. Older liver donor grafts were historically associated with poor outcomes and higher discard rates, but clinical protocols, organ allocation, and the donor pool have changed in the last 15 years.

Objective: We sought to evaluate trends in demographics, discard, and outcomes of older liver donors (OLDs, age≥70) and OLD recipients in a large national cohort.

Design: Prospective cohort study between 1/1/2003- 12/31/2016 in the United States.

Setting: The Scientific Registry of Transplant Recipients includes data on all transplant recipients in the United States, submitted by members of the Organ Procurement and Transplantation Network.

Participants: We studied 4,127 older liver donor grafts, 3,350 liver-only older donor recipients, 78,990 younger liver donors (age 18-69) grafts, and 64,907 liver-only younger donor recipients.

Exposures: Year of liver transplant and donor age.

Main outcomes and measures: Graft discard using multilevel logistic models and posttransplant outcomes (graft loss, mortality) using Cox proportional hazards models.

Results: After adjusting for donor characteristics other than age and accounting for OPO-level variation, older liver donor grafts were more than 2-times as likely to be discarded compared to younger liver donor grafts in each era (2003-2006 aOR: $_{1.68}1.97_{2.31}$, 2007-2009 aOR: $_{2.17}2.55_{3.01}$, 2010-2013 aOR: $_{1.68}2.04_{2.46}$, and 2013-2016 aOR: $_{1.96}2.37_{2.86}$; all p<0.001). Furthermore, transplants with older liver donor grafts represented a progressively lower proportion of all adult liver transplants, from 6.0% (n=258) in 2003 to 3.2% (n=211) in 2016 (p=0.001). However, outcomes in older liver donor recipients improved dramatically over time, with 40% lower graft loss risk (aHR: $_{0.53}0.60_{0.68}$, p<0.001) and 41% lower mortality risk (aHR: $_{0.52}0.59_{0.68}$, p<0.001) in

2010-2016 versus 2003-2009; this was well beyond the general temporal improvements in younger liver donors recipients (interaction p=0.03 and p=0.04, respectively).

Conclusions and relevance: Over the past 15 years, graft loss and mortality for older liver donor recipients improved dramatically, yet older liver donor graft discard remains more than two-fold increased and transplantation with older liver donor grafts decreased. Expansion of the donor pool through broader utilization of older liver donor grafts might be reasonable.

INTRODUCTION

Over 14,000 patients are currently on the United States liver transplant (LT) waitlist, yet only 8,082 LTs were performed in 2017.[2] Each year more than 10% of liver waitlist candidates die awaiting transplantation,[3] making the donor shortage a significant public health problem.[4,5] The disparity between the number of available liver donors and the demand of the LT waitlist has motivated novel ways to expand the donor pool. One controversial approach that has been cautiously used over the past 3 decades is utilization of older liver donors (OLDs; age≥70).[6-8] However, this potential donor pool is becoming increasingly more relevant and timely, as nearly 15% of the U.S. population is projected to be older than age 70 by 2030.[9] With continued attention to the use of OLD grafts and the donor shortage, utilization of OLD grafts has likely evolved. A description of the temporal trends in OLD graft discard and OLD recipient outcomes could inform clinical decision-making and expansion of this potential donor pool.

OLD grafts have historically been associated with graft loss and recipient mortality, which has led to reluctance to transplant these organs.[10-14] For this reason, OLD grafts only accounted for 4.3% of all liver donors from 2007-2011[15] with substantial center-level variation in OLD transplantation, ranging from 0-33% of all transplanted grafts.[16] While several single-center studies reported more routine use of OLDs and showed similar graft and patient survival regardless of donor age, these studies were limited by small sample size.[17-20] Furthermore, a more up-to-date exploration of national changes in OLD grafts is necessary, as temporal changes in OLD graft utilization and recipient outcomes have likely changed with evolving donor and recipient demographic trends (increasing age of LT recipients[22] and donors,[23,24] indication for

LT[22,25]), treatment for HCV with direct-acting antivirals, and changes in liver allocation policy (e.g. Share 35, hepatocellular carcinoma exception points).

To inform clinical practice with OLD grafts, we used national registry data to: 1) quantify trends in discard and utilization of OLD grafts, 2) quantify organ procurement organization (OPO) level variation in OLD graft discard, 3) characterize the changing landscape of OLD grafts and their recipients, and 4) describe trends over the last 15 years in graft loss and mortality for OLD recipients. Finally, for context, we compared trends in liver graft discard and posttransplant outcomes between OLDs and younger liver donor (YLDs).

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR) with available follow-up through March 2017. The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the U.S. submitted by members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[68] Mortality and graft loss were augmented through linkage with the Social Security Master Death File, data from Centers for Medicare and Medicaid Services (CMS), and waitlist data. The Health Resources and Services Administration (HRSA), the U.S. Department of Health and Human Services, provides oversight to the activities of OPTN and SRTR contractors. This study was acknowledged as non-human subjects research by the Johns Hopkins Medicine IRB (NA_00042871).

Study population

We identified 4,127 OLD grafts (liver grafts from older liver donors age ≥70) recovered for LT and 3,350 deceased liver-only OLD recipients (recipients of LTs from donors age ≥70) between January 1, 2003 and December 31, 2016. Also, we identified 78,990 YLD grafts (liver grafts from younger liver donors age 18-69) grafts recovered for LT and 64,907 deceased liver-only YLD recipients (recipients of LTs from donors age 18-69) in the same time period. We empirically grouped recipients into four time strata to reflect changes in allocation policy and general evolution of immunosuppression regimens: 2003-2006, 2007-2009, 2010-6/18/2013 and 6/19/2013-2016. We divided the recent periods at 6/18/2013 to evaluate trends before and after implementation of the Share 35 policy change, which increased regional sharing of liver allograft offers to patients with Model for End-Stage Liver Disease (MELD) score ≥35. Calculated MELD score is laboratory MELD, comprised of sodium, bilirubin, international normalized ratio, and creatinine, at time of transplant. Allocation MELD score is reported as the allocation score at time of transplant. The MELD score is a measure of disease severity and likely survival in patients awaiting liver transplantation. Recipients with missing body mass index (BMI; 3.1%) and missing cold ischemia time (3.8%) were excluded from the analysis.

OLD graft discard over time

We estimated the percentage of liver graft discard (defined as recovered but not transplanted) according to donor age in each time stratum. To characterize the change over time in OLD graft discard, we ran a multilevel logistic regression model with random intercept with an interaction between donor age and time stratum. This model also accounted for underlying variation across OPOs. All models were adjusted for donor cause of death, sex, race, donation after cardiac death, and Hepatitis C virus [69].

OPO-level variation in OLD graft discard

To characterize the variation in OLD graft discard across OPOs, we ran a multilevel logistic regression model with random intercept for OPO among only OLD grafts and calculated each OPOs individual rate of OLD graft discard, adjusted for donor race, gender, BMI, HCV, cause of death, and DCD. The intraclass correlation coefficient (ICC) from this model quantifies the variance in OLD graft discard explained by the OPO where the OLD graft was recovered. We calculated the probability that an OLD graft was discarded for each OPO. From this model, we derived the national average probability of discard and the probability of discard within the highest utilizing OPOs (lowest quartile of OLD graft discard). We then estimated the number of OLD grafts that would not have been discarded if all OPOs discarded at or below the national average and separately if all OPOs discarded at or below the lowest quartile of OLD graft discard. In other words, how many additional OLDs would have been used for transplant if OLDs were discarded at rates observed in high utilizing OPOs.

OLD recipients over time

We calculated the percentage of adult liver transplant recipients who received OLDs annually during the study period. Cuzick test of trend was used to compare changes in the number of OLD recipients over the study period. We compared the recipient, donor, and transplant characteristics of OLD recipients for each time stratum (see "Study Population" above).

Mortality and all-cause graft loss in OLD recipients over time

Mortality and all-cause graft loss were estimated at 1-, 3- and 5-years using the Kaplan-Meier method for each time stratum. The Kaplan-Meier method was also used to create unadjusted cumulative incidence curves of mortality and all-cause graft loss for each time stratum. Cox proportional hazards models for mortality and all-cause graft loss were adjusted recipient (sex, age, race, BMI, primary diagnosis, MELD, life support at LT, hepatocellular carcinoma [HCC], HCV, HIV status, diabetes status, primary insurance, portal vein thrombosis), donor factors (race, BMI, HCV, DCD), and transplant factors (cold ischemia time, shared organ status). To test whether temporal trends in mortality and graft loss differed between liver donor age groups, interactions between donor age (OLD and YLD) and each outcome were explored. For all models, proportional hazards assumptions were assessed with visual inspection of complementary log-log plots and Schoenfeld residuals.

Statistical analyses

Continuous variables were compared using t-tests and categorical variables were compared using χ^2 tests. Race was reported by clinicians to the OPTN. Confidence intervals are reported as per the method of Louis and Zeger.[70] All analyses were two-tailed and α was set at 0.05. All analyses were performed using STATA 14.2/MP (College Station, Texas).

RESULTS

Study population: OLDs

We identified 4,127 OLD grafts (liver grafts from OLDs) recovered for LT. Among OLD grafts recovered across the entire study period (between 2003-2016), 54% were aged 70-74, 33% were

75-79, 11% were 80-84, and 2% were ≥85 (Table 1A). Among 747 discarded OLD grafts, 51% of OLDs were aged 70-74, 33% of OLDs were 75-79, 13% of OLDs were 80-84, and 3% of OLDs were ≥85 (Table 1B). Among 3,350 utilized OLDs for liver-only OLD recipients, 55% of OLDs were aged 70-74, 33% of OLDs were 75-79, 10% of OLDs were 80-84, and 2% of OLDs were ≥85.

Changing landscape of recovered and discarded OLD characteristics

The average donor BMI of recovered OLD grafts increased from 26.1 in 2003-2006 to 28.0 in 2013-2016 ($p<0.001$). Recent OLDs were less likely to be Caucasian (69.9% in 2013-2016 vs. 80.6% in 2003-2006, $p<0.001$) and less likely to be DCD grafts (0.1% in 2013-2016 vs. 0.7% in 2003-2006, $p=0.008$) (Table 1A). Similarly, the average BMI of discarded OLDs increased from 26.7 in 2003-2006 to 28.7 in 2013-2016 ($p=0.008$). Recently discarded OLD grafts were less likely to be from Caucasian OLDs (73.7% in 2013-2016 vs. 80.8% in 2003-2006, $p=0.03$)(Table 1B).

OLD graft discard over time

OLD graft discard increased from 11.6% in 2003, to a peak of 24.5% in 2008, and down to (but still higher than 2003) 15.4% in 2016; OLD graft discard was higher every year in the study period compared to YLD graft discard (2003: 11.6% vs. 8.0%, 2008: 24.5% vs. 13.1%, 2016: 15.4% vs. 9.3%) (Figure 1A). After adjustment, OLD grafts were more than twice as likely to be discarded compared to YLD grafts in each era (2003-2006 aOR: $_{1.68}1.97_{2.31}$, 2007-2009 aOR: $_{2.17}2.55_{3.01}$, 2010-2013 aOR: $_{1.68}2.04_{2.46}$, and 2013-2016 aOR: $_{1.96}2.37_{2.86}$; all $p<0.001$).

OPO-level variation in OLD and YLD graft discard

Among the 58 OPOs in the United States, OLD graft discard ranged widely from 0-35.3% with a median OLD graft discard of 15.1% (IQR:9.8-25.0%). The ICC was 0.057, meaning that only 5.7% of the variation in OLD graft discard was explained by OPO (Figure 1B). The OPO-specific odds ratios of OLD discard ranged from 0.31 (95%CI:0.17-0.58) to 2.69 (2.20-3.29) compared to the national odds of OLD discard (OR=1). Four (6.9%) of 58 OPOs had a statistically significantly higher odds ratio and four had statistically significantly lower odds ratio of OLD discard as compared to the national average (Figure 1B). If all OPOs discarded OLD grafts at or below the 25th percentile of discard, 277 more OLD grafts would have been used: a 34% reduction in OLD graft discard. If all OPOs discarded at or below the national average, 177 more OLD grafts have been used: a 24% reduction in OLD graft discard.

Among the 58 OPOs in the United States, YLD graft discard ranged from 3.2-20.7% a median YLD graft discard of 9.3% (IQR:7.3-12.4%). The ICC was 0.096, meaning that only 9.6% of the variation in YLD discard was attributed to the OPO level. The OPO-specific odds ratios of YLD discard ranged from 0.23 (95%CI: 0.17-0.33) to 2.23 (95%CI: 1.70-2.93) compared to the national odds of YLD discard (OR=1). Six (10.3%) of 58 OPOs had a statistically significantly higher odds ratio and twenty-seven (46.6%) had statistically significantly lower odds ratio of younger liver donor discard as compared to the national average (Figure 1C).

Study population: OLD recipients

The average age of 3,350 OLD recipients (recipients of OLD grafts) was 57.6 years, 37.6% were female, and 73.8% were Caucasian (Table 2). The average calculated MELD score at time of LT

for OLD recipients was 19 (SD=8). The indications for LT were alcoholic cirrhosis (21.2%), HCV (13.7%), HCC (18.6%), nonalcoholic steatohepatitis (10.0%), primary biliary cirrhosis (5.0%), and primary sclerosing cholangitis (5.0%).

Changing landscape of OLD recipients

The number of OLD recipients steadily declined from 258 in 2003 to 211 in 2016 (Figure 2); the percentage of OLD recipients among all adult liver recipients also decreased from 6.0% to 3.2% ($p=0.001$). The average age of OLD recipients increased from 55.9 years in 2003 to 59.8 years in 2016 ($p<0.001$). Among recipients of OLD grafts, the percent of older (age≥65) OLD graft recipients increased over the study period from 2003 to 2016 from 9.3% to 20.2%. Among OLD recipients from 2013-2016 versus 2003-2006, sex (female: 38.4% vs. 37.9%, $p=0.94$), BMI (28.1 vs. 28.2 kg/m^2, $p=0.07$), and race (Caucasian: 73.0% vs. 74.6%, $p=0.26$) did not differ significantly. Additionally, the average calculated MELD score for OLD recipients at time of LT did not change (18 vs. 18, $p=0.80$), but the average allocation MELD score increased (25 vs. 21, $p<0.001$). Recent OLD recipients were more likely to have non-alcoholic steatohepatitis (16.9% in 2013-2016 vs. 4.1% in 2003-2006) or HCC (22.6% vs. 10.6%) and less likely to have HCV (11.5% vs. 20.0%) as the primary indication for LT ($p<0.001$) (Table 2).

Recently transplanted OLDs were more likely have higher BMI (27.8 vs. 25.9 kg/m^2, $p<0.001$). Also, recently transplanted OLDs were more likely to have anoxia (13.5% vs. 5.1%, $p<0.001$) and head trauma (17.1% vs. 12.5%, $p<0.001$) as the cause of death (Table 2).

Mortality in OLD recipients over time

Mortality in both OLD and YLD recipients improved over time (Figures 3A, 3C). In OLD recipients from 2003-2009 to 2010-2016, 1-year mortality improved from 18% to 11%, 3-year from 28% to 18%, and 5-year from 37% to 23%. In YLD recipients, from 2003-2009 to 2010-2016, 1-year mortality improved from 13% to 11%, 3-year from 22% to 14%, and 5-year from 28% to 21%. The improvements in mortality over time were greater in OLD recipients (interaction p=0.04)(Figure 3C): OLD recipients from 2010-2016 were at a 41% lower risk of mortality compared to OLD recipients from 2003-2009 (aHR: $_{0.52}0.59_{0.68}$, p<0.001), and YLD recipients from 2010-2016 were at a 31% lower risk of mortality compared to 2003-2009 (aHR: $_{0.66}0.69_{0.71}$,p<0.001).

All-cause graft loss in OLD recipients over time

Like mortality, graft loss in OLD and YLD recipients improved over time (Figures 3B, 3D). In OLD recipients from 2003-2009 to 2010-2016, 1-year graft loss improved from 23% to 15%, 3-year from 34% to 22%, and 5-year from 43% to 27%. In YLD recipients from 2003-2009 to 2010-2016, 1-year graft loss improved from 16% to 11%, 3-year from 26% to 19%, and 5-year from 32% to 24%. The improvements in graft loss over time were more marked in OLD recipients (interaction p=0.03; Figure 3D): OLD recipients from 2010-2016 were at a 40% lower risk of graft loss compared to OLD recipients from 2003-2009 (aHR: $_{0.53}$ $0.60_{0.68}$, p<0.001) and YLD recipients from 2010-2016 were at a 30% lower risk of mortality compared to 2003-2009 (aHR: $_{0.68}$ $0.70_{0.72}$, p<0.001).

DISCUSSION

In this national study of 4,427 recovered OLD grafts and 3,350 OLD recipients between 2003-2016, we observed decreasing utilization of OLD grafts with concomitant significant improvements in graft loss and mortality for recipients of these organs. OLD graft discard increased from 11.6% to 15.4% over the study period, and the proportion of OLD transplants performed among all LTs decreased from 6.0% to 3.2% ($p=0.001$). However, during the same time period, graft loss and mortality dropped by more than half (aHR: 0.47 and 0.44, both $p<0.001$), and improvements in graft loss and mortality for OLD recipients over time were significantly higher than improvements seen in YLD recipients.

Our findings of increased OLD graft discard from 2003-2016 are consistent with findings from Orman et al. of increased discard of all adult liver donors grafts from 2003-2010[24] along with worsening donor quality over time due to donor obesity, donor diabetes, and DCDs.[71] Our findings of high OLD graft discard and wide OPO-level variation of OLD graft utilization are consistent with previous studies that examined variation in OLD and DCD graft use at the OPO level (0-35.3% of adult donor LTs performed)[16] and OLD grafts used by UNOS region (0.9-12.9% of adult donor LTs performed).[72] However, we expand on these findings and show that, after accounting for other donor characteristics, only 5.7% of the variation in OLD graft discard can be explained by OPO. Further, we found that if all OPOs performed at least at the national average for OPO discard, 177 more OLD grafts would have been available for LT.

Our findings of improved posttransplant mortality and graft loss over time may be due to several factors including patient care, surgical technique, or improved donor: recipient matching. We previously identified a recipient phenotype, a *preferred recipient*, who does not incur additional risk associated with OLD graft use.[73] *Preferred recipients* are first-time transplant recipients over the age

of 45 with BMI<35, non-status 1 registration, CIT<8 hours, and an indication for liver transplantation other than HCV. We recently validated this *preferred recipient* phenotype and found that 28.4% of OLD grafts went to preferred recipients in 2006, but this increased to 59.1% in 2013, meaning that indeed OLD grafts are more frequently being transplanted in recipients who do not incur additional risk of graft loss or mortality with OLD grafts.[74] These *preferred recipients* represent a potential group of recipients that could be used for broader utilization of OLD grafts. Exclusion of a potential organ donor should not be based on age alone, but donor age should be evaluated with donor:recipient matching and consideration of potential cold ischemia time.

Strengths of this study include a large, national cohort of OLD grafts and OLD recipients dating back to the implementation of the MELD allocation system. However, one notable limitation is the inability to determine if the improvement in outcomes was due to improved posttransplant care or improved OLD graft candidate selection.[73,74] Judicious recipient selection to potentially increase OLD graft utilization is imperative; we do not advocate that every candidate receive an OLD graft. While the overall improvement in outcomes for OLD recipients is encouraging, further study is needed to determine the etiologies of this improvement. Additionally, we cannot quantify the potential expansion of the donor pools with increased OLD utilization because most potential OLDs were not evaluated by the organ procurement organizations, and discard rates are likely underestimated.

In conclusion, there is a continued decline in OLD graft utilization despite improving outcomes for OLD recipients over time. Though outcomes for all LT recipients have improved over time, there has been a more marked improvement in OLD recipients. These trends may suggest the

transplant community has improved selection of who should receive OLD grafts and care for OLD recipients, and there may be room for more liberal and broader utilization of OLDs to expand the donor pool. These findings can guide OPO evaluation of potential donors, transplant surgeon utilization of OLDs, and patient clinical decision-making.

Table 1. Characteristics of 4,127 recovered older liver donor (OLD) grafts and 747 discarded OLD grafts from 2003-2016.

Recovered OLD grafts	**2003-2006**	**2007-2010**	**2011-6/2013**	**7/2013-2016**	**p value**
N	**1,379**	**987**	**856**	**905**	
Donor age, years+	75.1 ±4.0	75.1 ±4.2	74.7 ±3.9	74.3 ±3.6	0.002
Female, %	55	53.6	55.5	53.7	0.82
Donor BMI, kg/m^2 +	26.1 ±5.0	26.7 ±5.4	27.8 ±5.6	28.0 ±5.9	<0.001
Race, %					<0.001
Caucasian	80.6	77.4	80.4	69.9	
African American	9.9	11.4	12.3	15.5	
Hispanic	6.9	7.8	4.3	10.3	
Asian	2.1	2.9	2.9	4.3	
Hepatitis C, %	0.4	0	0.5	0.4	0.23
Cause of death, %					<0.001
Anoxia	5.7	7.5	10.4	13.9	
Head trauma	12.4	14	13.8	16.6	
Cerebrovascular accident	80.6	77.3	75	68.2	
Donation after cardiac death, %	0.7	0.1	0	0.1	0.008
Discarded OLD grafts	**2003-2006**	**2007-2010**	**2011-6/2013**	**7/2013-2016**	**p value**
N	**219**	**220**	**156**	**152**	
Donor age, years+	75.6 ±4.1	75.7 ±4.6	75.2 ±3.8	74.3 ±3.9	0.004
Female, %	53.9	52.3	57.1	55.3	0.82
Donor BMI, kg/m^2 +	26.7 ±5.3	27.8 ±6.2	28.0 ±5.9	28.7 ±6.3	0.008
Race, %					0.03
Caucasian	80.8	77.7	83.7	73.7	
African American	8.7	13.2	8.3	7.9	
Hispanic	7.8	5.9	4.5	10.5	
Asian	1.8	2.3	4.5	7.8	
Hepatitis C, %	0	0	1.3	0.7	0.17

Cause of death, %					0.54
Anoxia	9.1	10	14.1	15.8	
Head trauma	11.9	10.9	11.5	13.8	
Cerebrovascular accident	78.1	78.2	73.1	68.4	
Donation after cardiac death, %	1.4	0.5	0	0.7	0.42

[+]mean ± standard deviation

BMI= body mass index

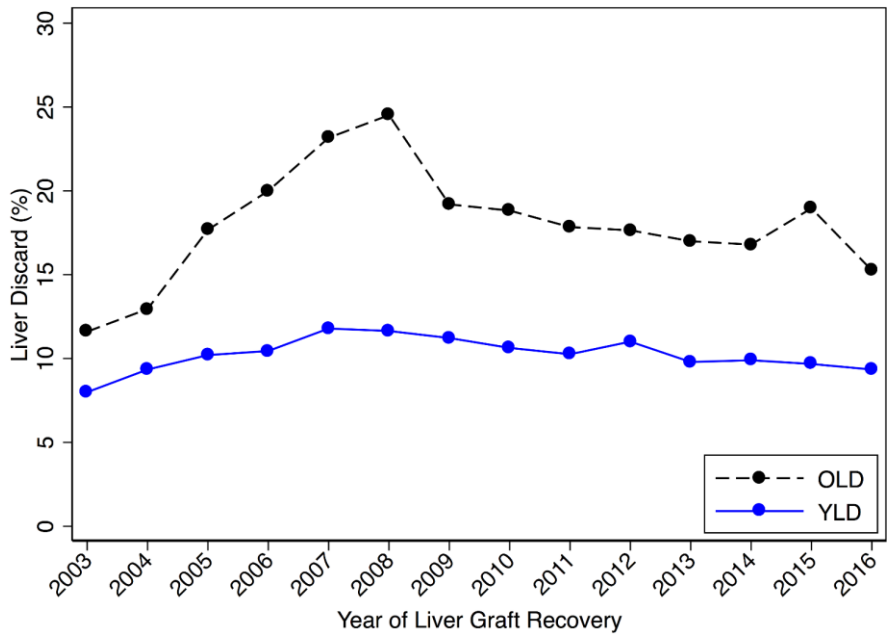
Table 2. Characteristics of older liver donor (OLD) recipients from 2003-2016.

	2003-2006	2007-2010	2011-6/2013	7/2013-2016	p value
N	1,147	758	698	747	
OLD recipient characteristic					
Age, years+	55.9 ±9.7	57.6 ±9.5	58.2 ±9.3	59.8 ±8.5	< 0.001
Female, %	37.9	37.2	37.3	38.4	0.94
BMI, kg/m^2 +	28.2 ±7.4	28.2 ±6.1	28.3 ±5.8	28.1 ±5.4	0.07
Race, %					0.26
Caucasian	74.6	73.7	73.6	73.0	
African American	6.3	6.5	6.0	5.4	
Hispanic	14.2	12.3	12.4	13.6	
Asian	3.9	6.4	7.2	6.8	
Indication for liver transplant, %					<0.001
Hepatitis C virus	20.0	10.3	9.6	11.5	
Alcoholic cirrhosis	21.2	21.6	21.4	20.9	
Non-alcoholic steatohepatitis	4.1	10	12.9	16.9	
Hepatocellular carcinoma	10.6	23.2	22.1	22.6	
Primary biliary cirrhosis	4.9	5.1	5.6	4.1	
Primary sclerosing cholangitis	4.7	5.2	5.6	4.8	
Calculated MELD score+	18 ±8	18 ±8	18 ±9	18 ±8	0.80
Allocation MELD score+	21 ±7	22 ±6	24 ±7	25 ±6	<0.001
Status 1/1A, %	4.4	3.9	2.2	0.9	<0.001
ICU prior to LT, %	11.4	8.2	7.1	6.2	0.001
Previous transplant, %	3.5	2.4	1.6	1.5	0.02
Portal vein thrombosis, %	2.2	2.2	3.6	6.4	<0.001
Diabetes mellitus, %	26.2	30.4	33.2	32.9	<0.001
Transplant characteristic					
Cold ischemia time, hours+	7.7 ±3.5	7.2 ±2.9	6.3 ±2.6	5.7 ±1.9	<0.001
Shared, %	47.4	45.9	38.7	39.0	<0.001

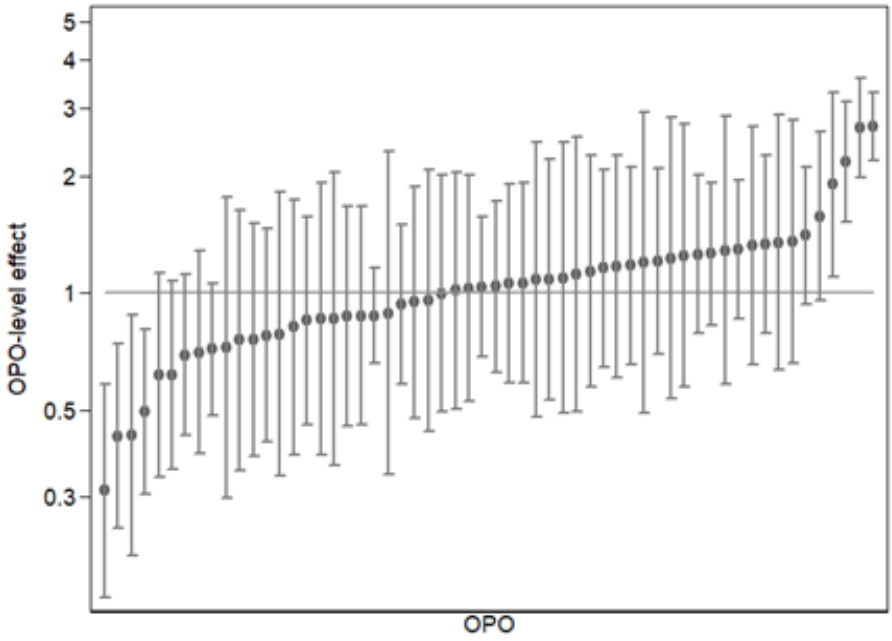
+mean ± standard deviation

BMI= body mass index, ICU= intensive care unit, MELD= model for end-stage liver disease

(a)


Liver Discard (%)
0
5
10
15
20
25
30
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
Year of Liver Graft Recovery
OLD
YLD

(b)


OPO-level effect
5
4
3
2
1
0.5
0.3
OPO

(c)

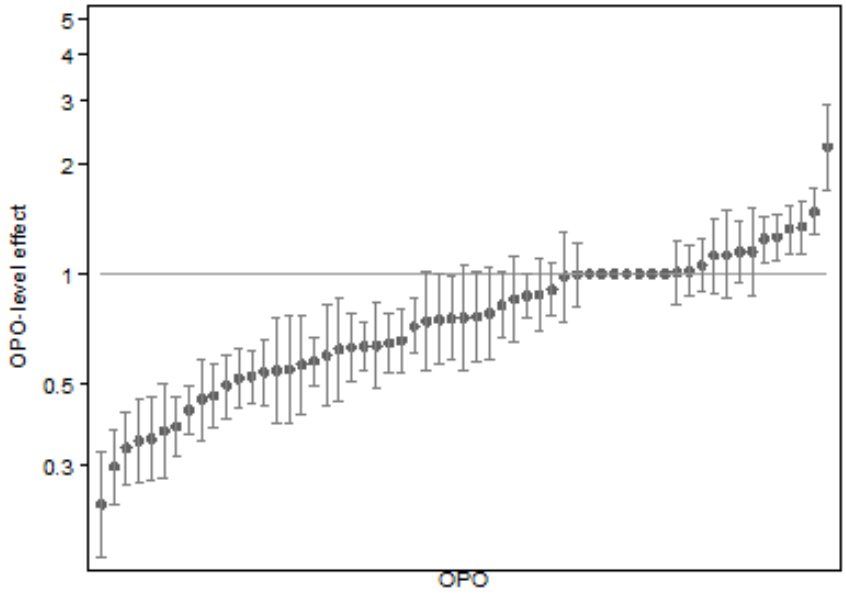


Figure 1. (a) Percent of discarded older liver donor (OLD) and younger liver donor [1] grafts by year of liver graft recovered. OLD grafts were more than 2-times as likely to be discarded compared to YLD grafts in each era (2003-2006 aOR: $_{1.68}1.97_{2.31}$, 2007-2009 aOR: $_{2.17}2.55_{3.01}$, 2010-2013 aOR: $_{1.68}2.04_{2.46}$, and 2013-2016 aOR: $_{1.96}2.37_{2.86}$; all $p<0.001$) after adjusting for sex, race, BMI, cause of death, DCD, and HCV status and accounting for OPO level variation.

(b) Relative odds of OLD graft discard by organ procurement organization (OPO) compared to national average (horizontal line). Each dot represents the relative risk of OLD graft discard for each OPO in the United States with 95% confidence interval.

(c) Relative odds of YLD graft discard by OPO compared to national average (horizontal line). Each dot represents the relative risk of YLD graft discard for each OPO in the United States with 95% confidence interval.

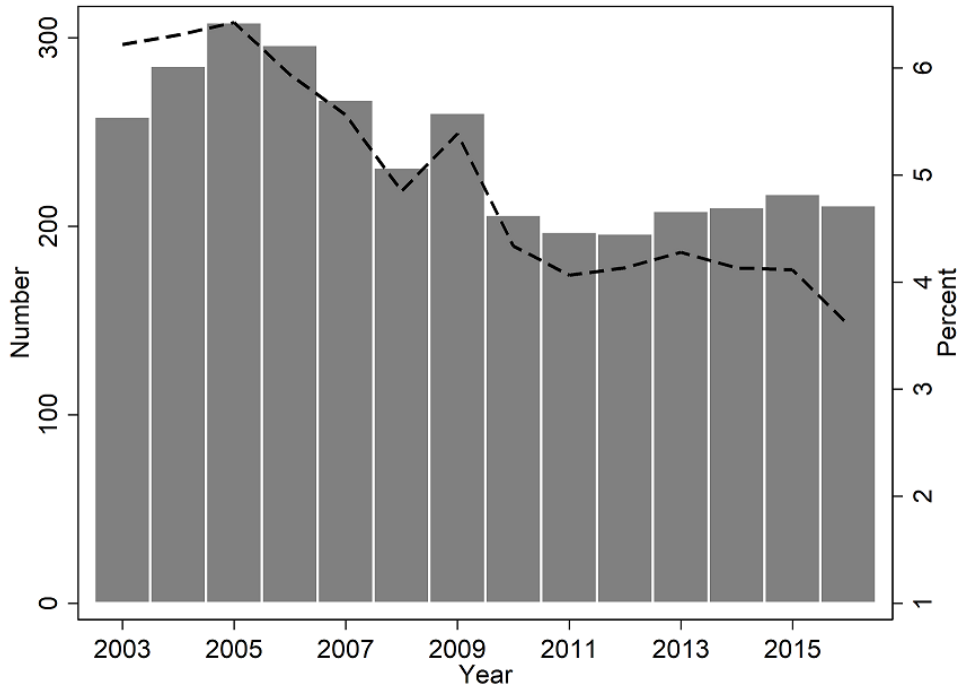
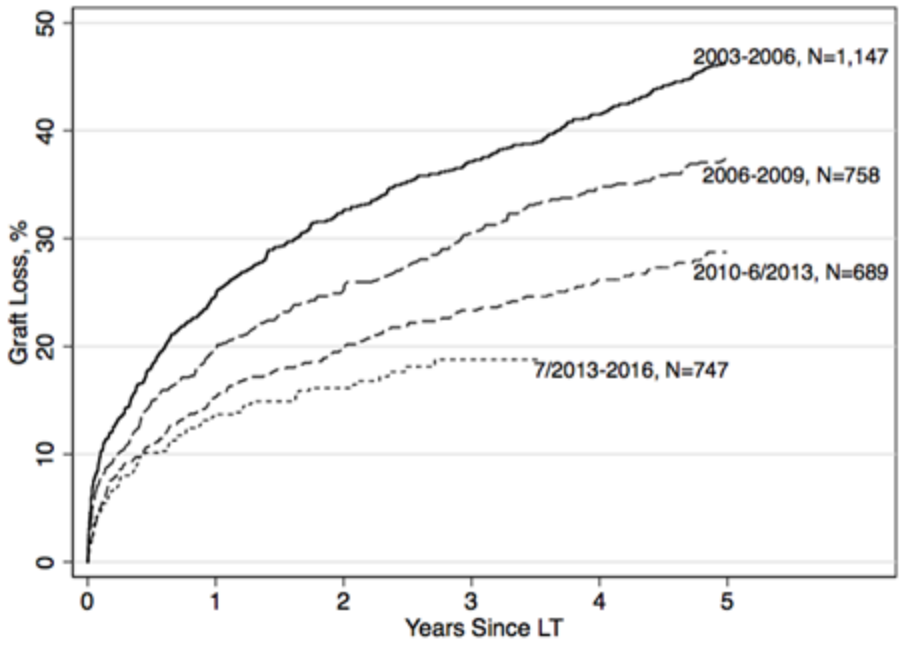
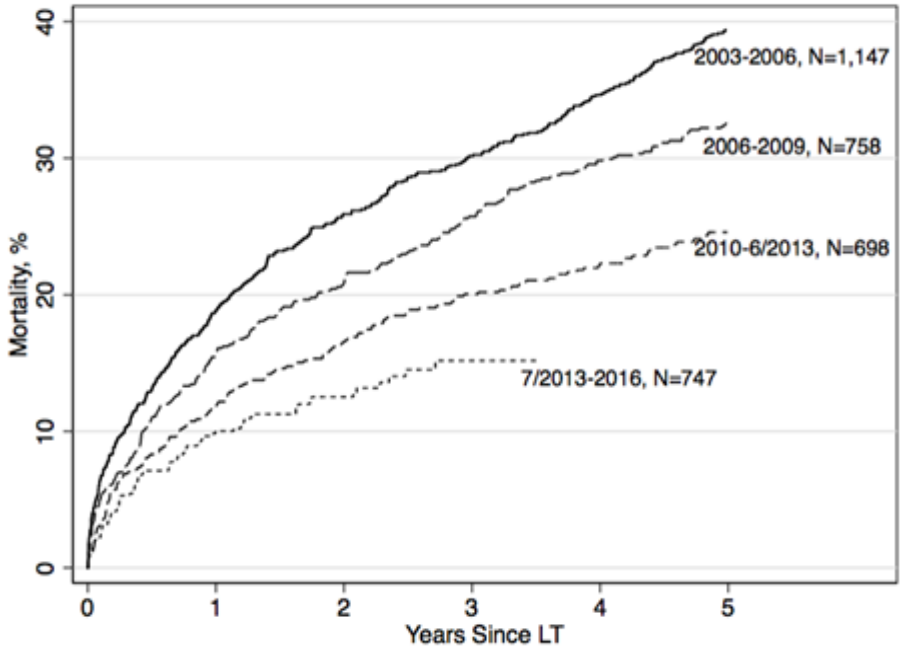


Figure 2. Trends in utilization of older liver donor (OLD) grafts according to year of liver transplant in OLD recipients. The number of transplanted OLD recipients is shown as a bar (left y-axis), and the percentage of OLDs among all adult liver grafts is shown as a line (right y-axis).

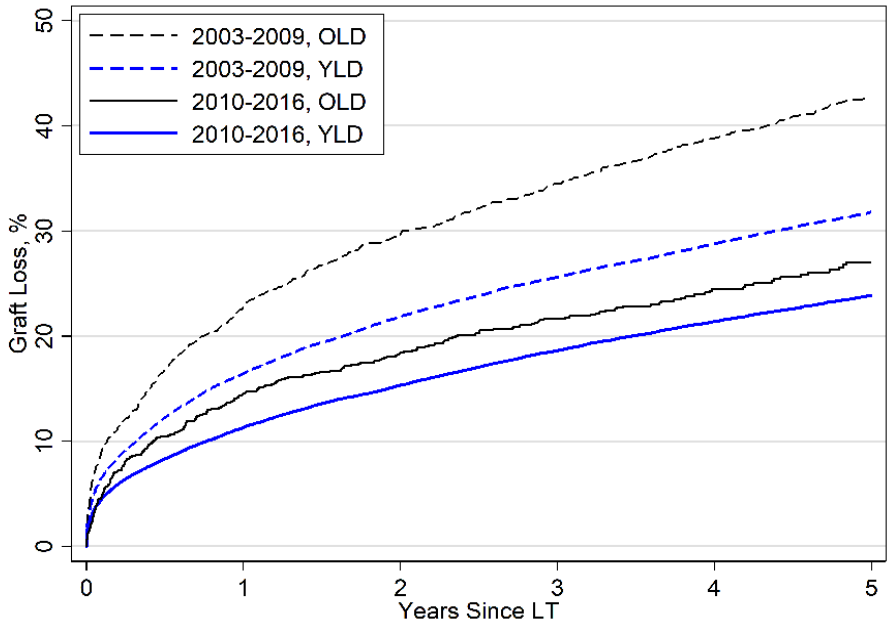
(a)


Graft Loss, %
0
10
20
30
40
50
0
1
2
3
4
5
Years Since LT
2003-2006, N=1,147
2006-2009, N=758
2010-6/2013, N=689
7/2013-2016, N=747

(b)


Mortality, %
0
10
20
30
40
0
1
2
3
4
5
Years Since LT
2003-2006, N=1,147
2006-2009, N=758
2010-6/2013, N=698
7/2013-2016, N=747

(c)



(d)

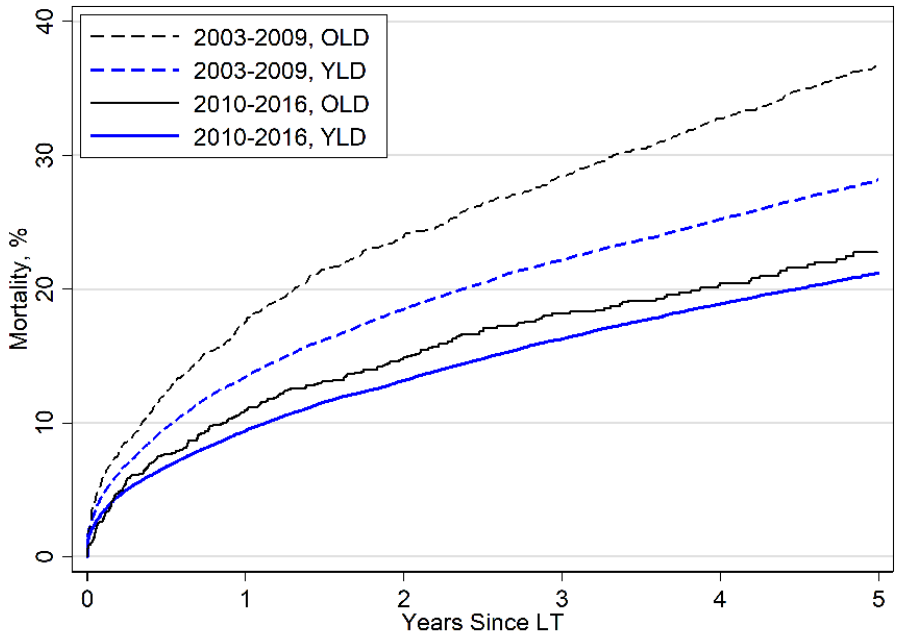


Figure 3. Cumulative incidence of mortality (a) and all-cause graft loss (b) in older liver donor (OLD) recipients. The year and number of liver transplant (LT) recipients is seen to the right of the curve. Cumulative incidence of mortality (c) and all-cause graft loss (d) in older liver donor (OLD) and younger liver donor [1] recipients. The most recent time periods were split at 6/18/2013 after the allocation policy implementation of Share35.

Chapter 3. National Trends in Liver Transplantation Among Older Adults

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ABSTRACT

Background: The burden of end-stage liver disease in older adults has increased; understanding trends in liver transplantation (LT) and outcomes for older recipients is imperative for evaluation, counseling, and appropriate referral of this vulnerable group of older adults.

Study design and setting: We studied 8,627 older (age≥65) deceased donor liver-only transplant recipients using data from the Scientific Registry of Transplant Recipients (1/1/2003-12/31/2016). We evaluated temporal changes in recipient, donor, and transplant characteristics. We also evaluated post-LT length of stay (LOS), acute rejection, graft loss, and mortality using logistic regression and Cox proportional hazards.

Results: LT in older adults increased almost 5-fold from 263 in 2003 (9.5% of total LT that year) to 1,144 in 2016 (20.7% of total LT). Recent recipients were more likely to be female, African American, and have a higher BMI and MELD score. Hepatitis C, non-alcoholic steatohepatitis, and hepatocellular carcinoma were the most common indications for LT in recent recipients. Comparing those in 2013-2016 to those in 2003-2006, odds of LOS>2 weeks decreased 34% (adjusted odds ratio [aOR]:0.66, 95%CI:0.57-0.76, *P*<.001), 1-year acute rejection decreased 30% (aOR:0.70, 95%CI:0.56-0.88, *P*=.002), all-cause graft loss decreased 54% (adjusted hazard ratio [aHR]:0.46, 95%CI:0.40-0.52, *P*<.001), and mortality decreased 57% (aHR:0.43, 95%CI:0.38-0.49, *P*<.001).

Conclusion: Despite the substantial increase in number and severity of older adults undergoing LT, LOS, rejection, graft loss, and mortality have significantly decreased over time. These trends can help guide appropriate LT referral and counseling in older adults with end-stage liver disease.

INTRODUCTION

The burden of end-stage liver disease (ESLD) in older adults (aged ≥65) in the United States (US) is increasing,[22,26-28] and older adults comprise 23.8% of the current liver transplant (LT) waitlist, up from 8% in 2002.[22,29] The increase in older adults with ESLD disease is driven by the aging population with hepatitis C virus cirrhosis along with the increase in nonalcoholic steatohepatitis and hepatocellular carcinoma, which typically affect older adults.[27,28,30,31] Historically, older adults were denied access to LT because of poor posttransplant survival,[32-34] but there are more recent reports of LT in older adults, including small reports of LT even in octogenarians.[35,36]

It is possible that advances in immunosuppression regimens and surgical techniques [37-40] may be leading to improved LT outcomes in older adults. However, older adults are uniquely susceptible after LT given increased comorbidity, higher prevalence of frailty, and physical impairment.[41-43] Among older LT candidates and recipients, physical impairment, frailty, and older age are associated with an increased risk of mortality.[22,42,44-46] Additionally, older adults have immunosenescence, leading to lower tolerance of post-LT immunosuppression. [47-49] Therefore, improvements in modern immunosuppression may not translate to improved posttransplant outcomes over time in older recipients. Further, poor outcomes in older LT recipients are typically due to cardiac complications, malignancy, and infection,[32,33,50] so surgical and immunosuppression changes do not necessarily translate into improved outcomes for older recipients. A better understanding of the trends over time in outcomes for older LT recipients is warranted for appropriate LT referral, evaluation, and counseling prior to transplantation.

In light of the aging ESLD population, we sought to evaluate and understand the temporal trends in LT and post-LT outcomes for older recipients. To inform clinical practice, we used

national registry data to: 1) characterize the changing landscape of LT in older adults, and 2) describe the trends over the last 15 years in LT length of stay, acute rejection, graft loss, and mortality for older recipients.

METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR) external release made available in March 2017. The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States submitted by members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[68] All-cause graft loss and mortality were augmented through linkage with the Social Security Master Death File, data from Centers for Medicare and Medicaid Services (CMS), and waitlist data. The Health Resources and Services Administration (HRSA), the United States Department of Health and Human Services, provides oversight to the activities of OPTN and SRTR contractors.

Study Population

We identified 8627 older (age ≥65) deceased donor liver-only transplant recipients between January 1, 2003 and December 31, 2016 using data from SRTR. We grouped these recipients by year of LT into four strata for empirical reasons and to reflect changes in allocation policy and general evolution of immunosuppression regimens: 2003-2006, 2007-2009, 2010-6/18/2013 and 6/19/2013-2016. We divided the recent time periods at 6/18/2013 to evaluate trends before and after implementation of the Share 35 policy change, which increased regional liver allograft offers to patients with MELD score ≥35. The annual number and percent of liver transplants

for older recipients was examined over time. Donor, recipient, and transplant characteristics were examined using t tests for continuous variables and χ^2 tests for categorical variables.

Outcomes

LOS was defined as the duration of hospitalization during the initial transplant episode and analyzed as a binary variable ≤2 weeks or >2 weeks using adjusted multiple logistic regression; a cut-off previously used in abdominal solid organ transplantation.[54,75] Acute rejection within the first year of LT was analyzed as a binary variable using adjusted multiple logistic regression. All-cause graft loss and mortality were estimated at 1-, 3- and 5-years using the Kaplan-Meier method for each time stratum. Kaplan-Meier methods were also used to create unadjusted cumulative incidence curves of all-cause graft loss and mortality. Cox proportional hazards models for all-cause graft loss and mortality were used to adjust for changes in recipient, donor, and transplant characteristics. Proportional hazards assumptions were confirmed with visual inspection of complementary log-log plots and Schoenfeld residuals.

Statistical Analyses

To ensure proper risk adjustment, we adjusted each of the regression models for standard factors accounted for in the SRTR program specific reports. This included recipient factors—sex, age, race, body mass index [67], primary diagnosis, life support, hepatocellular carcinoma, non-hepatocellular carcinoma malignancy, hepatitis C virus, HIV status, diabetic, primary insurance, portal vein thrombosis, and split LT)—and donor factors—age, race, BMI, hepatitis C virus, donation after cardiac death, ABO compatibility, cold ischemia time. All analyses were two-tailed and α was set at 0.05. All analyses were performed using STATA 14.2/MP for Linux (College Station, Texas).

RESULTS

Study Population

Among 58,598 adult LT recipients, 8627 (14.7%) were older LT recipients between 2003-2016; 78% were aged 65-69, 20.1% were aged 70-74, 1.6% were aged 75-79, and 0.1% were aged ≥80. Also, 36.1% were female, and 6.4% were African-American (Table 1).

Increase in LT in Older Adults

The annual number of LTs performed in older adults increased substantially throughout the study period (Figure 1A). In 2016, 1144 older adults received LTs (20.7% of all LT recipients), up from 263 older LT recipients in 2003 (9.5% of all LT recipients).

Changing Landscape of LT in Older Adults

LT recipients shifted toward older ages over time (Figure 1B). Older LT recipients became more likely to be male (66.0% in 2013-2016 vs 61.1% in 2003-2006, P =.006), African American (7.8 % vs 3.9%, P <.001), have MELD ≥30 (34.2% vs 13.0%, P <.001), have portal vein thrombosis (14.6% vs 5.0%, P <.001), and have non-alcoholic steatohepatitis (19.5% vs 5.8%) or hepatocellular carcinoma (28.9% vs 18.4%) as their indication for LT (Table 1). In addition, older LT recipients became more likely to receive a hepatitis C virus positive donor (5.3% vs 1.2%, p<0.001) or DCD donor (7.2% vs 4.8%, P=.003), and became less likely to receive a nationally shared donor (4.1% vs 10.6%, P <.001) (Table 1).

Length of Stay over Time

Median (interquartile range) LOS decreased from 10 (7-18) days in 2003-2006 to 9 (6-16) days in 2013-2016. LOS >2 weeks for older LT recipients decreased from 30.8% in 2003-2006 to 28.0%

in 2013-2016. After adjusting for donor, recipient, and transplant factors, the odds for LOS >2 weeks in 2013-2016 was 34% lower than in 2003-2006 (adjusted odds ratio [aOR]:0.66, 95% CI:0.57-0.76, *P* <.001) (Table 3).

Acute Rejection over Time

One-year acute rejection decreased from 14.8% in 2003-2006 to 9.7% in 2013-2016. After adjusting for donor, recipient, and transplant factors, one-year acute rejection in 2013-2016 was 30% lower than in 2003-2006 (aOR:0.70, 95% CI:0.56-0.88, *P* =.002) (Table 3).

All-Cause Graft Loss over Time

Graft survival in older LT recipients also improved over time (Figure 2A). One-year survival improved from 80% in 2003-2006 to 90% in 2013-2016; 3-year survival improved from 71% to 84%, and 5-year from 63% to 70% (Table 2). After adjusting for donor, recipient, and transplant factors, graft failure in 2013-2016 was 54% lower than it was in 2003-2006 (adjusted hazard ratio [aHR]:0.46, 95% CI:0.40-0.52, *P* <.001) (Table 3).

Mortality over Time

Patient survival in older LT recipients improved steadily over time (Figure 2B). One-year survival improved from 82% in 2003-2006 to 91% in; 3-year survival improved from 73% to 86%, and 5-year from 65% to 72% (Table 2). After adjusting for donor, recipient, and transplant factors, mortality in 2013-2016 was 57% lower than it was in 2003-2006 (aHR:0.43, 95% CI:0.38-0.49, *P* <.001) (Table 3).

DISCUSSION

In this national study of 8627 older LT recipients between 2003-2016, we have identified a changing landscape in transplantation for older adults, with a dramatic increase in number of LTs performed and a significant improvements in LOS, acute rejection, graft survival, and patient survival. There was almost a five-fold increase in the number of older adults who underwent LT from 2003 (N=263) to 2016 (N=1144), and older adults accounted for 20.7% of total LT recipients in 2016. Older LT recipients were more likely to be male, African American, have higher a MELD score and portal vein thrombosis in 2013-2016 as compared to 2003-2006. Also, recent older recipients were more likely to undergo LT for hepatitis C virus, non-alcoholic steatohepatitis, or hepatocellular carcinoma, and more likely to receive a hepatitis C virus positive or donation after cardiac death graft compared to older LT recipients in 2003-2006. Despite an increase in the severity of liver disease and number of LTs performed in older recipients, from 2003 to 2016 there were significant improvements in acute rejection (aOR: 0.70, P=.002) and shorter LOS (aOR: 0.66, P<.001) along with graft loss and mortality (aHR: 0.46 and 0.43, both P<.001).

Our findings of a significant increase in the number of older adults undergoing LT are consistent with reports of increasing numbers of older adults undergoing kidney, heart, and lung transplantation.[76,77] These studies described a substantial rise in the number and proportion of older adults undergoing transplantation, with up to 18.4% of kidney transplant recipients over the age of 65.[76] Our findings are also consistent with a report of increased LT in recipients over the age of 60 by Su et al; we extended their study by evaluating the trends over time in the characteristics and outcomes of older LT recipients and found that, despite the changing demographics, outcomes have dramatically improved.[22] Also, the temporal improvement we observed in graft and patient survival for older LT recipients is consistent with improvement in graft and patient survival for older KT recipients,[76] supporting our hypothesis that

improvements in immunosuppression might play a role. Finally, we show a dramatic improvement in long-term outcomes for older LT recipients that is different from a recent paper that showed no improvement in long-term outcomes for LT recipients of all ages.[78] However, this report did not stratify outcomes by age, but the majority of LT recipients are under age 65, so it seems to be driven by younger patients.

The strengths of this study include a large, unbiased, national cohort of LT recipients (i.e. every recipient in the United States) dating back to the implementation of the MELD allocation system. While we are limited by the general coarseness of comorbidity data in the national registry, it is unlikely that differences in comorbidities would explain the dramatically observed improvement in outcomes seen in recent years, especially given that older LT recipients are now sicker than those in the past (so any potential bias would be toward the null).

LT in older recipients increased dramatically in the last 15 years, with improvements in length of stay, acute rejection, graft survival, and patient survival in these recipients. Older patients with ESLD and their providers should be aware of these findings, and increased age *per se* should not prohibit access to LT in older adults.

Table 1. Characteristics of the older liver transplant (LT) recipients from 2003-2016.

Characteristic	2003-2006 N=1453	2007-2009 N=1544	2010- 6/2013 N=2222	7/2013- 2016 N=3408	*P* value
Recipient characteristic					
Age (years), mean± SD	68.0± 2.7	67.8± 2.6	67.8± 2.5	67.6± 2.4	.001
Female, %	38.9	37.2	36.9	34.0	.006
BMI, mean± SD	27.4± 4.9	27.9± 5.3	28.0± 5.1	28.4± 5.1	<.001
Race, %					
White	77.7	74.1	73.8	73.8	<.001
African American	3.9	5.1	6.7	7.8	
Indication for LT, %					
HCV cirrhosis	16.5	12.6	15.8	18.1	<.001
Alcoholic cirrhosis	12.6	14.1	12.7	13.0	
NASH	5.8	13.0	14.2	19.5	
HCC	18.4	27.9	29.1	28.9	
Cholestatic liver disease	10.0	8.3	7.8	6.7	
Non-cholestatic cirrhosis	26.4	18.2	13.8	8.6	
MELD, %					
<10	3.0	1.4	0.6	0.4	<.001
10-19	28.3	20.7	12.7	11.4	
20-29	53.8	62.7	58.3	52.9	
30-39	11.1	10.6	20.2	27.5	
≥40	1.9	3.6	6.4	6.7	
Status 1/1A	1.9	1.1	1.7	1.2	
Life support (prior to LT)	2.8	3.1	4.7	5.3	<.001
Ascites, %	2.0	2.0	2.0	1.9	.001
Albumin (g/dL)	1.1	1.1	1.1	1.2	<.001
Portal vein thrombosis, %	5.0	8.9	14.3	14.6	<.001
Comorbidities, %					
HIV	0.1	0.1	0.1	0.2	.79
HCV	27.5	27.6	30.2	32.6	<.001
Diabetes mellitus	31.0	34.5	33.5	37.4	<.001
Liver transplant characteristic					
Cold ischemia time (hours), %					
0-8	72.3	80.6	88.4	88.5	<.001

9-11	18.0	14.2	9.8	9.7	
≥12	9.7	5.2	1.8	1.8	
ABO incompatible, %	0.5	0.5	0.7	1.0	.08
Split graft, %	1.2	1.9	1.7	1.5	.37
Donor characteristic					
Age, %					<.001
<18	6.2	6.2	5.1	5.1	
18-39	28.8	32.8	34.6	36.5	
40-49	18.7	17.5	16.9	17.1	
50-59	19.0	18.3	20.2	20.3	
60-69	15.4	13.8	15.0	14.3	
≥70	12.0	11.5	8.2	6.7	
Female, %	44.9	40.2	43.1	40.8	.02
Race, %					
White	71.6	64.4	66.0	65.7	<.001
African American	14.3	17.2	19.4	18.8	
DCD, %	4.8	6.4	5.4	7.2	.003
HCV, %	1.2	1.8	2.3	5.3	<.001

HCV= hepatitis C virus, NASH= nonalcoholic steatohepatitis, HCC= hepatocellular carcinoma, DCD= donation after cardiac death

Table 2. Patient and all-cause graft survival at 1-, 3-, and 5-year in older recipients according to year of liver transplantation (LT).

Year of LT	Older recipients (N= 8,627)			
	N	%		
		1-year	3-year	5-year
Graft survival				
2003-2006	1453	80	71	63
2007-2009	1544	85	74	67
2010-06/18/2013	2222	85	76	70
06/19/2013-2016	3408	90	84	--
Patient survival				
2003-2006	1453	82	73	65
2007-2009	1544	87	76	69
2010-06/18/2013	2222	86	78	72
06/19/2013-2016	3408	91	86	--

*****The two latest time periods were split at 6/18/2103 after the allocation policy implementation of Share35. This policy increases regional liver allograft offers to patients with MELD score ≥35.

Table 3. Length of stay, one-year acute rejection, all-cause graft loss, and mortality for older liver transplant (LT) recipients.

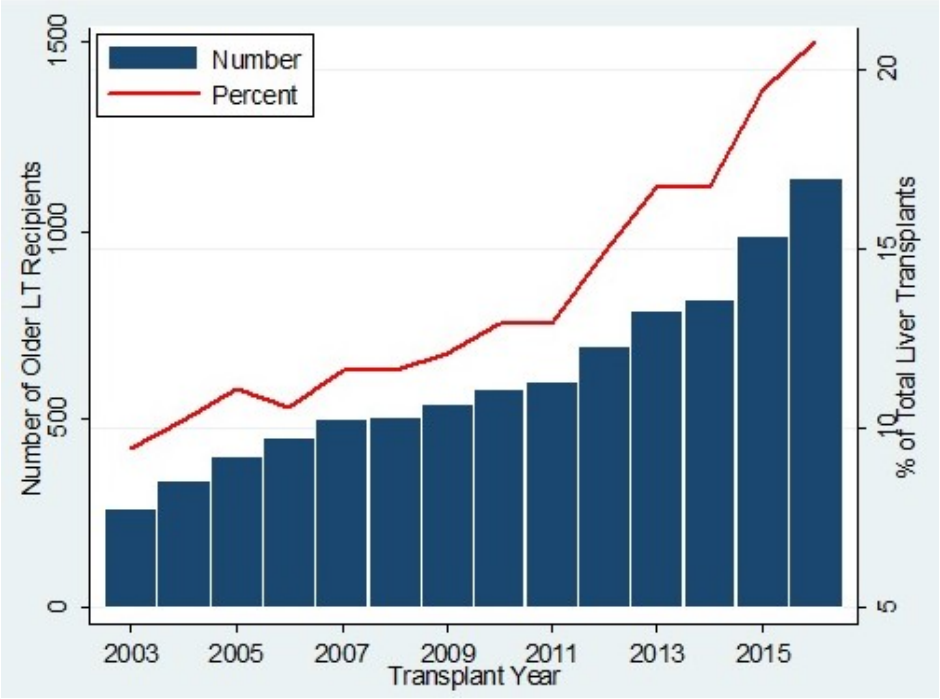
Year of LT	Older recipients (N= 8,627)	
Length of stay >2 weeks	N	aOR (95% CI) *P* value
2003-2006	1453	Reference
2007-2009	1544	0.83 (0.71, 0.98) *P*=.03
2010-06/18/2013	2222	0.73 (0.63, 0.85) *P*<.001
06/19/2013-2016	3408	0.66 (0.57, 0.76) *P*<.001
One-year acute rejection	N	aOR (95% CI) *P* value
2003-2006	1453	Reference
2007-2009	1544	1.00 (0.79, 1.27) *P*=.99
2010-06/18/2013	2222	0.74 (0.58, 0.93) *P*=.01
06/19/2013-2016	3408	0.70 (0.56, 0.88) *P*=.002
All-cause graft loss	N	aHR (95% CI) *P* value
2003-2006	1453	Reference
2007-2009	1544	0.83 (0.75, 0.92) *P*=.001
2010-06/18/2013	2222	0.68 (0.61, 0.75) *P*<.001
06/19/2013-2016	3408	0.46 (0.40, 0.52) *P*<.001
Mortality	N	aHR (95% CI) *P* value
2003-2006	1453	Reference
2007-2009	1544	0.83 (0.75, 0.93) *P*=0.001
2010-06/18/2013	2222	0.67 (0.60, 0.75) *P*<.001
06/19/2013-2016	3408	0.43 (0.38, 0.49) *P*<.001

Adjusted odds ratios (aORs) of one-year acute rejection loss and length of stay >2 weeks (relative to 2003-2006) in older were estimated using logistic regression. Adjusted hazard ratios (aHRs) of mortality and graft loss (relative to 2003-2006) in older recipients were estimated using Cox models. aHRs and aORs were adjusted for recipient factors (sex, age, race, body mass index (BMI), primary diagnosis, life support, hepatocellular carcinoma (HCC), non-HCC malignancy,

hepatitis C virus [69], HIV status, diabetic, primary insurance, portal vein thrombosis, and split LT), and donor factors (age, race, BMI, HCV, donation after cardiac death (DCD), ABO compatibility, as well as donor and recipient geography).

*****The two latest time periods were split at 6/18/2103 after the allocation policy implementation of Share35. This policy increases regional liver allograft offers to patients with MELD score ≥35.

(a)



(b)

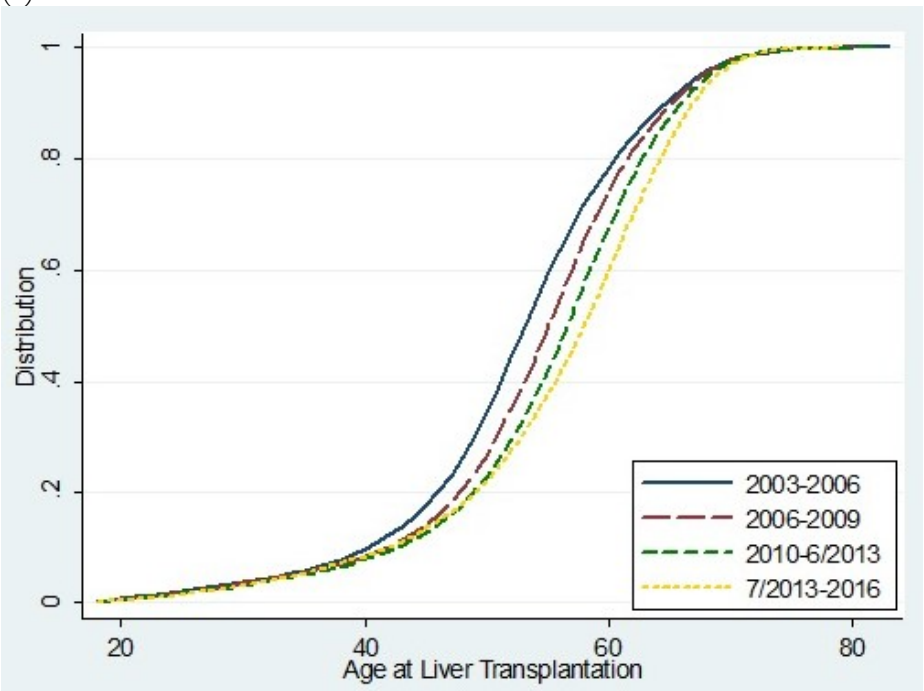
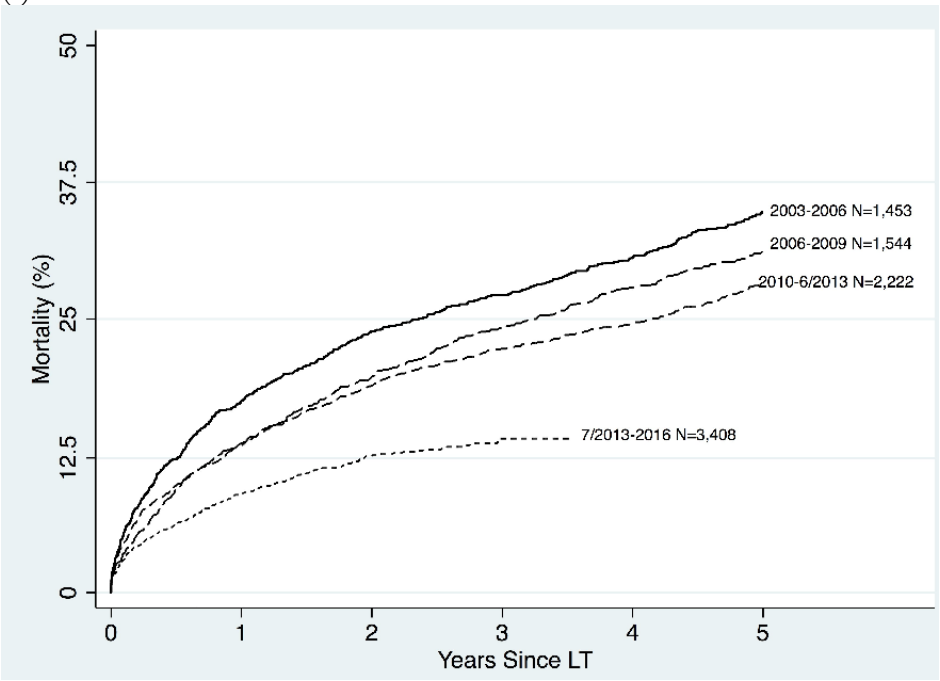


Figure 1. Trends in 8,627 older liver transplant (LT) recipients according to year of transplant. (a) The number of older LT recipients is shown as a bar (left y-axis), and the percentage of total older LT recipients among 58,598 adult LT recipients is shown as a line (right y-axis). (b) For all older LT recipients from 2003-2016, the nested cumulative distribution of age at the time of LT is displayed according to year of transplant.

(a)



(b)

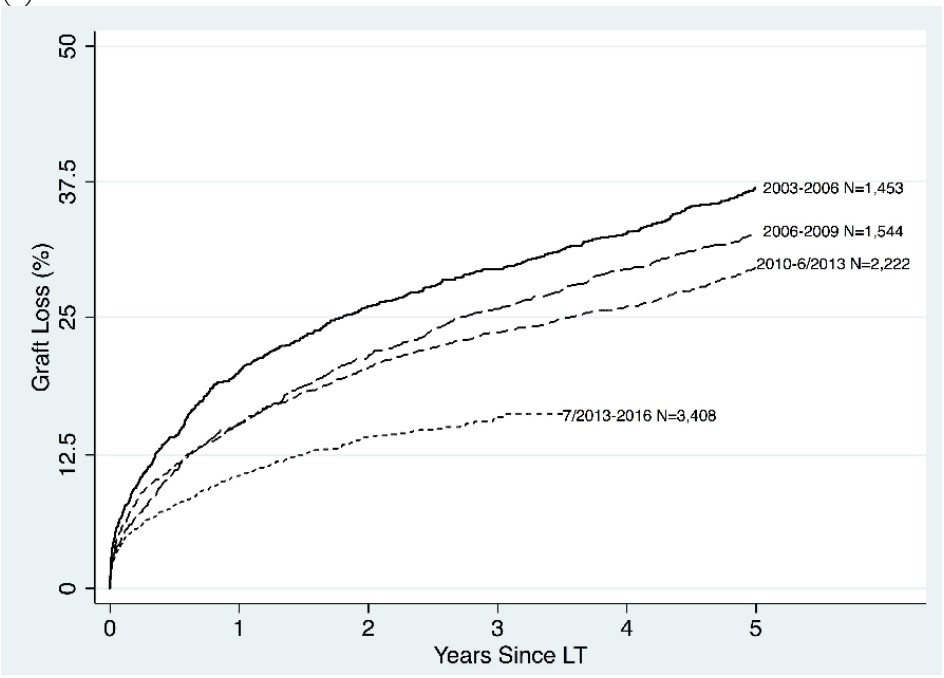


Figure 2. Cumulative incidence of (a) all-cause graft loss and (b) mortality in older LT recipients by year. The year and number of LT recipients is seen to the right of the curve. The most recent time periods were split at 6/18/2013 after the allocation policy implementation of Share35. This policy increases regional liver allograft offers to patients with MELD score ≥35 to direct allografts to sicker candidates.

Chapter 4. Multi-Center Study of Age, Frailty, and Waitlist Mortality Among Liver Transplant Candidates

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ABSTRACT

Objective: To determine if the association of frailty and waitlist mortality varies by candidate age.

Background: Frailty, a construct developed in geriatrics, is a state of decreased physiologic reserve, and is associated with mortality while awaiting liver transplantation (LT). However, older candidates have high comorbidity burden and less physiologic reserve, so the relationship between frailty and waitlist mortality may vary by candidate age.

Methods: We studied adults listed for LT at two transplant centers. The Liver Frailty Index (LFI; grip strength, chair stands, balance) was measured at evaluation, with frailty defined as LFI≥4.5. We compared the prevalence of frailty in older (≥65y) and younger (18-64y) candidates. We studied the association between frailty, age, interaction between the two, and waitlist mortality using competing risks regression adjusted for sex, BMI, and MELD.

Results: Among 882 LT candidates, 16.6% were ≥65y. Older candidates were more likely to be frail (33.3% vs. 21.7%, p=0.002). Older age (adjusted subhazard ratio [aSHR]: 2.16, 95%CI: 1.51-3.09, p<0.001) and frailty (aSHR: 1.92, 95%CI: 1.38-2.67, p<0.001) were independently associated with higher risk of waitlist mortality. However, the association between waitlist mortality and frailty did not vary by candidate age (aSHR of frailty for younger patients:1.90, 95%CI: 1.28-2.80, p=0.001; aSHR of frailty for older patients: 1.98, 95%CI: 1.07-3.67, p=0.03; p-interaction=0.9).

Conclusions: Older candidates experienced higher rates of frailty than younger candidates. However, regardless of age, frailty was associated with nearly two-fold increased risk of waitlist mortality. Our data support the applicability of the frailty concept to the whole LT population and can guide the development of prehabilitation programs targeting frailty in LT patients of all ages.

INTRODUCTION

Frailty, a measure of physiologic reserve and increased vulnerability to stressors, was initially described by gerontologists in older community dwelling adults.[51] Frailty was subsequently examined in older general surgery patients,[52] kidney transplant candidates and recipients,[41,49,53-59] and recently in liver transplant candidates and recipients, [44,60-64] where it was found to be associated with adverse outcomes in these populations. The Liver Frailty Index (LFI), comprised solely of performance-based measures (grip strength, balance testing, and chair stands), was developed in patients with cirrhosis evaluated for transplantation, and predictive validity was assessed with calculation of waitlist mortality.[44,60] The LFI improves risk prediction for waitlist mortality over the Model for End-stage Liver Disease (MELD) (c-statistic: 0.80 vs. 0.76). Up to 25% of liver transplant candidates are frail;[44,60] beyond waitlist mortality,[44] frailty is associated with increased hospitalizations[64] and depression[61] in liver transplant candidates and longer length of stay and hospitalized days in liver transplant recipients.[62]

While there is a higher prevalence of frailty in older adults, there is also a greater burden of comorbidities[41-43] and an increased prevalence of functional impairment in older adults.[42] Older candidates may therefore, because of comorbidity burden and underlying functional impairment, have a different association between frailty and waitlist mortality as compared to younger candidates. Yet, studies of frailty in liver transplant candidates have not examined whether there is effect modification by candidate age on the association between frailty and waitlist mortality: in other words, whether frailty has the same impact on younger patients as it does on older patients.[44,60] As the average age of waitlisted liver candidates and liver transplant recipients continues to increase,[22,66] it is even more important to understand this effect.

To clarify and quantify the interaction of candidate age and frailty on mortality on the liver transplant waitlist, we sought to quantify the prevalence of frailty, compare individual elements of the LFI score, and quantify the association of frailty and waitlist mortality, in older and younger liver transplant candidates.

METHODS

Study population

This was a prospective, longitudinal cohort study of 882 participants, aged 18 years or older, who were being evaluated in the outpatient setting for liver transplant at University of California San Francisco (n=759) from March 2012 to April 2018 or Johns Hopkins Hospital (n=123) from August 2016 to May 2018. We excluded participants with hepatocellular carcinoma (n=500) because their waitlist mortality was expected to differ substantially from participants with other causes of liver failure. Participants with severe hepatic encephalopathy (n=20), as defined by the time to complete the Numbers Connection Test >120 seconds were excluded.[42,44] We defined older candidates as aged≥65, a commonly used age cut-off.[42,66,79] The University of California San Francisco Institutional Review Board and Johns Hopkins Institutional Review Board approved the study.

Data collection

We measured the LFI as described below. Additional participant characteristics were abstracted from the electronic medical record (age, sex, race, indication for liver transplant, body mass index [BMI], MELD score, diabetes, hypertension, coronary artery disease, history of stroke, ascites [none, mild/moderate, refractory], and hepatic encephalopathy). Hepatic encephalopathy was defined as time >60 seconds to complete the Numbers Connection Test as previously used

in liver candidate cohorts.[42,44] Physicians were not aware of the measured frailty scores at liver transplant evaluation.

Frailty

We studied the LFI as previously defined in liver transplant candidates.[60,62] The LFI is composed of three components that include grip strength, balance testing, and chair stands. These objective measures were recorded at the time of clinic liver transplant evaluation using the following:

1. Grip strength: average of three trials in the subject's dominant hand using a hand dynamometer, measured in kilograms
2. Chair stands: measured as the number of seconds it takes to stand from seated in a chair five times with the subject's arms folded across the chest
3. Balance testing: measured as the number of seconds that a subject can balance in three positions (feet side-to-side, semi-tandem, and tandem) for a maximum of ten seconds each

The LFI was calculated (www.liverfrailtyindex.ucsf.edu):

(-0.330 x gender-adjusted grip strength) + (-2.529 x number of chair stands per second) + (-0.040 x balance time) + 6

Standard cutoffs were used to define robust (LFI<3.2), prefrail (3.2 to <4.5), and frail (LFI≥4.5).[60]

Waitlist mortality

Among liver transplant candidates, the risk of waitlist mortality was estimated at 6 months, 1 year, and 3 years using a competing risk framework by candidate age (older [age≥65] vs. younger [age18-64]) and frailty status with transplantation as a competing risk. Also, a competing risk framework was used to create unadjusted cumulative incidence curves of waitlist mortality by

candidate age and frailty status. The log rank test of equality was used to compare unadjusted cumulative incidence curves. Transplantation was considered a competing risk for waitlist mortality, and the time origin was date of liver transplant listing. Subhazard ratios of waitlist mortality by candidate age were obtained using the Fine and Gray method for competing risks.[80] The final multivariable model was selected for optimal parsimony by minimizing the Akaike Information Criteria (AIC) and included adjustment for sex, body mass index [67], and MELD score. To test whether waitlist mortality varied by frailty status, an interaction between candidate age and frailty was evaluated using a Wald test. Additionally, we quantified the risk of waitlist associated with each individual parameter of the LFI and included an interaction between candidate age and LFI component.

Statistical analyses

Comparison of candidate characteristics was performed using chi-squared test for categorical variables and t-tests or Wilcoxon rank sum for continuous variables. All analyses were two-tailed and α was set at 0.05. All analyses were performed using Stata 14.2/MP (College Station, Texas).

RESULTS

Baseline characteristics of the entire cohort

Among the 882 liver transplant candidates, 43.0% were female, 60.1% were Caucasian, and 16.6% were older (age≥65). The median (interquartile range [IQR]) was 56 (49-60) years for younger candidates and 67 (66-68) years for older candidates ($p<0.001$). The age range of older candidates was 65-75 years with 10% of the candidates being age 70 or greater. Older candidates were as likely to be Caucasian (69.3% vs. 59.6%), Hispanic (19.1% vs. 24.2%), or African American (4.1% vs. 3.8%) ($p=0.1$) compared to younger candidates. Older candidates had lower

MELD scores (median 17 vs. 18, p=0.01) and were more likely to have NASH as the indication for liver transplant (26.0% vs. 15.0%, p=0.02), hypertension (55.2% vs. 37.9%, p<0.001), diabetes (39.9% vs. 28.3%, p<0.01), and coronary artery disease (12.4% vs. 5.4%, p=0.002). Additionally, older candidates were more likely to have hepatic encephalopathy (29.9% vs. 16.2%, p<0.001) but similarly likely to have ascites (moderate: 31.9% vs. 29.4%, refractory: 5.6 vs. 7.1%, p=0.7).

Older liver transplant candidates were more likely to be frail (33.3% vs. 21.7%, p=0.002) and have higher LFI scores (4.3 vs. 3.9, p<0.001) than younger liver transplant candidates at evaluation.

Baseline characteristics by frailty status

Among the 735 younger liver transplant candidates, frail candidates had a similar average age (54.3 years vs. 53.1 years, p=0.2), similar BMI (29.4 vs. 29.2, p=0.9), and were more likely to be female (52.3% vs. 40.2%, p=0.01) than nonfrail candidates. Frail candidates were just as likely to be Caucasian (63.6% vs. 59.4%), Hispanic (22.0% vs. 23.7%), or African American (2.9% vs. 4.1%) (p=0.7) compared to nonfrail candidates. Younger frail candidates were more likely to have alcoholic cirrhosis (29.9% vs. 24.5%, p=0.001) and NASH (21.7% vs. 13.2%, p=0.001), but less likely to have HCV (26.8% vs. 34.6%, p=0.001) and cholestatic disease (7.1% vs. 16.4%, p=0.001) as the indication for liver transplant than nonfrail candidates. Also, younger frail candidates were more likely to have higher MELD scores (20 vs. 18, p<0.001), diabetes (41.3% vs. 24.1%, p<0.001), hepatic encephalopathy (27.5% vs. 13.1%, p<0.001), mild/moderate ascites (35.6% vs. 27.7%, p<0.001), and refractory ascites (13.1% vs. 5.3%, p<0.001) than nonfrail candidates. Younger frail candidates were just as likely to have history of stroke (1.3% vs. 1.6%,

p=0.8), hypertension (40.0% vs. 37.3%, p=0.5), and coronary artery disease (5.0% vs. 5.6%, p=0.8) compared to younger nonfrail candidates (Table 1).

Among the 147 older liver transplant candidates, frail candidates had a similar average age (67.1 years vs. 67.3 years, p=0.6) and similar BMI (30.0 vs. 28.9, p=0.3) compared to nonfrail candidates. Older frail candidates were more likely to have alcoholic cirrhosis (32.7% vs. 19.6%) and NASH (28.6% vs. 24.7%), but less likely to have HCV (24.5% vs. 33.0%) and cholestatic disease (8.2% vs. 11.3%) as the indication for liver transplant than nonfrail candidates. Also, older frail candidates had higher average MELD scores (19 vs. 16, p=0.03) and were more likely to have mild/moderate ascites (44.7% vs. 25.8%, p=0.03) and refractory ascites (8.5% vs. 4.1%, p=0.03) than nonfrail candidates. Older frailer candidates were just as likely to have diabetes (40.4% vs. 37.8%, p=0.8), stroke (2.1% vs. 2.0%, p=0.9), hypertension (44.7% vs. 60.2%, p=0.1), coronary artery disease (14.9% vs. 11.2%, p=0.5), and hepatic encephalopathy (34.7% vs. 27.6%, p=0.4) as nonfrail candidates (Table 1).

At the time of liver transplant evaluation, 23.5% of candidates were frail and 16.2% of candidates were robust. Older candidates were more likely to be frail (33.3% vs. 21.7%, p=0.002) and less likely to be robust (4.8% vs. 18.4%, p<0.001) compared to younger candidates (Figure 1). Additionally, older candidates had higher LFI scores (average 4.3 vs. 3.9, p<0.001) along with poorer median performance for each component of the LFI: male grip strength (30.3 kg vs. 34.0 kg, p<0.001) and female grip strength (18.9 vs. 20.7, p=0.004), balance testing (30 [25-30] vs. 30 [30-30] seconds, p<0.001), and chair stands (13.7 vs. 12.2 seconds, p<0.001) compared to younger candidates (Table 2).

Waitlist mortality

Waitlist mortality was higher in older candidates compared to younger liver transplant candidates (log rank p<0.001). The cumulative incidence of waitlist mortality estimated by competing risk framework for older versus younger liver transplant candidates was 13.6% (n=20) vs. 7.3% (n=54) at 6 months, 23.0% (n=34) vs. 12.6% (n=93) at 1 year, and 42.5% (n=62) vs. 24.9% (n=185) at 3 years after listing. After adjustment for candidate sex, BMI, and MELD score, older liver transplant candidates had a 2.2-fold higher risk of waitlist mortality (adjusted subhazard ration [aSHR]: 2.16, 95%CI: 1.51-3.09, p<0.001) compared to younger liver transplant candidates.

Waitlist mortality was higher in frail candidates compared to nonfrail liver transplant candidates (log rank p<0.001). The cumulative incidence of waitlist mortality for frail versus nonfrail liver transplant candidates was 14.8% (n=31) vs. 6.5% (n=44) at 6 months, 25.2% (n=53) vs. 11.4% (n=77) at 1 year, and 46.7% (n=98) vs. 23.1% (n=157) at 3 years after listing. After adjustment for candidate age (as continuous variable), sex, BMI, and MELD score, frailty was independently associated with a significantly higher risk of waitlist mortality (aSHR: 1.92, 95%CI: 1.38-2.67, p<0.001). However, the association between waitlist mortality and frailty did not vary by candidate age (p interaction=0.9): Frail older candidates had a higher risk waitlist mortality compared to nonfrail older candidates (aSHR: 1.98, 95%CI: 1.07-3.67, p=0.03), as well as frail younger candidates compared to nonfrail younger candidates (aSHR: 1.90, 95%CI: 1.28-2.80, p=0.001).

Additionally, after assessment of each component of the LFI individually, the risk of waitlist mortality decreased by 25% for each 1 unit increase in gender adjusted Z-score for grip strength (aSHR: 0.75, 95%CI: 0.64-0.88, p<0.001), and this association did not vary by candidate age (interaction p=0.8). The risk of waitlist mortality decreased by 6% for each second increase in

balance tests (aSHR: 0.94, 95%CI: 0.92-0.97, p<0.001), and this association did not vary by candidate age (interaction p=0.7). There was no association between waitlist mortality and chair stands time (aSHR: 1.02, 95%CI: 0.99-1.04, p=0.1), and this did not vary by candidate age (interaction p=0.2).

DISCUSSION

In this two-center prospective cohort study of frailty in 882 liver transplant candidates, we found older candidates were more likely to be frail, less likely to be robust, and had worse performance for all components of the LFI (grip strength, balance, chair stands) than younger candidates. Additionally, we found frail candidates were two-fold more likely to die on the waitlist. However, the impact of frailty did not vary by candidate age.

Less than one in ten older community dwelling adults are frail using the Fried frailty phenotype[51] and the prevalence of frailty increases with age,[81] yet nearly one in five liver transplant candidates, of all ages, are frail using Fried frailty phenotype.[44] Using the Liver Frailty Index, a cirrhosis-specific measure of frailty, we found one-third of older liver transplant candidates were frail. Our finding that frailty is more common in older liver transplant candidates compared to younger liver transplant candidates (33.3% vs. 21.6%, p=0.002) is similar to that seen in kidney transplant candidates (age≥65: 23.7% for age≥65 vs. 15.5% for age 18-55), with older kidney transplant candidates at a 2.2-fold increased odds of being frail compared to younger kidney transplant candidates.[58]

Not surprisingly, frail candidates are at a higher risk of waitlist mortality, and the quantification of this risk with an objective tool such as LFI is critical for identification of patients who are at

high risk of waitlist mortality *independent* of MELD-Na. Importantly, in this large cohort of 147 older liver transplant candidates, we did not find the association between frailty and waitlist mortality to vary by age. This finding expands upon our understanding of the concept of frailty in patients with cirrhosis – frailty captures something more than just age-related phenomena (e.g., muscle wasting and decreased physiologic reserve that is associated with aging itself), although the effects of chronologic aging may make it more likely that an older adult will display the frail phenotype. Frailty is a measure of physiologic reserve more than age and MELD-Na alone. The effects of cirrhosis that contribute to this manifestation of frailty exert as powerful an impact in younger adults with respect to the outcome of waitlist mortality.

Strengths of our study include the fact that this is a large, prospective cohort of frailty at two centers with distinctly different patient populations, along with granular ascertainment of candidate characteristics and long-term outcome follow-up. One notable limitation of this study is the enrollment of only outpatients, and our findings are not necessarily generalizable to inpatient liver transplant candidates. However, these are two distinct groups when thinking about a prehabilitation intervention prior to liver transplant, and inpatient liver transplant candidates would likely not be suitable candidates for a prehabilitation program. Another limitation is the use of the LFI is not directly comparable to other more general measures of frailty, such as the Fried frailty phenotype. Notably, the LFI includes only performance-based measurements, whereas the Fried frailty phenotype is a construct of frailty that likely better captures underlying physiologic reserve.

In conclusion, older liver transplant candidates are more likely to be frail by the Liver Frailty Index and have lower scores across all components of the LFI. Frailty is associated with waitlist mortality, irrespective of candidate age. These findings strengthen with the conceptual

framework and biological underpinnings of frailty. Interventions to mitigate frailty in liver transplant candidates awaiting transplantation should be explored.

Table 1. Characteristics of 882 liver transplant (LT) waitlist candidates by frailty status and age.

	Younger, nonfrail	**Younger, frail**	**Older, nonfrail**	**Older, frail**
N	575	160	98	49
Age, years*	53.1 (9.3)	54.3 (8.2)	67.3 (2.2)	67.1 (1.6)
Female, %	40.2	52.3	46.9	40.8
BMI, kg/m^2*	29.2 (5.7)	29.4 (6.7)	28.9 (5.4)	30.0 (6.1)
Race, %				
Caucasian	57.3	62.5	70.4	67.4
Black	4.2	2.5	4.1	4.1
Hispanic	24.9	21.9	17.4	22.5
Asian	5.4	3.8	3.1	2.0
Other	8.3	9.4	5.1	4.1
Indication for LT, %				
Alcoholic cirrhosis	24.5	29.9	19.6	32.7
NASH	13.2	21.7	24.7	28.6
HCV	34.6	26.8	33.0	24.5
Cholestatic disease	16.4	7.1	11.3	8.2
Other	11.3	14.7	11.3	6.1
MELD Na*	18.0 (5.4)	19.9 (7.0)	16.2 (5.0)	18.6 (6.8)
Diabetes, %	24.1	41.3	37.8	40.4
Stroke, %	1.6	1.3	2.0	2.1
Hypertension, %	37.3	40.0	60.2	44.7
CAD, %	5.6	5.0	11.2	14.9
Hepatic encephalopathy, %	13.1	27.5	27.6	34.7
Ascites, %				
None	67.0	51.3	70.1	46.8
Mild/moderate	27.7	35.6	25.8	44.7
Refractory	5.3	13.1	4.1	8.5

*average (standard deviation)

Table 2. Scores for individual components of the Liver Frailty Index (LFI) by candidate age (older: age ≥65 years and younger: age 18-64 years).

	Younger	**Older**	**p value**
LFI*	3.9 ±0.8	4.3 ±0.8	<0.001
Grip strength- Male, kg¥	34.0 (27.7-40.7)	30.3 (25.0-36.7)	<0.001
Grip strength- Female, kg¥	20.7 (17.0-25.3)	18.9 (15.7-23.3)	0.004
Balance, sec¥	30 (30-30)	30 (25-30)	<0.001
Chair stand, sec¥	12.2 (9.2-16.2)	13.7 (11.2-16.9)	<0.001

*average ± standard deviation
¥median (interquartile range)

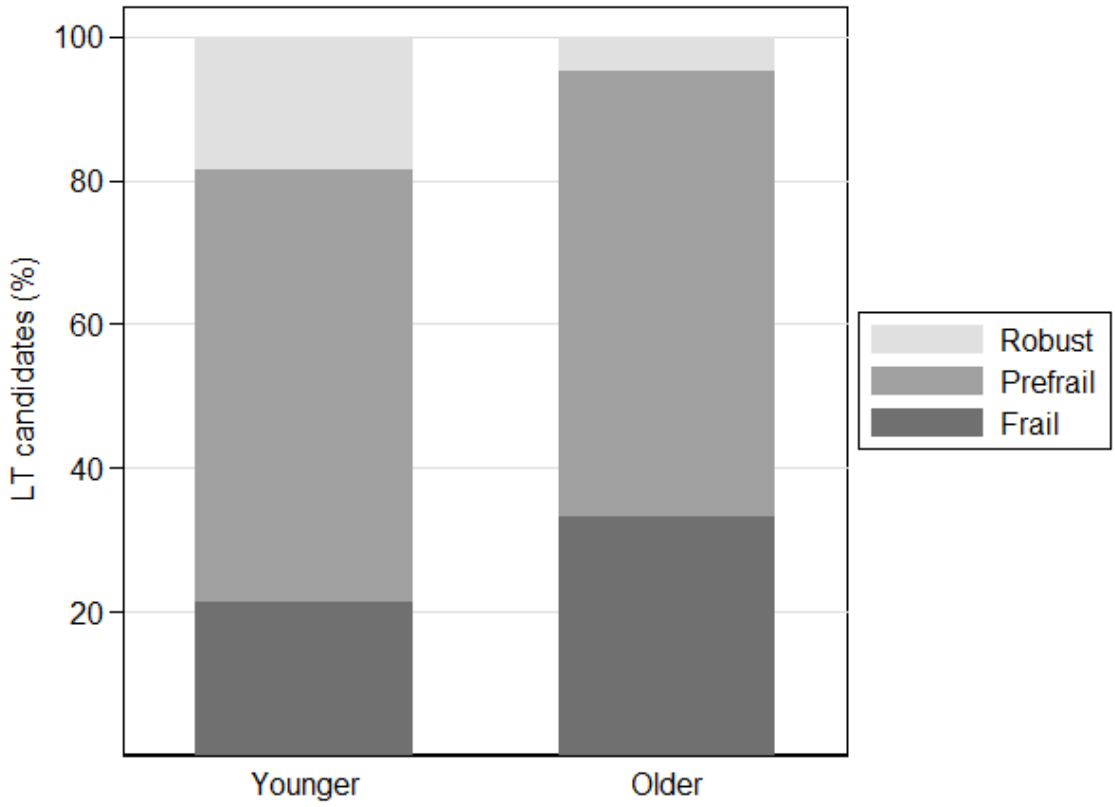

Figure 1. Prevalence of frailty by candidate age (older: age ≥65 and younger: age 18-64).

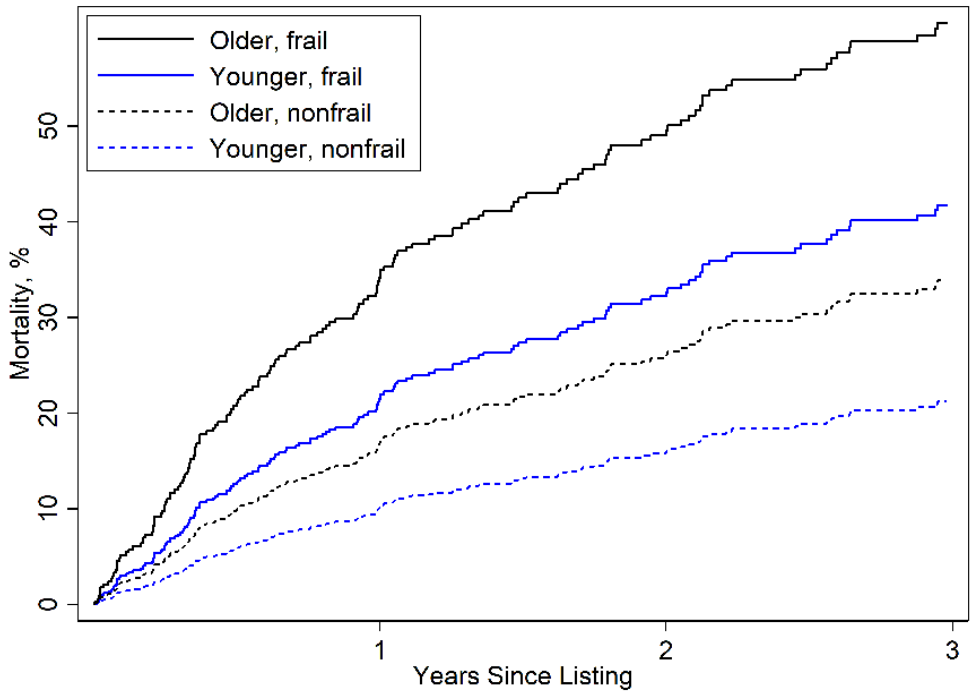

Figure 2. Cumulative incidence of waitlist mortality by frailty status (liver frailty index ≥4.5) in older (age ≥65) and younger (age 18-64) candidates. Transplant was treated as a competing risk.

Chapter 5. Conclusion

This work examined several challenges regarding use of older liver donors and liver transplantation for older recipients. First, the discard of older liver donors and outcomes for recipients of older liver donors over time compared to younger counterparts have never been previously examined. From our national registry study of 4,427 older liver donor grafts, we found that older liver donor graft utilization is declining (6.0% to 3.2%, p=0.001) and older liver donor graft discard is increasing (11.6% to 15.4%, p<0.001) since 2003. Discard of older liver donors is nearly two-fold higher for every year since 2003 compared to younger liver donors, and additionally we found that only 5.7% of older liver donor discard is associated with the organ procurement organization level. Among the 3,350 older liver donor recipients from 2003-2016, we found the risk of all-cause graft loss and mortality decreased by half (all-cause graft loss aHR [adjusted hazard ratio]: 0.60, 95%CI: 0.58-0.68, p<0.001, mortality aHR: 0.59, 95%CI: 0.52-0.68, p<0.001). Further, these improvements in all-cause graft loss and mortality for older liver donor recipients are more marked than improvements seen in younger liver donor recipients (all-cause graft loss p interaction=0.03, mortality p interaction= 0.04). These trends may suggest the transplant community has improved the selection of and care for recipients of older liver donors, and there may be room for more liberal and broader utilization of older liver donor grafts to expand the donor pool. These findings can guide organ procurement organization evaluation of potential donors, transplant surgeon utilization of older liver donors, and patient clinical decision-making.

Our findings of decreased utilization of older liver donor grafts are important because acceptance of older liver donor graft offers provide a survival benefit for candidates over remaining on the waitlist and waiting for a younger donor offer that may never come. Our recent

work showed that acceptance of an older liver donor graft confers survival benefit (2-fold decreased risk of mortality) for waitlist candidates across all MELD scores (MELD 15-40), especially in high MELD candidates (MELD 35-40).[21] Notably, both older (age≥65) and younger (age 18-64) candidates derived a survival benefit from older liver donor graft acceptance.[21] Patients and providers should carefully weigh the consequences of declining an older liver donor graft offer, as one-fourth of candidates die on the waitlist without undergoing transplantation after such a decline.[21] These findings can guide future clinical decision making for transplant providers and improve patient counseling in considering offers. Urging for increased utilization of older liver donor grafts must be taken into context with donor-recipient matching. Our previous work identified, through a full, formal donor-recipient interaction analysis, a *preferred* phenotype of recipients who incurred no additional risk of graft loss or mortality through acceptance of an older liver donor graft: recipient age>45, recipient BMI<35, indication for transplant other than Hepatitis C, and cold ischemia time <8 hours.[73] We recently validated this *preferred* recipient phenotype, showing that, 13 years later, recipients with this phenotype still have similar outcomes with livers from older versus younger donors, and that use of older liver donor grafts for preferred recipients has increased over time.[74] Thus, it seems that the transplant community has utilized donor-recipient matching for transplantation of older liver donor grafts, which is encouraging. Notably, this thesis work demonstrated that age of older liver donor recipients increased over time and the percent of older (age≥65) recipients of older liver donor grafts increased over the study period from 2003 to 2016 from 9.3% to 20.2%.

Another key component of future increased utilization of older liver donor grafts will likely need to come at the organ procurement organization level. Organ procurement organization performance and efficiency are evaluated by the number of procurements performed divided by

the number of eligible deaths (donation after brain death donors aged <70 years).[16] Thus, donors aged 70 and greater are considered ineligible donors, and organ procurement organization pursuit of ineligible donors is not specifically tracked. The conversion rates of ineligible donors into organ donors have not been quantified. As we urge the transplant community and organ procurement organizations to increase the procurement and utilization of potential older liver donors, the number of potential older liver donors will need to be quantified as an important first step.

From our national registry study of 8,627 older liver transplant recipients, we found that the number of liver transplant recipients aged≥65 increased nearly five-fold from 2003 (N=263) to 2016 (N=1,144), and older adults accounted for 20.7% of total liver transplant recipients in 2016. Older liver transplant recipients were more likely to be male, African American, have higher a MELD score and portal vein thrombosis in 2013-2016 as compared to 2003-2006. Also, recent older recipients were more likely to undergo liver transplantation for hepatitis C virus, non-alcoholic steatohepatitis, or hepatocellular carcinoma, and more likely to receive a hepatitis C virus positive or donation after cardiac death graft compared to older liver transplant recipients in 2003-2006. Despite an increase in the severity of liver disease and number of LTs performed in older recipients from 2003 to 2016, there were significant improvements in acute rejection (aOR: 0.70, 95%CI:0.56-0.88, p=0.002) and shorter length of stay (aOR: 0.66, 95%CI:0.57-0.76, p<0.001) along with lower risks of graft loss (aHR: 0.46, 95%CI:0.40-0.52, p<0.001) and mortality (aHR: 0.43, 95%CI: 0.38-0.49, p<0.001). These trends can help guide appropriate referral for liver transplantation and counseling in older adults with end-stage liver disease, and increased age *per se* should not prohibit access to liver transplantation in older adults.

As increased age alone should not be a deterrent for liver transplantation candidacy, there are common concerns surrounding liver transplantation in older adults. One consequence seen with aging is immunosenescence or decline of the immune system and response. This attenuated immune response seen in older adults leads to increased susceptibility to infections, cancer, and autoimmune diseases,[82,83] but also leads to lower rates of acute rejection after transplantation.[84] Age-related changes in the immune system, along with differences in drug absorption, metabolism, and excretion, make immunosuppression management for older transplant recipients a distinct entity from younger transplant recipients.[85] Thus, immunosuppression management in older liver transplant recipients is a key component to post-transplant management. The ability to find a balance between higher enough immunosuppression levels to prevent rejection, but low enough immunosuppression levels to decrease the risk of infections and malignancy, which are more common in older transplant recipients, is a difficult task. Further research into optimal immunosuppression dosing for older liver transplant recipients is necessary. Another concern regarding transplantation of older adults is the higher comorbidity burden and functional impairment seen in this population. While pre-transplant clearance for comorbidities, such as cardiac, vascular, or renal disease, is a key step prior to listing for liver transplantation, these tests may not capture the underlying physical or functional reserve of a patient. Additionally, patients without any comorbidity, yet a decreased physiologic or functional reserve, may not be identified through standard testing. An adjunct to conventional candidacy testing and identification of vulnerable candidates may be through the Liver Frailty Index.

Finally, in our two-center prospective cohort of 882 liver transplant candidates, we found older candidates were more likely to be frail (33.3% vs. 21.7%, $p=0.002$), less likely to be robust (4.8% vs. 18.4%, $p<0.001$), and had worse performance for all components of the Liver Frailty Index (grip strength, balance, chair stands) than younger candidates. Additionally, we found frail

candidates were two-fold more likely to die on the waitlist (aHR: 2.16, 95%CI: 1.51-3.09, p<0.001). However, the impact of frailty did not vary by candidate age (p interaction= 0.9). These findings strengthen with the conceptual framework and biological underpinnings of frailty. Interventions to mitigate frailty in liver transplant candidates awaiting transplantation should be explored.

It should be noted that frailty measured by the Liver Frailty Index in this thesis work includes only performance-based measurements (grip strength, balance testing, and chair stands). Thus, the data presented are not use of the Liver Frailty Index is not directly comparable to other more general measures of frailty, such as the Fried frailty phenotype. Additionally, the Liver Frailty Index may not capture the true physiologic reserve of a candidate; however, it does identify patients at increased risk of waitlist mortality and other poor outcomes.

These results have spurred a number of future scientific projects including older liver donors and older liver transplant recipients. For instance, the identification of specific characteristics of older liver donors and recipients will allow us to appropriately transplant these grafts along with quantification of survival benefit for older liver donor recipients and subgroup analysis to identify recipients who would benefit from transplantation with an older donor versus waiting for a younger donor. Donor-recipient matching will allow increased utilization of older liver donor grafts in the preferred recipients. Also, the number of potential older liver donors will need to be quantified as an important step to increase utilization, and this will take buy in from the organ procurement organizations and the transplant community. With increased utilization of older liver donors, more candidates will be able to undergo liver transplantation, and the hope is that there will be a reduction in waitlist mortality. The improvements in mortality, graft loss, rejection, and length of stay for older liver transplant recipients are encouraging. As older

candidates become a larger portion of the liver transplant waitlist, we will need to look into survival benefit of transplantation with certain donor characteristics (high BMI donors, older donors, donation after cardiac death donors) to ensure appropriate donor-recipient matching in these candidates and that they derive a survival benefit undergoing transplantation. With the prospective frailty cohort focused on functional testing, we will be able to start prehabilitation interventions to potentially improve a candidate's functional status while awaiting transplantation. Also, we will be able to quantify the association between frailty, as measured by the Liver Frailty Index, and outcomes such as graft loss, mortality, readmissions, and quality of life after liver transplantation.

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Curriculum Vitae

March 6, 2019

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DEMOGRAPHIC AND PERSONAL INFORMATION

Current Appointments

2014-present Halsted General Surgery Resident, Johns Hopkins University
2016-present Research Fellow, Johns Hopkins Bloomberg School of Public Health

Personal Data

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Education and Training

2010	BS, Biochemistry; *cum laude*, University of Texas/ Austin TX
2014	MD, Medicine, University of Texas at Houston Medical School / Houston TX
2019	PhD Candidate, Clinical Investigations, Johns Hopkins Bloomberg School of Public Health / Baltimore MD (primary mentors: Dorry Segev, MD PhD; Mara McAdams-DeMarco PhD)
2022	General Surgery Resident, Johns Hopkins University / Baltimore MD

Professional Experience

06/2008 – 05/2010	Research Assistant, University of Texas Department of Chemistry / Austin TX
05/2011 – 05/2014	Research Assistant, M.D. Anderson Cancer Center / Houston TX
08/2011 – 05/2014	Tutor for Step I medical board exam, University of Texas at Houston Medical School/ Houston TX
08/2011 – 05/2014	Medical Student tutor: physiology, anatomy, biochemistry, histology, Instructor, University of Texas at Houston Medical School/ Houston TX
05/2012	Medical Mission trip, Samaritan's Purse/ Port-Au-Prince Haiti
08/2012	Medical Mission trip, Samaritan's Purse/ Cite Soliel Haiti
07/2016 – present	Course Instructor, Medical Student Surgery Clerkship, Johns Hopkins University / Baltimore MD

PUBLICATIONS:

Original Research

1. **Haugen CE**, Chu NM, Ying H, Warsame F, Holscher CM, Desai NM, Jones MR, Norman SP, Brennan DC, Garonzik-Wang J, Walston JD, Bingaman AW, Segev DL,

McAdams-DeMarco M. Frailty and Access to Kidney Transplantation. *Clin J Am Soc Nephrol.* 2019 Mar 19. PMID: 30890577

2. **Haugen CE**, Holscher CM, Luo X, Bowring MG, Orandi BJ, Thomas AG, Garonzik-Wang J, Massie AB, Philosophe B, McAdams-DeMarco M, Segev DL. Assessment of Trends in Transplantation of Liver Grafts from Older donors and Outcomes of Recipients of Liver Grafts from Older Donors, 2003-2016. *JAMA Surg.* 2019 Feb 13. PMID:30758494
3. Chu NM, Deng A, Ying H, **Haugen CE**, Garonzik Wang JM, Segev DL, McAdams-DeMarco MA. Dynamic Frailty Before Kidney Transplantation- Time of Measurement Matters. *Transplantation.* 2019 Feb 4. PMID: 30753177
4. **Haugen CE**, Ishaque T, Sapirstein A, Cauneac A, Segev DL, Gentry S. Geographic Disparities in Liver Supply/Demand Ratio Within Fixed-Distance and Fixed-Population Circles. *Am J Transplant.* 2019 Feb 12. PMID: 30748095
5. **Haugen CE**, Luo X, Holscher CM, Bowring MG, DiBrito SR, Garonzik-Wang J, McAdams-DeMarco M, Segev DL. Outcomes in Older Kidney Transplant Recipients After Prior Non-Kidney Transplants. *Transplantation.* 2019 Feb 4. PMID: 30747853
6. Chu NM, Gross AL, Shaffer AA, **Haugen CE,** Norman SP, Xue WL, Sharrett AR, Carlson MC, Bandeen-Roche K, Segev DL, McAdams-DeMarco M. Frailty and Changes in Cognitive Function after Kidney Transplantation. *J Am Soc Nephrol.* 2019 Jan 24. PMID: 30679381
7. **Haugen CE**, McAdams-DeMarco M, Holscher CM, Ying H, Gurakar A, Garonzik-Wang J, Cameron AC, Segev DL, Lai JC. Multi-Center Study of Age, Frailty, and Waitlist Mortality Among Liver Transplant Candidates. *Ann Surg.* 2019 Jan 18. PMID: 30672803
8. Lai JC, Rahimi R, Verna EC, Kappus MR, Dunn MA, McAdams-DeMarco M, **Haugen CE**, Volk ML, Duarte-Rojo A, Ganger DR, O'leary JG, Dodge JL, Ladner D, Segev DL. Frailty Associated with Waitlist Mortality Independent of Ascites and Hepatic Encephalopathy in a Multi-Center Study. *Gastroenterology.* 2019 Jan 17. PMID: 30668935
9. **Haugen CE,** Bowring GB, Holscher CM, Jackson KR, Garonzik-Wang J, Cameron AC, Philosophe B, McAdams-DeMarco M, Segev DL. Survival Benefit of Accepting Livers from Deceased Donors Over 70 Years Old. *Am Journal Transplant.* 2019 Jan 7. PMID: 30614634
10. Pérez Fernández M, Martínez Miguel P, Ying H, **Haugen CE**, Chu NM, Rodríguez Puyol DM, Rodríguez-Mañas L, Norman SP, Walston JD, Segev DL, McAdams-DeMarco MA. Comorbidity, Frailty, and Waitlist Mortality among Kidney Transplant Candidates of All Ages. *Am J Nephrol.* 2019 Jan 9;49(2):103-110. PMID: 30625489
11. Holscher CM, Locham SS, **Haugen CE**, Bae S, Segev DL, Malas MB. Transplant Waitlisting Attenuates the Association between Hemodialysis Access Type and Mortality. *J Nephrol.* 2019 Jan 2. PMID: 30604152
12. **Haugen CE**, Holscher CM, Warsame F, Garonzik-Wang J, Pozo M, McAdams-DeMarco M, Segev DL. Trends in Liver Transplantation Among Older Adults in the United States. *J Am Geriatr Soc.* 2018 Dec;66(12):2321-2326. PMID: 30325004
13. McAdams-DeMarco MA, Ying H, Van Pilsum Rasmussen S, Schrack J, **Haugen CE**, Chu NM, González Fernández M, Desai N, Walston JD, Segev DL. Prehabilitation Prior to Kidney Transplantation: Results from a Pilot Study. *Clin Transplant.* 2018 Nov 21:e13450. PMID: 30462375
14. Holscher CM, Jackson K, Thomas AG, **Haugen CE,** DiBrito SR, Covarrubias K, Gentry SE, Ronin M, Waterman AD, Massie AB, Garonzik Wang J, Segev DL. Temporal changes in the composition of a large multicenter clearing house: Do the hard-to-match accumulate? *Am J Transplant.* 2018 Nov;18(11):2791-2797. PMID: 30063811

15. Holscher CM, Ishaque T, Garonzik Wang JM, **Haugen CE**, DiBrito SR, Jackson KR, Muzaale AD, Massie AB, Al Ammary F, Ottman SE, Henderson ML, Segev DL. Living Donor Postnephrectomy Kidney Function and Recipient Graft Loss: A Dose-Response relationship. *Am J Transplant*. 2018 Nov;18(11):2804-2810.
16. Nastasi AJ, Bryant TS, Le JT, Schrack J, Ying H, **Haugen CE,** Fernández MG, Segev DL, McAdams-DeMarco MA. Pre-kidney transplant lower extremity impairment and transplant length of stay: a time-to-discharge analysis of a prospective cohort study. *BMC Geriatr*. 2018 Oct 19;18(1):246. PMID: 30340462
17. Ishaque T, Massie AB, Bowring MG, **Haugen CE,** Ruck JM, Halpern SE, Waldram MM, Henderson ML, Garonzik Wang J, Cameron AM, Philosophe B, Ottmann S, Rositch AF, Segev DL. Liver Transplantation and Waitlist Mortality for HCC and non-HCC Candidates Following the HCC Policy Exception Change. *Am J Transplant*. 2018 Oct 12. PMID: 30312530
18. Konel JM, Warsame F, Ying H, **Haugen CE**, Mountford A, Chu NM, Crews DC, Desai NM, Garonzik-Wang JM, Walston JD, Norman SP, Segev DL, McAdams-DeMarco MA. Depressive Symptoms, Frailty, and Adverse Outcomes Among Kidney Transplant Recipients. *Clin Transplant*. 2018 Oct;32(10):e13391. PMID: 30152107
19. DiBrito SR, **Haugen CE**, Holscher CM, Olorundare IO, Alimi Y, Segev DL, Garonzik-Wang J. Complications, Length of Stay, and Cost of Cholecystectomy in Kidney Transplant Recipients. *Am J Surg*. 2018 Oct;216[67]:694-698.
20. Holscher CM, Kmd SB, Thomas AG, Henderson ML, **Haugen CE**, DiBrito SR, Muzaale AD, Garonzik Wang JM, Massie AB, Lentine KL, Segev DL. Early Hypertension and Diabetes after Living Kidney Donation: A National Cohort Study. *Transplantation*. 2018 Sep 21. PMID: 30247449
21. **Haugen CE,** King EA, Bae S, Bowring MG, Holscher CM, Garonzik-Wang J, McAdams-DeMarco M, Segev DL. Early Hospital Readmission in Older and Younger Kidney Transplant Recipients. *Am J Nephrol*. 2018 Sep 18;48[67]:235-241. PMID: 30227406
22. Warsame F, Ying H, **Haugen CE**, Thomas AG, Crews DC, Shafi T, Jaar B, Chu NM, Segev DL, McAdams-DeMarco MA. Intradialytic Activities and Health-related Quality of Life Among Hemodialysis Patients. Warsame F, *Am J Nephrol*. 2018;48(3):181-189. PMID: 30176670
23. Holscher CM, Leanza J, Thomas AG, Waldram MM, **Haugen CE**, Jackson KR, Bae S, Massie AB, Segev DL. Anxiety, Depression, and Regret of Donation in Living Kidney Donors. *BMC Nephrol*. 2018 Sep 4;19(1):218. PMID: 30180815
24. **Haugen CE**. Thomas AG. Massie AB. Garonzik-Wang J. Segev DL. Minimizing Risk Associated with Older Liver Donors by Matching to Preferred Recipients: A National Registry and Validation Study. *Transplantation*. 2018 Sep;102(9):1514-1519. PMID:29570165
25. Thomas AG, Ruck JM, Shaffer AA, **Haugen CE**, ScM HY, Warsame F, Chu N, Carlson MC, Gross AL, Norman SP, Segev DL, McAdams-DeMarco M. Kidney Transplant Outcomes in Recipients with Cognitive Impairment: A National Registry and Prospective Cohort Study. *Transplantation*. 2018 Aug 27. PMID: 30153224
26. DiBrito SR, Alimi Y, Olorundare IO, Holscher CM, **Haugen CE**, Segev DL, Garonzik-Wang J. Outcomes Following Colorectal Resection in Kidney Transplant Recipients. *J Gastrointest Surg*. 2018 May 7. PMID: 29736667
27. Warsame F, **Haugen CE**, Ying H, Garonzik-Wang JM, Desai NM, Hall RK, Kambhampati R, Crews DC, Purnell TS, Segev DL, McAdams-DeMarco MA. Limited Health Literacy and Adverse Outcomes Among Kidney Transplant Candidates. *Am J Transplant*. 2018 Jul 1. PMID: 29962069

28. **Haugen CE,** Mountford A, Warsame A, Berkowitz R, Bae S, Thomas A, Brown C, Brennan D, Neufeld K, Carlson M, Segev DL, McAdams-DeMarco M. Incidence, Risk Factors, and Sequelae of Post-Kidney Transplant Delirium. *JASN*. 2018 Jun;29(6):1752-1759. PMID: 29685884
29. Henderson ML, Adler JT, Van Pilsum Rasmussen SE, Thomas AG, Herron PD, Waldram MM, Ruck JM, Purnell TS, DiBrito SR, Holscher CM, **Haugen CE**, Alimi Y, Konel JM, Eno AK, Garonzik Wang JM, Gordon EJ, Lentine KL, Schaffer RL, Cameron AM, Segev DL. How Should Social Media Be Used in Transplantation? A Survey of The American Society of Transplant Surgeons. *Transplantation.* 2018 Apr 21. PMID: 29684002
30. McAdams-DeMarco MA, Ying H, Thomas AG, Warsame F, Shaffer AA, **Haugen CE,** Garonzik-Wang JM, Desai NM, Varadhan R, Walston J, Norman SP, Segev DL. Frailty, Inflammatory Markers, and Waitlist Mortality Among Patients with End-Stage Renal Disease in a Prospective Cohort Study. *Transplantation*. 2018 Oct;102(10):1740-1746. PMID: 29677074
31. Holscher CM, Jackson K, Chow EK, Thomas AG, **Haugen CE,** DiBrito SR, Purcell C, Ronin M, Waterman AD, Garonzik Wang J, Massie AB, Gentry SE, Segev DL. Kidney Exchange Match Rates in a Large Multicenter Clearinghouse. *Am J Transplant*. 2018 Jun;18(6):1510-1517. PMID: 29437286
32. Luo X, Leanza J, Massie AB, Garonzik-Wang JM, **Haugen CE,** Gentry SE, Ottmann SE, Segev DL. MELD as a metric for survival benefit of liver transplantation. *Am J Transplant*. 2018 May;18(5):1231-1237. PMID: 29316310
33. Luo X, Massie AM, **Haugen CE**, Choudhury R, Ruck JM, Shaffer AA, Zhou S, Segev DL, Garonzik-Wang JM. Baseline and Center-level Variation in Simultaneous Liver-Kidney Listing in the United States. *Transplantation.* 2018 Apr;102[67]:609-615. PMID: 29077659
34. McAdams-DeMarco MA, Olorundare IO, Ying H, Warsame F, **Haugen CE**, Hall R, Garonzik-Wang JM, Desai NM, Walston JD, Norman SP, Segev DL. Frailty and Post-kidney Transplant Health-Related Quality of Life. *Transplantation*. 2018 Feb;102(2):291-299. PMID: 28885489
35. Van Pilsum Rasmussen S, Konel J, Warsame F, Ying H, Buta B, **Haugen C**, King E, DiBrito S, Varadhan R, Rodríguez-Mañas L, Walston JD, Segev DL, McAdams-DeMarco MA. Engaging clinicians and patients to assess and improve frailty measurement in adults with end stage renal disease. *BMC Nephrol.* 2018 Jan 12;19(1):8. PMID: 29329515
36. Bowring MG, Ruck JM, **Haugen CE**, Massie AB, Segev DL, Gentry SE. Deceased-donor liver size and the sex-based disparity in liver transplantation. *Transplantation.* 2017 Nov;101(11):e329. PMID:28737603
37. Nastasi AJ, McAdams-DeMarco MA, Schrack J, Ying H, Olorundare I, Warsame F, Mountford A, **Haugen CE,** Fernández MG, Norman SP, Segev DL. Pre-Kidney Transplant Lower Extremity Impairment and Post-Transplant Mortality. *Am J Transplant.* 2017 Jul 15. PMID: 28710900
38. McAdams-DeMarco MA, Ying H, Olorundare I, King EA, **Haugen C**, Buta B, Gross AL, Kalyani R, Desai NM, Dagher NN, Lonze BE, Montgomery RA, Bandeen-Roche K, Walston JD, Segev DL. Individual Frailty Components and Mortality in Kidney Transplant Recipients. *Transplantation*. 2017 Sep;101(9):2126-2132. PMID: 27779573
39. McAdams-DeMarco MA, King EA, Luo X, **Haugen C**, DiBrito S, Shaffer A, Kuirka LM, Desai NM, Dagher NN, Lonze BE, Montgomery RA, Walston J, Segev DL. Frailty, Length of Stay and Mortality in Kidney Transplant Recipients: A National Registry and Prospective Cohort Study. *Annals of Surgery.* 2017 Dec;266(6):1084-1090. PMID:

27655240

40. Lee BP, Chen PH, **Haugen C,** Hernaez R, Philosophe B, Dagher N, Moore SA, Li Z, Cameron AM. Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis. *Annals of Surgery.* 2017 Jan;265(1):20-29. PMID: 27280501
41. Francis AM, **Haugen CE**, Grimes LM, Crow JR, Yi M, Mittendorf EA, Bedrosian I, Caudle AS, Babiera GV, Krishnamurthy S, Kuerer HM, Hunt KK. Is Sentinel Lymph Node Dissection Warranted for Patients with a Diagnosis of Ductal Carcinoma In Situ? *Ann Surg Oncol.* 2015 Dec;22(13):4270-9. PMID: 25905585
42. Shackford SR, Kahl JE, Calvo RY, Kozar RA, **Haugen CE,** Kaups KL, Kagle K, Tibbs BM, Mutto S, Rizzo A, Lormel C, Shackford MC, Burlew CC, Moore EE, Cogbill TH, Kallies KJ, Haan JM, Ward J. Gunshot wounds and Blast Injuries of the Face Are Associated with Significant Morbidity and Mortality: Results of a 10 Year Multi-Institutional Study of 740 Patients. Journal of Trauma and Acute Care. 2014 Feb; 76(2): 347-52. PMID: 24398775
43. Alatrash G, Mittendorf EA, Sergeeva A, Sukhumalchandra P, Qiao N, Zhang M, St. John LS, Ruisaard K, **Haugen CE,** Al-Atrache Z, Jakher H, Philips AV, Ding X, Chen JQ, Wu Y, Patenia RS, Bernatchez C, Vence LM, Radvanyi LG, Hwu P, Clise-Dwyer K, Ma Q, Lu S, Molldrem JJ. Broad Cross-Presentation of the Hematopoietically Derived PR1 Antigen on Solid Tumors Leads to Susceptibility to PR1-Targeted Immunotherapy. (Featured on the cover). *Journal of Immunology*. 2012 Dec; 189: 5476-5484. PMID: 23105141

Book Chapters

1. **Haugen CE,** Cameron AM. Portal Hypertension and the Role of Shunting Procedures. In: Cameron JC, Cameron AM (eds), Current Surgical Therapy, Chapter 73, 12th ed.

Editorials

1. DiBrito SR, Holscher CM, **Haugen CE**, Leeds I, Jackson K, Overton H, King E, Haut E. The Modern Surgeon Scientist. *Ann Surgery.* 2018 Dec;268(6):e88-e89.
2. **Haugen CE**, Segev DL. Letter to the Editor: Donor-Recipient Matching is Important but Age Matching Alone is Insufficient. *Transplantation*. 2019 Feb 4. PMID: 30747853

FUNDING

EXTRAMURAL Funding

Current:

01/2017 – 07/2019	"Novel Frailty Phenotype in Older dults with End-stage Renal Disease"
	Ruth L Kirschstein National Research Service Award, F32
	#F32AG053025
	NIA, NIH
	$221,970
	Principal Investigator, 95% effort

Previous:

02/2019	Travel Award: Controversies in Transplantation
	Breckenridge CO
	$1,500
02/2018	Travel Award: Controversies in Transplantation
	Breckenridge CO
	$1,500

11/2017 Travel Award: NIDUS Delirium Boot Camp
Boston MA
$1,000

11/2016 –12/2016 Renal Epidemiology Grant
#T32DK007732
Co-investigator
Larry Appel MD, PI

SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES

System Innovation and Quality Improvement efforts within JHMI:

07/2017 Team organizer and analyst QI project/2% effort; Johns Hopkins Department of Surgery, Role of Lymph Node Biopsy Service Versus Core Needle.

ORGANIZATIONAL ACTIVITIES

Journal peer review activities

2018- present American Journal of Transplantation, Ad hoc reviewer
2018- present Clinical Transplantation, Ad hoc reviewer

Administrative Appointments

2018 - present General Surgery Representative, House Staff Council, Johns Hopkins Hospital
2016 - present Interviewer, General Surgery Residency Admissions Committee, Johns Hopkins Hospital
2014 - 2017 Representative, General Surgery Residency Review Committee, Johns Hopkins Hospital

Professional Societies

08/2014 – present American College of Surgeons, resident member
09/2015 – present Association of Academic Surgeons, resident member
09/2015 – present American Society of Transplant Surgeons, resident member
07/2017 – present American Association for the Study of Liver Diseases
08/2010 – 07/2014 American College of Surgeons, medical student member

RECOGNITION

Awards, Honors

2009 Chemistry Development Award, University of Texas at Austin
2009 Phi Beta Kappa
2011 M.D. Anderson Summer Research Fellowship Award
2016-2018 Poster of Distinction, Academic Transplant Congress
2017 Young Investigator, NIA/NIH
2017 Emerging Liver Scholar Award, AASLD
2017 Best Project Proposal, NIDUS Delirium Bootcamp
2018 Poster of Distinction, American Society of Transplant Surgeons
2018 Best Poster, Center on Aging and Health Showcase

Invited Talks

Local

07/2017 "Navigating the Program", Graduate Training Program in Clinical Investigation, Johns Hopkins Bloomberg School of Public Health, Baltimore MD

National

07/2017 "Association of Cognitive Impairment and Sex on Listing for Kidney Transplantation", Young Investigators Forum, NIA/NIH, Bethesda MD

OTHER PROFESSIONAL ACCOMPLISHMENTS

Oral/Podium Presentations

1. **Haugen CE,** Bowring GB, Holscher CM, Jackson KR, Garonzik-Wang J, Cameron AC, Philosophe B, McAdams-DeMarco M, Segev DL. "Survival Benefit of Accepting Livers from Deceased Donors Over 70 Years Old." American Society of Transplant Surgeons, Miami, January 2019.
2. **Haugen CE**, McAdams-DeMarco, Ying H, Segev DL, Lai JC. "Multi-center Study of Frailty, Age, and Waitlist Mortality Among Liver Transplant Candidates." American Association for the Society of Liver Diseases, San Francisco, November 2018.
3. **Haugen CE,** Bowring GB, Holscher CM, Jackson KR, Garonzik-Wang J, Cameron AC, Philosophe B, McAdams-DeMarco M, Segev DL. "Turn Down for What: Outcomes Associated with Declining an Older Liver Donor." American College of Surgeons, Boston, October 2018.
4. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Trends in Liver Transplantation with Older Liver Donors." The Transplantation Society, Madrid, Spain, July 2018.
5. **Haugen CE,** Ying H, Gross A, Segev D, McAdams-DeMarco M. Inflammatory Frailty Index and Mortality after Kidney Transplantation. The Transplantation Society, Madrid, Spain, July 2018.
6. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Trends in Liver Transplantation with Older Liver Donors." American Transplant Congress, Seattle WA, June 2018.
7. **Haugen CE,** Ying H, Gross A, Segev D, McAdams-DeMarco M. Inflammatory Frailty Index and Mortality after Kidney Transplantation. American Transplant Congress, Seattle WA, June 2018.
8. **Haugen CE,** Mountford A, Warsame A, Berkowitz R, Bae S, Thomas A, Brown C, Brennan D, Neufeld K, Carlson M, Segev DL, McAdams-DeMarco M. Incidence, Risk Factors, and Sequelae of Post-Kidney Transplant Delirium. Renal Disease Interest Group, Baltimore MD, April 2018.
9. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Trends in Liver Transplantation with Older Liver Donors." Controversies in Transplantation, Breckenridge CO, February 2018
10. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Trends in Liver Transplantation with Older Liver Donors." Academic Surgical Congress, Jacksonville FL, January 2018.
11. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Outcomes in Older Kidney Transplant Recipients with Prior Non-Kidney Transplants." Academic Surgical Congress, Jacksonville FL, January 2018.

12. Haugen CE, Ying H, **McAdams-Demarco M**, Segev DL. "Impact of Cognitive Impairment on Kidney Transplant Listing." American Transplant Congress, Chicago IL, May 2017.

Posters

1. **Haugen CE**, Ishaque T, Sapirstein A, Segev DL, Gentry S. Geographic Disparities in Liver Supply/Demand Ratio within Fixed-distance and Fixed-population circles. American Society of Transplant Surgeons. Miami, FL, January 2019.
2. **Haugen CE,** Chu N, Ying H, Warsame F, Holscher CM, Norman S, Bingaman A, Segev DL, McAdams-DeMarco M. Frailty and Access to Kidney Transplantation. American Society of Transplant Surgeons. Miami, FL, January 2019.
3. **Haugen CE**, McAdams-DeMarco, Ying H, Segev DL, Lai JC. "Multi-center Study of Frailty, Age, and Waitlist Mortality Among Liver Transplant Candidates." American Society of Transplant Surgeons. Miami, FL, January 2019.
4. **Haugen CE,** Mountford A, Warsame A, Berkowitz R, Bae S, Thomas A, Brown C, Brennan D, Neufeld K, Carlson M, Segev DL, McAdams-DeMarco M. Incidence, Risk Factors, and Sequelae of Post-Kidney Transplant Delirium. American Transplant Congress. Seattle, WA, June 2018.
5. **Haugen CE,** Ying H, Lai J, McAdams-DeMarco M, Segev D. Frailty and Liver Transplantation. American Transplant Congress. Seattle, WA, June 2018.
6. **Haugen CE,** Mountford A, Warsame A, Berkowitz R, Bae S, Thomas A, Brown C, Brennan D, Neufeld K, Carlson M, Segev DL, McAdams-DeMarco M. Incidence, Risk Factors, and Sequelae of Post-Kidney Transplant Delirium. Center on Aging and Health Showcase. Baltimore, MD, April 2018.
7. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Bowring MG. Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Trends in Liver Transplantation with Older Liver Donors." Controversies in Transplantation. Breckenridge, CO, March 2018.
8. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Trends in Liver Transplantation with Older Liver Donors." American Society of Transplant Surgeons, Miami FL, January 2018.
9. **Haugen CE,** Luo X, Thomas AG, Holscher CM, Garonzik-Wang JM, McAdams-DeMarco M, Segev DL. "Outcomes in Older Kidney Transplant Recipients with Prior Non-Kidney Transplants." American Society of Transplant Surgeons, Miami FL, January 2018.
10. Haugen CE, Qiong H, **Holscher C**, Pozo M, McAdams-Demarco M, Segev DL. "Trends in Liver Transplantation Among Older Adults with ESLD." American College of Surgeons, San Diego CA, October 2017.
11. **Haugen CE**, Ying H, McAdams-Demarco M, Segev DL. "Impact of Sex on Kidney Transplant Listing." National Institutes of Health, Bethesda MD, July 2017.
12. **Haugen CE**, Qiong H, Pozo M, McAdams-Demarco M, Segev DL. "Trends in Liver Transplantation Among Older Adults with ESLD." American Transplant Congress, Chicago IL, May 2017.
13. **Haugen CE**, Ying H, McAdams-Demarco M, Segev DL. "Impact of Cognitive Impairment on Kidney Transplant Listing." American Society of Transplant Surgeons, Miami FL, January 2017.

14. Francis AM, Yi M, Mittendorf EA, **Haugen CE**, Bedrosian I, Caudle AS, Meric-Bernstam F, Babiera G, Krishnamurthy S, Kuerer HM, Hunt KK. "Utility of Sentinel Lymph Node Dissection in Ductal Carcinoma in Situ." Society of Surgical Oncology Conference, Washington D.C., March 2013.
15. **Haugen CE,** Al Atrache Z, Hussain A, Sukhumalchandra P, Xiao H, Alatrash G, Molldrem JJ, Mittendorf EA. "Uptake of soluble inflammatory mediators neutrophil elastase (NE) and proteinase 3 (P3) results in cross-presentation of the P3- and NE-derived peptide PR1 by solid tumors." AWS Conference STARR Poster Competition, San Francisco CA, October 2011.
16. **Haugen CE**, Kutcha C, Dalke A. Subacute meningoencephalitis with ocular findings. Pediatric Neurology Grand Rounds. Houston TX July 2012.

Community Services

2006-2008	Volunteer, Brackenridge Hospital, Critical Decision Unit, 4hrs per week / Austin TX
2006-2010	Volunteer, Ronald McDonald House, 1hr per week / Austin TX
05-08/2010	Volunteer, Wounded Warriors, 8 hrs/week/ Houston TX
2011-2014	Volunteer, Way Station Homeless Shelter, 2 hrs/week/ Houston TX

Brief Biosketch

Dr. Christine E. Haugen was born on November 24, 1987 in San Antonio, Texas and raised in Houston, Texas. She attended the University of Texas at Austin, where she was in the Chemistry/Biochemistry Honors Program. Dr. Haugen conducted basic science research in the chemistry laboratory of Dr. Jonathan Sessler, studying and synthesizing porphyrins as drug delivery molecules. She graduated *cum laude* in 2010 with a B.S. in Biochemistry. Dr. Haugen pursued medical school at the University of Texas at Houston Medical School. Outside of her coursework, she worked in a cancer immunology lab at M. D. Anderson with Drs. Kelly Hunt and Elizabeth Mittendorf, where she fell in love with the field of surgery. Dr. Haugen also was involved in medical student tutoring, ran review board review courses, and served on medical missions in Haiti. In 2014, she began her General Surgery residency at The Johns Hopkins Hospital. After receiving a National Institute of Health Ruth L. Kirschstein F32 National Research Service Award, Dr. Haugen joined the Epidemiology Research Group in Organ Transplantation, led by Dr. Dorry Segev, to pursue her PhD in Clinical Investigations at the Johns Hopkins Bloomberg School of Public Health. After completing her clinical training, she plans to pursue a fellowship in abdominal transplant surgery. In her free time, Dr. Haugen enjoys traveling, snowboarding, the outdoors, and spending time with her friends, family, and her dog, Liam.