Multicenter Study of Age, Frailty, and Waitlist Mortality Among Liver Transplant Candidates

Christine E. Haugen, MD, Mara McAdams-DeMarco, PhD,*† Courtenay M. Holscher, MD,* Hao Ying, MHS,* Ahmet O. Gurakar, MD,‡ Jacqueline Garonzik-Wang, MD, PhD,* Andrew M. Cameron, MD, PhD,* Dorry L. Segev, MD, PhD,*† and Jennifer C. Lai, MD, MBA§*

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 2 transplant centers. The liver frailty index (grip strength, chair stands, balance) was measured at evaluation, with frailty defined as liver frailty index ≥ 4.5. We compared the prevalence of frailty in older ($\geq$65 yr) and younger (18–64 yr) candidates. We studied the association between frailty, age, interaction between the 2, and waitlist mortality using competing risks regression adjusted for sex, BMI, and MELDNa.

Results: Among 882 LT candidates, 16.6% were ≥ 65 years. 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 2-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.

Keywords: frailty, liver transplantation, older adults

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From the *Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD; †Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD; ‡Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; and §Department of Medicine, University of California San Francisco, San Francisco, CA.

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Reprints: Jennifer C. Lai, MD, MBA, Associate Professor of Medicine, University of California San Francisco, 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143. E-mail: Jennifer.c.lai@ucsf.edu.

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Frailty, a measure of physiologic reserve and increased vulnerability to stressors, was initially described by gerontologists in older community dwelling adults.[1] Frailty was subsequently examined in older general surgery patients,[2] kidney transplant candidates and recipients,[3–10] and recently in liver transplant candidates and recipients,[11–16] 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 and validated in patients with cirrhosis evaluated for transplantation[11,12] and improves risk prediction for waitlist mortality over the Model for End-stage Liver Disease Sodium (c-statistic: 0.80 vs 0.76). Up to 25% of liver transplant candidates are frail;[11,12] beyond waitlist mortality,[12] frailty is associated with increased hospitalizations[15] and depression[13] in liver transplant candidates and longer length of stay and hospitalized days in liver transplant recipients.[14]

While there is a higher prevalence of frailty in older adults, there is also a greater burden of comorbidities[9,17,18] and an increased prevalence of functional impairment in older adults.[17] Older candidates may therefore, because of comorbidity burden and underlying functional impairment, have a more marked association between frailty and waitlist mortality as compared with 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.[11,12] As the average age of waitlisted liver candidates and liver transplant recipients continues to increase,[19,20] 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.[12,17] We defined older candidates as aged $\geq$65, a commonly used age cutoff.[17,20,21] 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), MELDNa 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.[12,17] 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.[11,14] The LFI is composed of 3 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 3 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 3 positions (feet side-to-side, semitandem, and tandem) for a maximum of 10 seconds each

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

$(-0.330 \times \text{sex-adjusted grip strength}) + (-2.529 \times \text{number of chair stands per second}) + (-0.040 \times \text{balance time}) + 6$

Standard cutoffs were used to define robust (LFI<3.2), prefrail (3.2–<4.5), and frail (LFI ≥ 4.5).[11]

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 (age 18–64)] and frailty status. 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.[22] The final multivariable model was selected for optimal parsimony by minimizing the Akaike Information Criteria and included adjustment for sex, BMI, and MELDNa score. To test whether waitlist mortality varied by frailty status, an interaction between candidate age and frailty was explored 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 2-tailed and α was set at 0.05. All analyses were performed using Stata 14.2/MP (College Station, TX).

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 ($P < 0.001$). Older candidates were just 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 with younger candidates. Older candidates had lower MELDNa 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 vs 53.1 yrs, $P = 0.2$), 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 (62.5% vs 57.3%), Hispanic (21.9% vs 24.9%), or African American (2.5% vs 4.2%) ($P = 0.7$) compared with younger 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 MELDNa 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 with younger nonfrail candidates (Table 1).

Among the 147 older liver transplant candidates, frail candidates had a similar average age (67.1 vs 67.3 yrs, $P = 0.6$) and similar BMI (30.0 vs 28.9, $P = 0.3$) compared with 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 MELDNa 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 with younger candidates (Fig. 1). Additionally, older candidates had

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, Yrs*	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/ethnicity, %				
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).

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 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) sec, $P < 0.001$], and chair stands (13.7 vs 12.2 sec, $P < 0.001$) compared with younger candidates (Table 2).

Waitlist Mortality

Waitlist mortality was higher in older candidates compared with younger liver transplant candidates (log rank $P < 0.001$). The cumulative incidence of waitlist mortality for older versus younger liver transplant candidates was 13.6% (n = 20) versus 7.3% (n = 54) at 6 months, 23.0% (n = 34) versus 12.6% (n = 93) at 1 year, and

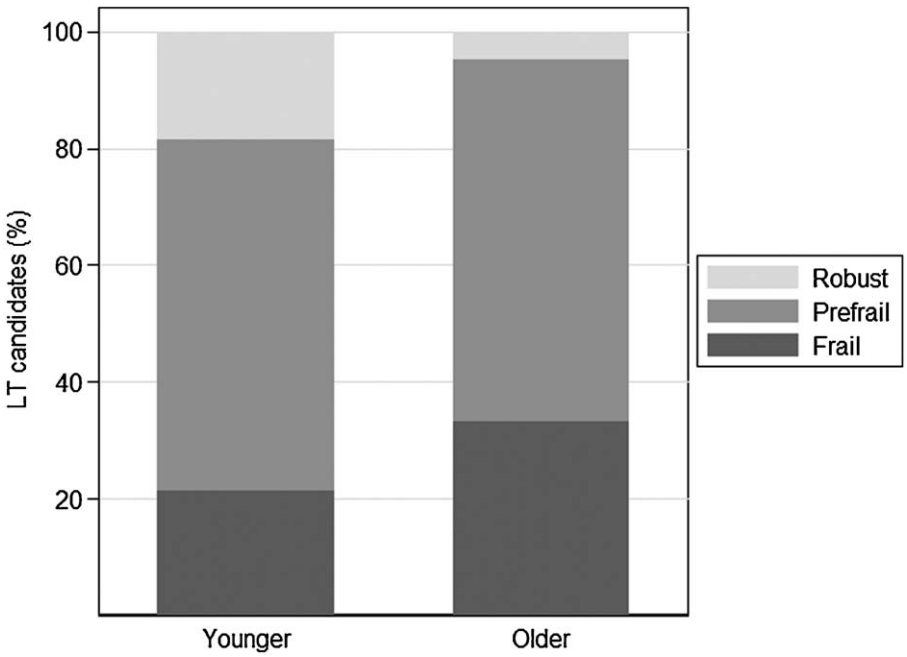

FIGURE 1. Prevalence of frailty by candidate age (older: age ≥ 65 and younger: age 18–64).

TABLE 2. Scores for Individual Components of the Liver Frailty Index (LFI) by Candidate Age (Older: Age ≥ 65 yrs and Younger: Age 18–64 yrs)

	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).

42.5% (n = 62) versus 24.9% (n = 185) at 3 years after listing. After adjustment for candidate sex, BMI, and MELDNa 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 with younger liver transplant candidates (Fig. 2).

Waitlist mortality was higher in frail candidates compared with 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) versus 6.5% (n = 44) at 6 months, 25.2% (n = 53) versus 11.4% (n = 77) at 1 year, and 46.7% (n = 98) versus 23.1% (n = 157) at 3 years after listing. After adjustment for candidate age, sex, BMI, and MELDNa 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 with nonfrail older candidates (aSHR: 1.98, 95% CI: 1.07–3.67, $P = 0.03$), as well as frail younger candidates compared with nonfrail younger candidates (aSHR: 1.90, 95% CI: 1.28–2.80, $P = 0.001$).

Additionally, 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 2-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 2-fold more likely to die on the waitlist. However, the impact of frailty did not vary by candidate age.

Less than 1 in 10 older community dwelling adults are frail using the Fried frailty index[1] and the prevalence of frailty increases with age,[23] yet nearly 1 in 5 liver transplant candidates, of all ages, are frail using Fried frailty index.[12] Using the Liver Frailty Index, a cirrhosis-specific measure of frailty, we found one-third of older liver transplant candidates were frail, not surprisingly, a nearly 5-fold higher prevalence than community dwelling older adults. Our finding that frailty is more common in older liver transplant candidates compared with 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 with younger kidney transplant candidates.[9]

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

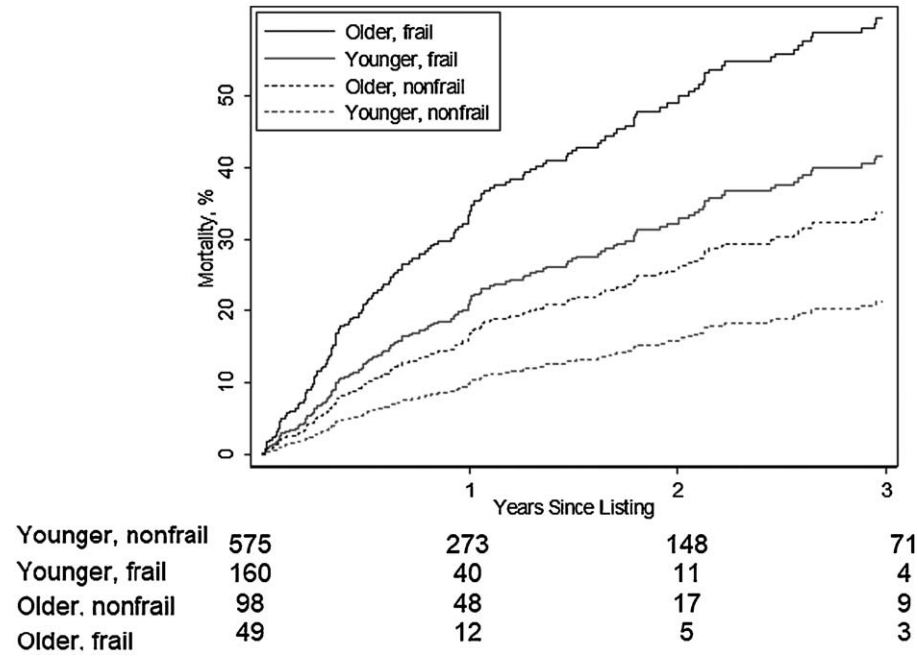

FIGURE 2. Cumulative incidence of waitlist mortality by frailty status (liver frailty index ≥4.5) in older (age ≥65) and younger (age 18–64) candidates. Transplant was treated as a competing risk.

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 (eg, 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 2 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 2 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.

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.

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