Liver Transplant Survival Index for Patients with Model for End-Stage Liver Disease Score $\geq$ 35: Modeling Risk and Adjusting Expectations in the Share 35 Era

Justin A Steggerda, MD, Irene K Kim, MD, FACS, Tsuyoshi Todo, MD, Darren Malinoski, MD, FACS, Andrew S Klein, MD, FACS, Matthew B Bloom, MD, FACS

BACKGROUND: The Share 35 policy for liver allocation prioritizes patients with Model for End-Stage Liver Disease (MELD) scores $\geq$ 35 for regional sharing of liver allografts. To better assess donor-recipient interactions and inform expectations, this study identified factors affecting graft survival independent of MELD score and derived a risk index for transplantation in the MELD $\geq$ 35 population.

STUDY DESIGN: The United Network for Organ Sharing (UNOS) STAR database was evaluated for deceased donor liver transplants with recipients' MELD $\geq$ 35, between January 2006 and June 2016. Data were randomly split into test and validate cohorts. Four individual models of graft survival spanning 90 days to 5 years were evaluated with univariate and multivariate Cox proportional hazards analyses against donor- and recipient-specific characteristics. Significant factors were compiled to generate the Liver Transplant Survival Index (LTSI-35), and survival analyses were performed.

RESULTS: Five risk groups (very low, low, moderate, high, and severe) were identified, with 1-year graft survival rates of 90.8% $\pm$ 0.2%, 89.3% $\pm$ 0.3%, 85.0% $\pm$ 0.3%, 79.8% $\pm$ 0.3%, and 70.3% $\pm$ 0.4% ($p < 0.001$ across groups), respectively. The greatest risk of graft loss was associated with donation after circulatory death (DCD) donors (1-year hazard ratio [HR] = 1.61 [95% CI 1.26 to 2.05], $p = 0.001$), recipients' requiring ventilator support (HR 1.32 [95% CI 1.17 to 1.51], $p < 0.001$), and recipient portal vein thrombosis (HR 1.21 [95% CI 1.03 to 1.42], $p = 0.003$). Subgroup analysis revealed increased risk of graft loss with graft macrosteatosis $\geq$ 30% on pre-donation biopsy at 90 days (HR 1.64 [1.33 to 1.99], $p < 0.001$).

CONCLUSIONS: The LTSI-35 identifies risk factors for graft loss in a high-MELD population which, when combined, may portend worse outcomes. The LTSI-35 may be used to influence donor selection, organ allocation, and to inform expectations for allograft survival. (J Am Coll Surg 2019;228:437−452. © 2018 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Implementation of the Share 35 rule in 2013 prioritized patients awaiting liver transplantation with Model for End Stage Liver Disease (MELD) scores $\geq$ 35 for regional sharing of available liver allografts.[1-3] This policy has resulted in decreased waitlist mortality for MELD $\geq$ 35 candidates,[4] receipt of higher-quality organs, as measured by donor risk index (DRI),[5] and improved 1-year graft survival in MELD $\geq$ 35 recipients compared with the pre-Share 35.[6] Despite these beneficial effects of Share 35, patients with MELD $\geq$ 35 continue to have worse post-transplant outcomes than those with MELD scores < 35.

Disclosure Information: Nothing to disclose.

Presented at the Southern Surgical Association 130th Annual Meeting, Palm Beach, FL, December 2018.

Received December 7, 2018; Accepted December 10, 2018.

From the Department of Surgery (Steggerda, Kim, Todo, Klein, Bloom), Divisions of Transplant Surgery (Kim, Todo, Klein), and Trauma and Critical Care Surgery (Bloom), Cedars-Sinai Medical Center Los Angeles, CA; and the Division of Trauma and Critical Care Surgery (Malinoski), Oregon Health and Science University, Portland, OR.

Correspondence address: Justin A Steggerda, MD, Department of Surgery, Cedars-Sinai Medical Center, 8700 Beverly Blvd, North Tower, Suite 8215, Los Angeles, CA 90048. email: justin.steggerda@cshs.org

https://doi.org/10.1016/j.jamcollsurg.2018.12.009
ISSN 1072-7515/18

Abbreviations and Acronyms

AUROC = area under the receiver operating characteristic curve
BAR = Balance of Risk score
CIT = cold ischemic time
DCD = donation after circulatory death
D-MELD = donor-Model for End-Stage Liver Disease
DRI = donor risk index
HR = hazard ratio
LTSI-35 = Liver Transplant Survival Index-Model for End-Stage Liver Disease 35
SOFT = Survival Outcomes Following Liver Transplantation score

Although some of the difference in graft survival may be attributable solely to severity of liver disease, MELD score alone has been found to have poor predictive ability for survival after liver transplantation.[7] To better account for additional contributory factors, the interaction between donors and recipients has been previously investigated. The Survival Outcomes Following Liver Transplantation (SOFT) score included donor and recipient factors, but focused only on early outcomes and used recipients with a broad range of MELD scores.[8] The Donor-MELD incorporated donor age with MELD score, but left out other recipient factors that may contribute to graft and patient survival, and again included recipients with a broad range of MELD scores.[9] Lastly, the Balance of Risk (BAR) score showed good predictive ability, but was based on factors found significant in the SOFT score and, like the previous 2 scoring strategies, was calculated across a wide range of MELD scores.[10] Furthermore, Schlegel and colleagues[11] recently examined multiple scoring systems in a population of MELD $\geq$ 30 recipients and found only BAR and SOFT scores to have predictive ability based on a single score cut-off.

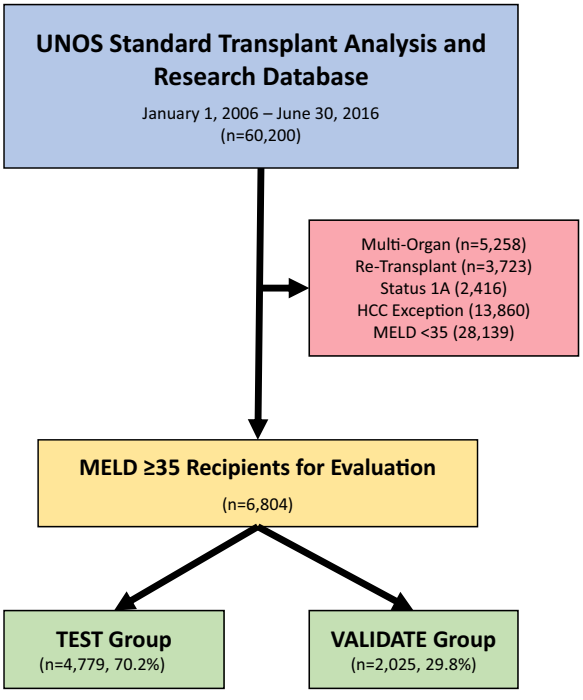


Figure 1. Liver Transplant Survival Index-Model for End-Stage Liver Disease (MELD) 35 (LTSI-35) population determination. This flow chart represents the identification and breakdown of 60,200 liver transplant recipients identified in the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research database to 6,804 recipients with MELD scores $\geq$ 35 used in the derivation and validation of the LTSI-35 recipients. HCC, hepatocellular carcinoma.

Recipients with MELD scores $\geq$ 35 represent a unique and extremely ill population, and there is a paucity of data on factors affecting graft survival in these patients. Therefore, this study aimed to identify donor- and recipient-specific factors associated with short- and long-term graft survival in recipients with MELD scores $\geq$ 35, and create a risk score to stratify patients at high risk of poor outcomes. These findings may be used to influence donor and recipient selection to improve transplantation outcomes and inform expectations of graft survival in a high-MELD population.

METHODS

Patient population

The United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) database was reviewed for all liver transplants in the United States with MELD $\geq$ 35 recipients, between January 2006 and June 2016. Exclusion criteria included Status 1A recipients, retransplants, and multivisceral transplants due to inconsistent allocation policies, as well as recipients with diagnosis of hepatocellular carcinoma (HCC) who received tumor exception points, which may not accurately quantify severity of illness (Fig. 1). Transplants with missing data from variables included in multivariable models were additionally excluded. Donor, procurement, and recipient-specific variables were extracted for evaluation. Adjusted graft survival was calculated for transplantations with adequate available follow-up only.

Regression modeling

The primary aim of this study of this study was to identify factors associated with acute and long-term graft failure after liver transplantation. Recipient death and retransplantation were similarly considered graft failure. Living

patients with functioning graft at last known follow-up were censored observations.

For Cox regression modeling and Kaplan-Meier analyses, a random number generator was used to create test and validate populations in a 70/30 distribution, respectively.[12] Individual models of graft survival were created for graft survival truncated and right censored at 90 days, 1 year, 3 years, and 5 years. Univariate Cox proportional hazards analysis was performed to identify characteristics associated with graft survival, and factors with p value < 0.10 were included in their respective multivariable model. Multivariable Cox proportional hazards modeling was performed in the test population using a manual stepwise regression,[13] excluding factors where p value was > 0.05.

Variables that remained significant in the validate population from each model were then combined into a single model of 5-year graft survival to develop an overall risk-index for recipients with MELD $\geq$ 35, known as the Liver Transplant Survival Index-35 (LTSI-35). Scores were normalized using a natural log and multiplier. The equation comprising the LTSI-35 is as follows:

LTSI-35 = 10 × ln (exp[(donor age × 0.0151) + (donor BMI × 0.0046) + (0.2885 if DCD donor) + (−0.0354 if CIT 8 to <12 hours; 0.2175 if CIT $\geq$ 12 hours) + (Recipient age × 0.0169) + (0.1164 if acute liver failure; −0.1413 if cryptogenic cirrhosis/nonalcoholic steatohepatitis [CC/NASH]; −0.2721 if cholestatic liver disease; −0.0409 if cirrhosis; −0.0382 if congenital/metabolic liver disease; −0.2709 if alcoholic liver disease; −0.0455 if hepatitis B-related liver disease; 0.0756 if hepatitis C-related liver disease; 0.1941 if hepatocellular carcinoma) + (0.1154 if previous abdominal surgery) + (−0.0614 if known portal vein thrombosis) + (0.2884 if ventilator support at transplant) + (0.1142 if dialysis within week before transplant)]).

From the LTSI-35 scores, 5 risk groups were identified using a symmetric distribution from the median LTSI-35 score: very low risk (0 to 15th percentile), low risk (15th to 35th percentile), moderate risk (35th to 65th percentile), high risk (65th to 85th percentile), and severe risk (85th to 100th percentile). Validation of the LTSI-35 was performed using Kaplan-Meier analysis to compare LTSI-35 performance between test and validate populations. Logistic regression was used to evaluate risk of graft loss across LTSI-35 risk groups.

Performance of the LTSI-35 was compared with previously published SOFT and BAR scores.[8,10] All MELD $\geq$ 35 recipients were included for comparison. Scores were calculated according to published equations. Logistic regression was performed for graft survival at 90 days, 1 year, and 3 years, and area under receiver operator curve (AUROC) was calculated for each score at all time points.

Evaluation of pre-donation biopsy cohort

Univariate analysis identified graft macrosteatosis $\geq$ 30% as significant predictor of graft loss. Because not all donors undergo pre-transplant biopsy and to avoid selection bias, transplants with pre-donation biopsy were considered for subgroup analysis to evaluate the impact of donor macrosteatosis on graft survival in a high-MELD population. Multivariable analysis was performed as previously described within this cohort.

Data analysis

Variables were compared across groups using *t*-tests, chi-square, 1-way analysis of variance (ANOVA), and Wilcoxon rank-sum tests, as appropriate. A value of $p < 0.05$ was considered significant. Data are presented as means ± standard deviation, unless otherwise noted. All modeling and statistical analyses were performed using JMP Pro 13.0 software (SAS).

RESULTS

Transplant characteristics

Within the 10-year evaluation period, 6,804 transplants in MELD $\geq$ 35 recipients were identified for analysis. Transplants were divided into test (n = 4,779, 70.2%) and validate (n = 2,025, 29.8%) cohorts for multivariate analysis. Select donor-, procurement-, and recipient-related characteristics for all MELD $\geq$ 35 transplants are presented in Table 1. Test and validate cohorts were compared, with no significant differences identified. Additional variables evaluated in all models are presented in eTable 1. For all MELD $\geq$ 35 recipients, 90-day graft survival was 90.1%; it dropped to 81.7% at 1 year and 70.6% at 3 years. Notably, of patients who experienced graft loss within the first year after transplantation, 58.9% were lost within the first 90 days after transplantation. Five-year follow-up showed 64.0% graft survival among all recipients.

Multivariable regression analysis

Variables found to be significant predictors of graft failure for both the test and validate populations are shown in Figure 2. Notably, not all variables that were significant in the test population remained significant in the smaller validate cohort. Furthermore, the composition of significant variables changed for each time point evaluated.

Final multivariable models for each time point are presented in Table 2 (complete unadjusted and adjusted

Table 1. Selected Characteristics for Donors and Recipients Evaluated in the Creation of the Liver Transplant Survival Index-Model for End-Stage Liver Disease 35

Variable	All MELD ≥ 35 (n = 6,804)	Test (n = 4,779)	Validate (n = 2,025)	p Value
Donor characteristics				
Age, y, mean ± SD, median (IQR)	39.4 ± 15.2 39 (26–52)	39.3 ± 15.2 39 (25–51)	39.6 ± 15.3 39 (26–52)	0.42
Sex, female, n (%)	2,666 (39.2)	1,879 (39.3)	787 (38.9)	0.74
Ethnicity*				0.54
Blood type*				0.49
BMI, kg/m^2	27.1 ± 5.8	27.2 ± 5.9	26.9 ± 5.5	0.06
Liver biopsy done	2,027 (29.8)	1,400 (29.3)	627 (30.9)	0.17
≥30% Macrosteatosis	128 (6.9)	91 (7.1)	37 (6.4)	0.69
Donor medical/social history, n (%)				
Diabetes	669 (9.8)	454 (9.5)	215 (9.8)	0.17
Hypertension	2,054 (30.2)	1,447 (30.3)	607 (30.0)	0.82
Prior malignancy	175 (2.6)	122 (2.6)	53 (2.6)	0.87
Previous myocardial infarction	196 (2.9)	131 (2.7)	65 (3.2)	0.30
Procurement variables, n (%)				
DCD Donor	206 (2.8)	130 (2.5)	76 (3.3)	0.06
CIT Groups				0.78
<8 h	5,299 (72.7)	3,676 (72.8)	1,623 (72.5)	
8 to <12 h	1,778 (24.4)	1,224 (24.2)	554 (24.8)	
>12 h	211 (2.9)	150 (3.0)	61 (2.7)	
Recipient characteristics				
Age, y, mean ± SD, median (IQR)	53.2 ± 10.0 55 (48–60)	52.7 ± 10.3 55 (4–60)	52.7 ± 10.4 54 (47–60)	0.94
Sex, female, n (%)	2,647 (35.8)	1,855 (36.2)	792 (34.8)	0.27
Ethnicity*				0.34
Blood type*				0.88
Recipient diagnosis*				0.50
Recipient medical/social history, n (%)				
HCV-positive	2,420 (35.6)	1,734 (36.3)	686 (33.9)	0.06
Previous abdominal surgery	2,624 (38.6)	1,824 (38.2)	800 (39.6)	0.30
PV thrombosis	716 (10.5)	510 (10.7)	206 (10.2)	0.57
Mechanical ventilation	1,065 (15.7)	750 (15.7)	315 (15.6)	0.91
Dialysis before transplantation	3,162 (46.5)	2,248 (47.0)	914 (45.1)	0.15
Adjusted graft survival, n (%)				
90-d	5,755 (90.1)	4,047 (90.4)	1,708 (89.6)	0.36
1-y	4,394 (81.7)	3,095 (82.1)	1,299 (80.6)	0.20
3-y	2,491 (70.6)	1,759 (71.0)	732 (69.9)	0.52
5-y	1,213 (64.0)	861 (64.1)	352 (63.8)	0.89

*See eTable 1.
CIT, cold ischemic time; DCD, donation after circulatory death; HCV, hepatitis c virus; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; PV, portal vein.

hazard ratios are presented in eTable 2A-D). The greatest risk of graft loss at any time point was associated with donation after circulatory death (DCD) donors. Donor BMI was a significant predictor of graft failure at 90 days, but was not significant at any other time points. Cold ischemic time (CIT) was also significant only in the 90-day model ($p < 0.001$), with increased HR for longer durations of CIT. Donor age was not significant in the 90-day survival model, but was significant at all later time points. Previous abdominal surgery or need for ventilator support were significant at all time points. Interestingly, requiring dialysis in the week before transplantation was a significant predictor of late graft loss only.

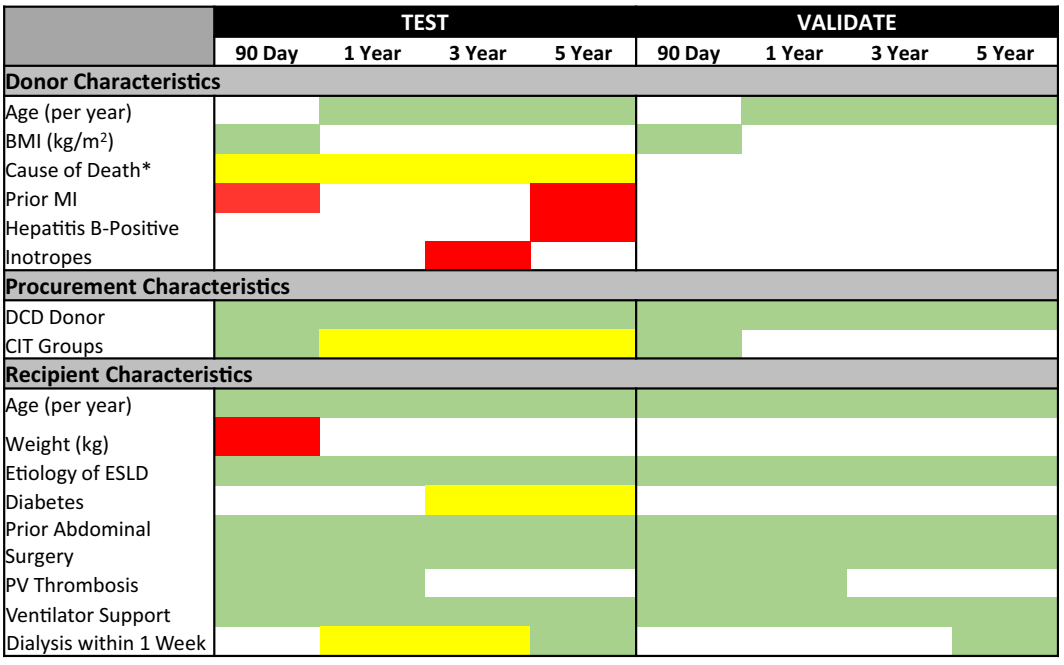


Figure 2. Variation in characteristics associated with graft loss of multiple durations of follow-up. Four independent multivariable models were created to evaluate factors associated with graft failure at 90 days, 1 year, 3 years, and 5 years. Models were created in a test population (70% of total) and fitted in a smaller validate population (30%). Green boxes indicate factors that were significant in both test and validate populations. *Cause of death divided into trauma/anoxia, CVA, and other. Yellow boxes indicate factors that were significant in only the test population with p value <0.01; red boxes indicate factors significant in only the test population with p value <0.05. CIT, cold ischemic time; DCD, donation after circulatory death; ESLD, end-stage liver disease; PV, portal vein.

Creation, validation, and performance of Liver Transplant Survival Index—Model for End-Stage Liver Disease 35

Adjusted hazard ratios and beta-coefficients for LTSI-35 are presented in Table 3. The mean LTSI-35 score for all patients was 16.7 ± 3.8. Distribution of scores and risk groups are presented in eTable 3. There was no difference between test and validate cohorts in either mean LTSI-35 score or risk group population.

Graft survival times were assessed by Kaplan-Meier analysis comparing risk groups (Fig. 3A). Because median graft survival was not reached, time to 25% graft loss was evaluated and found to vary significantly across risk groups—252 days in the severe-risk groups, 656 days in the high-risk group, and 1,386 days in the moderate-risk group; this level of graft loss was not achieved in the very low- or low-risk groups ($p < 0.001$). Adjusted graft survival was also assessed for each time point and was significantly different across risk groups for each follow-up duration (Fig. 3B, $p < 0.001$). At 90 days, graft survival ranged from 94.2% ± 0.2% in the very low-risk group to 83.4% ± 0.4% in the severe-risk group. At 1 year, graft survival was 89.8% ± 0.3% in the very low- and 88.3% ± 0.3% in the low-risk groups; it decreased to 77.9% ± 0.4% and 67.8% ± 0.5% in the high- and severe-risk groups, respectively. By 5 years, graft survivals were still 78.1% ± 0.5% and 73.3% ± 0.5% in the very low and low risk groups, respectively. However, in the high-risk group graft survival had dropped to 58.1% ± 0.6% and was even lower in the severe-risk group (45.1% ± 0.6%, $p < 0.001$ comparing all risk groups for all time points).

Logistic regression was used to determine the risk of graft loss at each specified time point across groups. Odds ratios for graft failure are presented in Table 4, with the moderate-risk group used as the reference group. Recipients in the LTSI-35 severe-risk group had a greater than 2-fold risk of graft loss at 90 days, and even higher risk at 1 year, 3 years, and 5 years. Those in the low- and very low-risk groups were at significantly lower risk of graft loss, compared with the moderate-risk group, at all time points.

The LTSI-35 was validated using Kaplan-Meier survival analysis to compare test and validate cohorts within each risk group, and significant differences were identified (eFig. 1). Adjusted graft survival rates for test and validate

Table 2. Adjusted Hazard Ratio at 4 Follow-up Durations

	90-d			1-y			3-y			5-y		
Variable	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Donor characteristics												
Age, per y				1.01	1.01−1.02	<0.001	1.01	1.00−1.02	<0.001	1.01	1.01−1.02	<0.001
BMI, per kg/m^2	1.03	1.01−1.06	0.01									
Procurement characteristics												
DCD Status	1.65	1.24−2.20	0.002	1.61	1.26−2.05	0.001	1.34	1.05−1.71	0.02	1.32	1.05−1.66	0.02
Cold ischemic time*			0.04									
8 to <12 h	1.05	0.79−1.39										
≥12 h	1.28	0.84−1.99										
Recipient characteristics												
Age	1.03	1.01−1.04	<0.001	1.02	1.01−1.04	<0.001	1.02	1.01−1.03	<0.001	1.02	1.01−1.03	<0.001
Etiology of ESLD†			0.05			0.05			<0.001			<0.001
Acute	0.37	0.10−1.30		0.52	0.23−1.17		0.52	0.26−1.02		0.68	0.38−1.21	
CC/NASH	0.91	0.60−1.38		0.99	0.72−1.36		1.10	0.83−1.45		1.05	0.81−1.37	
Cholestatic	0.58	0.33−1.01		0.54	0.34−0.84		0.67	0.46−0.97		0.73	0.51−1.03	
Cirrhosis, not specified	1.33	0.77−2.29		1.08	0.68−1.69		0.87	0.56−1.34		0.86	0.57−1.31	
Congenital/metabolic	0.74	0.30−1.84		0.61	0.29−1.29		0.57	0.29−1.12		0.49	0.25−0.98	
Alcohol	1.08	0.75−1.55		0.96	0.72−1.28		0.93	0.72−1.21		0.91	0.71−1.16	
Hepatitis C	1.16	0.85−1.60		1.20	0.95−1.53		1.27	1.03−1.57		1.25	1.02−1.53	
Hepatitis B	1.17	0.51−2.65		0.99	0.50−1.96		0.80	0.41−1.59		0.74	0.38−1.48	
Hepatocellular carcinoma	1.03	0.64−1.65		1.27	0.90−1.79		1.38	1.02−1.87		1.44	1.08−1.92	
Previous abdominal surgery	1.28	1.11−1.47	<0.001	1.19	1.06−1.33	0.003	1.17	1.06−1.28	0.002	1.15	1.05−1.26	0.003
Portal vein thrombosis	1.30	1.07−1.57	0.01	1.21	1.03−1.42	0.03						
Ventilator support at transplantation	1.27	1.07−1.50	0.007	1.32	1.17−1.51	<0.001	1.30	1.16−1.46	<0.001	1.24	1.11−1.38	<0.001
Dialysis within 1 wk before transplantation										1.15	1.05−1.26	0.004

*Reference group is cold ischemic time < 8 hours.
†Reference groups is other causes.
CC/NASH, cryptogenic cirrhosis/nonalcoholic steatohepatitis; DCD, donation after circulatory death; ESLD, end-stage liver disease; HR, hazard ratio.

Table 3. Liver Transplant Survival Index-Model for End-Stage Liver Disease 35 Regression Coefficients and Hazard Ratio

Characteristic	β Regression coefficient	Adjusted HR	95% CI	p Value
Donor characteristic				
Age, per y	0.0151	1.02	1.01−1.02	<0.001
BMI, per kg/m^2	0.0046	1.00	0.99−1.01	0.38
Procurement characteristics				
DCD Status	0.2885	1.33	1.15−1.56	<0.001
Cold ischemic time*				0.01
8 to <12 h	-0.0354	0.97	0.84−1.10	
≥12 h	0.2175	1.24	1.00−1.55	
Recipient characteristic				
Age	0.0169	1.02	1.01−1.02	<0.001
Etiology of ESLD†				<0.001
Acute	0.1664	1.18	0.87−1.61	
CC/NASH	-0.1413	0.87	0.73−1.03	
Cholestatic	-0.2721	0.76	0.61−0.95	
Cirrhosis (not specified)	0.0409	1.04	0.82−1.32	
Congenital/metabolic	-0.0382	0.96	0.71−1.30	
Alcohol	-0.2709	0.76	0.64−0.90	
Hepatitis C	0.0756	1.08	0.95−1.23	
Hepatitis B	-0.0455	0.96	0.68−1.33	
Hepatocellular carcinoma	0.1941	1.21	1.01−1.46	
Previous abdominal surgery	0.1154	1.12	1.06−1.19	<0.001
Known portal vein thrombosis	-0.0614	0.94	0.86−1.03	0.20
Ventilator support at transplantation	0.2884	1.33	1.24−1.44	<0.001
Dialysis within 1 wk at transplantation	0.1142	1.12	1.05−1.19	<0.001

*Reference group for cold ischemic time is <8 h.
†Etiology of ESLD reference group is "other causes."
CC/NASH, cryptogenic cirrhosis/nonalcoholic steatohepatitis; DCD, donation after circulatory death; ESLD, end-stage liver disease; HR, hazard ratio.

data cohorts were also assessed, and no significant differences were observed for any time point (eTable 4).

Multiple scoring systems have been developed to predict graft survival in the liver transplant population. A recent review of these scoring systems found only the SOFT score and BAR score performed well in populations with MELD scores ≥ 30.[11] We evaluated the performance of the LTSI-35 against SOFT and BAR scores at predicting 90-day, 1-year, and 3-year graft survival in the MELD > 35 population (Fig. 4). Area under the receiver operating characteristic curve (AUROC) was similar between all 3 scoring systems at 90 days post-transplantation; however, at 1 year and 3 years post-transplant, the LTSI-35 had higher AUROC than both SOFT and BAR scores.

Pre-donation biopsy and donor macrosteatosis

Recipients of livers with pre-donation biopsy results showing macrosteatosis ≥ 30% had decreased graft survival compared with those with lower levels of macrosteatosis at 90 days (76.0% vs 90.2%, p < 0.001) and 1 year (81.2% vs 71.6%, p = 0.02, Fig. 5A). At 3 years and 5 years of follow-up, there was a trend toward worse graft survival, which did not reach statistical significance. Univariate analysis showed that macrosteatosis ≥ 30% was significant predictor of graft survival at 90 days (HR 2.69 [range 1.72 to 3.79], p < 0.001) and 1 year (HR 1.79 [range 1.23 to 2.53], p < 0.001), but was not significant at 3 years or 5 years. Donor livers with macrosteatosis ≥ 30% were found to have an adjusted HR of 1.64 ([range 1.33 to 1.99], p < 0.001) for graft failure at 90 days. This HR dropped to 1.39 ([range 1.16 to 1.67], p < 0.001) at 1 year (Fig. 5B, C). Donor BMI and recipient age became nonsignificant when macrosteatosis was included as variable in the 90-day model; however, recipient age remained significant at 1 year. Recipient etiology of end-stage liver disease also became nonsignificant at both time points when macrosteatosis was introduced into the model.

DISCUSSION

The Share 35 policy was implemented in response to findings that liver transplant candidates with MELD ≥ 35

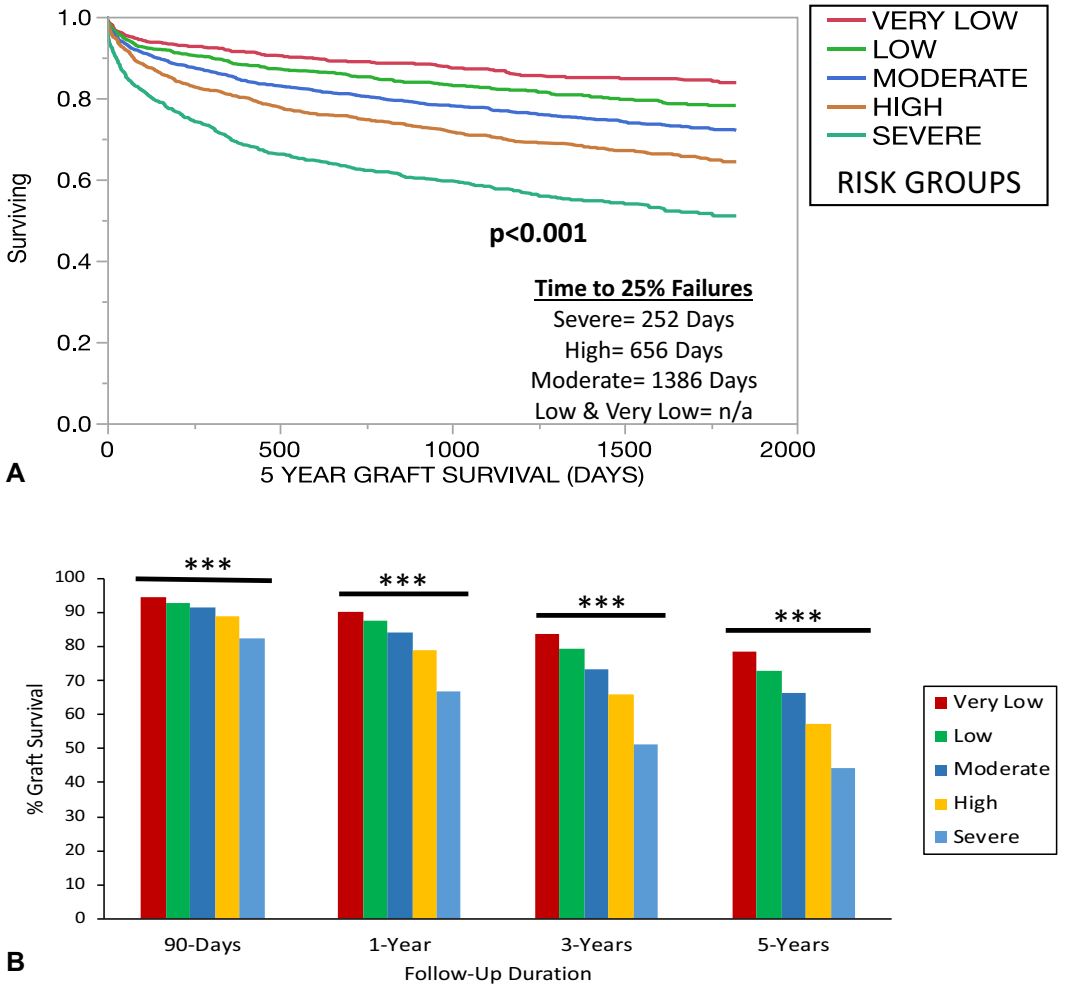


Figure 3. Liver Transplant Survival Index-Model for End-Stage Liver Disease (MELD)-35 (LTSI-35) risk group distribution and associated graft survival. (A) Kaplan-Meier survival curves show a significant difference across all 5 LTSI-35 risk groups for graft survival ($p < 0.001$). Graft survival was truncated to 5 years with right-censored data for patients lost to follow-up with functioning grafts. Time to 25% failure was recorded for 3 risk groups that reached this level of graft loss. (B) Adjusted rates of graft survival were compared across risk groups for 90 days, 1 year, 3 years, and 5 years of graft survival. Rates of graft loss were significant different across all groups at all time points (*** for $p < 0.001$). n/a, not applicable.

had a waitlist mortality that was similar to that of patients with acute fulminant liver failure.[4] Initiation of this policy facilitated regional sharing of deceased donor liver allografts for high-MELD recipients and has resulted in an increased proportion of transplants for MELD $\geq$ 35 recipients,[14] with higher quality donor organs and

Table 4. Odds Ratios for Graft Failure by Liver Transplant Survival Index-Model for End-Stage Liver Disease 35 Risk Group

Variable	90-d	1-y	3-y	5-y
Very low risk, OR (95% CI)	0.64 (0.46–0.88)	0.60 (0.45–0.79)	0.53 (0.40–0.70)	0.54 (0.38–0.76)
Low risk, OR (95% CI)	0.79 (0.60–1.03)	0.70 (0.56–0.89)	0.73 (0.58–0.93)	0.70 (0.52–0.94)
Moderate risk, % graft survival	Reference, 91.2	Reference, 84.1	Reference, 73.3	Reference, 65.7
High risk, OR (95% CI)	1.36 (1.08–1.72)	1.50 (1.24–1.83)	1.46 (1.19–1.79)	1.38 (1.06–1.80)
Severe risk, OR (95% CI)	2.07 (1.64–2.61)	2.51 (2.07–3.07)	2.45 (1.98–3.04)	2.34 (1.74–3.13)
p Values*	<0.001	<0.001	<0.001	<0.001

*p Values assessed for entire model at each time point.
OR, odds ratio.

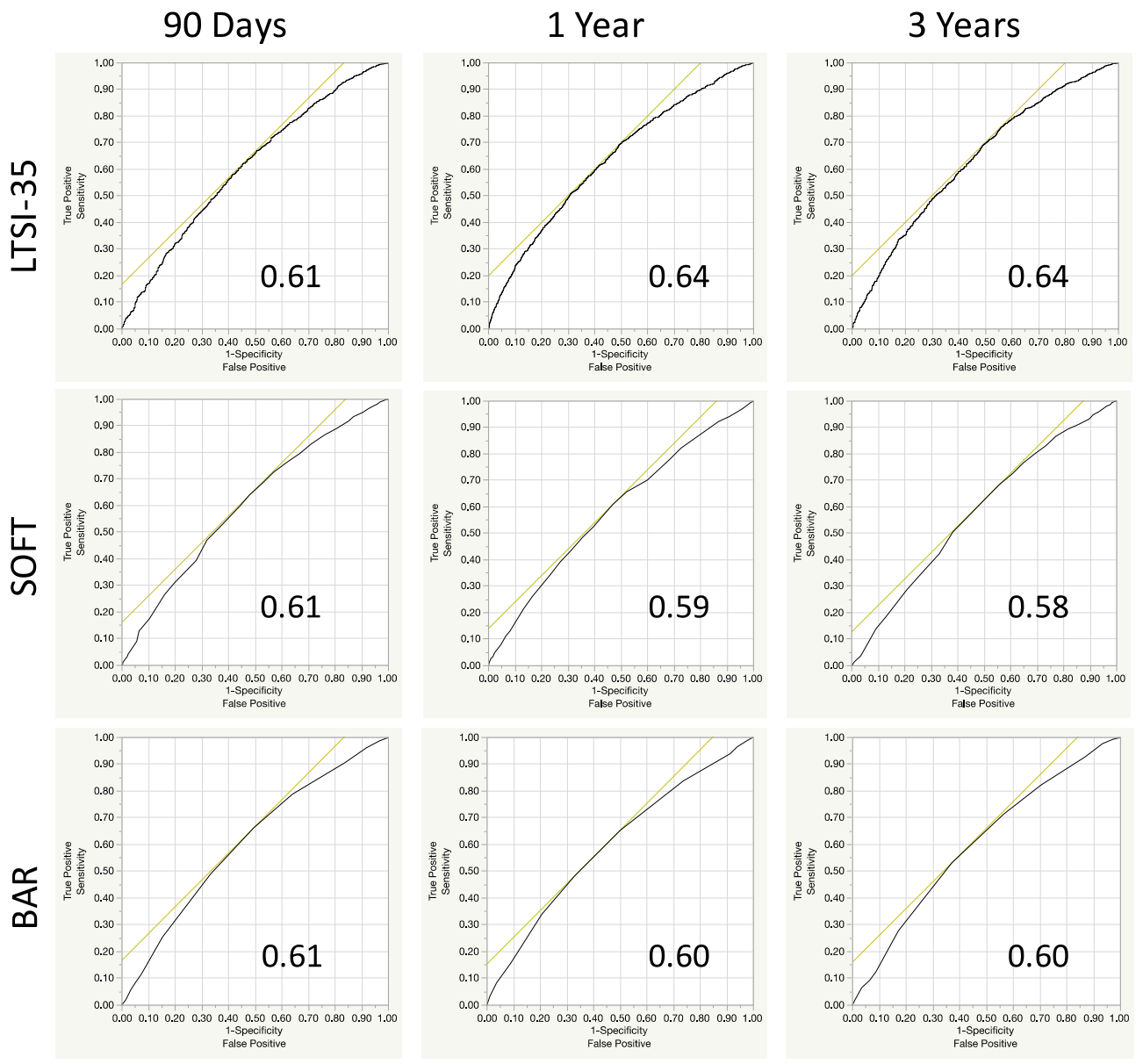


Figure 4. Comparison of Liver Transplant Survival Index (LTSI)-35 performance with other risk scores for MELD $\geq$ 35 recipients. Area under receiver operating curve (AUROC) was calculated for the LTSI-35, Survival Outcomes Following Transplantation (SOFT), and Balance of Risk (BAR) scores, predicting graft survival at 90 days, 1 year, and 3 year time points. AUROC are reported for each score.

improved 1-year survival.[6] Despite this, the average post-transplant survival is worse in recipients with MELD $\geq$ 35 compared with those with lower MELD scores; however, the variables contributing to this difference are widely unknown. Using multivariable models for early and late graft survival, with data from transplants collected over a 10-year period in MELD $\geq$ 35 recipients, this study identifies donor- and recipient-specific factors that are significantly associated with graft survival in this severely ill population. Furthermore, we produced the LTSI-35, which stratifies donor-recipient pairs with associated risks of graft loss. Finally, this study reports the increased risk of graft loss with donor macrosteatosis, specifically in a high-MELD population.

The notion that sicker patients require higher-quality organs to optimize outcomes has driven organ allocation for liver transplantation. Although donor organ quality may be measured by DRI, clinical application of the

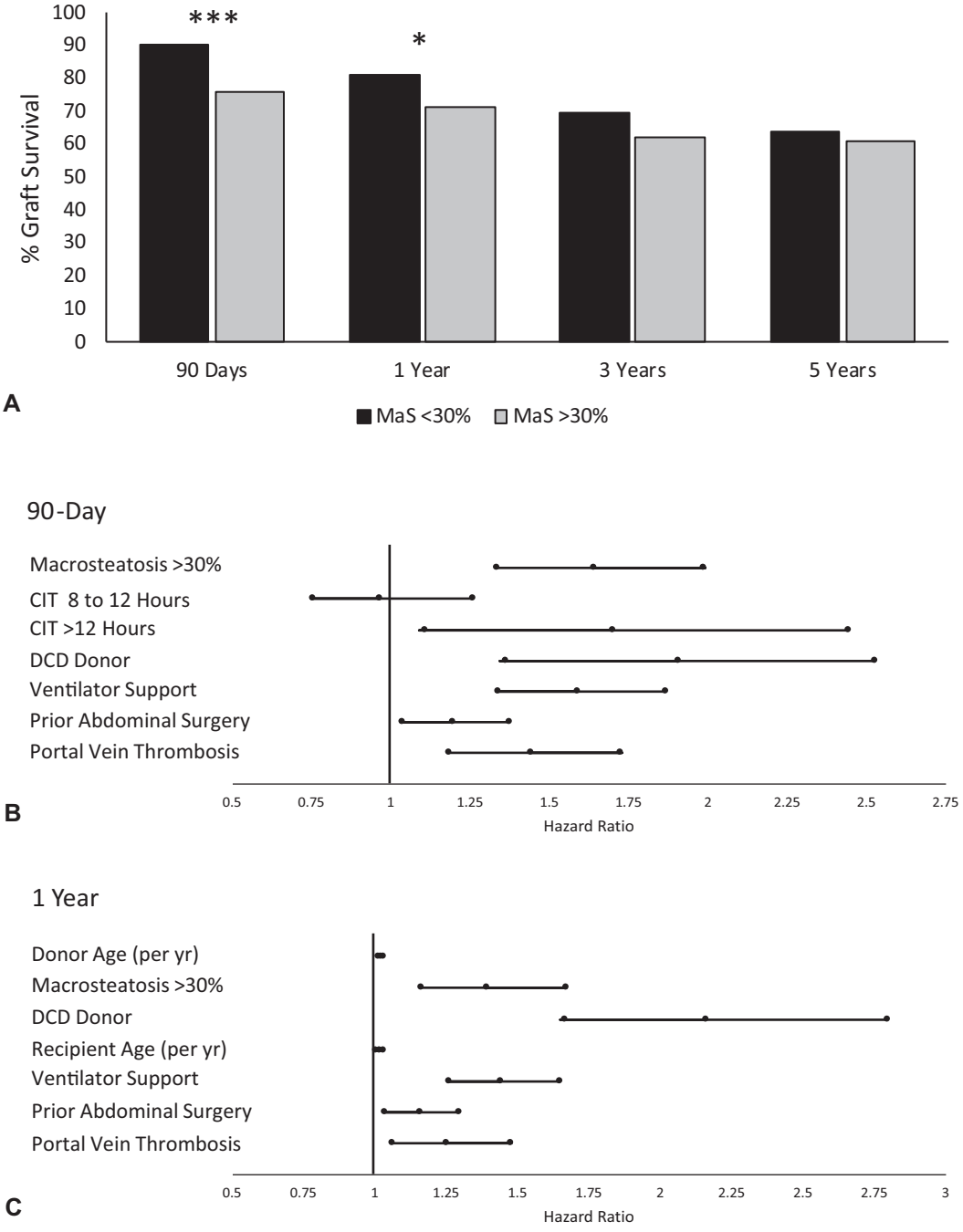


Figure 5. Evaluation of pre-transplant biopsy and macrosteatosis. Subgroup analysis of donors with a pre-transplant biopsy evaluated the effects of macrosteatosis $\geq$ 30% on graft loss. (A) Adjusted graft survival was compared between recipients with donor biopsy showing macrosteatosis $\geq$ 30% and those with macrosteatosis $<$ 30% (*** for $p < 0.001$, * for $p < 0.05$). (B and C) Multivariable analysis showed that macrosteatosis was a significant risk factor for early graft loss in high-MELD recipients. Forest plots show hazard ratios (HR) with 95% confidence intervals for models incorporating macrosteatosis at 90 days and 1 year. CIT, cold ischemic time; DCD, donation after circulatory death; MaS, macrosteatosis.

DRI has been found to be limited.[15] Critics of the DRI point out that it includes factors that should have no bearing on organ outcomes (ie donor ethnicity), and large variability has been reported with respect to post-transplant survival.[16] Donor risk index may be a useful tool by which to compare potential donors, but it lacks

recipient characteristics, which may ultimately drive transplantation outcomes.

Four models of graft survival—at 90 days, 1 year, 3 years, and 5 years—are presented here, and the only significant donor-specific characteristics affecting outcomes at any time point were age and BMI, when assessed in our smaller validation cohort. We found that donor cause of death was significant in our test population at all time points, but dropped out in the smaller validation cohort, which may be explained by the high proportion of "other" causes of death. Other donor-specific variables, such as previous myocardial infarction, hepatitis B viral positivity, or inotrope requirement before donation were found to have a significant p value (<0.05) in the test population, but again, were not significant in the validate population. These characteristics, particularly a previous myocardial infarction or inotrope requirement, may indicate a sicker donor, but do not ultimately associate with outcomes. Additionally, some variables may be loosely associated with graft failure solely by evaluation in a large population; however, through re-evaluation in the smaller validate cohort, we eliminated factors that did not have a consistently strong influence on allograft outcomes. Two procurement-specific variables were associated with allograft survival. Donation after circulatory death was significant at all time points, while cold ischemic time was significant only for early graft survival. Others who have found that prolonged cold ischemic time is associated with higher rates of early allograft dysfunction support this finding for cold ischemic time.[17,18]

This study found that prevailing factors associated with graft survival were primarily recipient specific. Recipient age, certain etiologies of end-stage liver disease, and requiring ventilator support at time of transplantation were found to be significant risk factors for graft loss at all time points evaluated. Nearly 16% of the population required ventilator support at the time of transplantation, which was associated with an increased risk of graft loss of 24% to 32% at any time. Ventilator dependence has been previously identified in a small study as a risk factor for graft loss.[8,19] This is a notable difference from the SOFT score, which examined recipients across a broad range of MELD scores, wherein only 3.9% were ventilator dependent pre-transplant, and it was not found to be a predictor of graft loss.[8] In our final LTSI-35 model, ventilator support was found to have an HR of 1.33 (range 1.24 to 1.44, $p < 0.001$), similar to the risk of using a DCD organ. These findings indicate that requiring ventilator support may be a marker for futility in liver transplantation in high-MELD recipients, identifying patients who are at markedly increased risk of graft loss or death after transplantation. To overcome this risk and optimize outcomes, it could be argued that intubated patients should not have any other significant risk factors, such as previous abdominal surgery or portal vein thrombosis. Moreover, non-DCD, nonmacrosteatotic organs with short cold ischemic times should be used for mechanically ventilated patients.

Our models also found that recipient portal vein thrombosis is a risk factor for early graft loss; however, it is not significant for late graft loss. The association between portal vein thrombosis and allograft loss is unclear. Previous studies, including a meta-analysis, have shown no increased risk of graft loss in the presence of portal vein thrombosis.[20,21] Conversely, in the preallocation SOFT score, portal vein thrombosis was given 5 points, indicating a high risk. The derivation of preallocation SOFT and SOFT scores, however, followed outcomes for only 6 months and controlled for MELD in regression modelling while using recipients with a broad range of scores.[8] Notably, none of these studies examined portal vein thrombosis in the high-MELD population alone. Our study confirmed this risk in a high-MELD population and showed that this risk extends up to 1-year post-transplantation.

We found that dialysis at the time of transplantation is a risk factor only for later-term graft survival. Nearly half of the MELD $\geq$ 35 population (46.5%) required dialysis within the week before transplantation. Unfortunately, neither the reason for dialysis nor the use of dialysis after transplantation are provided in this database, making it difficult to draw further conclusions regarding the role of dialysis in long-term graft dysfunction. Still, these findings of differential risks and variable risk factors affecting short- and long-term survival may be used to direct concern and guide perioperative care in liver transplant recipients.

Macrosteatosis in the donor liver has been associated with prolonged ICU and hospital stays and increased risk of primary nonfunction or graft loss.[22-24] Although some reports have shown acceptable outcomes using grafts with $\geq$30% macrosteatosis, many of these studies have been done in low-MELD (<25) populations[22] or in populations with high rates of hepatitis-B associated end-stage liver disease.[25,26] In the MELD $\geq$ 35 population, we found that macrosteatosis $\geq$ 30% in the donor liver is associated with a 60% increased risk of graft loss at 90 days and a 40% increased risk of graft loss by 1 year. However, we also found that this was not a risk factor for later-term graft outcomes. These findings suggest that donor livers with macrosteatosis $\geq$ 30% should be used sparingly in high-MELD recipients; however, in

the absence of other significant risk factors (ie ventilator support, prolonged cold ischemic time, etc), these organs may be used with caution and should have close clinical follow-up for early signs of graft failure.

Predicting outcomes for individuals after transplantation is difficult due to the high number of post-transplantation factors that may contribute to graft loss, such as transfusion requirements, duration of ICU stays, development of infection or rejection, disease recurrence, medication noncompliance, etc. The LTSI-35 stratifies patients into 5 risk groups based solely on variables available at the time of transplantation, and it associates those groups with risks of graft loss at both early and late time points. Measured across the groups, differences in graft survival were significant by Kaplan-Meier analysis and adjusted rates of graft survival for each of the time points measured. The concurrence between our test and validation cohorts within each risk group supports the statistical reliability of our model.

Extracted from the 4 individual models, the variables contained within the LTSI-35 are primarily recipient based. This indicates that a broad range of donors should be considered for transplantation in these high-risk individuals, with the exception of very old donors, those with macrosteatosis $\geq$ 30% on biopsy, or DCD donors. We also found that very long cold ischemic time ($\geq$12 hours) carried significant risk, but this risk was lessened with shorter periods of cold ischemia.

Unfortunately, these findings beg the question—if the majority of risk is inherent to the recipient, is this a measure of futility in transplantation? One-year graft survival ranged from 90.4% to 64.5% across all risk groups. Five-year survival rates were as high as 77.4% to 77.9% and 72.4% to 75.9% in the very low and low risk groups, respectively. The moderate risk group had 90-day and 1-year survival rates of 90.2% to 91.7% and 83.0% to 84.6%, respectively. These rates of graft survival are acceptable and achievable. However, compared with moderate risk recipients, high risk recipients had 36% to 50% increased risk of graft loss, and severe risk recipients had risk of graft loss up to 2.5 times higher at any time point. The contributing risk factors in these very high-risk individuals should be thoroughly reviewed, and both donors and recipients should be optimized to maximize outcomes when pursuing transplantation for these cases.

Previous studies have examined the role of donor and recipient factors on post-transplant outcomes. Recently, 6 published scoring systems for post-transplant outcomes were reviewed and compared for performance in recipients with MELD scores of 30 or higher. Only 2—the SOFT and BAR scores—were able to identify high- and low-risk groups based on a predefined cutoff score. Comparison of the LTSI-35 against the SOFT and BAR scores showed it performed better at 1 year and 3 years, while having equivalent performance at 90 days post-transplant in a MELD $\geq$ 35 population. The University of California-Los Angeles (UCLA) group has also published the Futility Risk Score (UCLA-FRS), which was modeled using recipients with MELD $\geq$ 40 for 90-day graft survival or in-hospital mortality.[27] This model had good predictive ability within the UCLA population, reporting a c-statistic of 0.72. Unfortunately, many of the variables included in that model were not available in the STAR database, and comparison with the LTSI-35 was not possible. Although the AUROC was only 0.64 at 1 year and 3 years, the LTSI-35 represents the best available model for the high-MELD population using UNOS-derived data.

The implications of these findings are multiple. First, identification of recipients falling into the severe risk group at time of transplantation may better direct care because they require more frequent clinical evaluation, given their increased risk of graft loss. Outside of the operating room, this risk index may better inform patients and families of expected outcomes and guide the surgeon's discussion for such expectations. Last, organizations such as the Centers for Medicare and Medicaid Services (CMS), the United Network for Organ Sharing (UNOS), and The Joint Commission use patient and graft survival as key metrics for programmatic review. These data are also used by insurance companies to identify centers of excellence and determine which programs are deemed qualified to provide transplantation services for patients. The LTSI-35 provides a tool that uses defined and weighted deceased donor and recipient attributes to accurately and quantitatively adjust outcomes against expectations. Although the LTSI-35 was developed as an adjunct for better clinical decision making, integration of the LTSI-35 into the reporting of center-specific outcomes may decrease the disincentives associated with placing transplants in high-MELD recipients.

Our study is not without its limitations. First, this is a retrospective review of nationally collected data. These large databases are subject to input error, missing data, and a large portion of the population being lost to follow-up without exact dates of death or graft loss. Right-censored data is a significant limitation to predicting outcomes in medical studies and biostatistics, leading to difficulties in modeling. Similarly, patient death or graft loss is not a common occurrence, even in this high-MELD population. It has been shown that when populations do not reach 50% failure or death, modeling is similarly difficult. We have attempted to overcome

these limitations by identifying risk groups and associating groups with rates of graft loss, rather than predicting graft survival on an individual, patient-specific level.

CONCLUSIONS

Transplantation in high-MELD recipients carries significant inherent risk. Here we have identified specific donor, procurement, and recipient characteristics that are associated with increased risk of graft loss in this severely ill population. Showing higher AUROC for 1-year and 3-year graft survival than SOFT and BAR scores, the LTSI-35 represents an advancement in models for predicting graft loss in a high-MELD population. The LTSI-35 may be used to inform risks of graft loss for both short- and long-term outcomes and identify patients with multiple risk factors, where use of specific donor organs or limiting cold-ischemic time, may alleviate some of the risk for transplantation, leading to improved outcomes in this MELD $\geq$ 35 population. Finally, the LTSI-35 represents a model to risk adjust expectations against outcomes for transplant center metrics, ultimately promoting transplantation in sicker individuals and/or the use of marginal organs to increase the number of transplantations and patients served.

Author Contributions

Study conception and design: Steggerda, Kim, Bloom
Acquisition of data: Steggerda, Kim, Bloom
Analysis and interpretation of data: Steggerda, Kim, Bloom
Drafting of manuscript: Steggerda, Kim, Todo, Klein, Bloom
Critical revision: Steggerda, Kim, Todo, Malinoski, Klein, Bloom

Acknowledgment: The authors would like to thank Catherine Bresee, MS, a biostatistician in the Biostatistics Core at Cedars-Sinai Medical Center (Los Angeles, CA), for her advisory role in the performance of data analysis and manuscript preparation.

REFERENCES

1. Sharma P, Schaubel DE, Gong Q, et al. End-stage liver disease candidates at the highest model for end-stage liver disease scores have higher wait-list mortality than status-1A candidates. Hepatology 2012;55:192–198.
2. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567–580.
3. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
4. Chapman WC. The new lottery ticket: Share 35. Liver Transpl 2016;22:393–395.
5. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant 2006;6:783–790.
6. Kwong AJ, Goel A, Mannalithara A, Kim WR. Improved post-transplant mortality after Share 35 for liver transplantation. Hepatology 2018;67:273–281.
7. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. PLoS One 2013;8:e80661.
8. Rana A, Hardy MA, Halazun KJ, et al. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. Am J Transplant 2008;8:2537–2546.
9. Ikegami T, Imai D, Wang H, et al. D-MELD as a predictor of early graft mortality in adult-to-adult living-donor liver transplantation. Transplantation 2014;97:457–462.
10. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. Ann Surg 2011;254:745–753; discussion 753.
11. Schlegel A, Linecker M, Kron P, et al. Risk assessment in high- and low-MELD liver transplantation. Am J Transplant 2017; 17:1050–1063.
12. Harrell F. Regression coefficients and scoring rules. J Clin Epidemiol 1996;49:819.
13. Collett D. In: Modelling Survival Data in Medical Research. Third edition. Boca Raton: CRC Press, Taylor & Francis Group; 2015.
14. Massie AB, Chow EK, Wickliffe CE, et al. Early changes in liver distribution following implementation of Share 35. Am J Transplant 2015;15:659–667.
15. Mataya L, Aronsohn A, Thistlethwaite JR Jr, Friedman Ross L. Decision making in liver transplantation–limited application of the liver donor risk index. Liver Transpl 2014;20:831–837.
16. Flores A, Asrani SK. The donor risk index: a decade of experience. Liver Transpl 2017;23:1216–1225.
17. Sibulesky L, Li M, Hansen RN, et al. Impact of cold ischemia time on outcomes of liver transplantation: a single center experience. Ann Transplant 2016;21:145–151.
18. Stahl JE, Kreke JE, Malek FA, et al. Consequences of cold-ischemia time on primary nonfunction and patient and graft survival in liver transplantation: a meta-analysis. PLoS One 2008;3:e2468.
19. Yuan H, Tuttle-Newhall JE, Chawa V, et al. Prognostic impact of mechanical ventilation after liver transplantation: a national database study. Am J Surg 2014;208:582–590.
20. John BV, Konjeti R, Aggarwal A, et al. Impact of untreated portal vein thrombosis on pre and post liver transplant outcomes in cirrhosis. Ann Hepatol 2013;12:952–958.
21. Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. J Hepatol 2012;57: 203–212.
22. McCormack L, Petrowsky H, Jochum W, et al. Use of severely steatotic grafts in liver transplantation: a matched case-control study. Ann Surg 2007;246:940–946; discussion 946–948.
23. Baccarani U, Adani GL, Isola M, et al. Steatosis of the graft is a risk factor for posttransplantation biliary complications. Transplant Proc 2009;41:1313–1315.

24. Seifalian AM, Chidambaram V, Rolles K, Davidson BR. In vivo demonstration of impaired microcirculation in steatotic human liver grafts. Liver Transpl Surg 1998;4:71–77.
25. Gao F, Xu X, Ling Q, et al. Efficacy and safety of moderately steatotic donor liver in transplantation. Hepatobiliary Pancreat Dis Int 2009;8:29–33.
26. Li J, Liu B, Yan LN, et al. Reversal of graft steatosis after liver transplantation: prospective study. Transplant Proc 2009;41:3560–3563.
27. Petrowsky H, Rana A, Kaldas FM, et al. Liver transplantation in highest acuity recipients: identifying factors to avoid futility. Ann Surg 2014;259:1186–1194.

Discussion

DR WILLIAM C CHAPMAN (St Louis, MO): In this report, the liver transplant group from Cedars-Sinai Medical Center in Los Angeles used the United Network for Organ Sharing (UNOS) STAR database to evaluate results for liver transplantation in patients with very high illness acuity score, namely Model for End-Stage Liver Disease (MELD) score ≥ 35, receiving transplants between 2006 and 2016. The authors conducted an analysis with the test group and subsequent validation cohort, and demonstrated that 5 risk groups could be identified with stratification of 1-year graft survival rates ranging from 90% in the very lowest risk to only 70% in those with the high-risk outcomes for graft loss. In addition, they identified factors associated with graft loss, including donors that arose from donation after cardiac death (DCD) recipients who were on mechanical ventilation before transplantation, and recipients with portal vein thrombosis. In addition, they identified graft macrosteatosis $> 30\%$ as a significant risk factor for graft loss at 90 days.

While the results of this large data set do appear to nicely separate outcomes in this cohort, please detail how this information can be used on an individual case basis. For example, many would argue that DCD donors should never be used in a MELD > 35 recipient. What is your practice at Cedars-Sinai Medical Center in this regard? In many respects, the same argument could be made for increased macrosteatosis. In other words, this type of donor should probably not be used in that very sickest cohort of patients. Do these variables play a role in your current individual patient selection for transplantation? Please detail which patients should perhaps not be considered for transplantation in the MELD $>$ 35 cohort. Are there such patients for whom transplantation may be futile, and in such measures, should this not be undertaken, and should this be decided on a policy level? In other words, a national level. On the other hand, for those patients who might have a 50% survival prediction, those patients have a 0% survival prediction without transplantation. How should we approach this group?

Is there a formula for clinicians to use the liver transplant survival index (LTSI) on a day-to-day basis for an individual case calculation, or does this modeling only appear in the large cohort of data? The formula provided in this manuscript is logarithmic and appears to be very complex. Perhaps you can comment on whether this plays a role in such cases at your institution.

DR ANDREW CAMERON (Baltimore, MD): Share 35, as described, was really a policy tweak enacted by UNOS in 2013 to effectuate more efficient sharing of organs across state lines for the sickest patients, those with a MELD score > 35. High-quality organs have therefore been going more and more to those patients over the last 5 years, and thus the reanalysis of this subgroup presented today. To do so, the authors used data from the last 10 years, most of which preceded the Share 35 era, but nonetheless identified DCD donors, intubated recipients, portal vein thrombus, and maybe fatty grafts as risk factors for poor outcomes in these high MELD patients.

Is this new info? Did anything change with Share 35, or did we already know pre-Share 35 that these factors—DCDs and intubated recipients—did worse? Likewise, do these same predictors not bode worse outcomes in patients with a MELD < 35? Is there anything specific about them as there are to patients with high MELD, or are they simply poor prognostic indicators for any patient about to have a liver transplant?

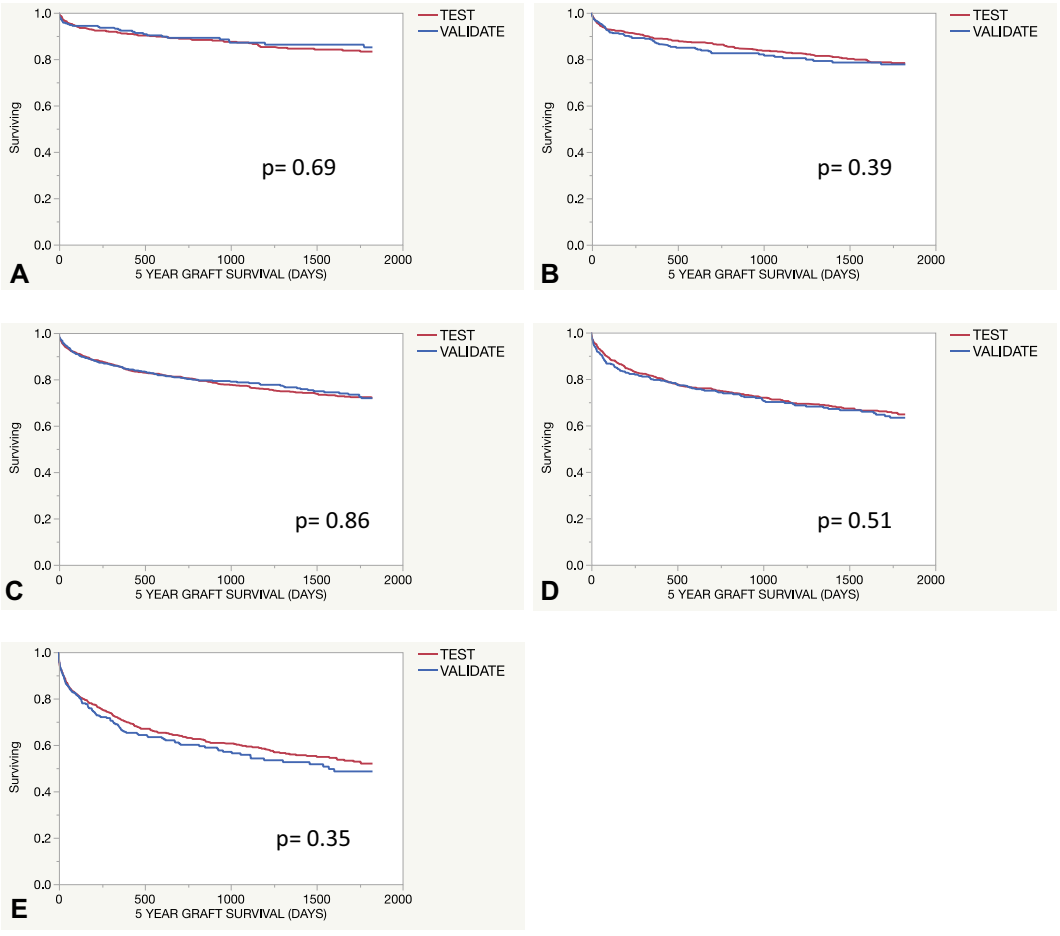
Are these predictors identified just because they are what we have captured in the UNOS database? Can the authors think of any other factors that would have been important to look at to predict survival that are not in the UNOS database? For example, liver biopsy was available in only a subset of patients, but was found to be an important predictor in this cohort, as one might have guessed.

The most important question this work raises is brought forward by the authors in their manuscript and by Dr Chapman. There is a patient in the ICU at Cedars who is high MELD, has been allocated an organ by Share 35, and is also high risk by their new metric. This patient has 0% chance of survival without a liver transplant and 70% chance of survival with a liver transplant. The family thinks that is a miracle, and that is why they came to Cedars. Will you tell them, "No, the liver is better used elsewhere"? I would like them to take a stand on their findings right now as to what they will do at Cedars and how to make policy now that we are better understanding futility. This is interesting, important work, and their discussion is very thoughtful, but until we decide to do something differently, it is just math.

DR RONALD W BUSUTTIL (Los Angeles, CA): In the study presented here, Dr Klein and his colleagues investigated both donor and recipient factors as possible predictors of graft loss in the highest acuity patients, with MELD > 35. They are using retrospective data from the UNOS STAR registry, which has been accumulated over a 10-year period.

While many of the variables studied were significant only at certain time points or were not impactful in the validation group, factors identified with the highest risk of graft loss in the final modeling were DCD donors, donation after cardiac death, pre-transplant, mechanical ventilation, and, surprisingly, recipient portal vein thrombosis.

Now, some of these factors that have been found significant, such as portal vein thrombosis, are difficult to mitigate in high-



eFigure 1. Validation of Liver Transplant Survival Index-Model for End-Stage Liver Disease (MELD) 35 (LTSI-35) in risk groups. Kaplan-Meier survival curves were compared between test and validate populations (70/30 derivation of all MELD $\geq$ 35 recipients) for 5-year graft survival using LTSI-35 risk groups. No differences between test and validate populations were identified in any group. (A) Very low-risk group; (B) low-risk groups; (C) moderate-risk group; (D) high-risk group; (E) severe-risk group.

eTable 1. All Donor and Recipient Characteristics

Characteristic	All MELD ≥ 35 (n = 6,804)	Test (n = 4,779)	Validate (n = 2,205)	p Value
Donor characteristic				
Age, y, mean ± SD, median (IQR)	39.4 ± 15.2, 39 (26–52)	39.3 ± 15.2, 39 (25–51)	39.6 ± 15.3, 39 (26–52)	0.42
Sex, female, n (%)	2,666 (39.2)	1,879 (39.3)	787 (38.9)	0.74
Ethnicity, n (%)				0.54
White	4,310 (63.4)	3,044 (63.7)	1,266 (62.5)	
Black	1,028 (15.1)	730 (15.3)	298 (14.7)	
Hispanic	1,193 (17.5)	814 (17.0)	379 (18.7)	
Asian	165 (2.4)	117 (2.5)	48 (2.4)	
Other	108 (1.6)	74 (1.6)	34 (1.7)	
Blood type, n (%)				0.49
O	3,723 (54.7)	2,617 (54.8)	1,106 (54.6)	
A	2,684 (39.5)	1,888 (39.5)	796 (39.3)	
B	338 (5.0)	238 (5.0)	100 (5.0)	
AB	59 (0.9)	36 (0.8)	23 (1.1)	
Height, cm, mean ± SD	171.6 ± 10.3	171.5 ± 10.3	171.8 ± 10.2	0.31
Weight, kg, mean ± SD	79.9 ± 18.6	80.1 ± 18.8	79.5 ± 18.0	0.25
BMI, kg/m^2, mean ± SD	27.1 ± 5.8	27.2 ± 5.9	26.9 ± 5.5	0.06
≥30, n (%)	1,726 (25.4)	1,237 (25.9)	489 (24.2)	0.13
Liver biopsy done, n (%)	2,027 (29.8)	1,400 (29.3)	627 (30.9)	0.17
≥30% MaS, % of biopsied donors	128 (6.9)	91 (7.1)	37 (6.4)	0.69
Cause of death, DRI, n (%)				0.06
Trauma/anoxia, median (IQR)	4,180 (61.4)	2,935 (61.4)	1,245 (61.5)	
CVA, median (IQR)	2,454 (36.1)	1,711 (35.8)	743 (36.7)	
Other, median (IQR)	170 (2.5)	133 (2.8)	37 (1.8)	
Donor medical/social history, n (%)				
Diabetes	669 (9.8)	454 (9.5)	215 (9.8)	0.17
Hypertension	2,054 (30.2)	1,447 (30.3)	607 (30.0)	0.82
Previous malignancy	175 (2.6)	122 (2.6)	53 (2.6)	0.87
Previous myocardial infarction	196 (2.9)	131 (2.7)	65 (3.2)	0.3
Pre-donation cardiac arrest	434 (6.4)	319 (6.7)	115 (5.7)	0.13
CDC high risk	1,046 (15.4)	753 (15.8)	293 (14.5)	0.19
HCV-positive	101 (1.5)	71 (1.5)	30 (1.5)	0.99
HBV-positive	259 (3.8)	168 (3.5)	91 (4.5)	0.06
EBV-positive	5,981 (87.9)	4,201 (87.9)	1,780 (87.9)	0.99
CMV-positive	4,341 (63.8)	3,028 (63.4)	1,313 (64.8)	0.25
Cigarette smoker	1,445 (21.2)	1,009 (21.1)	436 (21.5)	0.7
Drug use	2,909 (42.8)	2,048 (42.9)	861 (42.5)	0.81
Donor management				
Serum BUN, median (IQR)	16 (11–25)	16 (11–25)	16 (11–25)	0.55
Serum Cr, median (IQR)	1.0 (0.8–1.5)	1.0 (0.8–1.5)	1.0 (0.8–1.6)	0.96
Serum AST, median (IQR)	42 (25–78)	42 (25–76)	43 (25–82.5)	0.68
Serum ALT, median (IQR)	34 (21–66)	34 (21–66)	34 (21–65)	0.14
Serum bilirubin, median (IQR)	0.7 (0.4–1.1)	0.7 (0.4–1.1)	0.7 (0.4–1.0)	0.81
Blood pH, median (IQR)	7.41 (7.36–7.45)	7.41 (7.36–7.45)	7.41 (7.36–7.45)	0.8
Transfusions, n (%)				0.47
None	4,029 (54.5)	2,794 (54.5)	1,235 (54.3)	
1 to 5 U	2,293 (31.0)	1,584 (30.9)	709 (31.2)	

(Continued)

eTable 1. Continued

Characteristic	All MELD ≥ 35 (n = 6,804)	Test (n = 4,779)	Validate (n = 2,205)	p Value
6 to 10 U	618 (8.4)	415 (8.1)	203 (8.9)	
>10 U	454 (6.1)	329 (6.4)	125 (5.5)	
Unknown	3 (0.04)	2 (0.04)	1 (0.04)	
DDAVP, n (%)	1,199 (16.2)	834 (16.3)	365 (16.1)	0.84
Anti-hypertensives, n (%)	1,962 (26.5)	1,387 (27.1)	575 (25.3)	0.12
Diuretics, n (%)	4,762 (64.4)	3,332 (65.0)	1,430 (62.9)	0.08
Steroids, n (%)	5,456 (73.8)	37,87 (73.9)	1,669 (73.4)	0.67
T3, n (%)	50 (0.7)	33 (0.7)	17 (0.8)	0.54
T4, n (%)	4,431 (65.1)	3,078 (64.4)	1,353 (66.9)	0.06
Vasodilators, n (%)	996 (14.6)	703 (14.7)	293 (14.5)	0.82
Heparin, n (%)	6,537 (96.1)	4,592 (96.1)	1,945 (96.1)	0.95
Vasopressin, n (%)	4,169 (61.3)	2,912 (60.9)	1,257 (62.1)	0.37
Insulin, n (%)	4,520 (66.4)	3,159 (66.1)	1,361 (67.2)	0.38
Inotropes, n (%)	3,468 (51.0)	2,431 (50.9)	1,037 (51.2)	0.81
Procurement variables				
DCD Donor, n (%)	206 (2.8)	130 (2.5)	76 (3.3)	0.06
Split liver, n (%)	37 (0.5)	24 (0.5)	13 (0.6)	0.59
Cold ischemic time, h, mean ± SD, median (IQR)	6.7 ± 2.7, 6.3 (5−8)	6.7 ± 2.7, 6.4 (5−8)	6.8 ± 2.9, 6.3 (5−8)	0.88
CIT group, n (%)				0.78
<8 h	5,299 (72.7)	3,676 (72.8)	1,623 (72.5)	
8 to <12 h	1,778 (24.4)	1,224 (24.2)	554 (24.8)	
>12 h	211 (2.9)	150 (3.0)	61 (2.7)	
Recipient characteristic				
Age, y, mean ± SD, median (IQR)	53.2 ± 10.0, 55 (48−60)	52.7 ± 10.3, 55 (47−60)	52.7 ± 10.4, 54 (47−60)	0.94
Sex, female, n (%)	2,647 (35.8)	1,855 (36.2)	792 (34.8)	0.27
Ethnicity, n (%)				0.34
White	4,813 (65.1)	3,335 (65.1)	1,478 (65.0)	
Black	750 (10.1)	505 (9.9)	245 (10.8)	
Asian	293 (4.0)	217 (4.2)	76 (3.3)	
Hispanic	1,429 (19.3)	989 (19.3)	440 (19.4)	
Other	112 (1.5)	78 (1.5)	34 (1.5)	
Blood type, n (%)				0.88
O	3,600 (48.7)	2,501 (48.8)	1,099 (48.4)	
A	2,706 (36.6)	1,875 (36.6)	831 (36.6)	
B	873 (11.8)	595 (11.6)	278 (12.2)	
AB	218 (3.0)	153 (3.0)	65 (2.9)	
Height, cm, mean ± SD	171.4 ± 10.3	171.4 ± 10.3	171.6 ± 10.2	0.57
Weight, kg, mean ± SD	86.1 ± 21.0	85.5 ± 20.9	85.6 ± 20.8	0.83
BMI, kg/m^2, mean ± SD	29.2 ± 6.4	29.0 ± 6.3	29.0 ± 6.4	0.99
≥30 kg/m^2, n (%)	2,956 (39.5)	2,059 (40.2)	897 (39.5)	0.57
Location at transplantation, (n %)				0.67
Not hospitalized	4,883 (66.0)	3,394 (66.2)	1,489 (65.5)	
Hospitalized	1,420 (19.2)	965 (18.8)	455 (20.0)	
ICU	1,079 (14.6)	755 (14.7)	324 (14.3)	
Waitlist time, d, median (IQR)	15 (5−114)	15 (5−117)	17 (5−106)	0.98

(Continued)

eTable 1. Continued

Characteristic	All MELD ≥ 35 (n = 6,804)	Test (n = 4,779)	Validate (n = 2,205)	p Value
Recipient diagnosis, n (%)				0.5
Acute liver failure	218 (3.2)	150 (3.1)	68 (3.4)	
CC/NASH	983 (14.5)	704 (14.7)	279 (13.8)	
Cholestatic	629 (9.3)	293 (6.1)	127 (6.3)	
Cirrhosis, not specified	420 (6.2)	293 (6.1)	127 (6.3)	
Congenital/metabolic	239 (3.5)	170 (3.6)	69 (3.4)	
Alcohol	1,393 (20.5)	955 (20.0)	438 (21.6)	
Hepatitis B	190 (2.8)	142 (3.0)	48 (2.4)	
Hepatitis C	2,060 (30.3)	1,457 (30.5)	603 (29.8)	
HCC	615 (9.0)	443 (9.3)	172 (8.5)	
Other	56 (0.8)	36 (0.8)	20 (1.0)	
Recipient medical/social history				
Previous malignancy, n (%)	624 (9.2)	453 (9.5)	171 (8.4)	0.18
Diabetes, n (%)	1,479 (21.7)	1,056 (22.1)	423 (20.9)	0.29
HBV-positive, n (%)	1,376 (20.2)	981 (20.5)	395 (19.5)	0.36
HCV-positive, n (%)	2,420 (35.6)	1,734 (36.3)	686 (33.9)	0.06
EBV-positive, n (%)	4,163 (61.2)	2,934 (61.4)	1,229 (60.7)	0.59
CMV-positive, n (%)	4,560 (67.0)	3,219 (67.4)	1,341 (66.2)	0.37
Prior abdominal surgery, n (%)	2,624 (38.6)	1,824 (38.2)	800 (39.6)	0.3
Previous TIPS, n (%)	695 (10.2)	501 (10.5)	194 (9.6)	0.27
PV thrombosis, n (%)	716 (10.5)	510 (10.7)	206 (10.2)	0.57
Encephalopathy, n (%)	5,649 (83.0)	3,971 (83.1)	1,678 (82.9)	0.83
Ascites, n (%)	6,270 (92.2)	4,403 (92.1)	1,867 (92.2)	0.96
Mechanical ventilation, n (%)	1,065 (15.7)	750 (15.7)	315 (15.6)	0.91
Dialysis prior to transplantation, n (%)	3,162 (46.5)	2,248 (47.0)	914 (45.1)	0.15
Serum albumin, mg/dL, median (IQR)	3.2 (2.7−3.8)	3.2 (2.7−3.8)	3.2 (2.7−3.8)	0.52

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CC/NASH, cryptogenic cirrhosis/nonalcoholic steatohepatitis; CDC, Centers for Disease Control; CIT, cold ischemic time; CMV, cytomegalovirus; CR, creatinine; CVA, cerebrovascular accident; DCD, donation after circulatory death; DDAVP, desmopressin; DRI, Donor Risk Index; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MaS, macrosteatosis; MELD, Model for End-Stage Liver Disease; PV, portal vein; TIPS, transjugular intrahepatic portovenous shunt.

eTable 2. Cox Proportional Hazards Models for Graft Survival at Four Follow-Up Time Points

	Unadjusted			Adjusted		
Graft survival	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
90 d						
Donor characteristic						
BMI, per kg/m^2	1.01	1.00−1.02	0.04	1.03	1.01−1.06	0.01
Procurement characteristic						
DCD Status	1.56	1.19−2.01	0.002	1.65	1.24−2.20	0.002
Cold ischemic time*			0.003			0.04
8 to <12 h	1.20	1.06−1.35		1.05	0.79−1.39	
≥12 h	1.34	0.99−1.76		1.28	0.84−1.99	
Recipient characteristic						
Age	1.02	1.02−1.03	<0.001	1.03	1.01−1.04	<0.001
Etiology of ESLD†			<0.001			0.05
Acute	1.01	0.70−1.47		0.37	0.10−1.30	
CC/NASH	0.85	0.69−1.05		0.91	0.60−1.38	
Cholestatic	0.79	0.61−1.02		0.58	0.33−1.01	
Cirrhosis, not specified	1.08	0.83−1.42		1.33	0.77−2.29	
Congenital/metabolic	1.03	0.72−1.47		0.74	0.30−1.84	
Alcohol	0.77	0.63−0.93		1.08	0.75−1.55	
Hepatitis C	0.80	0.68−0.94		1.16	0.85−1.60	
Hepatitis B	0.96	0.64−1.44		1.17	0.51−2.65	
Hepatocellular carcinoma	0.93	0.73−1.19		1.03	0.64−1.65	
Previous abdominal surgery	1.33	1.20−1.49	<0.001	1.28	1.11−1.47	<0.001
Portal vein thrombosis	1.33	1.13−1.55	0.001	1.30	1.07−1.57	0.01
Ventilator support at transplantation	1.85	1.63−2.09	<0.001	1.27	1.07−1.50	0.007
1 y						
Donor characteristic						
Age, per y	1.01	1.01−1.02	<0.001	1.01	1.01−1.02	<0.001
Procurement characteristic						
DCD Status	1.53	1.19−1.95	0.002	1.61	1.26−2.05	0.001
Recipient characteristic						
Age	1.02	1.02−1.03	<0.001	1.02	1.01−1.04	<0.001
Etiology of ESLD†			<0.001			<0.001
Acute	0.90	0.65−1.24		0.52	0.23−1.17	
CC/NASH	0.89	0.75−1.06		0.99	0.72−1.36	
Cholestatic	0.74	0.60−0.92		0.54	0.34−0.84	
Cirrhosis, not specified	0.99	0.79−1.25		1.08	0.68−1.69	
Congenital/metabolic	0.96	0.71−1.29		0.61	0.29−1.29	
Alcohol	0.79	0.67−0.92		0.96	0.72−1.28	
Hepatitis C	1.02	0.89−1.15		1.20	0.95−1.53	
Hepatitis B	1.19	0.60−1.21		0.99	0.50−1.96	
Hepatocellular carcinoma	1.10	0.89−1.15		1.27	0.90−1.79	
Previous abdominal surgery	1.31	1.19−1.45	<0.001	1.19	1.06−1.33	0.003
Portal vein thrombosis	1.29	1.10−1.50	0.002	1.21	1.03−1.42	0.03
Ventilator support at transplantation	1.79	1.59−2.02	<0.001	1.32	1.17−1.51	<0.001
3 y						
Donor characteristic						
Age, per year	1.01	1.01−1.02	<0.001	1.01	1.00−1.02	<0.001
Procurement characteristics						
DCD Status	1.53	1.19−1.95	0.002	1.34	1.05−1.71	0.02

(Continued)

eTable 2. Continued

	Unadjusted			Adjusted		
Graft survival	**HR**	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Recipient characteristic						
Age	1.02	1.02−1.03	<0.001	1.02	1.01−1.03	<0.001
Etiology of ESLD[†]			<0.001			<0.001
Acute	0.85	0.63−1.14		0.52	0.26−1.02	
CC/NASH	0.98	0.84−1.13		1.10	0.83−1.45	
Cholestatic	0.77	0.63−0.93		0.67	0.46−0.97	
Cirrhosis, not specified	0.93	0.75−1.14		0.87	0.56−1.34	
Congenital/metabolic	0.83	0.62−1.10		0.57	0.29−1.12	
Alcohol	0.78	0.68−0.90		0.93	0.72−1.21	
Hepatitis C	1.13	1.01−1.26		1.27	1.03−1.57	
Hepatitis B	0.87	0.64−1.18		0.80	0.41−1.59	
Hepatocellular carcinoma	1.32	1.12−1.54		1.38	1.02−1.87	
Previous abdominal surgery	1.54	1.32−1.80	<0.001	1.17	1.06−1.28	0.002
Ventilator support at transplantation	2.05	1.11−1.51	<0.001	1.30	1.16−1.46	<0.001
5 y						
Donor characteristic						
Age, per year	1.01	1.01−1.02	<0.001	1.01	1.01−1.02	<0.001
Procurement characteristics						
DCD Status	1.97	1.48−2.55	<0.001	1.32	1.05−1.66	0.02
Recipient characteristic						
Age	1.02	1.02−1.03	<0.001	1.02	1.01−1.03	<0.001
Etiology of ESLD[†]			<0.001			<0.001
Acute	0.92	0.71−1.21		0.68	0.38−1.21	
CC/NASH	0.98	0.85−1.13		1.05	0.81−1.37	
Cholestatic	0.78	0.65−0.93		0.73	0.51−1.03	
Cirrhosis, not specified	0.92	0.75−1.12		0.86	0.57−1.31	
Congenital/metabolic	0.80	0.61−1.05		0.49	0.25−0.98	
Alcohol	0.79	0.69−0.90		0.91	0.71−1.16	
Hepatitis C	1.13	1.02−1.26		1.25	1.02−1.53	
Hepatitis B	0.81	0.60−1.10		0.74	0.38−1.48	
Hepatocellular carcinoma	1.35	1.16−1.57		1.44	1.08−1.92	
Previous abdominal surgery	1.36	1.21−1.54	<0.001	1.15	1.05−1.26	0.003
Ventilator support at transplantation	1.98	1.72−2.27	<0.001	1.24	1.11−1.38	<0.001
Dialysis within 1 wk at transplantation	1.42	1.25−1.60	<0.001	1.15	1.05−1.26	0.004

*Reference group is cold ischemic time < 8 h.
[†]Reference groups is "other causes."
CC/NASH, cryptogenic cirrhosis/nonalcoholic steatohepatitis; DCD, donation after circulatory death; ESLD, end-stage liver disease; HR, hazard ratio.

eTable 3. Distribution of Liver Transplant Survival Index-Model for End-Stage Liver Disease-35 Scores and Risk Group Stratification

Variable	All MELD ≥ 35	Test	Validate	p Value
LTSI-35, mean ± SD, median (IQR)	16.7 ± 3.8, 16.7 (14.0–19.3)	16.6 ± 3.7, 16.7 (14.0–19.3)	16.6 ± 3.8, 16.6 (14.0–19.3)	0.55
LTSI-35 risk group, score, n (%)				0.89
Very low risk, <12.7	1,012 (15.7)	699 (14.9)	313 (15.7)	
Low risk, 12.8 to <15.1	1,307 (19.5)	924 (19.7)	383 (19.2)	
Moderate risk, 15.1 to <18.2	2,056 (30.7)	1,445 (30.7)	611 (30.6)	
High risk, 18.2 to <20.5	1,341 (20.0)	935 (19.9)	406 (20.3)	
Severe risk, ≥20.5	984 (14.7)	697 (14.8)	287 (14.4)	

IQR, interquartile range; LTSI-35, Liver Transplant Survival Index-Model for End-Stage Liver Disease (MELD) 35.

eTable 4. Graft Survival in Liver Transplant Survival Index Risk Groups

	Very low risk, n (%)		Low risk, n (%)		Moderate risk, n (%)		High risk, n (%)		Severe, n (%)	
Survival	**Test**	**Validate**	**Test**	**Validate**	**Test**	**Validate**	**Test**	**Validate**	**Test**	**Validate**
90 d	611 (94.4)	268 (93.7)	797 (92.9)	325 (93.1)	1,238 (91.7)	531 (90.2)	783 (88.7)	342 (87.9)	563 (83.8)	226 (82.5)
1 y	454 (89.6)	198 (90.4)	632 (88.8)	249 (87.1)	961 (84.6)	420 (83.0)	596 (78.2)	262 (77.1)	407 (69.1)	156 (64.5)
3 y	283 (84.2)	116 (82.9)	365 (79.2)	132 (78.1)	538 (73.8)	235 (72.1)	330 (65.5)	153 (64.6)	209 (53.1)	83 (52.2)
5 y	137 (77.4)	55 (79.7)	184 (72.4)	63 (75.9)	264 (67.0)	112 (62.9)	156 (55.9)	80 (62.9)	92 (47.7)	32 (39.0)