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A Clinical Tool to Guide Selection and Utilization of Marginal Donor Livers With Graft Steatosis in Liver Transplantation

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Background. Donor liver biopsy (DLBx) in liver transplantation provides information on allograft quality; however, predicting outcomes from these allografts remains difficult. **Methods.** Between 2006 and 2015, 16691 transplants with DLBx were identified from the Standard Transplant Analysis and Research database. Cox proportional hazard regression analyses identified donor and recipient characteristics associated with 30-d, 90-d, 1-y, and 3-y graft survival. A composite model, the Liver Transplant After Biopsy (LTAB) score, was created. The Mini-LTAB was then derived consisting of only donor age, macrosteatosis on DLBx, recipient model for end-stage liver disease score, and cold ischemic time. Risk groups were identified for each score and graft survival was evaluated. *P* values <0.05 were considered significant. **Results.** The LTAB model used 14 variables and 5 risk groups and identified low-, mild-, moderate-, high-, and severe-risk groups. Compared with moderate-risk recipients, severe-risk recipients had increased risk of graft loss at 30 d (hazard ratio, 3.270; 95% confidence interval, 2.568-4.120) and at 1 y (2.258; 1.928-2.544). The Mini-LTAB model identified low-, moderate-, and high-risk groups. Graft survival in Mini-LTAB high-risk transplants was significantly lower than moderate- or low-risk transplants at all time points. **Conclusions.** The LTAB and Mini-LTAB scores represent guiding principles and provide clinically useful tools for the successful selection and utilization of marginal allografts in liver transplantation.

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Liver transplantation (LT) represents the sole curative option for patients with end-stage liver disease (ESLD); however, there remains a persistent unmet need for donor

organs. To overcome the deficit in available allografts, the utilization of marginal organs has been widely promoted. However, this movement is balanced by the need to maintain excellent recipient outcomes.

Donor liver biopsy (DLBx) is used to evaluate questionable or marginal donors and provides information on fibrosis, necrosis, and levels of macrosteatosis (MaS). Historically, allografts with high levels of MaS, typically defined as >30%, have been associated with early allograft dysfunction (EAD), primary nonfunction (PNF), and worse outcomes overall.¹⁻³ Despite this, multiple single-center studies have shown successful allograft and patient survival with the use of highly steatotic allografts, even up to 90% MaS.⁴⁻⁷ This has been further supported by a recent study showing that allografts with MaS >30% have better survival in the current transplant era compared with those used 10 y ago.⁸ Separately, our group showed equivalent 1-y graft survival for liver allografts with up to 50% MaS when used in recipients with model for end-stage liver disease (MELD) scores <33 and up to 40% MaS in higher MELD recipients.⁹ Together, these findings support the use of increasingly steatotic allografts with attention to recipient selection.

The influence of donor characteristics on transplant outcomes was first described by the Donor Risk Index (DRI).¹⁰ While difficult to calculate, this score has been additionally critiqued for its overall poor predictive ability.¹¹ In 2011, de Graaf et al¹² showed that severe allograft MaS >30% carried a

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greater impact on graft survival than the DRI alone. Attempts to include graft MaS into scoring systems predicting graft survival have been undertaken; however, these are limited by the incorporation of organs with MaS >30% into a single risk group.^{3,13} This unfortunately limits the ability to apply these scoring systems, in light of new findings supporting the use of higher MaS organs.

The aim of the present study is to develop a simple, clinically useful, scoring system to risk stratify LT for marginal donors undergoing DLBx. By identifying donor and recipient characteristics significantly associated with increased risk of graft loss, we created the Liver Transplant After Biopsy (LTAB) score, as well as a more clinically useful Mini-LTAB, to risk stratify donor–recipient pairs in LT after DLBx.

MATERIALS AND METHODS

Study Population

The Organ Procurement and Transplant Network Standard Transplant Analysis and Research database was evaluated to identify all LTs where DLBx was performed between January 2006 and June 2015. Exclusion criteria included pediatric recipients (<18 y old), donation after circulatory death (DCD) donors, multivisceral and split-LTs, and those with missing data. During the study period, 60 200 LTs were performed in the United States. After applying exclusion criteria, a study population of 16 691 transplants (27.7%) with biopsy results was identified for analysis. Using computerized random number generation, transplants were randomly divided into test and validate cohorts representing 70% and 30% of the study population, respectively. Donor and recipient characteristics were collected and analyzed, including age, gender, ethnicity, blood type, body mass index (BMI), viral status for Epstein-Barr virus, cytomegalovirus, hepatitis B virus, and hepatitis C virus (HCV). Cold ischemic time (CIT) for each transplant was collected. Donor-specific variables include biopsy results with percent MaS, history of hypertension, diabetes, prior myocardial infarction, history of cigarette or drug use, and Center for Disease Control classification as a high-risk donor. Recipient-specific variables include laboratory-based MELD-sodium (MELD-Na) score, cause of liver disease, history of diabetes, prior abdominal surgery, portal vein thrombosis (PVT), prior transjugular intrahepatic portosystemic shunt placement, and need for dialysis or mechanical ventilation at time of transplant.

LTAB Model Creation and Validation

Cox proportional hazards models were developed within the test cohort to evaluate graft survival at 4 time points: 30 d, 90 d, 1 y, and 3 y posttransplant. Graft survival was defined, using the determination set forth by Feng et al¹⁰ during derivation of the DRI, as graft loss requiring retransplantation or patient death, whichever came first.

A composite model was then created using variables that were significantly associated with graft survival at 2 or more time points. The composite model was then again evaluated within the test cohort to assess hazard ratios (HRs) for each variable at 30 d, 90 d, 1 y, and 3 y after transplant. HRs were collected from each model and a weighted average was calculated—30% for 30-d graft survival, 30% for 90-d graft survival, 25% for 1-y graft survival, and 15% for 3-y graft survival.

The LTAB score was then created by allocating points based on weighted HRs. The LTAB score represented the sum of all points with a natural log transformation to normalize the distribution of scores across transplants. Risk groups were then calculated by proportion of transplants, such that the lowest 10% of scores were deemed very low risk, 10% to 35% as low risk, 35% to 65% as moderate risk, 65% to 90% as high risk, and >90% as severe risk.

Test and validate cohorts were evaluated for risk of graft loss across risk groups using Cox proportional hazards models and Kaplan-Meier (KM) survival analysis. Area under receiver operator curve (AUROC) was used to evaluate predictive abilities of scoring system at each time point after transplantation.

Mini-LTAB Model Derivation

To create a clinically useful tool, the Mini-LTAB was derived from the LTAB score to include only 4 clinically relevant variables. The score was calculated using the formula:

Mini-LTAB = Donor age (1 point/y) + Graft MaS (1 point/% MaS) + MELD-Na Score (1 point/point) + CIT (10 points for every hour after 4 h)

Scores were used to create 3 clinically useful risk groups: low risk, moderate risk, and high risk based on score distribution and interquartile range. Graft survival was again assessed in test and validate cohorts by risk group using proportional hazard regression analysis and KM survival analysis, and AUROC was calculated at 30 d, 90 d, 1 y, and 3 y after transplant.

Statistical Analyses

Single-variable analyses were performed using the Student *t* test or analysis of variance, as appropriate. Pearson's chi-square analyses were used with multiple categorical variables. Graft survival was assessed using KM survival analyses with log-rank evaluation to determine statistical differences between multiple groups. Logistic regression models were used to evaluate risk of early and late graft loss. Odds ratios with 95% confidence intervals (CIs) for likelihood of graft loss at each time point are reported. United Network for Organ Sharing region of transplant and year of transplant were included in all regression modeling, both of which have previously been shown to influence organ utilization and outcomes among highly steatotic organs.^{9,14} All statistical analyses were performed using JMP Pro 14.1 software (SAS Institute Inc., Cary, NC). *P* values <0.05 were considered significant. Bonferroni corrections were applied for multiple comparisons, with minimum *P* values <0.0001.

RESULTS

Population Characteristics

During the study period, 16 691 adult LTs were identified with DLBx. After randomization, a test cohort of 11 600 transplants and a validate cohort of 5091 transplants were created. Table 1 presents selected characteristics from the study population (complete characteristics are presented in Table S1, SDC, <http://links.lww.com/TXD/A400>). Notably, there were no statistical differences between the test and validate cohorts.

Donor median age was 51 y (interquartile range [IQR], 40–61 y), whereas recipient median age was slightly older

TABLE 1.
Selected characteristics of transplants with donor liver biopsy

Characteristics	All transplants (n = 16 691)	Test cohort (n = 11 600)	Validate cohort (n = 5091)	P
Donor characteristics				
Age, median (IQR), y	51 (40–61)	51 (40–61)	51 (40–60)	0.28
Gender, female, n (%)	7745 (46.4%)	5406 (46.6%)	2339 (45.9%)	0.43
Ethnicity				0.23
White	11 343 (68.0%)	7923 (68.3%)	3420 (67.2%)	
Black	3086 (18.5%)	2109 (18.2%)	977 (19.2%)	
Hispanic	1632 (9.8%)	1147 (9.9%)	485 (9.5%)	
Asian	408 (2.4%)	269 (2.3%)	139 (2.7%)	
Other	222 (1.3%)	152 (1.3%)	70 (1.4%)	
Body mass index, kg/m ²	28.2 (24.3–33.4)	28.2 (24.3–33.3)	28.3 (24.3–33.6)	0.37
MaS on biopsy (%)	5 (0–10)	5 (0–10)	5 (0–10)	0.41
Cause of death				0.93
Anoxia	4306 (25.8%)	3002 (25.9%)	1304 (25.6%)	
Trauma	3623 (21.7%)	2524 (21.8%)	1099 (21.6%)	
CVA/stroke	8377 (50.2%)	5811 (50.1%)	2566 (50.4%)	
Other	385 (2.3%)	263 (2.3%)	122 (2.4%)	
Diabetes	3221 (19.4%)	2219 (19.3%)	1002 (19.8%)	0.39
HCV positive	1367 (8.2%)	922 (8.0%)	445 (8.7%)	0.09
HBV positive	1511 (9.1%)	1060 (9.1%)	451 (8.9%)	0.58
EBV positive	14 368 (86.1%)	10 008 (86.3%)	4360 (85.6%)	0.27
CMV positive	11 353 (68.0%)	7932 (68.4%)	3421 (67.2%)	0.13
Transplant characteristics				
CIT groups				0.44
<4 h	1356 (8.3%)	938 (8.2%)	418 (8.4%)	
4–<6 h	4594 (28.0%)	3187 (28.0%)	1407 (28.1%)	
6–<8 h	5164 (31.5%)	3543 (31.1%)	1621 (32.4%)	
8–<10 h	3212 (19.6%)	2262 (19.8%)	950 (19.0%)	
10–<12 h	1357 (8.3%)	962 (8.4%)	395 (7.9%)	
≥12 h	727 (4.4%)	511 (4.5%)	216 (4.3%)	
Recipient characteristics				
Age, y	56 (51–62)	56 (51–61)	57 (51–62)	0.39
Gender, female	4987 (0.74)	3475 (30.0%)	1512 (29.7%)	0.74
Ethnicity				0.68
White	12 324 (73.8%)	8559 (73.8%)	3765 (74.0%)	
Black	1550 (9.3%)	1080 (9.3%)	470 (9.2%)	
Hispanic	1877 (11.3%)	1306 (11.3%)	571 (11.2%)	
Asian	702 (4.2%)	480 (4.1%)	222 (4.4%)	
Other	238 (1.4%)	175 (1.5%)	63 (1.2%)	
Body mass index, kg/m ²	28.1 (24.6–32.3)	28.1 (24.7–32.4)	28.1 (24.6–32.2)	0.61
MELD-Na score	21.6 (15.0–29.2)	21.6 (15.0–29.3)	21.3 (15.0–29.0)	0.16
Exception points				0.66
No exceptions	10 360 (62.1%)	7224 (62.3%)	3136 (61.6%)	
HCC exceptions	4677 (28.0%)	3239 (27.9%)	1438 (28.3%)	
Other exceptions	1654 (9.9%)	1137 (9.8%)	517 (10.2%)	
Prior abdominal surgery	7077 (43.2%)	4939 (43.3%)	2138 (42.8%)	0.58
Prior TIPS	1522 (9.3%)	1051 (9.2%)	471 (9.4%)	0.66
PV thrombosis	1629 (9.9%)	1139 (9.9%)	490 (9.8%)	0.74
Dialysis in week before Txp	1097 (6.4%)	772 (6.7%)	325 (6.4%)	0.54
Mechanical ventilation at Txp	613 (3.7%)	421 (3.6%)	192 (3.8%)	0.65

CIT, cold ischemic time; CMV, cytomegalovirus; CVA, cerebrovascular accident; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; MaS, macrosteatosis; MELD-Na, model for end-stage liver disease–sodium; PV, portal vein; TIPS, transjugular intrahepatic portovenous shunt; Txp, transplant.

at 56 y (IQR, 51–62 y). The distribution of MaS in test and validate cohorts is shown in Figure 1. Approximately 20% of donors had a history of diabetes. Notably, 8.2% of donors were HCV positive, and 9.1% were hepatitis B virus positive. Median terminal aspartate transaminase, alanine transaminase, and bilirubin were all within normal limits at 41, 33,

and 0.7, respectively. Donor and recipient characteristics by MaS on DLBx are reported in Table 2. Interestingly, 75% of transplants performed had MaS 10% or less, whereas only 10% had MaS above 25%.

Among recipients, the median MELD-Na score was 21.6 (IQR, 15–29.2). The most common cause of ESLD was

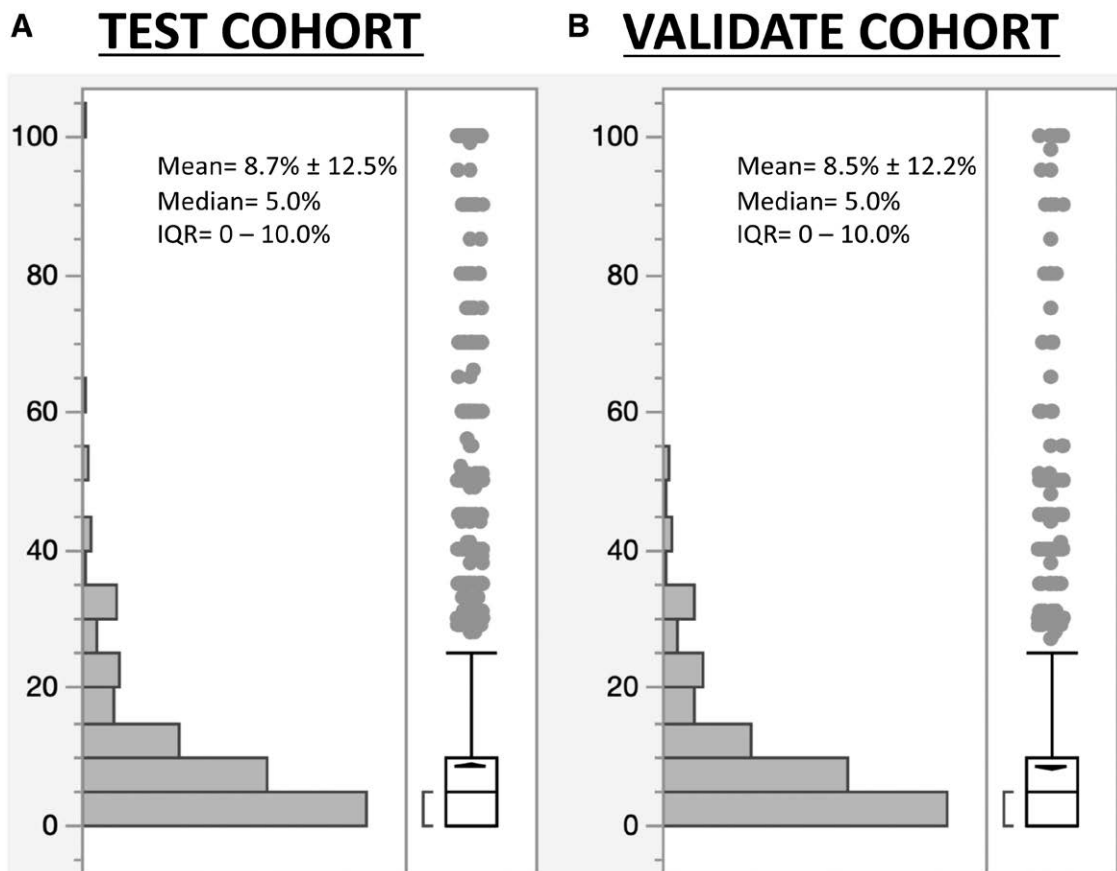


FIGURE 1. Distribution of macrosteatosis in test and validate cohorts. The distribution of macrosteatosis as assessed on donor liver biopsy is shown in test (A) and validate (B) cohorts. Mean with SD, median, and IQRs are reported. IQR, interquartile range.

hepatocellular carcinoma (n=4605 recipients; 27.6%), followed closely by HCV (n=4504; 27.0%), alcoholic liver disease (n=2113; 12.7%), and non-alcoholic steatohepatitis or cryptogenic cirrhosis (n=2039; 12.2%). PVT was present in about 10% of recipients, whereas 6.4% had received dialysis within the week before transplant and only 3.7% required ventilator support at time of transplant. Interestingly, Black people accounted for 18.5% of donors but only 9.3% of recipients.

Development of a Comprehensive Model for Graft Survival

The test cohort was evaluated to identify factors associated with short- and long-term graft survival. Multivariable Cox proportional hazards models were created for 30-d, 90-d, 1-y, and 3-y graft survival. Table 3 shows the characteristics significantly associated with allograft survival at each of the follow-up time points. Final regression models with associated HR and 95% CI are reported in Tables S2A–D (SDC, <http://links.lww.com/TXD/A400>). Notably, graft MaS was the only donor-specific characteristic associated with 30-d graft survival in this population, whereas donor cause of death and age were associated with graft survival from 90 d onward. CIT was associated with graft survival at 1 and 3 y but not early graft survival. Among recipients, MELD-Na score was associated with graft survival at all time points, as was a history of prior abdominal surgery, PVT, and requiring mechanical ventilator support at the time of transplant. Recipient age and ethnicity were associated with 1- and 3-y graft survival, whereas BMI was associated with early graft survival.

A comprehensive model was developed by identifying donor and recipient characteristics that were significantly associated with graft survival at 2 or more time points. The final model consisted of 14 variables: donors' age, cause of death, and history of diabetes; graft MaS; CIT; and recipients' age, ethnicity, BMI, MELD-Na score, exception point status, Epstein-Barr virus status, history of prior abdominal surgery, PVT, and need for ventilator support at time of transplant.

The comprehensive model was then evaluated in both test and validate cohorts for graft survival at 30 d, 90 d, 1 y, and 3 y. Tables S3A–D (SDC, <http://links.lww.com/TXD/A400>) report the results of these regression models with HR and 95% CI for each characteristic. As expected, some variables were not significantly associated with graft survival at each time point, but all variables remained significantly associated with graft survival at 2 or more time points. Interestingly, some variables were significant in the validate cohort but not in the test cohort, that is, donor age at 90 d. Conversely, donor cause of death was not significantly associated with 90-d graft survival.

LTAB Risk Score Creation and Evaluation

HRs for each variable from the test cohort were then combined, and a weighted average was calculated. The weighting placed importance on early graft survival with 30% given to 30-d and 90-d graft survival, 25% given to 1-y survival, and 15% to 3-y survival. A weighted HR was calculated and used to guide point allocation. Table 4 shows the weighted HR and associated points assigned to each variable. A natural log

TABLE 2.**Selected characteristics of transplants by macrosteatosis on allograft biopsy**

Characteristics	% Macrosteatosis on biopsy					P
	<10%	10–19%	20–29%	30–39%	>40%	
Donor characteristics						
Age, median (IQR), y	51 (40–61)	53 (43–61)	51 (43–59)	51 (43–60)	47 (36–55)	<0.001
Gender, female, n (%)	4783 (46.7%)	1299 (47.4%)	500 (43.7%)	343 (44.6%)	233 (45.1%)	0.19
Ethnicity ^a						
White	6921 (67.6%)	1890 (68.9%)	792 (69.2%)	540 (70.2%)	359 (69.4%)	<0.001
Black	2096 (20.5%)	416 (15.2%)	156 (13.6%)	106 (13.8%)	55 (10.6%)	
Hispanic	855 (8.4%)	317 (11.6%)	139 (12.2%)	93 (12.1%)	90 (17.4%)	
Asian	242 (2.4%)	81 (3.0%)	32 (2.8%)	20 (2.6%)	7 (1.4%)	
BMI, kg/m ²	27.3 (23.7–32.4)	29.9 (25.7–35.1)	31.1 (27.2–35.7)	31.0 (26.9–36.3)	30.2 (25.7–35.8)	<0.001
Cause of death						
Anoxia	2687 (26.2%)	689 (25.1%)	300 (26.2%)	180 (23.4%)	137 (26.5%)	0.025
Trauma	2218 (21.7%)	582 (21.2%)	240 (21.0%)	172 (22.4%)	136 (26.3%)	
CVA	5099 (49.8%)	1412 (51.5%)	585 (51.1%)	402 (52.3%)	224 (43.3%)	
Other	240 (2.3%)	59 (2.2%)	19 (1.7%)	15 (2.0%)	20 (2.3%)	
Hx of diabetes	1944 (19.1%)	587 (21.5%)	224 (19.8%)	162 (21.2%)	78 (15.3%)	0.004
Hx of HTN	5233 (51.4%)	1472 (54.0%)	628 (55.6%)	446 (58.5%)	219 (42.9%)	<0.001
CDC high risk	1386 (13.5%)	299 (10.9%)	105 (9.2%)	64 (8.3%)	69 (13.4%)	<0.001
Any drug use	3612 (35.3%)	926 (33.8%)	373 (32.6%)	259 (33.7%)	215 (41.6%)	0.004
HCV positive	960 (9.4%)	172 (6.3%)	66 (5.8%)	24 (3.3%)	23 (4.5%)	<0.001
HBV positive	1007 (9.8%)	226 (8.2%)	88 (7.7%)	49 (6.4%)	34 (6.6%)	<0.001
CIT, h	6.5 (5.0–8.3)	6.5 (5.2–8.4)	6.9 (5.3–8.6)	6.8 (5.3–8.5)	6.9 (5.3–8.7)	0.06
Recipient characteristics						
Age, median (IQR), y	56 (51–62)	56 (51–62)	57 (51–62)	57 (50–62)	56 (51–61)	0.27
Gender, female, n (%)	3181 (31.1%)	756 (27.6%)	314 (27.5%)	188 (24.5%)	140 (27.1%)	<0.001
Ethnicity ^a						
White	7595 (74.1%)	1973 (72.0%)	847 (74.0%)	592 (77.0%)	394 (76.2%)	0.20
Black	948 (9.3%)	273 (10.0%)	100 (8.7%)	53 (6.9%)	45 (8.7%)	
Hispanic	1138 (11.1%)	314 (11.5%)	126 (11.0%)	82 (10.7%)	51 (9.9%)	
Asian	409 (4.0%)	141 (5.1%)	55 (4.8%)	35 (4.6%)	19 (3.7%)	
BMI, kg/m ²	28.1 (24.6–32.3)	28.2 (24.7–32.3)	28.5 (25.0–32.8)	27.8 (24.7–32.6)	27.9 (24.8–32.6)	0.51
MELD-Na score	21.6 (15.0–29.2)	22.0 (15.0–29.8)	21.0 (14.6–29.2)	21.3 (14.7–28.0)	20.6 (15.3–27.6)	0.16
ESLD cause ^b						
NASH/CC	1209 (11.8%)	331 (12.1%)	155 (13.6%)	110 (14.3%)	67 (13.0%)	0.07
Alcohol	1263 (12.3%)	357 (13.0%)	150 (13.1%)	104 (13.5%)	75 (14.5%)	
HCV	2795 (27.3%)	735 (26.8%)	301 (26.3%)	190 (24.7%)	131 (25.3%)	
HCC	2833 (27.7%)	760 (27.7%)	321 (28.1%)	217 (28.2%)	150 (29.0%)	
Exception points						
No points	6342 (61.9%)	1680 (61.3%)	714 (62.4%)	497 (64.6%)	330 (63.8%)	0.65
HCC points	2893 (28.2%)	781 (28.5%)	306 (26.8%)	196 (25.5%)	136 (26.3%)	
Other points	1009 (9.9%)	281 (10.3%)	124 (10.8%)	76 (9.9%)	51 (9.9%)	
EBV positive	6406 (62.5%)	1769 (64.5%)	713 (62.3%)	510 (66.3%)	316 (61.1%)	0.08
Hx abdominal surgery	4342 (43.1%)	1151 (42.7%)	495 (44.1%)	301 (39.9%)	231 (45.4%)	0.30
PV thrombosis	1009 (10.0%)	281 (10.4%)	109 (9.6%)	75 (9.8%)	53 (10.3%)	0.95
On ventilator	394 (3.9%)	97 (3.5%)	37 (3.2%)	17 (2.2%)	12 (2.3%)	0.06

P values <0.05 are considered significant and marked in bold.

^aOther ethnicities not shown in table.

^bOther causes of ESLD not shown in table.

BMI, body mass index; CDC, Center for Disease Control; CIT, cold ischemic time; CVA, cerebrovascular accident; EBV, Epstein-Barr virus; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HTN, hypertension; Hx, history; IQR, interquartile range; MELD-Na, model for end-stage liver disease–sodium; PV, portal vein.

transformation was applied to normalize the score distribution and 5 risk groups were created with equal distribution from the median score. Figure 2A–D shows distributions of raw and transformed scores in both test and validate cohorts.

Graft survival was then assessed in both test and validate cohorts. Figure 3A and B shows KM survival curves by risk

group in both test and validate cohorts. Graft survival was compared between test and validate cohorts within each risk group, and no significant differences were identified (Figure S1A–E, SDC, <http://links.lww.com/TXD/A400>). Cox proportional hazard modeling was performed to assess graft survival at 30 d, 90 d, 1 y, and 3 y in both test and validate cohorts.

TABLE 3.**Factors associated with graft survival from 30 d to 3 y after transplant**

	30 d	90 d	1 y	3 y
Donor and procurement variables	<ul style="list-style-type: none"> • MaS on biopsy • Cold ischemic time 	<ul style="list-style-type: none"> • MaS on biopsy • Cause of death • Cold ischemic time • HCV positive 	<ul style="list-style-type: none"> • Age • Cause of death • Diabetes • Cold ischemic time 	<ul style="list-style-type: none"> • Age • Cause of death • Diabetes • Cold ischemic time
Recipient variables	<ul style="list-style-type: none"> • MELD-Na score • Body mass index • Exception points • Prior abdominal surgery • PV thrombosis • On mechanical ventilation 	<ul style="list-style-type: none"> • MELD-Na score • Body mass index • Exception points • Prior abdominal surgery • PV thrombosis • On mechanical ventilation 	<ul style="list-style-type: none"> • Age • Ethnicity • MELD-Na score • Exception points • EBV positive • Prior abdominal surgery • PV thrombosis • On mechanical ventilation • On dialysis 	<ul style="list-style-type: none"> • Age • Ethnicity • MELD-Na score • EBV positive • Cause of ESLD • Prior malignancy • Prior TIPS • Prior abdominal surgery • PV thrombosis • On mechanical ventilation

Inclusion in final model requires variables to be significantly associated with graft survival at 2 or more time points; factors meeting this requirement are bolded.

EBV, Epstein-Barr virus; ESLD, end-stage liver disease; HCV, hepatitis C virus; MaS, macrosteatosis; MELD-Na, model for end-stage liver disease–sodium; PV, portal vein; TIPS, transjugular intrahepatic portovenous shunt.

Table 5 reports the HR and 95% CI for graft survival at each time point by risk group. Moderate-risk transplants were considered the reference and showed 94% graft survival at 90 d, 87% at 1 y, and 75% at 3 y after transplants. Notably, severe-risk transplants had a >2.5-fold increased risk of graft loss at 30 and 90 d and >2-fold increased risk of graft loss at 1 y compared with moderate-risk transplants. This equated to graft survival of 87.4%–90.6% at 30 d and 74.2%–76.8% at 1 y. Very-low-risk and low-risk transplants had nearly 70% and 30% decreased risk of graft loss compared with moderate-risk transplants at these same time points.

Mini-LTAB Risk Score and Graft Survival

The LTAB risk score contains 14 variables found to be significantly associated with allograft survival after DLBx. To make a more clinically useful scoring system, the Mini-LTAB was created using 4 easily identified variables from the LTAB risk score: donor age, graft MaS, CIT, and recipient MELD-Na score. Together, these variables represent the Mini-LTAB, which is calculated by summation of the 4 variables with a slight modification to CIT (see Materials and Methods for calculation). Distribution of Mini-LTAB in the test and validate cohorts is presented in Figure S2A and B (SDC, <http://links.lww.com/TXD/A400>). Graft survival was then assessed within 10-point ranges at 30 d, 90 d, and 1 y (Figure 4A–C). As a simple risk score, 3 risk groups were identified according to IQR—low risk constituted the lowest 25% of scores (Mini-LTAB <130), moderate risk the middle 50% of scores (130 to <170), and high risk the top 25% of scores or scores >170. Additionally, all cases with recipients on mechanical ventilation or with PVT were considered high risk. Graft survival was assessed using KM survival analysis (Figure 5). Cox proportional hazards models were evaluated for graft survival at 30 d, 90 d, 1 y, and 3 y in both test and validate cohorts (Table 6). Notably, high-risk transplants had a 2-fold increased risk of graft loss at 30 d in both test and validate cohorts. Risk of graft loss was persistently elevated for high-risk transplants with a 50% increased risk at 1 y posttransplant. Importantly, the Mini-LTAB high-risk group identified 98.6% of severe-risk transplants according to LTAB score; cross-over between the

2 scoring system risk groups is shown in Figure S3 (SDC, <http://links.lww.com/TXD/A400>).

Multiple scoring systems have been developed to predict allograft survival in LT recipients. AUROC was calculated for both the LTAB and Mini-LTAB scores and determined to be 0.61 and 0.57, respectively (Figure S4, SDC, <http://links.lww.com/TXD/A400>). Two other popular scores, the Balance of Risk (BAR) and donor-MELD, were also assessed for predicting graft survival in this population of transplants after DLBx. The LTAB outperformed both of them, with AUROC of 0.56 for both BAR and donor-MELD scores.

DISCUSSION

Growing waitlists for LT in the United States have mandated efforts to increase the donor pool with the use of marginal or extended criteria donors. DLBx is a useful adjunct in the evaluation of marginal allografts by providing objective evidence of organ quality. Despite expansion of the donor pool, optimal utilization of marginal allografts remains in question. The purpose of this present study was to evaluate outcomes of allografts that had undergone donor biopsy. The LTAB and Mini-LTAB scores created here provide clinically useful tools to risk stratify transplantation of marginal organs after performance of DLBx.

Although 14 variables were identified for the LTAB score, the primary advantage of the Mini-LTAB lies in simplicity. In comparison with the LTAB score as well as other existing risk scores, that is DRI, BAR, and Futility Risk Score, the Mini-LTAB is easily calculated with few variables and simple addition. The factors included in the Mini-LTAB (donor age, allograft steatosis, recipient MELD score, and estimated CIT) are most similar to the BAR score, with the exception of retransplantation. Furthermore, the Mini-LTAB evaluates steatosis as a continuous variable rather than a categorical variable, allowing better differentiation between grafts with increased amounts of steatosis. Finally, apart from variables included in the Mini-LTAB, both recipients on mechanical ventilation and those with PVT were identified as high risk for 1-y graft loss. Although there is variation in the severity and sequelae of PVT, it was associated with a nearly 2-fold increased risk of graft loss at 30 d posttransplant and 70%

TABLE 4.
HRs and scoring system for the LTAB risk score

Characteristics	30 d HR	90 d HR	1 y HR	3 y HR	Weighted average ^a	Allocated points
Donor characteristics						
Age (per y)	1.003	1.004	1.006	1.007	1.005	1 pt/y
MaS on biopsy (per % steatosis)	1.01	1.007	1.003	1.001	1.006	1 pt/% MaS
Cause of death						
Anoxia	Reference					0 pts
Trauma	1.328	1.298	1.16	1.165	1.253	25 pts
Cerebrovascular accident	1.192	1.328	1.222	1.192	1.240	25 pts
Other	1.634	1.569	1.502	1.223	1.520	50 pts
Hx of diabetes	1.186	1.166	1.176	1.161	1.172	20 pts
Procurement characteristics						
Cold ischemic time						
<4 h	Reference					0 pts
4–<6 h	1.391	1.322	1.23	1.077	1.283	30 pts
6–<8 h	1.527	1.495	1.352	1.194	1.424	40 pts
8–<10 h	1.926	1.733	1.328	1.212	1.612	60 pts
10–>12 h	1.94	1.923	1.404	1.259	1.699	70 pts
≥12 h	2.858	2.327	1.636	1.443	2.066	100 pts
Recipient characteristics						
Age (per y)	1.002	1.006	1.014	1.007	1.007	1 pt/y
Body mass index (per kg/m ²)	1.023	1.02	1.005	0.999	1.014	1 pt/kg/m ²
Ethnicity						
White	Reference					0 points
Black	1.224	1.183	1.314	1.454	1.269	25 points
Hispanic	1.077	1.01	0.976	1.042	1.026	5 points
Asian	1.473	1.113	0.907	0.8	1.123	5 points
Other	0.72	0.638	0.925	0.899	0.796	0 points
MELD-Na score (per point)	1.02	1.028	1.026	1.018	1.024	2 pts/MELD-Na score
Exception points awarded						
No exception points						0 points
HCC exception points	1.201	1.154	1.245	1.373	1.243	25 points
Other exception points	1.818	1.642	1.445	1.292	1.549	50 points
EBV negative	0.895	0.879	0.848	0.91	0.883	10 points
Prior abdominal surgery	1.447	1.421	1.311	1.22	1.350	35 points
Portal vein thrombosis	2.052	1.785	1.684	1.395	1.729	75 points
On mechanical ventilation at time of transplant	3.759	3.049	2.36	1.965	2.783	250 points

Continuous variables: recipient age, MaS on biopsy, donor age awarded up to 100 points; MELD score up to 80 points; and BMI up to 50 points.

^aWeighted average = 30% 30-d survival, 30% 90-d survival, 25% 1-y survival, 15% 3-y survival.

BMI, body mass index; EBV, Epstein-Barr virus; HCC, hepatocellular carcinoma; HR, hazard ratio; Hx, history; LTAB, Liver Transplant After Biopsy; MaS, macrosteatosis; MELD-Na, model for end-stage liver disease–sodium.

increased risk of graft loss at 1 y. Though not a contraindication to LT, it should be considered as a significant risk factor when evaluating marginal grafts.

The LTAB and Mini-LTAB scores both incorporate donor and recipient variables. Donor and recipient matching is not a new concept in LT, particularly when using marginal allografts. Recent studies have shown improved outcomes when matching extended criteria organs (steatotic, older donor age, DCD, etc) with recipients with lower MELD scores and other favorable transplant factors.^{15–17} In particular, recipient factors associated with similar outcomes between allografts with and without MaS >30% include MELD score <24, low-risk recipients by BAR score, or institutional matching algorithms.^{18–20} MELD score is important for evaluating potential recipients as it reflects recipient severity of illness. High MELD recipients are less likely able to tolerate marginal grafts; however, multiple factors play a role in outcomes of LT. Incorporation of

MELD score in the LTAB and, importantly, in the Mini-LTAB reflects the donor–recipient interaction without setting firm cutoffs for recipient selection based on MELD score alone.

Understanding the interplay between components of the LTAB and Mini-LTAB scores allows transplant surgeons to better use DLBx. Hepatic steatosis is commonly identified at the procurement surgery and DLBx is used to evaluate the volume of steatosis in the donor liver. Steatosis is characterized as MaS or microsteatosis; however, only MaS has been found to have significant influence on allograft survival.²¹ Mild steatosis (<30% MaS) has long been considered acceptable for transplant without detriment to outcomes.²² The use of allografts with moderate (30%–60% MaS) or severe (>60%) steatosis has remained controversial. LT with moderately steatotic livers has been associated with increased transfusion requirements and longer intensive care unit and hospital stays.^{6,23} Importantly, allografts with increased levels of steatosis are

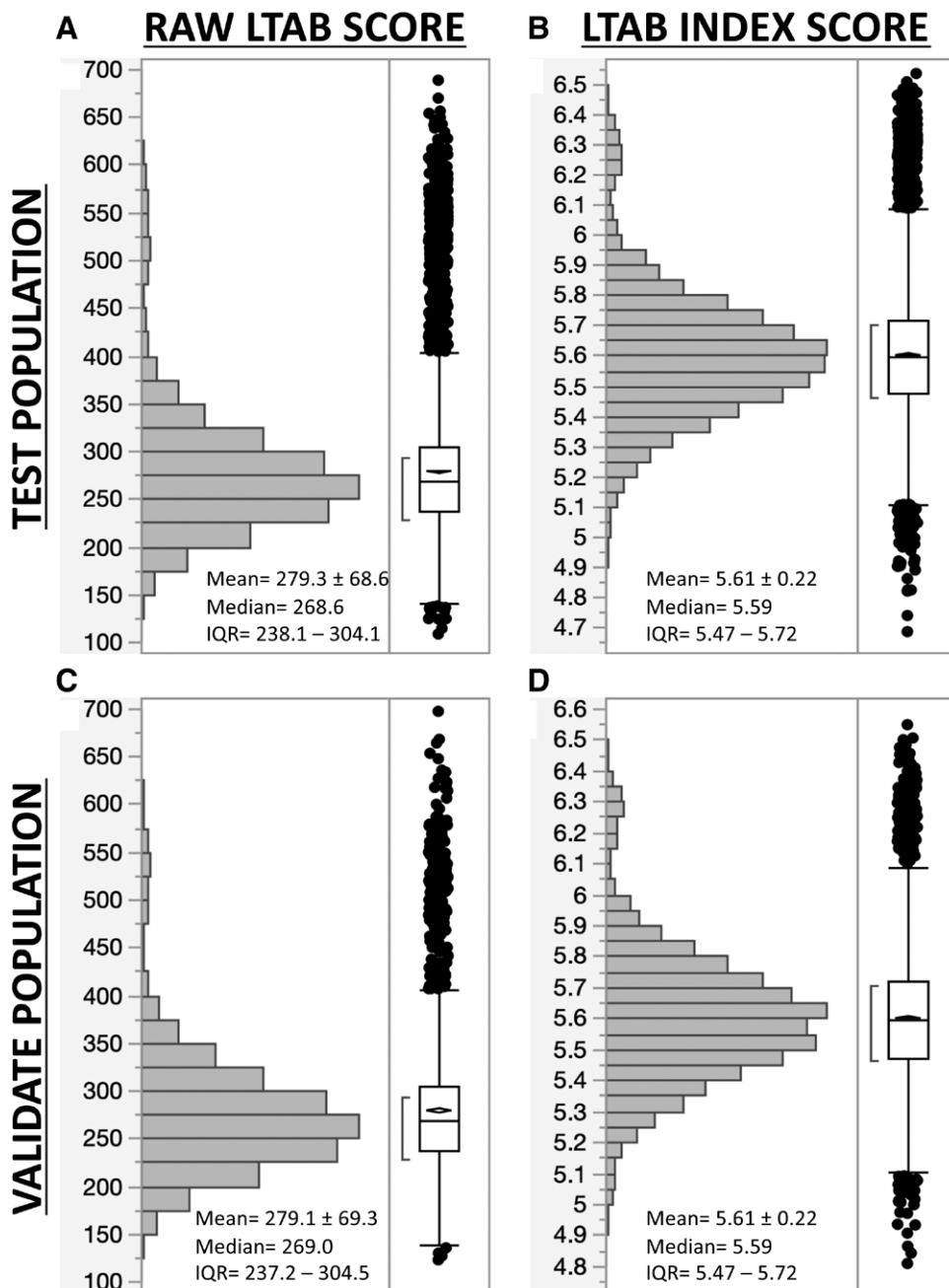


FIGURE 2. Distribution of LTAB scores and scoring index in test and validate cohorts. Raw LTAB scores were calculated for all patients in both test and validate cohorts. A natural log modification was applied to produce the LTAB index score with normal distribution. Means, medians, and IQRs are reported for each population. IQR, interquartile range; LTAB, Liver Transplant After Biopsy.

associated with postreperfusion syndrome and EAD.⁷ Severely steatotic organs (>60% MaS) have been associated with even higher rates of PNF (20%–50%) and EAD (25%–80%).^{12,24,25} Croome et al²⁶ best demonstrated the effects of postreperfusion syndrome by comparing allografts with moderate steatosis to those with mild (10%–20%) or no steatosis during LT, finding increased rates of hypotension requiring vasopressor use, cardiac arrest, renal dysfunction requiring renal replacement therapy, and need to return to the operating room in patients receiving grafts with moderate steatosis.

In contrast to these findings, multiple case series have reported the successful use of both moderately and severely steatotic allografts in LT. Rates of graft survival, PNF, and

biliary and ischemic complications were similar between moderately steatotic allografts and lean allografts.^{7,12,18,27,28} Baccarani et al² evaluated severely steatotic allografts and showed acceptably low rates of PNF (0%–3.8%) and 1-y graft survival (82%–94.7%). Wong et al²⁹ showed equivalent 1- and 3-y graft survival after LT with severely steatotic allografts, identifying lower MELD scores and short CIT as important factors to success. Croome et al²⁶ found no difference in 1-, 3-, or 5-y patient and graft survival between recipients of moderately steatotic allografts and those with mild or no steatosis. Recently, our own group evaluated the outcomes of allografts with DLBx, looking at smaller MaS groups to better determine thresholds for poor outcomes. In

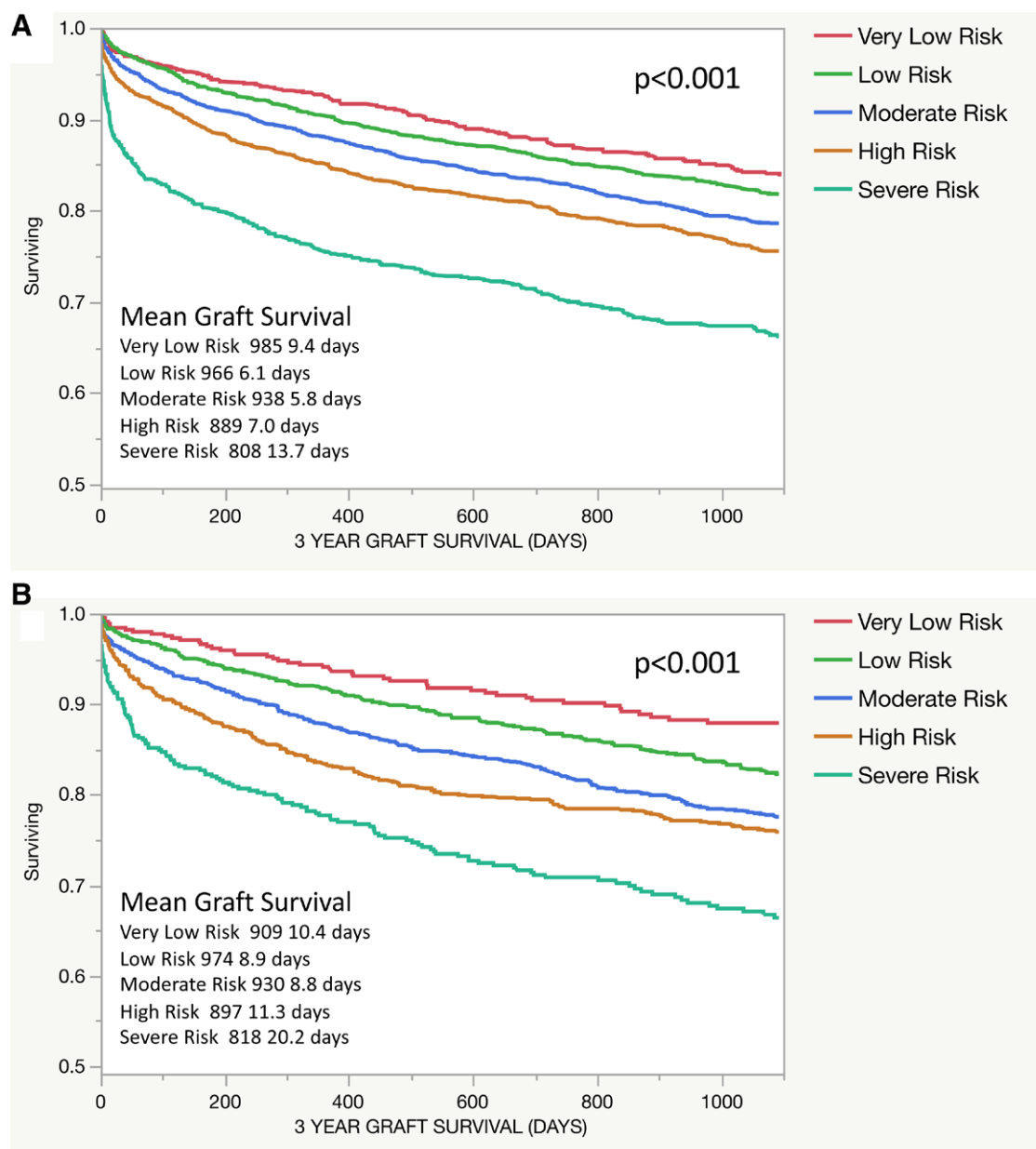


FIGURE 3. Three-year allograft survival by LTAB risk groups. LTAB risk groups were identified and 3-y graft survival was assessed by Kaplan-Meier survival curves in test cohort (A) and validate cohort (B). Mean graft survival is reported; P value assesses differences in graft survival across risk groups. LTAB, Liver Transplant After Biopsy.

that study, we showed equivalent 1-y graft survival between allografts transplanted without DLBx and those with $\leq 50\%$ MaS in recipients with MELD scores < 33 , as well as allografts with $\leq 40\%$ MaS in recipients with higher MELD scores.⁹ Altogether, these results support increasing the use of steatotic donor allografts with higher levels of MaS. However, it should be acknowledged that steatosis groups represent a range of fat content across 30%. Allografts with 35% to 40% MaS and those with 55% to 60% MaS are both considered under moderate steatosis but may have different rates of utilization and outcomes. Use of allografts with very high levels of MaS, $\sim 50\%$ MaS or higher, is uncommon and extreme care should be used by centers with experience in transplanting steatotic livers. Furthermore, recipient selection in paramount to achieving good outcomes and use of highly steatotic grafts should be avoided in patients with coronary artery disease,

atrial fibrillation, elderly recipients, and those with anticipation of prolonged hepatectomies or prolonged CIT.

The present study attempts to risk stratify LT with steatotic organs through use of a simple scoring system—the Mini-LTAB score. The factors included in the Mini-LTAB score were picked from a group of factors previously found to be associated with allograft survival after DLBx⁹; however, these factors are not unique to our study alone. De Graaf et al¹² showed that MaS was a stronger predictor of graft survival than the DRI. Spitzer et al³ attempted to incorporate donor MaS into a donor risk assessment, which included donor age, ethnicity, DCD status, CIT, and donor MaS (grouped as $< 20\%$, $20\%–30\%$, and $> 30\%$). Through multivariable analysis, the study showed that MaS $> 30\%$ carried a relative risk of 1.71 ($P = 0.007$) and MaS $20\%–30\%$ combined with CIT > 11 h had relative risk of 1.54 ($P = 0.03$).³ Dutkowski

TABLE 5.
Graft survival and associated HR in LTAB risk groups from 30 d to 3 y

		Very low risk (n = 1056)	Low risk (n = 2645)	Moderate risk (n = 3167)	High risk (n = 2621)	Severe risk (n = 1055)	P
Test cohort	30 d						
	Graft survival, n (%)	1028 (97.4%)	2576 (97.4%)	3042 (96.1%)	2475 (94.4%)	922 (87.4%)	<0.001
	HR	0.646	0.653	Reference	1.400	3.270	<0.001
	(95% CI)	(0.429-0.972)	(0.489-0.873)		(1.105-1.773)	(2.568-4.165)	
	90 d						
	Graft survival, n (%)	1009 (95.7%)	2516 (95.5%)	2962 (93.7%)	2407 (92.1%)	874 (83.1%)	<0.001
	HR	0.655	0.691	Reference	1.248	2.821	<0.001
	(95% CI)	(0.472-0.904)	(0.551-0.867)		(1.029-1.514)	(2.308-3.448)	
	1 y						
	Graft survival, n (%)	899 (91.4%)	2223 (89.6%)	2613 (87.3%)	2096 (84.6%)	744 (74.2%)	<0.001
	HR	0.659	0.802	Reference	1.241	2.258	<0.001
	(95% CI)	(0.521-0.833)	(0.684-0.939)		(1.077-1.430)	(1.928-2.644)	
	3 y						
	Graft survival, n (%)	575 (81.4%)	1426 (79.1%)	1673 (75.8%)	1321 (72.7%)	455 (62.4%)	<0.001
	HR	0.749	0.828	Reference	1.143	1.821	<0.001
(95% CI)	(0.629-0.891)	(0.733-0.936)		(1.021-1.280)	(1.595-2.079)		
Validate cohort	30 d						
	Graft survival, n (%)	503 (98.6%)	1101 (97.6%)	1296 (96.4%)	1089 (94.6%)	415 (90.6%)	<0.001
	HR	0.327	0.653	Reference	1.561	2.662	<0.001
	(95% CI)	(0.169-0.822)	(0.408-1.044)		(1.077-2.261)	(1.768-4.010)	
	90 d						
	Graft survival, n (%)	497 (98.0%)	1079 (96.1%)	1260 (94.2%)	1044 (90.9%)	391 (85.4%)	<0.001
	HR	0.336	0.675	Reference	1.632	2.688	<0.001
	(95% CI)	(0.174-0.650)	(0.466-0.978)		(1.217-2.189)	(1.938-3.730)	
	1 y						
	Graft survival, n (%)	450 (94.1%)	958 (90.1%)	1112 (87.5%)	891 (82.4%)	335 (76.8%)	<0.001
	HR	0.445	0.770	Reference	1.441	2.003	<0.001
	(95% CI)	(0.298-0.666)	(0.602-0.985)		(1.168-1.778)	(1.561-2.570)	
	3 y						
	Graft survival, n (%)	289 (86.3%)	607 (79.0%)	698 (75.3%)	576 (73.3%)	193 (63.1%)	<0.001
	HR	0.507	0.825	Reference	1.172	1.721	<0.001
(95% CI)	(0.379-0.679)	(0.685-0.993)		(0.988-1.390)	(1.405-2.108)		

CI, confidence interval; HR, hazard ratio; LTAB, Liver Transplant After Biopsy.

et al¹³ evaluated outcomes of steatotic livers by recipients BAR score, showing that allografts with >30% MaS showed favorable outcomes with recipients in the lowest BAR risk group. The LTAB and Mini-LTAB were compared with the BAR score by calculating AUROC for 1-y allograft survival. The Mini-LTAB and BAR score had similar AUROC of 0.57 and 0.56, respectively, whereas the complete LTAB score had a higher AUROC of 0.61. None of these AUROC are particularly excellent; however, they remain the most applicable scoring systems to this patient population. Although there is some overlap of factors between the BAR and LTAB scores, whittling them down to the 4 factors that comprise the Mini-LTAB is a mathematical representation of the guiding principles for successful selection and utilization of steatotic and marginal allografts in LT.

The clinical utility of the Mini-LTAB may be best explored with an example—consider an allograft with 30% MaS is identified in the operating room by DLBx. If this organ were from a 33-y-old donor, allocated to a recipient with MELD score of 24, and with an estimated 6h CIT, then the Mini-LTAB score would be 107 points (=30+33+24+20), placing this transplant in the low-risk cohort with an estimated 1-y graft survival of ~89%. Consider this same liver now from a 55-y-old donor for a patient with a MELD score of 30, and

now the score is 135 (=30+55+30+20), carrying moderate risk in LT and 1-y graft survival of ~88%. Finally, take this transplant and extend the CIT to 10h because of prolonged travel time or difficult hepatectomy. Now the Mini-LTAB score is 175 and the transplant is considered high risk with a 50% increased risk of graft loss at 1 y compared with low-risk transplants and an 81.9%–82.3% 1-y graft survival rate. The risk of graft loss may increase as the result of changes in multiple factors. The Mini-LTAB easily navigates these changes with a score that is easily calculated and recalculated as needed.

The impact of this study, along with recent literature showing acceptable outcomes with highly steatotic donors, cannot be understated. Jackson et al⁸ showed that allografts with higher levels of steatosis are being used more frequently and have better graft survival than those used 10 y ago. Furthermore, improvements in organ preservation with machine-based perfusion have improved outcomes for steatotic organs.^{30,31} Together, these studies depict a changing landscape of organ utilization and preservation. Unfortunately, machine-based perfusion strategies are not yet widely available, leaving room for improvements in organ utilization. Still, application of these preservation strategies, in addition to optimal donor–recipient pairing, may increase utilization of marginal

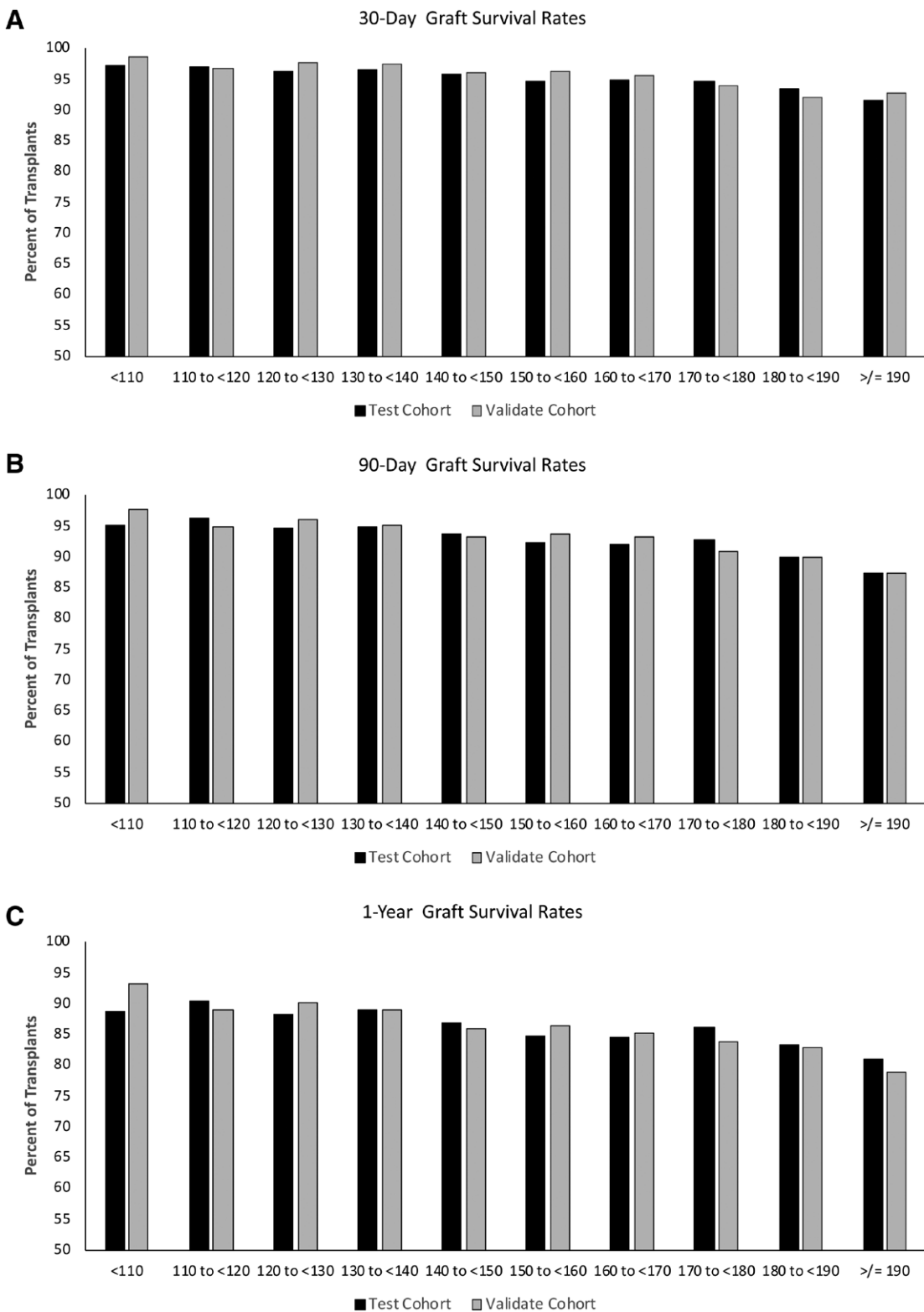


FIGURE 4. Allograft survival rates by Mini-LTAB score groups. Mini-LTAB scores were divided into 10-point increments and graft survival was assessed between test and validate cohorts at (A) 30 d, (B) 90 d, and (C) 1 y after transplant. There were no significant differences between test and validate cohorts within any score group, at any time point. LTAB, Liver Transplant After Biopsy.

steatotic organs to defervesce the waitlist for LT across the United States while maintaining acceptable outcomes in the future.

This study is not without its limitations. A primary limitation to this study is the variability in obtaining, processing,

and interpreting liver biopsy during LT.³² El-Badry et al³³ showed that variations in slide preparation may lead to differing appearances of final slides. Heller et al³⁴ compared analysis of frozen sections with analysis of permanent sections, finding clinically significant differences in 7% of cases.

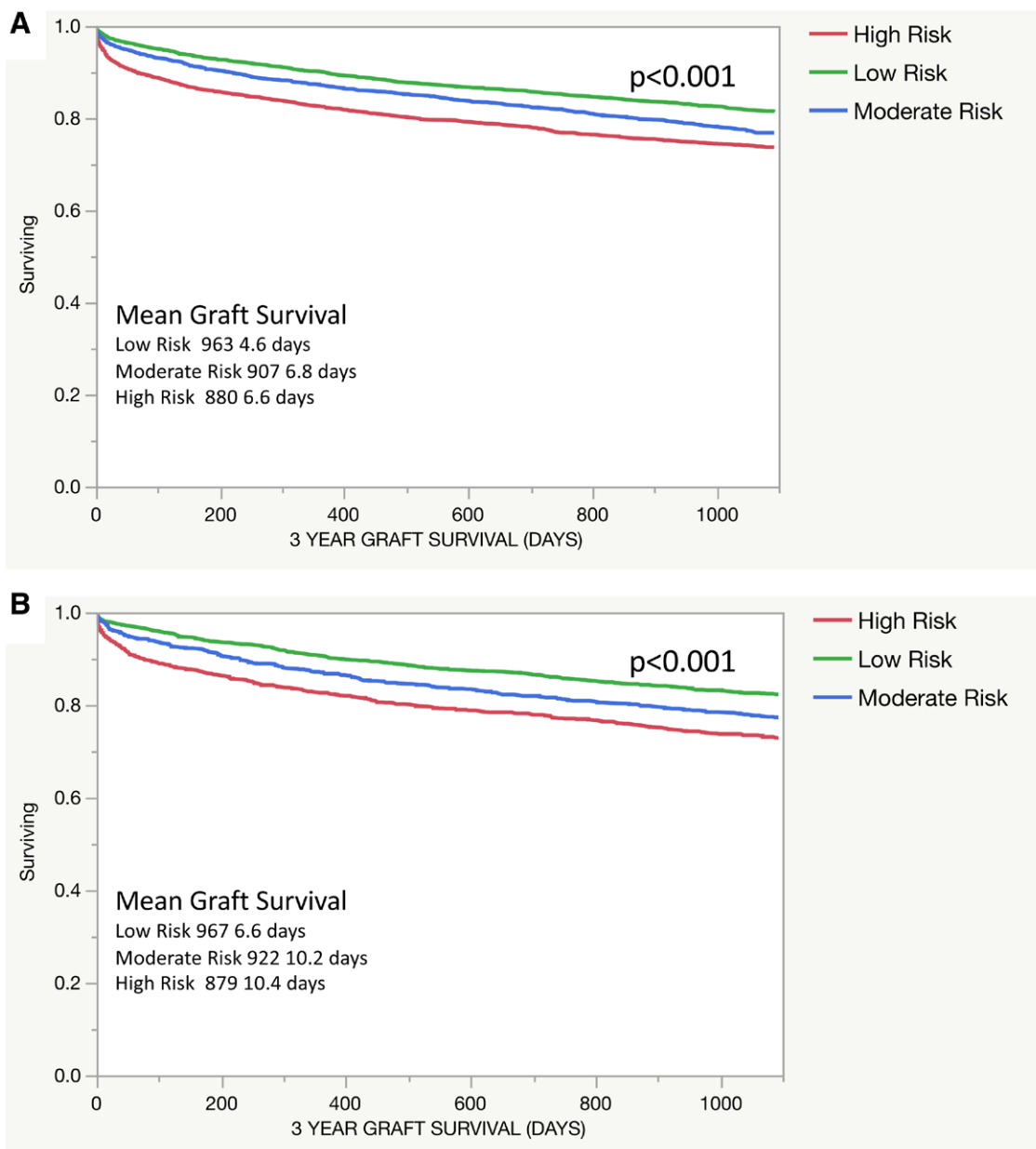


FIGURE 5. Three-year allograft survival by Mini-LTAB risk groups. Mini-LTAB risk groups were identified and 3-y graft survival was assessed by Kaplan-Meier survival curves in test cohort (A) and validate cohort (B). Mean graft survival is reported; P value assesses differences in graft survival across risk groups. LTAB, Liver Transplant After Biopsy.

Fiorentino et al³⁵ compared frozen and permanent sections of liver biopsies and associated outcomes, finding high rates of agreement between both preparations with regard to steatosis (coefficient of agreement=0.93); however, they found MaS was overestimated in 12.5%. They also found that only MaS and total steatosis identified on frozen section were associated with allograft outcomes, whereas other histological characteristics were not predictive. Nonetheless, many of the donor biopsies from organ procurements in the United States are performed and processed at small community hospitals. Consequently, they are not evaluated by experienced liver pathologists. Therefore, many centers rely on their own experienced pathologists to evaluate biopsies before making decisions on organ acceptance. Recently, Sun et al³⁶ reported superior performance of a neural network in evaluating whole

slide images of liver biopsies for quantifying steatosis when compared with an on-service pathologist. Ultimately, there are a number of factors that may influence the results of DLBx evaluation. Until advances in methods of specimen processing or evaluation become widely adopted, we must rely on assessment by surgeons and pathologists alike.

Other limitations to this study exist, including this being a retrospective study from a large national database. We recognize the limitations inherent to using such a database, such as incorrect or missing data. In this Organ Procurement and Transplant Network Standard Transplant Analysis and Research database, biopsy results are available for 27.7% of patients. The decision to perform liver biopsy introduces selection bias, which is mitigated by excluding transplants without biopsy results. Nonetheless, this is the largest and only national database for

TABLE 6.**Graft survival and associated HR for Mini-LTAB risk groups**

		Low-risk Mini-LTAB <130 (n = 2495)	Moderate-risk Mini-LTAB 130–169 (n = 4263)	High-risk Mini-LTAB ≥170 (n = 3913)	P
Test cohort	30 d				
	Survival, n (%)	2426 (97.2%)	4104 (96.3%)	3625 (92.6%)	<0.001
	HR (95% CI)	0.731 (0.552-0.967)	Reference	1.991 (1.644-2.412)	<0.001
	90 d				
	Survival, n (%)	2379 (95.5%)	4002 (94.2%)	3496 (89.5%)	<0.001
	HR (95% CI)	0.763 (0.611-0.954)	Reference	1.855 (1.585-2.171)	<0.001
	1 y				
	Survival, n (%)	2091 (89.8%)	3521 (87.6%)	3057 (82.3%)	<0.001
	HR (95% CI)	0.804 (0.688-0.938)	Reference	1.497 (1.333-1.682)	<0.001
	3 y				
	Survival, n (%)	1303 (79.2%)	2226 (76.7%)	1991 (70.9%)	<0.001
	HR (95% CI)	0.876 (0.779-0.986) (n = 1073)	Reference (n = 1934)	1.331 (1.212-1.463) (n = 1643)	<0.001
Validate cohort	30 d				
	Survival, n (%)	1051 (98.0%)	1875 (97.0%)	1534 (93.4%)	<0.001
	HR (95% CI)	0.659 (0.404-1.074)	Reference	2.218 (1.620-3.036)	<0.001
	90 d				
	Survival, n (%)	1033 (96.8%)	1826 (94.9%)	1467 (89.5%)	<0.001
	HR (95% CI)	0.613 (0.416-0.906)	Reference	2.130 (1.664-2.726)	<0.001
	1 y				
	Survival, n (%)	920 (91.2%)	1601 (87.8%)	1273 (81.9%)	<0.001
	HR (95% CI)	0.703 (0.550-0.899)	Reference	1.550 (1.301-1.847)	<0.001
	3 y				
	Survival, n (%)	570 (81.4%)	1017 (77.2%)	805 (70.4%)	<0.001
	HR (95% CI)	0.779 (0.647-0.939)	Reference	1.395 (1.211-1.607)	<0.001

CI, confidence interval; HR, hazard ratio; LTAB, Liver Transplant After Biopsy.

transplantation in the United States, and the large population size will likely average out minor errors. Second, the LTAB and Mini-LTAB scores were created and evaluated in a single population. Despite use of both test and validate cohorts, external validation in a separate population would add strength to its clinical use. Still, we believe its simplistic nature will allow it to be easily implemented in clinical practice, and it may serve to inform expectations of transplant while not being used as a predictive tool. The incorporation of CIT itself represents a minor limitation of the LTAB and Mini-LTAB scores. We recognize that exact CIT may not be known at time of organ procurement, but a range of reasonable estimates is usually possible based upon distance between donor and recipient, travel time, and status or location of the recipient.

The world of transplant is evolving at an incredible pace—with advancements in organ preservation and immunosuppression, treatments for HCV-infected recipients and donors, growing population of transplant registrants with non-alcoholic steatohepatitis, and the changing face of the donor population.³⁷⁻³⁹ To keep pace, the transplant community must adapt and progress, by finding new ways to grow the donor population and increase organ utilization without detriment to outcomes. Utilization of marginal organs represents 1 such way to grow the donor pool. The LTAB score is useful for evaluation of transplants using marginal organs undergoing DLBx. Furthermore, by focusing on 4 primary transplant characteristics, the Mini-LTAB score is a simple tool for clinicians to use in the evaluation and risk stratification of LT donor–recipient pairs. Together, these scores may be used to

inform decision making and organ selection and enhance discussions with recipients about postoperative outcomes.

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