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Predicting futile outcomes following deceased donor liver transplantation in non-HCC patients with MELD-Na score above 30: a retrospective international multicenter cohort study

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Introduction: In the current "sickest first" allocation policy for limited deceased liver grafts, identifying patients "too sick to transplant" before transplantation is crucial to optimize outcomes. This study aimed to predict futile outcomes following deceased donor liver transplantation (DDLT) in patients with model for end-stage liver disease-sodium (MELD-Na) scores ≥30.
Methods: This international multicenter study was conducted as part of the International Society of Liver Surgeons. We collected data from patients with a MELD-Na score of ≥30 who underwent DDLT. A total of 994 patients were enrolled between 2010 and 2021, including 654 from the Republic of Korea, 224 from the USA, and 116 from other regions. Futility was defined as death within 3 months or during the hospital stay following a DDLT. After exclusion, 160 (16.6%) patients were classified into a futile group and 803 (83.4%) into a non-futile group.
Results: The MELD-Na scores collected at three time points (listing, matching, and transplantation) were comparable between the groups ($P = 0.442$, $P = 0.180$, and $P = 0.554$, respectively). Regarding concomitant organ failure factors, the futile group showed a higher incidence of organ dysfunction across all measured parameters, including the use of mechanical ventilators, continuous renal replacement therapy (CRRT), pneumonia, bacteremia, and vasopressor use (all $P < 0.01$). Independent risk factors for futile outcome were recipient age (≥65 years), body mass index (<18.5 kg/m^2), mechanical ventilator use, CRRT (≥1 week), and prolonged intensive care unit stay before transplantation (≥2 weeks). The futility rate was 53.3% in patients with ≥3 risk factors ($P < 0.001$). We developed a nomogram to predict futility after DDLT based on multivariate regression analysis, which showed a better predictive power than previous models.
Conclusion: The risk factors and new nomogram, which adequately reflect concomitant organ failure before liver transplantation, could effectively predict the risk of futile outcomes after DDLT and contribute to decision-making regarding transplantation eligibility in clinical practice.

Keywords: deceased donor liver transplantation, futility, MELD-Na score, nomograms, treatment outcome

Introduction

Liver transplantation is the only life-saving treatment option for end-stage liver disease[1]. The number of patients on the liver transplant waitlist continues to increase globally[2], although the pool of living and deceased donors has remained stable for years. Consequently, the distribution of the limited number of

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deceased donor livers has led to a serious debate on achieving an appropriate balance between equity and efficiency. With the implementation of the model for end-stage liver disease (MELD) score in allocation systems, many countries have adopted a "sickest first" policy, prioritizing more critically ill patients[3,4]. Given that patients with high MELD scores, indicative of severe illness, are at a higher risk of concomitant organ failure[5], some of them deemed "too sick for transplant" could result in futile outcomes following liver transplantation, potentially in wasting of livers that could have been used in other patients with a concomitant domino effect in waitlist mortality.

Futility in liver transplantation has been defined as mortality within 3 months or in-hospital mortality[6]. Mitigating extremely poor clinical conditions with multiple organ failures within a short period of time is usually challenging. Therefore, it is of particular importance to identify patients who, despite receiving high-quality liver grafts and having no problems during the surgical procedure, are at high risk of futile transplantation. However, it is exceedingly difficult for transplant teams to deny liver transplantation based on the clinical condition of each patient on the waitlist. Although several studies have attempted to predict post-transplant outcomes based on pre-transplant factors[6-10], comprehensive multicenter studies analyzing complex multiorgan failures related to high MELD scores are limited.

Therefore, this international multicenter study aimed to identify the risk factors associated with futile outcomes following deceased donor liver transplantation (DDLT) in patients with a MELD-sodium (MELD-Na) score of ≥30 and to develop an easy-to-use and widely applicable nomogram for predicting futility. This study was reported according to the strengthening the reporting of cohort, cross-sectional and case–control studies in surgery criteria[11].

Materials and methods

Data collection

This international multicenter cohort study was conducted as part of the International Society of Liver Surgeons (ISLS) Study Group project. We collected comprehensive data from patients with MELD-Na scores ≥30 who underwent DDLTs. Recruitment was limited to institutions that performed ≥50 liver transplantations annually. Data were obtained from six institutions, namely, Korea University, Asan Medical Center, Mount Sinai Medical Center, Hospital das Clinicas, Samsung Medical Center, Yonsei University, and Centro Médico Nacional 20 de Noviembre. The study was approved by the Institutional Review Board and strictly adhered to the ethical guidelines of the Declaration of Helsinki and the Declaration of Istanbul.

Study population and definition of futility

Between 2010 and 2021, 994 patients from the six institutions were enrolled in this study. Patients who met the following criteria were included: (1) aged ≥18 years who received a DDLT and (2) a MELD-Na score ≥30 at the time of matching. Exclusion criteria were as follows: (1) status I, fulminant hepatic failure; (2) patients with hepatocellular carcinoma (HCC) identified during preoperative evaluation (irrespective of exception points), although an incidental diagnosis of HCC on pathological examination did not preclude enrollment; and (3) patients lost to follow-up within 1-year after the DDLT. Due to the variations in applying HCC exception points for each patient from different countries, we excluded patients diagnosed with HCC based on preoperative imaging studies. After the exclusion, 963 patients were included in the final analysis.

Futility was defined as death within 3 months or during a hospital stay following DDLT. Patients requiring re-transplantation were not included in the futility category, as these cases were more likely related to graft quality rather than the clinical condition of the recipient. Among the 963 patients analyzed, 160 (16.6%) and 803 (83.4%) were classified into the futile and non-futile groups, respectively. We performed a comparative analysis of the characteristics and clinical outcomes of the two groups. Furthermore, a risk factor analysis for futile transplantation was performed, from which we developed a nomogram to predict futility in DDLT.

Preoperative assessment

Preoperative assessments were performed to evaluate the extent of liver dysfunction and concomitant organ failure. The MELD-Na scores were systematically collected at three different time points: listing, matching, and transplantation. Factors reflecting concomitant organ failure were as follows: use of mechanical ventilation, assessment of oxygenation efficiency using SaO_2/FiO_2 or PaO_2 $/FiO_2$ ratios, type and duration of renal replacement therapy, pneumonia, bacteremia, use of vasopressors, and duration of an intensive care unit (ICU) stay before transplantation. The aim of this study was to comprehensively assess the effects of concomitant organ failure on patient survival and evaluate the risk factors for futility.

Statistical analysis

Continuous variables are presented as medians and ranges or as means with standard deviations, depending on whether the data followed a normal distribution. They were compared between groups using Student's *t*-test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. Categorical variables are presented as numbers with percentages and were compared using the χ^2 or Fisher's exact test, as appropriate. Repeated analysis of variance was performed to analyze the differences in the changes in MELD-Na scores over three time points between the groups. Overall survival rates were calculated using the Kaplan–Meier analysis and compared using the log-rank tests. Logistic regression analysis was used to assess the prognostic significance of variables for patient survival. Multivariate analysis was performed on factors with P values ≤ 0.1 in the univariate analysis.

To evaluate the calibration of the predictive model, a calibration curve was constructed using the bootstrap resampling method with 100 repetitions for internal validation. The curve was generated using the "rms" package in R, comparing predicted probabilities to observed outcomes. The apparent calibration curve and bias-corrected curve were derived to account for overfitting, and the ideal line served as a reference for perfect calibration. We performed the statistical analysis without imputing missing values. Specifically, we conducted a complete case analysis for significant risk factors in the multivariate regression analysis by eliminating missing values through close collaboration with participating centers. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS

Statistics for Windows (version 22.0; IBM Corp., Armonk, NY, USA) and R software (version 3.6.1; Vienna, Austria; "rms" and "pROC" packages).

Results

Baseline characteristics of recipients and donors

Baseline characteristics of recipients in the futile and non-futile groups are shown in Table 1. Median body mass index (BMI) was significantly lower in the futile group than in the non-futile group (23.9 [15.8–43.1] vs. 24.9 [16.5–42.1] kg/m^2, P = 0.041). Regarding the cause of liver transplantation, alcoholic liver disease was less prevalent in the futile group than in the non-futile group (46 [28.8%] vs. 299 [37.4%], P = 0.038). The MELD-Na scores collected at the three time points (listing, matching, and transplantation) were comparable between the groups (P = 0.442, P = 0.180, and P = 0.554, respectively). Furthermore, the proportion of patients showing an upward trend in the MELD-Na score at transplantation compared with that at matching did not differ between the futile and non-futile groups (62 [86.1%] vs. 354 [90.3%], P = 0.283). The distribution of the MELD-Na scores is demonstrated in Figure 1, and no significant difference was observed according to the time point between the groups (P = 0.706).

Regarding factors associated with concomitant organ failure, the futile group showed a higher incidence of organ dysfunction across all measured parameters, including the use of mechanical ventilators, continuous renal replacement therapy (CRRT), pneumonia, bacteremia, and use of vasopressors (all P < 0.01) (Table 1). However, the PaO_2/FiO_2 ratio and duration of ventilator support before transplantation were comparable between the futile and non-futile groups (225 [98–452] vs. 250 [97–394], P = 0.367 and 5[1-8] vs. 3[1-28] days, P = 0.865, respectively). The duration of CRRT before transplantation was also comparable between the two groups (5[1-30] vs. 5[1-30] days, P = 0.408).

Table 2 shows the baseline characteristics of donors between the two groups. All the donors in both groups were brain dead. The proportion of grafts with macrosteatosis exceeding 30% was comparable between the futile and non-futile groups (5

Table 1

Baseline characteristics of recipients in the futile and non-futile groups

	Futile group (*n* = 160)	Non-futile group (*n* = 803)	Total (*n* = 963)	*P* value
Age (years)	51.0 (±13.0)	49.5 (±12.7)	49.7 (±12.8)	0.013
Sex (female)	50 (31.2%)	274 (34.1%)	324 (33.6%)	0.483
BMI (kg/m^2)[a]	23.9 (15.8–43.1)	24.9 (16.5–42.1)	24.8 (15.8–43.1)	0.041
Cause of transplantation				
HBV	28 (17.5%)	168 (21.0%)	196 (20.4%)	0.316
HCV	12 (7.5%)	54 (6.8%)	66 (6.9%)	0.732
Alcoholic	46 (28.8%)	299 (37.4%)	345 (35.9%)	0.038
MASH	3 (1.9%)	40 (5.0%)	43 (4.5%)	0.081
Others	71 (44.4%)	244 (30.5%)	315 (32.8%)	0.001
MELD-Na score				
At listing	28.7 (±8.4)	28.0 (±7.8)	28.2 (±7.9)	0.442
At matching[a]	36 (30–48)	36 (30–55)	36 (30–55)	0.180
At transplantation	36.0 (±5.6)	36.4 (±5.0)	38.0 (±5.1)	0.554
DM	29 (22.3%)	154 (21.3%)	183 (21.5%)	0.797
HTN	30 (23.1%)	138 (19.1%)	168 (19.7%)	0.292
Hepatic encephalopathy (grade ≥3)	34 (21.5%)	103 (12.9%)	137 (14.3%)	0.005
Mechanical ventilator	53 (33.1%)	113 (14.1%)	166 (17.3%)	<0.001
CRRT	73 (45.6%)	203 (25.3%)	276 (28.7%)	<0.001
Pneumonia	26 (16.2%)	70 (8.7%)	96 (10.0%)	0.004
Bacteremia	37 (23.3%)	119 (14.9%)	156 (16.2%)	0.009
Vasopressor	47 (29.4%)	112 (13.9%)	159 (16.5%)	<0.001
Previous abdominal surgery	59 (37.1%)	185 (23.0%)	244 (25.4%)	<0.001
Previous TIPS[b]	3 (2.1%)	10 (1.4%)	13 (1.5%)	0.450
PVT	8 (5.6%)	45 (6.1%)	53 (6.1%)	0.820
ICU stay before transplantation (days)[a]	7 (0–62)	4 (0–110)	5 (0–110)	<0.001
BAR score[a]	16 (10–24)	15 (10–25)	16 (10–25)	<0.001
Pre-transplant laboratory finding				
WBC (10^3/L)	8.6 (±5.7)	7.6 (±6.5)	7.8 (±6.4)	0.212
Platelets (×10^3)[a]	53 (7–302)	59 (7–362)	58 (7–369)	0.002
Total bilirubin (mg/dL)	23.4 (±12.2)	20.8 (±12.3)	22.0 (±12.3)	0.262
Creatinine (mg/dL)[a]	1.86 (0.21–6.84)	2.00 (0.21–11.39)	1.96 (0.21–11.39)	0.179
PT-INR	2.86 (±1.62)	2.92 (±1.53)	2.91 (±1.54)	0.936
Na (mmol/L)[a]	137 (116–165)	136 (104–175)	136 (104–175)	0.001

BAR, balance of risk; BMI, body mass index; CRRT, continuous renal replacement therapy; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; HTN, hypertension; ICU, intensive care unit; MASH, metabolic dysfunction-associated steatohepatitis; MELD-Na, model for end-stage liver disease-sodium; PT-INR, prothrombin time-international normalized ratio; PVT, portal vein thrombus; TIPS, transjugular intrahepatic portosystemic shunt; WBC, white blood cell.

[a]Mann–Whitney.

[b]Fisher's exact.

Values are presented as median (range) or median (standard deviation) depending on whether the data followed a normal distribution for continuous data and *n* (%) for categorical data.

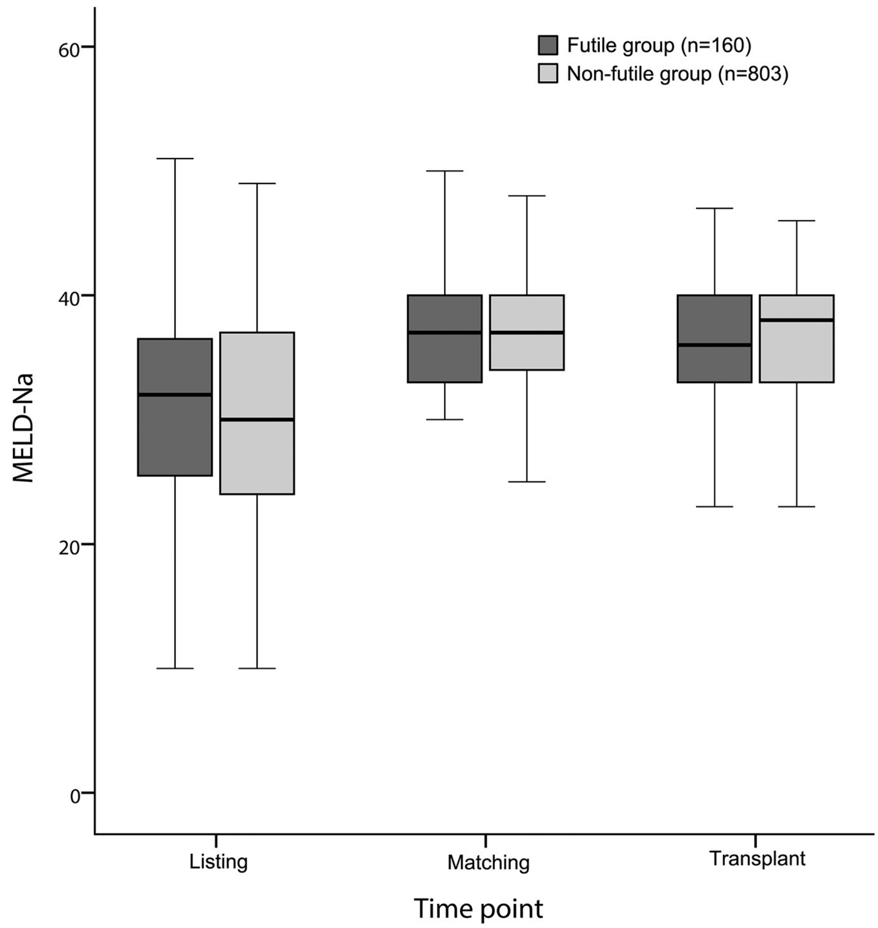

Figure 1. MELD-Na score at different time points (listing, matching, and transplant). There was no significant difference in MELD-Na score according to the time point between the groups (*P* = 0.706). MELD-Na, model for end-stage liver disease-sodium.

[6.7%] vs. 13 [4.2%], *P* = 0.361). The cold ischemic time was also comparable between the groups (347.7 [±130.2] vs. 328.0 (±122.2) min, *P* = 0.078). Furthermore, the donor risk index[12] showed no significant difference between the futile group and the non-futile group (1.49 [±0.27] vs. 1.52 [±0.34], *P* = 0.270).

Recipient outcomes

In the futile group, the causes of futility, defined as death within 3 months of liver transplantation or during hospitalization, were as follows: infectious complications in 87 (54.4%) patients, cardiovascular complications in 13 (8.1 %), cerebrovascular complications in 8 (5.0 %), graft failure in 12 (7.5 %), and unknown causes in 40 (25.0 %) patients (Fig. 2). The median time to futility was 27 days (range, 0–326 days).

Short-term clinical outcomes are shown in Table 3. Postoperative peak aspartate aminotransferase and alanine aminotransferase levels were significantly higher in the futile group than in the non-futile group (1541 [230–31 971] vs. 725 [250–30 820] IU/L, *P* < 0.001 and 694 [140–10 799] vs. 455 [190–8990] IU/L, *P* < 0.001, respectively). Major complications graded as Clavien–Dindo grade IIIA or above were significantly higher in the futile group than in the non-futile group (83 [51.9%] vs. 303 [37.7%], *P* = 0.001). Furthermore, infectious complications occurred more frequently in the futile group compared to the non-futile group (42 [44.7%] vs. 79 [13.9%], *P* < 0.001). Additionally, the number of patients requiring a re-laparotomy and re-transplantation was also higher in the futile group than in the non-futile group (44 [31.0%] vs. 115 [15.6%], *P* < 0.001, and 26 [16.2%] vs. 55 [6.8%], *P* < 0.001, respectively). Consequently, the median length of the ICU stay was significantly longer in the futile group than in the non-futile group (11 [0–166] vs. 6 [0–157] days, *P* < 0.001).

Risk factors associated with and development of a nomogram for predicting futility

Multivariate logistic regression analysis was performed to evaluate risk factors for futility (Table 4). Among the concomitant organ failure factors, the use of a mechanical ventilator (odds ratio 2.407 and 95% confidence interval [1.540–3.761], *P* < 0.001), CRRT (≥1 week, 2.839 [1.329–6.064], *P* = 0.007), and prolonged ICU stay before transplantation (≥2 weeks, 1.917 [1.049–3.501], *P* = 0.034) were independent risk factors for futility. Other significant factors included recipient age (≥65 years, 1.786 [1.097–2.907, *P* = 0.020] and BMI (<18.5 kg/m^2, 2.015 [1.118–3.632], *P* = 0.020). Significant differences in futility rate and overall survival were observed based

Table 2

Baseline characteristics of donors in the futile and non-futile groups

	Futile group (*n* = 160)	Non-futile group (*n* = 803)	Total (*n* = 963)	*P* value
Age (years)	45.9 (±15.3)	44.0 (±15.2)	44.3 (±15.2)	0.111
Sex (female)	57 (35.6%)	285 (35.5%)	342 (35.5%)	0.974
BMI (kg/m^2)	24.7 (±4.0)	24.7 (±4.7)	24.7 (±4.6)	0.873
Macrosteatosis (≥30%)[a]	5 (6.7%)	13 (4.2%)	18 (4.6%)	0.361
DCD	0 (0%)	0 (0%)	0 (0%)	—
Cause of death				0.130
Trauma	21 (24.1%)	116 (24.7%)	137 (24.6%)	
Anorexia	18 (20.7%)	147 (31.3%)	165 (29.7%)	
CVA	43 (49.4%)	175 (37.3%)	218 (39.2%)	
Others	5 (5.7%)	31 (6.6%)	36 (6.5%)	
Race				0.029
African American	10 (6.3%)	47 (5.9%)	57 (5.9%)	
American	19 (11.9%)	126 (15.7%)	145 (15.1%)	
Asian	127 (79.9%)	570 (71.0%)	697 (72.5%)	
Others	3 (1.9%)	60 (7.5%)	63 (6.5%)	
Partial/split transplantation[a]	4 (2.5%)	22 (2.7%)	26 (2.7%)	1.000
Cold ischemic time (min)	347.7 (±130.2)	328.0 (±122.2)	331.3 (±123.7)	0.078
Donor risk index	1.49 (±0.27)	1.52 (±0.34)	1.51 (±0.33)	0.270

BMI, body mass index; CVA, cerebrovascular accident; DCD, donation after circulatory death.
[a]Fisher's exact.
Values are presented as median (range) or median (standard deviation) depending on whether the data followed a normal distribution for continuous data and *n* (%) for categorical data.

on the number of risk factors in the multivariate analysis (Fig. 3). The futility rate was 11.3% for patients with no risk factors, 20.6% for those with one risk factor, 38.4% for those with two risk factors, and 53.3% for those with three or more risk factors ($P < 0.001$). The baseline characteristics and clinical outcomes of recipients and donors based on the number of risk factors are presented in Supplemental Digital Content (Table S1, http://links.lww.com/JS9/D902) and Table S2, http://links.lww.com/JS9/D902).

Figure 4A presents a nomogram developed to predict futility after a DDLT, accompanied by a receiver operating characteristic (ROC) curve assessing the predictive accuracy of the model (Fig. 4B). The nomogram included significant clinical predictors identified using the multivariate analysis, including recipient age, BMI (<18.5 kg/m^2), use of mechanical ventilation, duration of CRRT, and length of ICU stay before transplantation. The ROC curve analysis showed an area under the curve (AUC) of 0.70, demonstrating a good predictive ability of the nomogram.

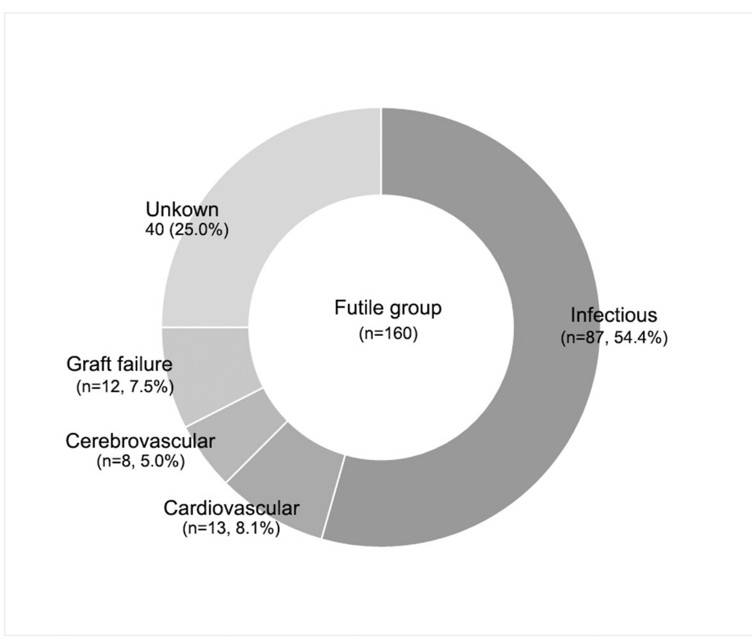

Figure 2. Cause of futility in the futile group.

Table 3

Clinical outcomes of recipients in the futile and non-futile groups

	Futile group (n = 160)	Non-futile group (n = 803)	Total (n = 963)	P value
Operation time (min)[a]	550 (277–1140)	510 (168–1019)	515 (168–1140)	0.207
Warm ischemic time (min)	42.6 (±34.8)	39.7 (±41.8)	40.2 (±40.7)	0.421
Transfusion (RBC, pint)[a]	11 (0–157)	10 (0–96)	10 (0–157)	0.011
Transfusion (FFP, pint)[a]	10 (0–146)	10 (0–77)	10 (0–146)	0.191
Peak AST (IU/L)[a]	1541 (230–31 971)	725 (250–30 820)	799 (230–31 971)	<0.001
Peak ALT (IU/L)[a]	694 (140–10 799)	455 (190–8990)	470 (190–10 799)	<0.001
Major complication (grade ≥IIIA)	83 (51.9%)	303 (37.7%)	386 (40.1%)	0.001
Biliary complication	2 (1.8%)	38 (5.9%)	40 (5.3%)	0.073
Vascular complication	12 (10.7%)	24 (3.7%)	36 (4.7%)	0.001
Bleeding complication	15 (16.0%)	81 (14.0%)	96 (14.3%)	0.617
Infectious complication	42 (44.7%)	79 (13.9%)	121 (18.0%)	<0.001
Respiratory complication	10 (10.6%)	69 (11.9%)	79 (11.8%)	0.717
Re-laparotomy	44 (31.0%)	115 (15.6%)	159 (18.1%)	<0.001
Re-transplantation	26 (16.2%)	55 (6.8%)	81 (8.4%)	<0.001
ICU stay (days)[a]	11 (0–166)	6 (0–157)	6 (0–166)	<0.001
Hospital stay (days)[a]	24 (0–326)	31 (2–646)	30 (0–646)	<0.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; FFP, fresh frozen plasma; ICU, intensive care unit; RBC, red blood cells.
[a]Mann–Whitney.
Values are presented as median (range) or median (standard deviation) depending on whether the data followed a normal distribution for continuous data and n (%) for categorical data.

This model had a better predictive power for futility after DDLT than the MELD-Na (AUC: 0.527) and balance of risk (BAR) (AUC: 0.594) scores (Fig. 4B). Furthermore, to assess the agreement between the predicted and actual outcomes, a calibration curve was constructed using the bootstrap method for internal validation (Fig. 5). The dashed diagonal line represents the performance of an ideal model, wherein the predicted outcome would correspond perfectly with the actual outcome. The dotted line represents the plot of the predicted values using the prediction model, while the solid line shows the results after correcting for bias due to overfitting through bootstrapping. Since there is a minimal difference between the dotted and solid lines, overfitting did not affect the prediction model. While the calibration curve does not align perfectly with the ideal prediction line, the overall similarity between the dashed line and the dotted line demonstrates the validity of this model in predicting futility.

Discussion

Deceased donor liver transplantation has remarkably improved, providing a vital chance for a new life for patients with end-stage liver disease and establishing a foundation for living donor liver transplantation[13]. The age-standardized prevalence of decompensated cirrhosis has risen to 132.5 per 100 000 individuals[2], consequently increasing the importance of liver transplantation globally. In Western countries, DDLT still accounts for >90% of all liver transplantations[14]. Unlike living donor liver transplantation, DDLT places a significant emphasis on priority allocation

Table 4

Univariate and multivariate logistic regression analyses for futile liver transplantation

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (≥65 years)	1.600 (1.009–2.537)	0.046	1.786 (1.097–2.907)	0.020
Sex (male)	1.140 (0.791–1.641)	0.483		
BMI (<18.5 kg/m^2)	2.149 (1.241–3.720)	0.006	2.015 (1.118–3.632)	0.020
Cause of transplantation (viral hepatitis)	0.872 (0.591–1.288)	0.492		
MELD-Na score (≥38)	1.170 (0.833–1.643)	0.364		
Hepatic encephalopathy (grade ≥3)	1.853 (1.203–2.854)	0.005	1.517 (0.941–2.445)	0.087
Concomitant organ failure				
Mechanical ventilator	3.020 (2.056–4.437)	<0.001	2.407 (1.540–3.761)	<0.001
CRRT (≥1 week)	2.396 (1.149–4.997)	0.020	2.839 (1.329–6.064)	0.007
Pneumonia	2.032 (1.249–3.304)	0.004		
Bacteremia	1.738 (1.146–2.635)	0.009		
Vasopressor	2.566 (1.730–3.807)	<0.001		
ICU stay before transplantation (≥2 weeks)	3.197 (1.875–5.452)	<0.001	1.917 (1.049–3.501)	0.034
Cold ischemic time (≥8 h)	1.678 (0.983–2.864)	0.058		
Donor risk index (≥1.5)	0.960 (0.576–1.602)	0.876		

BMI, body mass index; CI, confidence interval; CRRT, continuous renal replacement therapy; ICU, intensive care unit; MELD-Na, model for end-stage liver disease-sodium; OR, odds ratio.

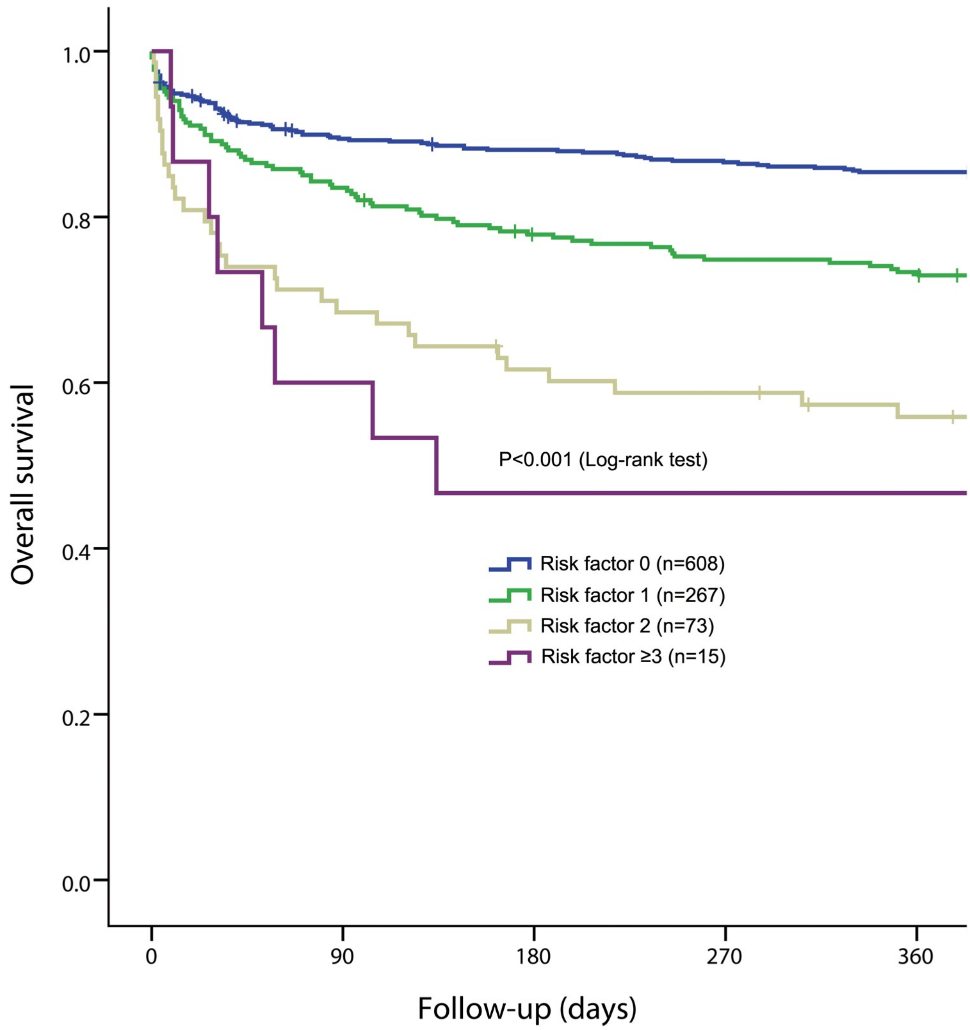

Figure 3. Overall survival according to the risk factors. Risk factors comprised recipient age ≥65 years, BMI <18.5 kg/m^2, use of mechanical ventilation, CRRT for >1 week, and ICU stay <2 weeks before transplantation. The Kaplan–Meier survival curves compare groups with zero, one, two, and three or more risk factors. Significant differences in survival are observed, with an increasing number of risk factors correlating with decreased survival ($P < 0.001$). BMI, body mass index; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

policies. Achieving balanced equity and efficiency in the distribution of limited deceased donor liver resources is a formidable challenge. Since the introduction of the MELD score for organ allocation in the USA in 2002[3,4], many countries have adopted this policy. The MELD-Na score has recently been used, despite controversies regarding its ability to reflect patient severity in certain groups[15,16]. Nonetheless, while these objective criteria prioritize equity under the "sickest first" policy, there remains a need to identify patients with extremely poor preoperative conditions to avoid futile transplantation. This critical decision rests solely on surgeons, necessitating more objective and high-evidence-level research to guide decision-making. Despite this, large-scale multicenter studies addressing this issue are still lacking. Therefore, this international multicenter study aimed to identify and quantify the risk factors for futile liver transplantation in patients with a MELD-Na score ≥30 to guide crucial decisions regarding transplantation eligibility.

The issue of futility of liver transplantation has been a longstanding concern, leading to the development of several scores for predicting futile transplantations. The most widely known among these is the UCLA futility risk score, which defines futility as death within 3 months or during hospitalization after a liver transplantation[6]. However, this applies only to patients with an MELD score of ≥40. This scoring system incorporates the MELD score, cardiac risk, age-adjusted Charlson Comorbidity Index, and pre-transplant septic shock as risk factors, with a futility rate of 50% for patients scoring ≥26. The pre-allocation survival outcomes following liver transplantation score, using the United Network for Organ Sharing (UNOS) data post-MELD score adoption, includes nearly 20 variables, making it difficult for routine use and less predictive despite its extensive data[7]. Similarly, the BAR score, also derived from UNOS data, does not adequately reflect concurrent organ failure, often accompanying liver failure, which leads to futility[8]. Moreover, the recently reported liver transplant risk score, even for high-risk groups, showed a 1-year mortality rate of 28.6%, which is insufficient to decisively determine futility[9]. To overcome the limitations of previous studies, our large-scale

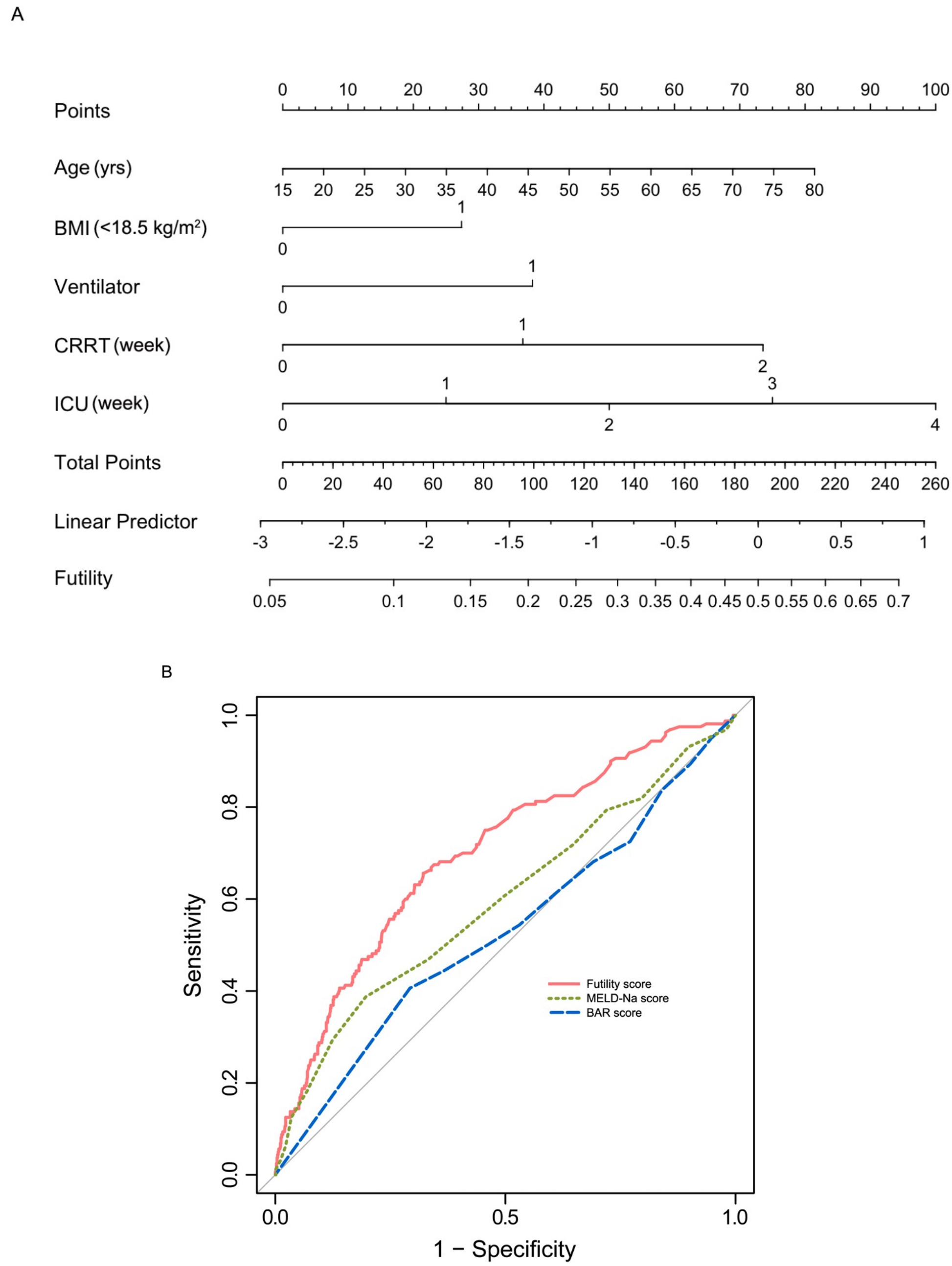

Figure 4. (A) Nomogram for predicting futility after DDLT and (B) the corresponding ROC curve. The nomogram includes significant clinical predictors for futility identified by multivariate logistic regression analysis. Our model had better predictive power for futility (AUC = 0.700) after DDLT than the MELD-Na (AUC = 0.594) and BAR scores (AUC = 0.527). AUC, area under the curve; BAR, balance of risk; DDLT, deceased donor liver transplantation; MELD-Na, model for end-stage liver disease-sodium; ROC, receiver operating characteristic.

international multicenter study focused exclusively on patients with a MELD score of ≥30. It comprehensively incorporates critical concomitant organ failure associated with futile liver transplantation and identifies predictive risk factors, resulting in an easy-to-apply, intuitive nomogram. Furthermore, our model demonstrated a better predictive power for futility than the MELD-Na and BAR scores.

Patients with high MELD-Na scores frequently experience acute deterioration of liver function[17]. Depending on the stage of liver disease and the presence of organ failure, patients can be categorized as having acute liver failure, compensated or decompensated liver cirrhosis, or acute-on-chronic liver failure (ACLF)[18]. Although various guidelines from Eastern and Western countries define these conditions differently[19-21], it is evident that patients with the highest priority for receiving liver grafts, due to their high MELD-Na scores, are more likely to experience concomitant organ failure. These organ or system failures associated with liver failure include the liver, kidneys, brain, lungs, and coagulation and circulatory systems. A study including patients with ACLF stage-3 (involving ≥3 organ

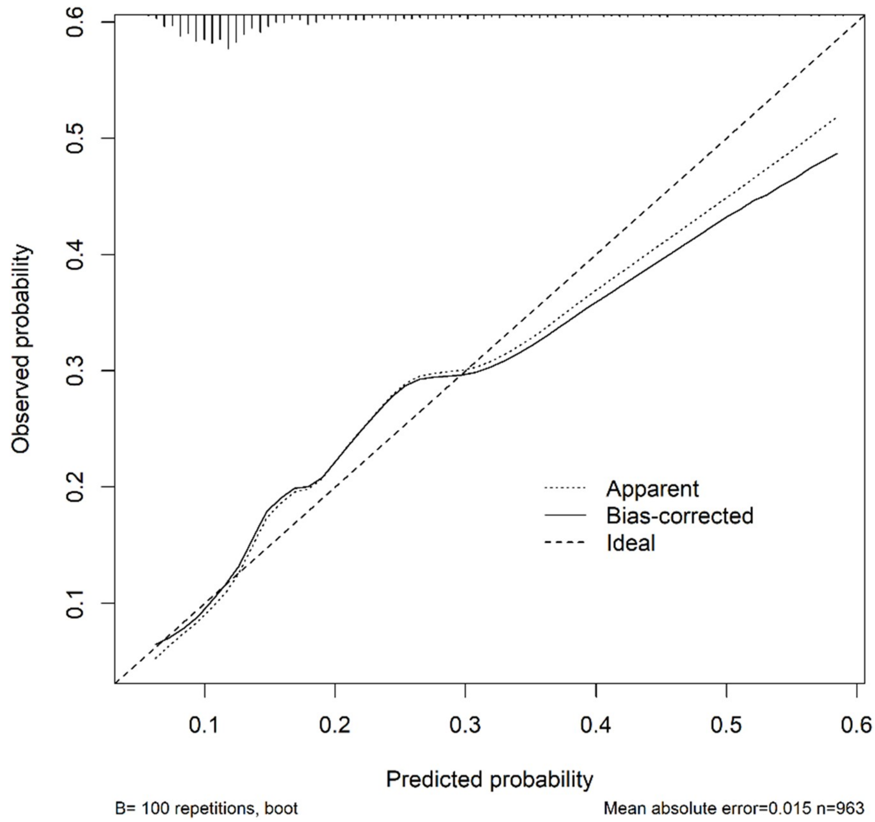

Figure 5. Calibration plot of the prediction model for futility. The calibration curve demonstrates the correlation between the predicted and observed futility rates after DDLT. The dashed diagonal line represents the performance of an ideal model. The solid line represents the actual model performance, comparing the predicted and observed futility rates using 100 bootstrap samples. Points below the diagonal line indicate over-prediction, while points above correspond to under-prediction. The plot shows a slight under- or overestimation of futility rates after DDLT, but the model was reasonably calibrated and predicted futility. DDLT, deceased donor liver transplantation.

failures) revealed a remarkably high 1-year survival rate of 83.9%, emphasizing the necessity of liver transplantation[18,22]. However, in regions where deceased donor grafts are extremely limited, it is not uncommon for patients with very high MELD-Na scores to undergo transplantation, even in those with ≥4 organ failures and experience futile outcomes.

In the multivariate logistic regression analysis for futility, the significant factors included recipient age (≥65 years), BMI (<18.5 kg/m^2), use of a mechanical ventilator, CRRT (≥1 week), and prolonged ICU stay before transplantation (≥2 weeks); which were appropriately reflected in the nomogram. In the current era of aging populations, it is not uncommon to perform liver transplantation in patients older than 70 years[13,23]. However, increasing recipient age negatively affects post-transplant outcomes and increases the risk of futility[24,25]. In particular, in cases of ACLF in which the patient's condition deteriorates rapidly, the limited functional reserve in older adult patients necessitates a comprehensive evaluation of other risk factors before deciding on transplantation. On the other hand, it is noteworthy that in our study cohort, which included only patients with MELD-Na scores ≥30, there was no difference in futility rates based on the MELD-Na score, nor was it an independent risk factor for futility. These results underscore the need for another model to predict post-transplantation outcomes in patients on waiting lists.

With regard to concomitant organ failure, it is evident that early mortality after liver transplantation increases with the number of organ failures, including liver and kidney; this risk is notably higher in ACLF settings[26-28]. In a consensus meeting involving 35 international transplant experts, it was reported that the type and number of organ failure played a critical role in the decision to delay or deny liver transplantation[29]. Specifically, there was a more lenient approach toward liver, kidney, and coagulation failures, whereas respiratory, circulatory, and metabolic failures were approached more strictly[30]. A high MELD-Na score indicates significant liver, kidney, and coagulation dysfunctions. The extent of additional concomitant organ failures is critical factor. Our study confirmed that the use of mechanical ventilation due to respiratory failure, the duration of CRRT, and ICU stay proportionally increased the risk. Although the incidences of vasopressor use and pre-transplant infections were higher in the futility group, they were not identified as risk factors in the final multivariate regression analysis, likely because of statistically significant interactions with other independent risk factors and the selective nature of the retrospective cohort. Furthermore, the thresholds for ventilator dependence (FiO_2 or PaO_2/FiO_2) and vasopressor doses vary considerably among clinicians, making standardization difficult. The risk factors and nomogram derived in this study cannot be used as absolute criteria for all patients. However, we should consider the risk of futility calculated in this study and comprehensively consider more detailed indicators and trends of life-threatening organ failure to determine transplant eligibility.

This study had few limitations. One limitation was the difficulty in incorporating more detailed variables of concomitant organ failure. Although we collected data on more specific factors, such as PaO_2/FiO_2, SaO_2/FiO_2, and the types and doses of vasopressors, the retrospective nature of the study resulted in a significant number of missing values, making it challenging to include these factors in the final analysis. Furthermore, a significant number of patients had unclear causes for transplantation, which may be a potential limitation of this large-scale retrospective study. Another limitation is the absence of donor factors in the final model. The donor risk index showed no difference between the futile and non-futile groups and was not identified as a risk factor for futility. This is likely because the patients in this study received DDLT from liver grafts with relatively low donor risk index scores. Nevertheless, this study's strength lies in its large-scale approach, comprising patients from both Eastern and Western populations and focusing exclusively on patients with MELD scores ≥30.

Conclusions

Independent risk factors for futile outcomes after DDLT in patients with MELD-Na scores ≥30 include recipient age, BMI, use of mechanical ventilation, prolonged CRRT, and ICU stay. The nomogram, which adequately reflects concomitant organ failure before liver transplantation, could predict the risk of futile transplantation and help establish individualized perioperative strategies to improve outcomes after DDLT.

Ethical approval

The study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB approval number: 2020AN0553), and strictly adhered to the ethical guidelines of the Declaration of Helsinki and the Declaration of Istanbul.

Consent

During the IRB approval process, informed consent was waived, considering the retrospective nature of this study and the fact that patient information is de-identified and poses no harm to the patients.

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Author contributions

H.-S.J., K.J.H., and D.-S.K.: conception and design; Y.-I.Y., G.-S. C., D-G.K., D.B., and H.P.: administrative support; K.-H.K., P. T., R.M., and D.B.: provision of study materials or patients; H.-S. J., Y.-I.Y., P.T., P.M.-C., J.K., D.-G.K., and C.F.-Z.: acquisition of data; H.-S.J., R.M., J.K., D.J.J., and K.J.H.: data analysis and interpretation; H.-S.J. and D.-S.K.: manuscript writing; K.-H.K., P.M.-C., W.A., G.-S.C., D.J.J., C.F.-Z., and H.P.: critical revision; all authors: final approval of manuscript.

Conflicts of interest disclosure

The authors have no conflicts of interest to disclose.

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Data availability statement

Because of the sensitive nature of the data collected for this study, the authors do not wish to make the data publicly available but are available from the corresponding author on reasonable request.

Presentation

None.

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