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A nomogram for prediction of early allograft dysfunction in living donor liver transplantation

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Abstract

Liver transplantation is the treatment of choice for end-stage liver diseases. However, early allograft dysfunction (EAD) is frequently encountered and associated with graft loss or mortality after transplantation. This study aimed to establish a predictive model of EAD after living donor liver transplantation. A total of 77 liver transplants were recruited to the study. Multivariate analysis was utilized to identify significant risk factors for EAD. A nomogram was constructed according to the contributions of the risk factors. The predictive values were determined by discrimination and calibration methods. A cohort of 30 patients was recruited to validate this predictive model. Four independent risk factors, including donor age, intraoperative blood loss, preoperative alanine aminotransferase (ALT), and reperfusion total bilirubin, were identified and used to build the nomogram. The c-statistics of the primary cohort and the validation group were 0.846 and 0.767, respectively. The calibration curves for the probability of EAD presented an acceptable agreement between the prediction by the nomogram and the actual incidence. In conclusion, the study developed a new nomogram for predicting the risk of EAD following living donor liver transplantation. This model may help clinicians to determine individual risk of EAD following living donor liver transplantation.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, DDLT = deceased donor liver transplantation, EAD = early allograft dysfunction, GGT = gamma-glutamyl transpeptidase, HCC = hepatocellular carcinoma, INR = international normalized ratio, LDH = lactate dehydrogenase, LDLT = living donor liver transplantation, LT = liver transplantation, MELD = model for end-stage liver disease, PRBC = packed red blood cell.

Keywords: early allograft dysfunction, liver transplantation, nomogram, prediction

1. Introduction

In patients with end-stage liver disease, liver transplantation (LT) has become increasingly standard among the treatment options.[1,2] In Western countries, transplanted organs are mostly obtained from brain stem-dead, heart-beating cadaveric donors. In 2017, there were 7715 cadaveric liver grafts transplanted in the United States.[3] In Asian countries, traditional religion and emotional issues limit the availability of deceased donors.[4] High waitlist mortality and liver disease progression from lengthy waiting times are major challenges in deceased donor LT (DDLT).[5]

As a result of a growing demand for LT and a scarcity of grafts from cadaveric or brain-dead donors, living donor liver donation appears to be the solution. In 1994, the first adult-to-adult living donor liver transplantation (LDLT) was performed in Hong Kong.[6] Adult LDLT decreases the healthcare costs spent on decompensated liver failure patients in the pretransplant phase. Patients on the waiting list for DDLT may deteriorate to a more debilitated state and have a high risk of mortality, while living donor recipients are generally in the earlier stage of liver disease.[7] Even though studies have shown comparable results in graft and recipient survival between LDLT and DDLT,[8,9] the incidence rate of early allograft dysfunction (EAD) is lower in LDLT than in DDLT.[10–13] Postoperative complications occurred more frequently in LDLT due to the greater technical complexity of the living donor graft.[14] Transplant clinicians have devoted their efforts to improving surgical techniques and refining postoperative management.[14] During the past few decades, LDLT has become an effective treatment for end-stage liver disease and acute liver failure.[15,16]

With an incidence as high as 27%, EAD represents one of the most common complications during post-transplantation care. EAD has been characterized as functional insufficiency after LT and has been attributed to donor factors and preservation injury.[12] The diagnosis of EAD is made in the presence of one or

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more of the following conditions: total bilirubin greater than or equal to 10 mg/dL on postoperative day 7, international normalized ratio ≥1.6 on postoperative day 7, and alanine or aspartate aminotransferases greater than or equal to 2000 IU/L within the first week.[17,18] The literature has identified numerous donor and recipient factors associated with EAD. In DDLT, risk factors included recipient ventilator use before LT, donor age, allograft steatosis, donor liver mass, donation after cardiac death, cold ischemia time, intraoperative packed red blood cell (PRBC) transfusion and operation time[11] whereas left lobe grafts, high donor body mass index (BMI), donor age, high preoperative bilirubin, and high portal perfusion pressure were risk factors for EAD among LDLT recipients.[12] To reduce the rate of EAD, there was a shift to the utility of right lobe grafts from traditionally using left lobe grafts.[19] Despite the technical principles of standardization, graft dysfunction remains a concern for most surgeons. Although the majority of EAD patients eventually recover, they are still at risk of longer intensive care unit and hospital stays,[20,21] graft loss, and greater morbidity and mortality.[22] Recently, a predictive model for EAD after LT was reported[2]; nevertheless, a predictive score for EAD after LDLT in the form of a nomogram has not been developed. In this study, we aimed to develop a nomogram examining donor and recipient characteristics in addition to blood biomarkers at different stages of transplantation to predict EAD.

2. Materials and methods

2.1. Patients

The study received prior approval from the Institutional Review Board of Chang Gung Memorial Hospital (IRB 103-5859A3) and was registered under The Australian New Zealand Clinical Trials Registry, ID number: ACTRN12615000446561. Informed written consent was obtained before LT. A total of 77 pairs of recipients and donors undergoing LDLT between May 2015 and April 2018 at Chang Gung Memorial Hospital (Taoyuan, Taiwan) were consecutively recruited to the study. Prospective recipients with a concurrent septic or shocked status, anticipated pulmonary hypertension with a preoperative pulmonary wedge pressure >35 mm Hg or refusal to provide informed consent were excluded from the study.

On the day of transplantation, the allograft was implanted with an anastomosis of the hepatic vein of the graft to the inferior vena cava of the recipient and an end-to-end reconstruction of the portal vein between the portal vein of the graft and the portal trunk of the recipient. Subsequent to graft reperfusion, the hepatic arteries of the donor and recipient were reconstructed under a microscope. Finally, duct-to-duct reconstruction was performed between the graft's hepatic duct and the recipient's common bile duct.[23]

Of the 77 recipients, 35 had hepatitis B virus-related cirrhosis, 26 had hepatitis C virus-related cirrhosis, 22 had alcoholic cirrhosis and the other 29 had hepatocellular carcinoma (HCC). From October 2018 to September 2019, a further validation cohort of 30 patients undergoing LDLT was recruited.

2.2. Data collection and variable definition

The biological model for end-stage liver disease (MELD) score was calculated on the day of transplantation in all cases. BMI was calculated by weight in kilograms divided by squared height in meters. Blood samples were collected from a peripherally indwelling arterial catheter in a serum separation tube (SST) (BD vacutainer, Franklin Lakes, NJ) at two time points: T1 before the induction of general anesthesia and T2 two hours into the neohepatic stage. The biochemical data, including albumin, creatinine (Cr), lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), were measured by the clinical laboratory within the hospital. Cold ischemia time (CIT) was defined as the time from the infusion of the cold preservation solution until the implantation of the liver allograft in the recipient. Warm ischemia time (WIT) was defined as the time from the start of the hepatic vein reconstruction to the portal reperfusion. The clinical outcomes after LT were assessed within 1 week of transplantation. The diagnosis of EAD was made for grafts meeting one or more of the following criteria[18]: international normalized ratio (INR) ≧1.6 on postoperative day 7, bilirubin level ≧10 mg/dL on postoperative day 7, and AST or ALT levels > 2000 IU/mL within the first 7 postoperative days.

2.3. Statistical analysis

Numerical variables such as age, BMI, height, weight, MELD score, blood loss, graft, graft recipient weight ratio (GRWR), PRBC, fresh frozen plasma (FFP), platelet, CIT, and WIT are presented as the mean and standard deviation. Categorical variables such as sex, blood type, status of virology, HCC, and chronic kidney disease are presented as the number and percentage. The significance of different variables was examined with independent *t* tests. A two-sided probability value of $<.05$ was considered significant.

Significant variables from the univariate test were selected and used as predictive variables in the multivariate logistic regression analysis. The optimal cut-off point of the numerical variables was determined by receiver operating characteristic (ROC) curve analysis. A point system ranging from 0 to 100 points was developed, and points were assigned in proportion to their estimated data coefficients. The variable assigned as 100 points had the largest beta coefficient, and the rest of the variables with different ratios to the largest one were assigned points accordingly. A chart for calculation was developed after the above procedures. Statistical analysis was performed using R open source software version 3.6.1 and the rms package for logistic regression and nomogram construction. Discrimination and calibration methods were used to assess the predictive accuracy of the constructed model. The concordance statistic (*c*-statistic) was the calculated area under the ROC curve (AUC). A C-statistic of more than 0.7 was regarded as fair, and more than 0.8 was regarded as good.

3. Results

3.1. Clinical characteristics of the patients

In the study cohort, the mean age of the donor and recipients was 32.52 years and 54.62 years, respectively. There were 45 (58.44%) male recipients and 32 (41.56%) female recipients. The incidence rates of EAD in the study and validation cohorts were 31.17% (24/77) and 30.00% (9/30), respectively. The clinical characteristics and laboratory data of the patients in the study and validation cohorts are presented in Table 1.

Table 1

Demographics and clinical characteristics of the primary cohort and validation cohort.

	Primary cohort (n = 77)		Validation cohort (n = 30)	
	Mean ± SD or n	%	Mean ± SD or n	%
Recipient				
Gender				
Male	45	58.44	22	73.33
Female	32	41.56	8	26.67
Age (years)	54.62 ± 8.73		56.63 ± 7.50	
BMI	25.29 ± 3.44		24.88 ± 3.97	
Height (m)	1.63 ± 0.08		1.66 ± 0.07	
Weight (kg)	67.51 ± 12.26		68.35 ± 12.23	
Blood type				
A	26	33.77	9	30
B	17	22.08	10	33.33
O	31	40.26	10	33.33
AB	3	3.90	1	3.33
MELD	18.27 ± 9.56		16.27 ± 7.03	
HBV (Yes/No)	35/42	45.45/54.55	18/12	60.00/40.00
HCV (Yes/No)	26/51	33.77/66.23	3/27	10.00/90.00
Alcoholism (Yes/No)	22/55	28.57/71.43	9/21	30.00/70.00
HCC (Yes/No)	29/48	37.66/62.34	13/17	43.33/56.67
ABO incompatibility (Yes/No)	13/64	16.88/83.12	2/28	6.67/93.33
CKD (Yes/No)	15/62	19.48/80/52	4/26	13.33/86.67
Donor				
Gender				
Male	29	37.66	15	50.00
Female	48	62.33	15	50.00
Age (years)	32.52 ± 8.23		30.87 ± 9.12	
BMI	22.96 ± 2.74		22.11 ± 4.64	
Height (m)	1.65 ± 0.08		1.67 ± 0.09	
Weight (kg)	63.04 ± 11.38		63.48 ± 10.30	
Blood type				
A	18	23.38	8	26.67
B	15	19.48	5	16.67
O	41	53.25	17	56.67
AB	3	3.90	0	0
Intra-operative factor				
Blood loss (mL)	2044.42 ± 1708.90		1904.67 ± 1976.03	
Graft (g)	635.26 ± 133.85		628.00 ± 135.58	
GRWR (%)	0.96 ± 0.25		0.96 ± 0.24	
PRBC (U)	9.22 ± 7.52		8.13 ± 8.39	
FFP (U)	12.83 ± 10.68		13.13 ± 10.04	
Platelet (U)	8.75 ± 9.24		11.20 ± 9.42	
CIT (minutes)	50.35 ± 33.67		48.60 ± 31.37	
WIT (minutes)	47.75 ± 35.30		17.00 ± 4.84	

BMI = body mass index, CIT = cold ischemia time, CKD = chronic kidney disease, FFP = fresh frozen plasma, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, GRWR = graft recipient weight ratio, MELD = model for end-stage liver disease, PRBC = packed red blood cell, WIT = warm ischemia time.

Based on the results of univariable analysis, potential risk factors for EAD including donor's age, recipient's MELD score, serum biomarkers such as total and direct bilirubin and ALT in addition to intraoperative blood loss were identified. All significant factors in the univariate analysis were used to build a multivariable logistic regression model. Donor's age, recipient's MELD score, preoperative serum ALT, reperfusion serum total bilirubin, and blood loss remained independent prognostic factors in the logistic model. The optimal cut-off value for blood loss was determined using ROC analysis and was 2902. The optimal cut-off values for T1 ALT and T2 total bilirubin were 58.9 and 11.1, respectively. Multivariate analysis (Table 2) showed that MELD score (OR 1.221; 95% CI 1.012–1.472; $P = .0367$), preoperative serum ALT ≧ 58.9 (OR 8.814; 95% CI 2.396–32.427; $P < .01$), reperfusion serum total bilirubin ≧11.1 (OR 0.561; 95% CI 0.315–1.000; $P = .0499$), donor age ≧45 years (OR 16.245; 95% CI 2.202–119.852; $P < .01$), and blood loss ≧2902 (OR 4.385; 95% CI 1.230–15.631; $P = .0226$) were significantly associated with EAD after LDLT.

3.2. Prognostic nomogram for the prediction of EAD

A nomogram incorporating the aforementioned significant risk factors was created (Fig. 1). As each of the three parameters in calculating the MELD score was considered individually, and the MELD score was excluded from the nomogram. Donor's age contributed the most and was assigned 100 points, whereas the rest of the variables were appointed points in proportion to their beta coefficients. By summing the total score and locating it on the total point scale, the probability of EAD can be estimated accordingly.

Table 2

Univariable analysis and logistic regression analysis.

Variable	Univariable analysis *P* value	Logistic regression analysis		
		Odds ratio	95% CI	*P*
Recipient				
Age (years)	.0541			
BMI	.9725			
MELD	.0380	1.221	1.012–1.472	.0367
T1 albumin (g/dL)	.6442			
T1 creatinine (mg/dL)	.1548			
T1 LDH (U/L)	.1114			
T1 total bilirubin (mg/dL)	.0031	0.948	0.670–1.341	.7627
T1 direct bilirubin (mg/dL)	.0052	0.981	0.602–1.601	.9398
T1 AST (U/L)	.1873			
T1 ALT (U/L)	.0370	8.814	2.396–32.427	.0011
T1 ALP (U/L)	.7769			
T2 albumin (g/dL)	.7149			
T2 creatinine (mg/dL)	.0770			
T2 LDH (U/L)	.0533			
T2 total bilirubin (mg/dL)	.0022	0.561	0.315–1.000	.0499
T2 direct bilirubin (mg/dL)	.0077	2.252	0.709–7.154	.1688
T2 AST (U/L)	.1908			
T2 ALT (U/L)	.6692			
T2 ALP (U/L)	.3906			
Total bilirubin T2/T1	.9550	1.201	0.641–2.251	.5671
ABO incompatibility	.9729			
Donor				
Age (years)	.0303	16.245	2.202–119.852	.0063
≧45				
<45				
BMI	.1130			
Intra-operative factor				
Blood loss (mL)	.0468	4.385	1.230–15.631	.0226
Graft (g)	.9562			
GRWR (%)	.3989			
≧0.8				
<0.8				
CIT (minutes)	.3307			
WIT (minutes)	.5796			

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CIT = cold ischemia time, GRWR = graft recipient weight ratio, LDH = lactate dehydrogenase, MELD = model for end-stage liver disease, WIT = warm ischemia time.

3.3. Validation and calibration of the nomogram

The ROC curves of the study and validation groups are plotted in Figure 2. The accuracy of this predictive model was tested by AUC. In the study cohort, the AUC for the established nomogram to predict EAD was 0.846. In the validation cohort, the AUC remained as high as 0.767 (Fig. 2). The calibration curve showed a steady distribution, which demonstrated a good estimation of agreement between the predicted probabilities and observed proportions (Fig. 3). The calibration plots presented acceptable agreement between the prediction by the nomogram and the actual incidence of EAD.

4. Discussion

EAD indicates poor graft function in the first week of LT, adversely influencing graft and patient outcomes. Several prognostic models have been reported, although these models emphasize only one or two factors and require complex calculations. In LDLT, a donor age of 50 years or older, a high MELD score, and HCV-positive status was associated with poor survival and hepatic artery resistance index was predictive of EAD.[4,24] Calculation models containing recipient and donor factors have been previously proposed to predict EAD after DDLT.[2] Indocyanine green plasma disappearance rate during reperfusion stage was also presented in the prediction of EAD and mortality after DDLT.[25] The contributing factors and mechanism for EAD are fundamentally different between LDLT and DDLT.[26] and creating a model that accurately assess the risk in developing EAD can be challenging. In comparison to these previously published models, we have designed a nomogram that is a precise, rapid and approachable to the transplant surgeons in assessing the risks of graft failure in LDLT recipients.

HCC development is a long process involving genetic changes over time. Histidine triad nucleotide-binding 2 (*HINT2*), has been studied as a tumor suppressor and found to be down-regulated in HCC, suggesting low *HINT2* expression predicts earlier tumor recurrence.[27] Other prognostic factor, the soluble form of programmed death ligand 1 (sPD-L1) on tumor cells, when elevated, has also been found to be prognostic indicator for poor outcome.[28] Huge HCC, defined as a tumor diameter greater or equal to 10 cm, complete resection was believed to be potentially curative; however, the approach and extent of

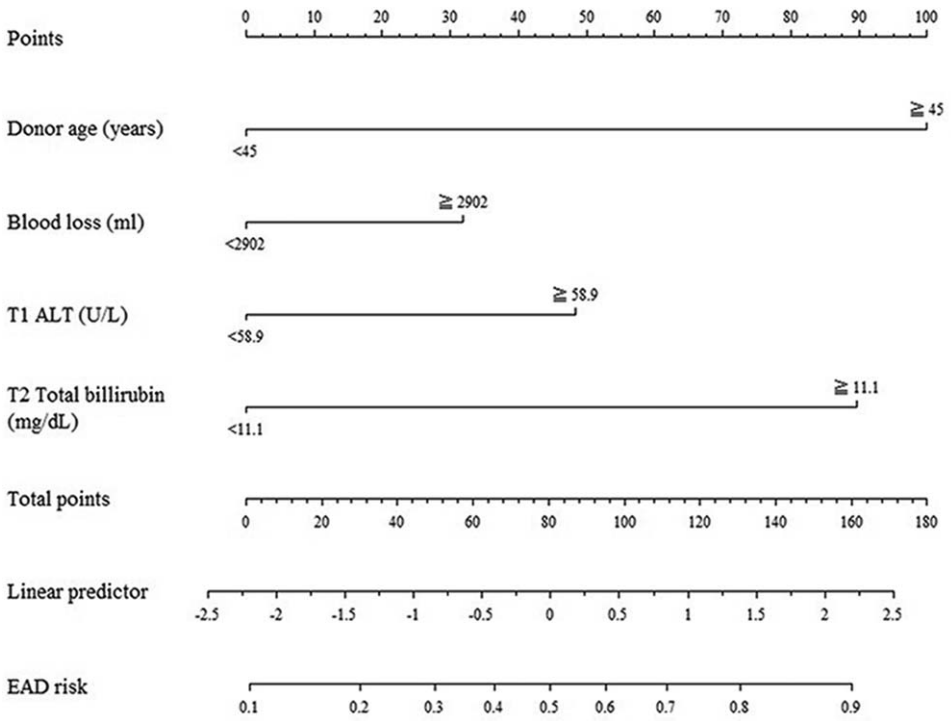

Figure 1. The nomogram for predicting the incidence of early allograft dysfunction following liver transplantation. ALT = alanine aminotransferase, EAD = early allograft dysfunction.

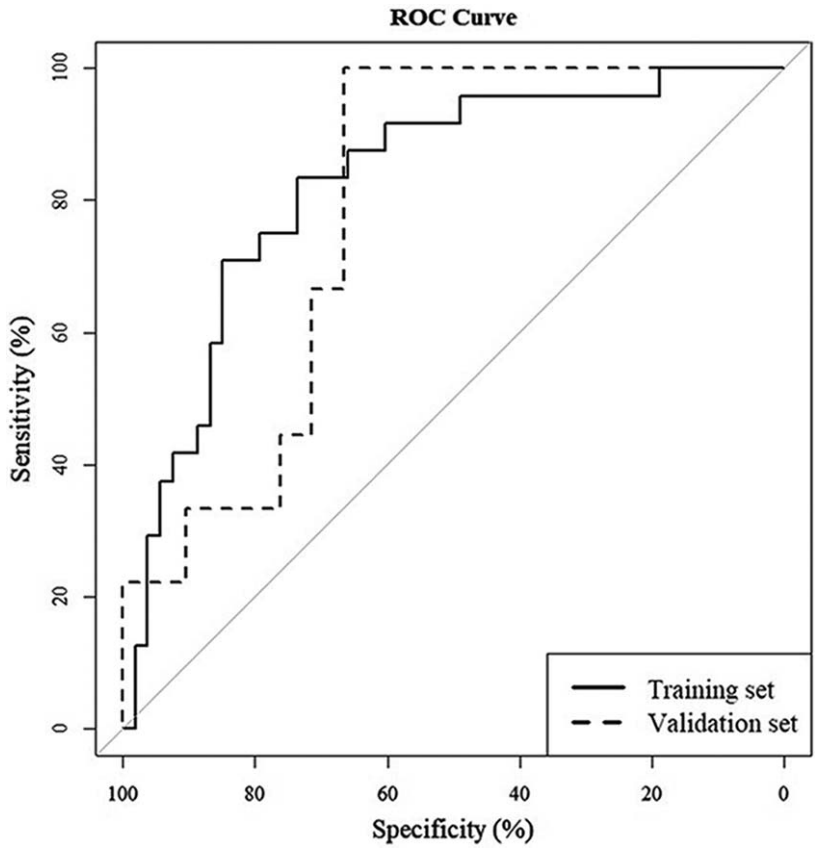

Figure 2. Receiver operating characteristic (ROC) curves. The area under the receiver operating characteristic curve (AUC) for the established nomogram to predict EAD for the study group was 84.6%. The AUC for the validation group was 76.7%.

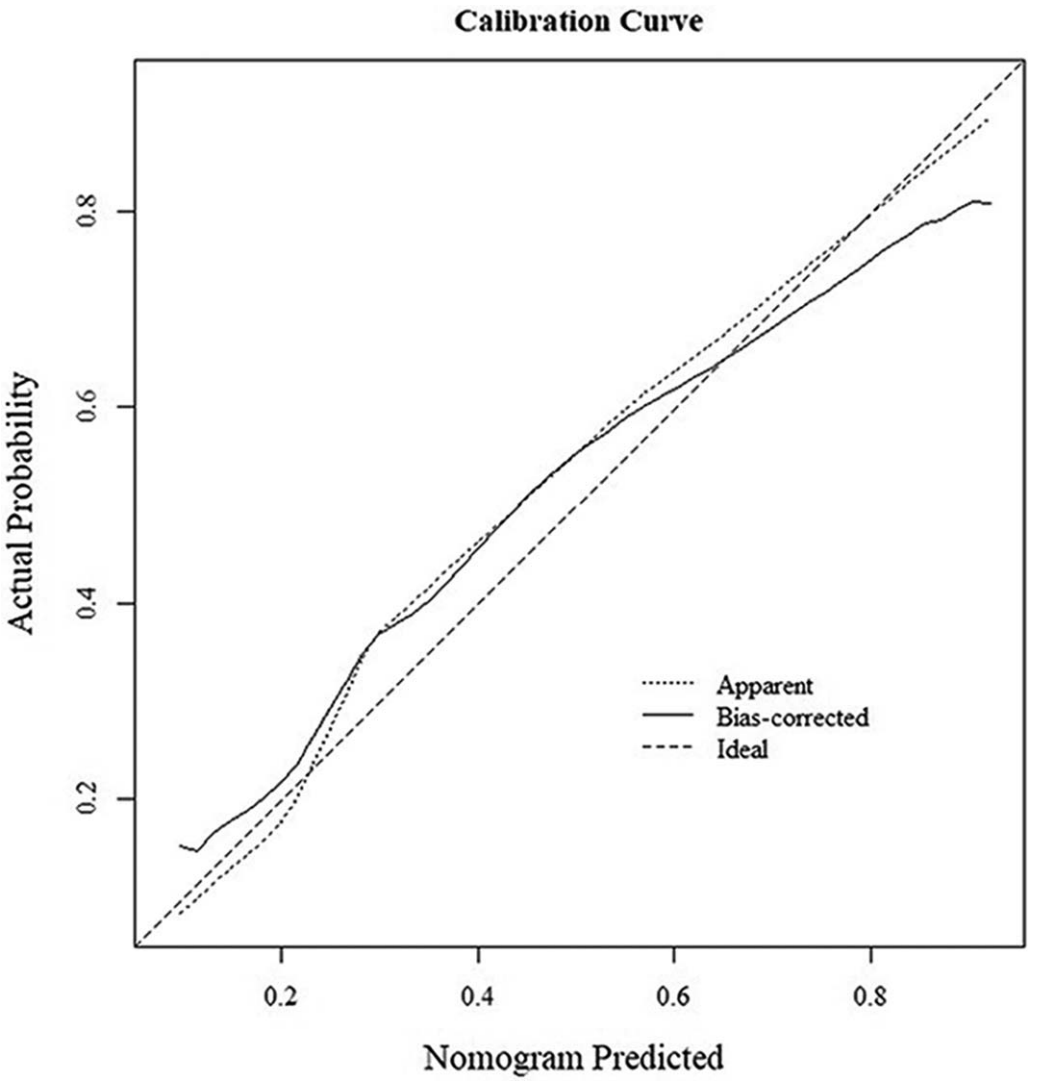

Figure 3. The calibration curves for predicting the incidence of early allograft dysfunction (EAD) following living donor liver transplantation in the primary cohort. The incidence rate predicted with the nomogram is plotted on the *x*-axis; the incidence rate of EAD is plotted on the *y*-axis. The 45-degree line indicates a perfect calibration model.

resection remain unclear. HCC with diaphragmatic invasion often requires tumor en bloc with part of the diaphragm is often resected and anterior approach is recommended in minimizing intraoperative bleeding.[29] In advanced HCC patients, LT offers the best long-term survival when compared to complete resection, often limited by the amount of the future liver remnant, is believed to offer better 1- and 3-year survival. When the liver functional reserve becomes doubtful, other treatments such as transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA) and liver transplantation are still available as treatment options. LT for HCC representing 15% to 50% of all LT and LT appears to be the best treatment for early and advanced stage HCC.[30,31]

Through univariable analysis and subsequent logistic regression regarding the donor, intraoperative parameters and recipient, we identified donor's age, intraoperative blood loss, preoperative ALT, and reperfusion serum total bilirubin as independent prognostic factors. The literature has suggested that aged donor grafts were associated with poorer graft survival at 3 months and 1 year and eventually recipient survival.[32,33] In contrast to the association with EAD, Kuramitsu et al reported that aged grafts had similar graft survival outcomes compared with younger grafts.[34] In the present study, older donor age (≧45 years) was significantly associated with EAD.

Intraoperative blood loss requiring massive blood transfusion often leads to coagulopathy, hypothermia, acidosis, and electrolyte abnormalities.[35] Both massive hemorrhage and transfusion are associated with an increased risk of mortality and morbidity after LT.[35,36] Intraoperative bleeding is also associated with an increased likelihood of tumor recurrence following LT for HCC.[37] Ikegami et al[38] examined 210 cases undergoing LDLT and reported that operative blood loss was significantly associated with early graft loss (10.7 ± 12.3 L vs 4.9 ± 5.8 L; $P = .003$). In the present study, blood loss of over 2902 mL was significantly predictive of EAD.

ALT is a liver enzyme indicative of hepatocellular injury or death.[39,40] Ioannou et al[41] reported that elevated ALT activity in the absence of viral hepatitis or excessive alcohol consumption

was related to an increased calculated risk of coronary heart disease. Ischemia-reperfusion injury has a great impact on liver function during LT, and increased serum transaminase levels were noted after reperfusion.[42] The ALT level might be elevated over 4 to 5 times the upper limit of the normal range in uncomplicated cases on postoperative day 1.[43] In contrast, Ardite et al[44] identified a peak serum ALT level of more than 2500 IU/mL within the first 3 postoperative days as initial graft dysfunction. Postoperative serum aminotransferases, including AST and ALT, were significantly associated with a higher rate of graft loss within 3 months.[45] A predictive index using the ratio of ALT and gamma-glutamyl transpeptidase (GGT) served as independent risk factors for EAD.[46] Preoperative and reperfusion indices were considered because the elevation of postoperative ALT may be multifactorial and nonspecific due to insufficient graft function. Although the detailed mechanism of action by which elevated ALT levels had a negative effect on the initial graft outcome remains unclear, the present study demonstrated that a preoperative ALT level >58.9 mg/dL was significantly associated with EAD. To the best of our knowledge, no previous study has revealed a relationship between preoperative ALT level and EAD. Future work is needed to further confirm this finding.

Bilirubin, the color constituent of bile, is a major end product of heme breakdown. The enterohepatic cycling of conjugated bilirubin is impaired in cholestatic and parenchymal liver diseases.[47] The literature has demonstrated that bilirubin concentration was elevated secondary to poor liver function, blood transfusion, and cholestasis after severe ischemia in the post-transplant period.[43] In LDLT, preoperative hyperbilirubinemia is associated with EAD after LDLT in the A2ALL cohort study[12] whereas in DDLT, high pretransplantation bilirubin levels are related to reduced ischemia-reperfusion injury and mortality rate.[48] Delayed hyperbilirubinemia or serum total bilirubin level > 20 mg/dL on postoperative day 7 is especially indispensable in the evaluation of primary graft dysfunction, which is highly associated with graft mortality.[38] There has been little investigation into the relationship between intraoperative clinical biochemistry data and transplantation outcome. The present study revealed that serum total bilirubin during the neohepatic stage may reflect the severity of ischemia and could predict the initial graft outcome immediately after LT.

There are some limitations that might interfere with the interpretation of this predictive model. First, this is a single center analysis with a small population. In addition, the study might be limited to Asian ethnicities and geographical areas. Future work is warranted to test this prediction model.

In conclusion, a new nomogram for predicting the risk of EAD following LDLT was developed. By using this model, surgeons can predict the risk of EAD soon after LDLT, and precautions for graft dysfunction could be taken as early as possible.

Author contributions

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