Blood loss during liver transplantation is a predictor of postoperative thrombosis

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ABSTRACT

Liver transplantation (LT) is an effective way to cure end-stage liver diseases (ESLDs), which have generally been regarded as examples of acquired bleeding disorders. However, postoperative thrombosis after LT is recognised and remains a life-threatening complication. This study aimed to show that blood loss during LT is a predictor of postoperative thrombosis and to establish a predictive model. We analysed the medical records of all patients who underwent LT at the First Affiliated Hospital of Xi'an Jiaotong University from January 2017 to April 2019 to identify the risk factors for post-transplant thrombosis. The predictive nomogram was established based on independent predictors identified by logistic regression analysis. Blood loss during LT of ≥31.25 mL/kg can predict postoperative thrombosis, and the nomogram achieved an accurate prediction.

KEYWORDS: liver transplantation, postoperative thrombosis, hepatic artery thrombosis, portal venous thrombosis, nomogram

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Introduction

Liver transplantation (LT) has become a curative way to improve the outcome of patients with end-stage liver diseases (ESLDs).[1] Coagulation disorders and bleeding issues in patients with ESLDs have been considered the dominant clinical problem for many years, but now thromboembolic complications are also recognised.[2,3] Inappropriate clotting is seen in hepatic artery thrombosis (HAT), portal vein thrombosis (PVT) and peripheral limb deep vein thrombosis (DVT). Furthermore, sometimes the inferior vena cava and the hepatic vein system may be affected.[4]

Better surgical and medical management of LT have improved the survival of patients. However, postoperative thrombosis remains a life-threatening complication. Although the incidence of HAT is relatively low and ranges between 1.2% and 6%, mortality after HAT approaches 30%.[5–8] The incidence of PVT is 1%–3%, which can lead to mesenteric ischaemia or even a negative impact on graft function and transplantation outcomes.[9,10] DVT has increasingly become an important cause of morbidity and mortality after major abdominal surgery in recent decades, but reports regarding the incidence and predictors of it in liver transplant recipients are still lacking.[11]

Bleeding during liver surgery could be surgical, coagulopathic or both.[12,13] Blood products commonly used to replace the blood lost include red blood cells (RBCs), fresh frozen plasma (FFP) and platelets.[2,14] Procoagulant proteins included in the haemostasis process are deficient in patients with ESLD due to innate protein synthetic dysfunction. The reduced production of haemostatic elements can be compensated for by off-setting factors that are associated with thrombosis (such as the high levels of the platelet adhesive protein, von Willebrand factor (vWF)).[15] Postoperative thromboembolic complications may be triggered by transfused blood products combined with compensatory mechanisms. Previous studies have shown that ≥7 units of blood received during the LT was significantly associated with early HAT ($p=0.017$), and patients were more likely to develop DVT if they received increased amounts of intraoperative FFP ($p<0.001$).[11,16]

Given the linear relationship between blood loss, blood products requirements and, subsequently, thromboembolic events, we hypothesised that the intraoperative blood loss during LT may be a factor relevant to postoperative thrombosis. Our study was conducted to show this, identify other possible predictors and construct a nomogram, which will be a useful tool to identify those who are at an increased risk of developing thrombosis after LT.

Materials and methods

Patients

The institutional review board approved this study. The medical records of all consecutive patients who underwent classic orthotopic LT at the organ transplantation unit of the First Affiliated Hospital of Xi'an Jiaotong University, China, from January 2017 to April 2019 were analysed. All of the liver grafts were from cardiac-dead donors. Patient demographics, perioperative factors and postoperative thrombosis were recorded carefully. The exclusion criteria were patients aged <18 years, incomplete clinical data, repeat transplants, multi-organ transplantation and cases who returned to theatre after LT. Patient follow-up was conducted until death, thrombosis or the end of the study period. During the entire follow-up, the occurrence of HAT, PVT, or upper and lower extremity DVT at any site were recorded. To examine the generalisability of the

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model, an independent cohort of patients who underwent LT in 2016 was enrolled, using the same inclusion and exclusion criteria. The patients were defined as the validation cohort of this study.

It is remarkable that the deceased donor livers in our study were all from donation after cardiocirculatory death. A suitable donation after cardiac death candidate is defined as a severely neurologically injured patient who is expected to expire within 60 minutes following life support measures withdrawal, guided by the University of Wisconsin Donation After Cardiac Death Evaluation Tool.[17]

At our centre, LT is performed by dedicated teams of surgeons and anaesthetists. In general, a haemoglobin concentration of 70 g/L was used as a transfusion trigger. However, in rapidly bleeding patients, the final haemoglobin threshold was 80 g/L. FFP was provided generally in a 1:1 ratio with RBCs. Additional FFP was guided by laboratory test results and microvascular bleeding. In our institution, platelets were rarely transfused because of the blood bank resource management policy. Since there were no specific defined target laboratory values for ESLD patients, transfusion of blood products was mainly based on clinical grounds at our centre.[18]

Postoperative prevention and diagnosis of thrombosis

All of the patients received nadroparin calcium once a day (OD) and alprostadil twice a day (BID) after LT during the intensive care unit (ICU) period for the prevention of thrombosis as soon as no evidence of haemorrhagic or bleeding tendency was found. Detection of thrombosis was performed by Doppler ultrasound (DUS; including DUS of the hepatic artery, portal vein and peripheral limb deep vein), this imaging examination was performed once a day during each patient's stay in the surgical ICU (SICU). When hepatic arterial and portal vein inflow were not observed, hepatic angiography and percutaneous transhepatic portography (PTP) were performed to reach a final diagnosis.

Statistical methods

Statistical analyses to identify the risk factors were performed with SPSS for Windows 22.0 (SPSS, Chicago, USA). Categorical data were expressed as numbers and percentages, quantitative variables were expressed as the median and interquartile range (IQR) or the mean and standard deviation (SD). The Pearson chi-squared test and Fisher exact test were used to compare qualitative variables, while Student's t-test or the Mann–Whitney *U* test was used for continuous independent variables. Variables that were associated with thrombosis issues in the univariate regression models ($p<0.1$) were then entered into a backward-stepwise multivariate logistic regression analysis to identify independent predictors, which were used to generate a prognostic model; $p<0.05$ was considered significant for these final analyses.

To assess the discriminatory power of blood loss volume and the prognostic power of the multivariable model, we constructed receiver operating characteristic (ROC) curves and measured the areas under the ROC curve (AUCs) for the prediction of thrombotic complications, which were converted into binary forms. The optimal cut-off point for the ROC analysis was determined using Youden's index, the point that gave the greatest sum of the specificity and sensitivity. The ROC curves were generated, and the differences in the AUCs were detected using MedCalc v15.0 (MedCalc Software, Ostend, Belgium).

Predictive nomogram

A nomogram was created using the *rms* package in R v3.6.0 (The R Foundation) based on the results of multivariate analysis. The performance of the nomogram was evaluated by the concordance index (C-index). The value of the C-index ranges from 0.5–1.0, with 0.5 indicating a random chance and 1.0 indicating a perfect ability to discriminate the outcome. The calibration curve was derived to illustrate the association between the actual and the predicted probabilities. The actual probability is plotted on the y axis; the nomogram-predicted probability of postoperative thrombosis is plotted on the x axis. A plot along the 45° line would indicate a perfectly calibrated model in which the predicted probabilities are identical to the actual outcomes. In preparation for the clinical use of the nomogram, the total scores of each patient were calculated to find an appropriate point to stratify patients into two groups (low- and high-predictive probabilities).

Results

Of the 253 patients in the primary database, 14 patients without complete clinical information, four patients who underwent repeat transplantation and three patients who had multi-organ transplantation were excluded. A total of 232 patients were eligible for our final analysis. The median age was 48 years (IQR 39–55), 176 (75.9%) patients were men and 60 (25.9%) patients had pre-transplant thrombosis. Overall, postoperative thrombotic events were diagnosed in 26 (11.2%) cases: HAT occurred in eight (3.5%) patients, PVT in nine (3.9%) patients and DVT in nine (3.9%) patients. Thrombosis occurred after a median time of 6 days (IQR 2–12) from LT.

Blood loss analysis related to the risk of thrombotic events

The study population was categorised according to the presence or absence of postoperative thrombosis. A higher blood loss volume (median of 32.8 mL/kg (IQR 17.9–61.5); $p<0.001$; Table 1) was associated with postoperative thrombosis after LT. Then, a ROC curve was plotted to verify the optimal cut-off value, which was 31.25 mL/kg (AUC 0.731; 95% confidence interval (CI) 0.669–0.787; sensitivity 53.85%; specificity 81.55%; Fig 1).

Table 1. Description of intraoperative blood loss during liver transplantation

	Total, n=232	No thrombosis, n=206	With thrombosis, n=26	p-value
Blood loss, mL/kg, median (IQR)	16.9 (10.1–28.9)	15.9 (9.8–27.9)	32.8 (17.9–61.5)	<0.001

IQR = interquartile range.

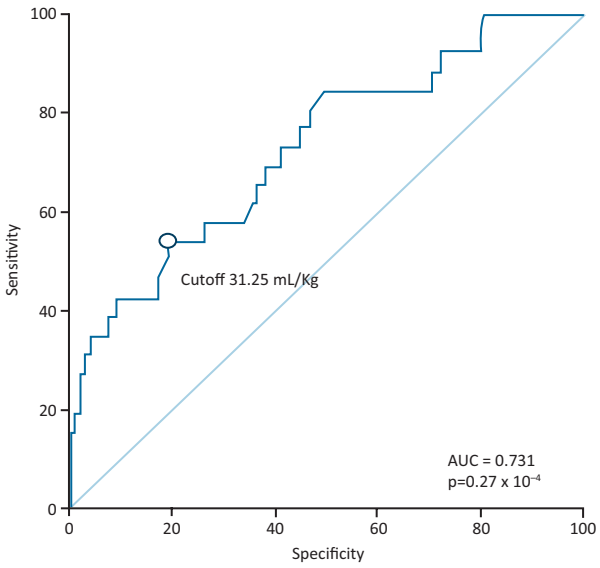

Fig 1. Receiver operating characteristic curve for the ability of blood loss to discriminate between patients with and without postoperative thrombosis. AUC = area under the curve.

Other predictors of postoperative thrombosis

Preoperative clinical donor characteristics, laboratory data and operative factors for all patients are shown in Tables 2 and 3, and supplementary material S1, Table S1. There were no significant differences between the patients grouped by sex, age, body mass index (BMI) or donor characteristics. Patients who developed thrombosis after LT were found to have a higher Model for End-stage Liver Disease (MELD) score (p=0.056), and a lower haemoglobin (p=0.007), RBC count (p=0.017), haematocrit (p=0.006) and fibrinogen (p=0.008). The diagnosis of primary hepatic carcinoma was associated with avoidance of thrombosis (p=0.061). In addition, a longer prothrombin time (PT; p=0.004), longer activated partial thromboplastin time (aPTT; p=0.031), higher international normalised ratio (INR; p=0.004) and higher D-dimer level (p=0.004) were detected in patients with thrombosis. In view of the potential impact that pre-transplant thrombosis can have on postoperative thrombosis, we performed an analysis. There were 60 patients who had pre-transplant thrombosis, and 10 (16.7%) in this subgroup developed postoperative thrombosis. This group of 60 patients had a non-significantly higher postoperative thrombosis rate compared with patients without any thrombosis before LT (10/60 (16.7%) vs 16/172 (9.3%); p=0.119).

Among the intraoperative factors, a longer surgery time (p=0.003) was associated with thrombosis. The infusion of ≥27.7 mL/kg of FFP, ≥26 mL/kg of RBCs and ≥10 units of cryoprecipitate intraoperatively increased the incidence of thrombosis significantly (p<0.001, p=0.001 and p=0.081, respectively). We also recorded the thromboelastography (TEG), but there was no significant difference.

All statistically significant factors in the univariate analysis (p<0.1) in our study were entered into the logistic regression model. As shown in Table 4, blood loss ≥31.25 mL/kg during the operation could predict thrombosis independently (hazard ratio (HR) 5.214; p=0.012). Other independent risk factors were the preoperative haematocrit level (HR 1.799; p=0.035) and the haemoglobin level (HR 1.856; p=0.013).

Multivariable prognostic model with independent factors

To evaluate whether the integration of blood loss and the preoperative levels of haemoglobin and haematocrit could improve the prediction of postoperative thrombosis, a multivariable joint ROC analysis was performed (Fig 2). The AUC was 0.822 (95%CI 0.765–0.869; p<0.001), which indicates that the multivariable model could forecast thrombosis. The predictive power was compared between the multivariable model and blood loss alone. The AUC of the multivariable model was significantly higher than the AUC of the blood loss model (0.822 vs 0.731; p=0.047).

Table 2. Clinical and donor characteristics of all study patients for thrombosis groups

	Total, n=232	No thrombosis, n=206	With thrombosis, n=26	p-value
MELD score, median (IQR)	15 (10–20)	15 (10–19)	18 (12–26.5)	0.056
Primary hepatic carcinoma, n (%)	73 (31.5)	69 (33.5)	4 (15.4)	0.061
Hemoglobin, g/L, mean (SD)	109.3 (24.4)	111 (24)	96.4 (23.9)	0.007
RBC count, × 10^{12}/L, median (IQR)	3.5 (3–4.1)	3.5 (3.0–4.2)	3.1 (2.6–3.5)	0.017
Haematocrit, %, median (IQR)	32 (27.9–37.5)	32.4 (28.2–38.1)	28.3 (23.8–33)	0.006
PT, seconds, median (IQR)	17.7 (15.7–20.9)	17.6 (15.5–20.5)	19.6 (17.1–27.8)	0.004
aPTT, seconds, median (IQR)	44.8 (40.2–51.4)	44.4 (39.9–50.4)	48.3 (42.5–58.1)	0.031
INR, median (IQR)	1.5 (1.3–1.8)	1.5 (1.2–1.8)	1.7 (1.4–2.6)	0.004
Fibrinogen, g/L, median (IQR)	1.8 (1.5–2.4)	1.8 (1.5–2.4)	1.6 (1–2)	0.008
D-dimer, mg/L, median (IQR)	1.8 (0.8–4.3)	1.7 (0.7–4.1)	3.6 (1.3–10.1)	0.004

aPTT = activated partial thromboplastin time; INR = international normalised ratio; MELD = Model for End-stage Liver Disease; PT = prothrombin time; RBC = red blood cell.

Table 3. Operative factors associated with postoperative thrombosis

	Total, n=232	No thrombosis, n=206	With thrombosis, n=26	p-value
Duration of surgery, hours, median (IQR)	6 (5.5–7)	6 (5.5–7)	7 (6–8.8)	0.003
Anhepatic phase, minutes, median (IQR)	50 (42–57)	51 (45–60)	51 (44–56)	0.391
HA anastomosis time, minutes, median (IQR)	40 (35–45)	40 (35–45)	40 (40–55)	0.096
Intraoperative blood transfusion				
RBC, mL/kg, median (IQR)	17.5 (8.1–26.2)	16.5 (7.4–25.3)	26 (18–40)	0.001
FFP, mL/kg, median (IQR)	18.2 (12.2–26.7)	16.7 (11.8–25.2)	27.7 (17.3–38.4)	<0.001
Cryoprecipitate, units, median (IQR)	5 (0–10)	5 (0–10)	10 (0–17)	0.081

FFP = fresh frozen plasma; HA = hepatic artery; RBC = red blood cell.

Construction and calibration of the nomogram

A nomogram was constructed with independent predictors of postoperative thrombosis (Fig 3). To use the nomogram, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each value (top plotting scale). The total points are calculated as the sum of points for each variable, and the probability of thrombosis is the corresponding number of total points on the nomogram (bottom plotting scale). The C-index of the nomogram was 0.716 (95%CI 0.603–0.829). In addition, the calibration plot showed good agreement between the prediction by nomogram and the actual observation (Fig 4).

Validation of the nomogram

The medical records of all consecutive patients who underwent LT in 2016 (n=83) at our centre were collected and defined as the validation cohort of this study to further estimate the value of the nomogram. The patients who underwent LT from January 2017 to April 2019 were defined as the primary cohort. The clinical and donor characteristics of the patients in the primary cohort and the validation cohort are listed in supplementary material S1, Table S1. Postoperative thrombosis after LT was found in 26 (11.2%) and eight (9.6%) patients in the primary cohort and the validation cohort, respectively. The ROC curve analysis was performed to validate the nomogram internally in the primary cohort (Fig 5a) and externally in the validation cohort (Fig 5b). In the primary cohort, the AUC was 0.718 (95%CI 0.655–0.775). In the validation cohort, the AUC was 0.652 (95%CI 0.539–0.754). There was no statistical significance between two AUCs (p=0.5832).

Risk of postoperative thrombosis based on the nomogram scores

According to Youden's method, the optimal cut-off value for the total nomogram scores was 65, and the sensitivity and specificity were 53.85% and 84.80%, respectively. The median value was 55, the sensitivity and specificity were 57.69% and 64.71%, respectively. However, considering that we cannot have both high sensitivity and high specificity, and the purpose of our nomogram is to correctly identify hypercoagulability (a high sensitivity) instead of to prevent false negativity (a high specificity), the median value of the nomogram scores was used as the cut-off. Patients with nomogram scores ≥55 were considered to have a high predictive probability of thrombosis. The sensitivity and specificity in differentiating between the presence and absence of thrombosis in the validation cohort were 50% and 66.22%, respectively.

Discussion

In this study, we evaluated the utility of intraoperative blood loss in predicting postoperative thrombosis after LT. Based on the multivariate logistic regression analysis, we identified independent variables. Patients who experienced blood loss ≥31.25 mL/kg and those who had a lower level of haematocrit and haemoglobin were more likely to develop thrombosis after LT. Next, we constructed a nomogram on the basis of these predictors. The nomogram's prediction was supported by the C-index (0.716; 95%CI 0.603–0.829), the calibration curve and the validation results.

Bleeding and postoperative thrombosis may seem like two contradictory, unrelated states. After Thomas E Starzl first devised using homografts to replace the decaying livers of patients with ESLD, most of the first 100 recipients died from uncontrolled bleeding.[19] In addition to the abnormal conventional coagulation function laboratory tests such as the PT, aPTT and the INR, patients with ESLD have generally been regarded as examples of acquired bleeding. However, this verdict has been challenged over the past 20 years, and a number of key changes in haemostatic pathways have been elucidated in patients with liver disease.

Table 4. Multivariate analysis of postoperative thrombosis

	p-value	B	SE	Wald	HR	95% CI
Total blood loss ≥31.25 mL/kg	0.012	1.651	0.657	6.325	5.214	1.440–18.884
Haemoglobin, g/L	0.013	–0.156	0.063	6.193	1.856	1.757–1.967
Haematocrit, %	0.035	0.587	0.279	4.437	1.799	1.042–3.107

B = beta coefficient; CI = confidence interval; HR = hazard ratio; SE = standard error.

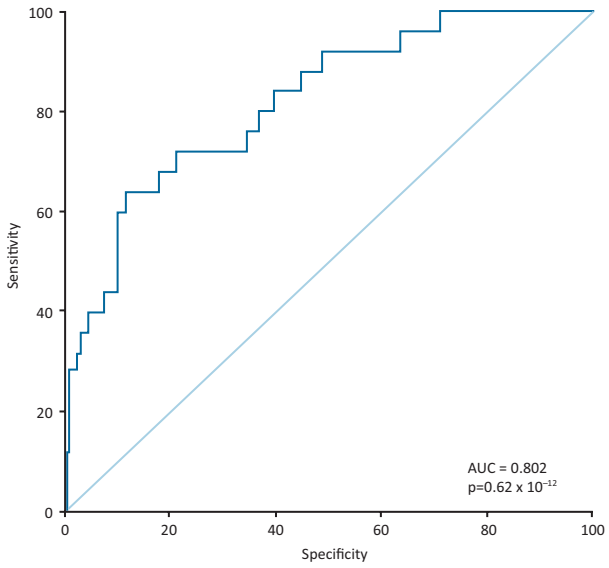

Fig 2. Receiver operating characteristic curve for the multivariable prognostic model with the independent factors. AUC = area under the curve.

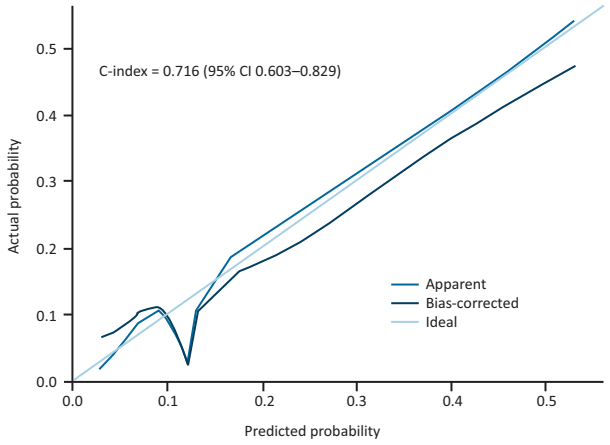

Fig 4. Calibration curve of the nomogram for the probability of postoperative thrombosis (bootstrap 1,000 repetitions). C-index = concordance index; CI = confidence interval.

The modern understanding of changes in the haemostatic system during ESLD involves a new balance between bleeding and clotting, and the balance may shift to either side, which could explain the occurrence of both bleeding and thrombotic events.[20] The normal haemostasis process contains three main components: primary haemostasis, secondary haemostasis and fibrinolysis, all of which are affected during ESLD. In stable liver diseases, the destruction of the clotting system can be remedied by off-setting factors.[2,13,21] In primary haemostasis, thrombocytopenia is the best-known change, and the quantitative deficits in platelet count are offset by increased vWF levels and low levels of the vWF-cleaving protease ADAMTS-13.[15] In secondary haemostasis, diminished levels of procoagulant factors II, V, VII, IX, X and XI, and fibrinogen are significantly offset by proportionally decreased levels of liver-derived anticoagulant factors (including protein C, protein S and heparin cofactor II) and elevated factor VIII. The levels of a series of activators in fibrinolysis are decreased accompanied by increased levels of tissue-plasminogen activator (tPA), which can be offset by low levels of plasminogen and elevated levels of tPA inhibitors (PAI-1). It is remarkable that the combination of decreased levels of protein C and elevated levels of factor VIII plays a significant role in the cirrhosis-induced hypercoagulable state.[22,23] The final effect of changes in fibrinolysis is hyperfibrinolysis, which is thought to contribute to the elevated levels of fibrin degradation products (such as D-dimer) and bleeding associated with advanced cirrhosis.[24] Clinicians should be aware of these changes and avoid correcting coagulation factors blindly in an attempt to reach normal levels.

Regarding rebalancing the haemostatic system, LT teams are regularly confronted with tough treatment decisions. Furthermore, all currently available conventional laboratory measures of haemostasis have significant limitations; for example, the PT and aPTT are only sensitive for procoagulant proteins factors I, II, V, VII, and X, and do not account for the deficiencies of anticoagulant factors such as protein C. The INR is a mathematical conversion of the PT, and some studies have reported that the use of INR fails to yield standardisation for reporting PT in patients with liver disease.[25] Furthermore,

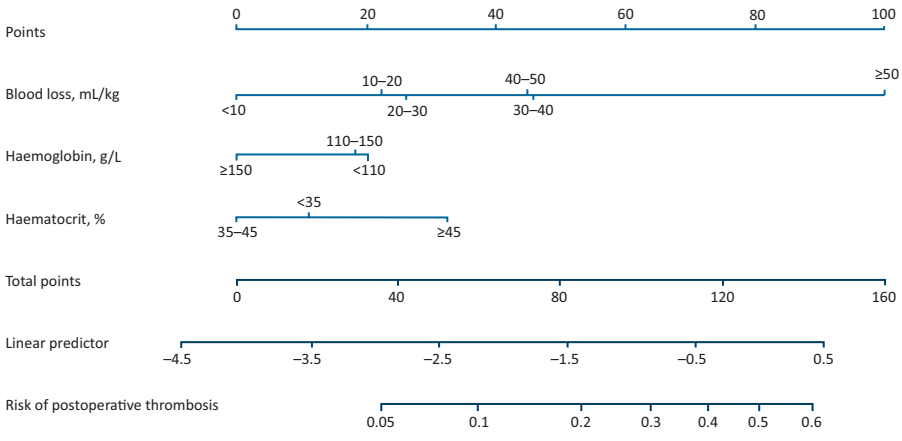

Fig 3. Postoperative prognostic nomogram to predict the probability of postoperative thrombosis after liver transplantation.

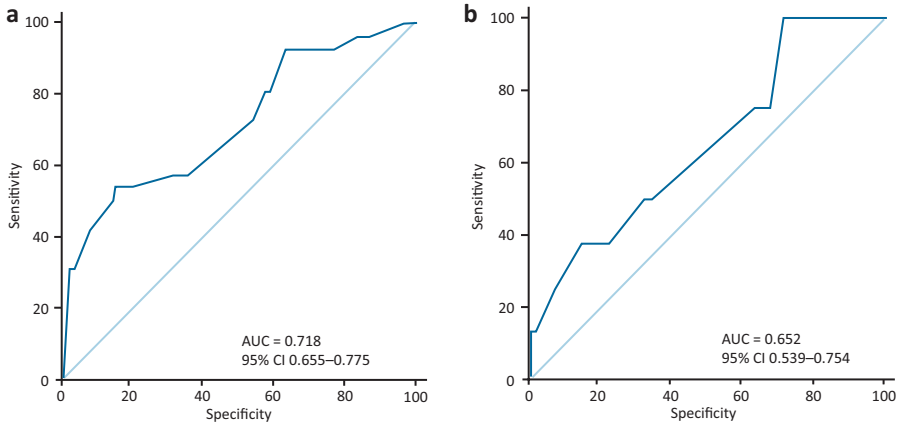

Fig 5. Receiver operating characteristic curves for predicting postoperative thrombosis. a) Primary cohort. b) Validation cohort. AUC = area under the curve; CI = confidence interval.

transfusing ESLD patients with several units of FFP to correct for the results of the INR tests does not actually change thrombin production, but may do harm by exacerbating portal hypertension.[26,27] The results shown in Tables 2 and 4 indicate that PT, aPTT, INR and D-dimer levels are higher in patients with postoperative thrombosis than in other groups, but the differences were not significant after multivariate analysis, which is in accordance with the therapeutic dilemma.

Increasing numbers of centres report transfusion-free LT because, based on previous studies, blood products transfusion in LT can increase the risk of bacterial infections, haemodialysis, longer ICU or hospital stays, cytomegalovirus infections and hypoxaemia.[28,29] An accurate preoperative evaluation and intraoperative management are urgently needed, and commercially available tools (such as TEG and rotational thromboelastometry (ROTEM)) can provide alternatives. Viscoelastic tests have been applied during the process of LT since the 1980s. However, Krzanicki *et al* found that a shortened R time did not predict hypercoaguability.[30] Additional studies are needed to evaluate whether TEG-based transfusions would be beneficial to identify patients who are at high risk of thrombosis and to establish a reasonable reference range. However, we did not get a significant difference in TEG.

The initiation of the procoagulant process may be triggered by another factor, ischaemia reperfusion injury (IRI), which is an inflammatory state.[31] Liver IRI has significant effects on the function of the transplanted liver. The cellular and molecular mechanisms of IRI in LT are numerous, which involve multiple cell types and molecular pathways. Interestingly, the cellular and molecular events can be correlated with clinical risk factors for IRI in LT, such as donor age, ischaemic times etc.[32] As our results show, there were no differences in donor age, warm ischaemia and cold ischemia time, or anhepatic phase (Table 3; supplementary material S1, Table S1). Consequently, we consider that the influences of the IRI on the postoperative thrombosis are consistent between the two groups in our study.

Some limitations of our study should be considered. First, only our centre was included. Despite this, we describe a methodological approach that can be translated to other practices. Second, all patients in our study received a donation after cardiocirculatory death graft, which may limit the generalisability to other programmes of our model. Still, our nomogram is limited by the failure to incorporate molecular factors. Further efforts are encouraged to improve this model.

Conclusion

Intraoperative blood loss can be used to identify recipients at great risk of developing thrombosis using a cut-off value of 31.25 mL/kg; the sensitivity is 53.85% and the specificity is 81.55%. Other independent risk factors after logistic regression are the preoperative haemoglobin and haematocrit level. We further established a nomogram for thromboembolic event prediction. By referring to the blood loss and the nomogram, clinicians could obtain more information for each recipient and provide more reasonable preventive treatment accordingly. ■

Supplementary material

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:
S1 – Clinical and donor characteristics tables.

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