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Original Article

L-GrAFT$_7$ has High Accuracy in Predicting Early Allograft Failure after Liver Transplantation: A Multicenter Cohort Study in China

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Abstract

Background and Aims: Increasing utilization of extended criteria donor leads to an increasing rate of early allograft failure after liver transplantation. However, consensus of definition of early allograft failure is lacking. ***Methods:*** A retrospective, multicenter study was performed to validate the Liver Graft Assessment Following Transplantation (L-GrAFT) risk model in a Chinese cohort of 942 adult patients undergoing primary liver transplantation at three Chinese centers. L-GrAFT (L-GrAFT$_7$ and L-GrAFT$_{10}$) was compared with existing models: the Early Allograft Failure Simplified Estimation (EASE) score, the model of early allograft function (MEAF), and the Early Allograft Dysfunction (EAD) model. Univariate and multivariate logistic regression were used to find risk factors of L-GrAFT high-risk group. ***Results:*** L-GrAFT$_7$ had an area under the curve of 0.85 in predicting 90-day graft survival, significantly superior to MEAF [area under the curve (AUC=0.78, p=0.044)] and EAD (AUC=0.78, p=0.006), while there was no statistical significance between the predicting abilities of L-GrAFT$_7$ and EASE (AUC=0.84, p>0.05). Furthermore, L-GrAFT$_7$ maintains good predicting ability in the subgroup of high-donor risk index (DRI) cases (AUC=0.83 vs. MEAF, p=0.007 vs. EAD, p=0.014) and recipients of donors after cardiac death (AUC=0.92 vs. EAD, p<0.001). Through multivariate analysis, pretransplant bilirubin level, units of packed red blood cells, and the DRI score were selected as independent risk factors of a L-GrAFT$_7$ high-risk group. ***Conclusions:*** The accuracy of L-GrAFT$_7$ in predicting early allograft failure was validated in a Chinese multicenter cohort, indicating that it has the potential to become an accurate endpoint of clinical practice and transitional study of machine perfusion.

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Keywords: Early allograft failure; Graft survival; Liver transplantation; Risk prediction model; Multicenter study.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUROC, area under the ROC curves; CIT, cold ischemia time; CI, confidence interval; DBD, donor after brain death; DBCD, donor after brain and cardiac death; DCD, donor after cardiac death; DRI, donor risk index; EAD, Early Allograft Dysfunction; EAF, early allograft failure; EASE, the Early Allograft Failure Simplified Estimation score; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR, interquartile range; L-GrAFT, the Liver Graft Assessment Following Transplantation risk model; LT, liver transplantation; MEAF, the model of early allograft function; MELD, the model of end-stage liver diseases; ROC, receiver operating characteristics; RRT, renal replacement therapy; uPRBCs, units of pack of red blood cells; WIT, warm ischemia time.

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Introduction

To deal with the imbalance between number of donors and recipients, use of extended criteria donor grafts has been introduced to the transplant community.[1–3] This has raised concerns of increasing the occurrence of allograft failure after liver transplantation (LT).[4,5] Early allograft dysfunction (EAD) was first defined by Deschênes *et al*.[6] It may lead to early allograft failure (EAF), which is defined as death or need for retransplantation within 90 days following transplantation.[7–10] EAF is not only impacted by inevitable ischemia-reperfusion injury during the operation, but is also associated with recipient factors in the model of end-stage liver diseases (MELD) era.[11] On the one hand, concerns of EAF has prompted the development of machine perfusion,[12,13] aiming at mitigating the ischemia-reperfusion injury. On the other hand, this

highlights the importance of an accurate measurement of early allograft function.

The most widely accepted method of predicting EAF was proposed by Olthoff *et al*.[14] using the EAD model, which includes postoperative serum bilirubin, international normalized ratio (INR) and aspartate aminotransferase or alanine aminotransferase as indicators in the recipient. Unfortunately, this binary model fails to meet the need for continuous assessment of graft function in the clinical arena. The model of early allograft function (MEAF) was established by Pareja *et al*.[7] to grade the allograft function as a continuous score. However, few studies have reported its accuracy in predicting postoperative graft failure.

Recently, two new models have been built with excellent C-statistics for predicting EAF. The Liver Graft Assessment Following Transplantation (L-GrAFT) risk model, proposed by Agopian *et al*.,[9] successfully predicted graft function within 90 days after transplantation based on 7 ($L\text{-}GrAFT_7$) or 10 ($L\text{-}GrAFT_{10}$) days of post-LT laboratory examination. In an external validation study in the USA,[15] the L-GrAFT model maintained its high accuracy. The Early Allograft Failure Simplified Estimation (EASE) score was developed by Avolio *et al*.[10] is a similar model, was also validated in an external cohort. Moreover, Chen *et al*.[16] compared the existing models in a single-center study in China, and shows that $L\text{-}GrAFT_7$ performed better in predicting 3-month graft survival than the MEAF and EAD models. Therefore, in this study, our primary objective was to validate the ability of L-GrAFT to predict EAF in a multicenter cohort.

Methods

Patient population

This retrospective multicenter study compared the L-GrAFT risk score with the EASE score, MEAF score, and the EAD model. Three Chinese centers participated in the study, the First Affiliated Hospital of Sun Yat-sen University, the Zhongshan People's Hospital and the First People's Hospital of Foshan. Previously collected data of all patients from January 1st, 2015 to December 31st, 2020 in these centers were included in the analysis. Adult patients undergoing primary LT were eligible. The exclusion criteria were under 18 years of age, recipients who underwent retransplantation, combined transplantation, living donor transplantation, and split transplantation. Patients with insufficient data for model calculation were also excluded.

The primary study outcome was as death or need for retransplant for any reason within 3 months after LT.[10] Allograft failure occurring in 6 months after transplantation was also recorded. Data collected to validate the existing models included four categories: (1) Recipient demographics (age, sex, body mass index, diagnosis of primary end-stage liver disease, hypertension and diabetes); (2) Pretransplant laboratory variables (total bilirubin, INR, creatinine, albumin, laboratory MELD score, requirement of renal replacement therapy, and mechanical ventilation before LT); (3) Donor and operative characteristics (donor age, sex, body mass index, graft type according to the Chinese classification,[17] donor risk index [DRI],[18] anhepatic phase during the operation, units of packed red blood cells [uPRBCs], cold ischemia time (CIT), and warm ischemia time); (4) Postoperative laboratory examination (aspartate aminotransferase, INR, total bilirubin and platelet for 10 days following transplantation, and alanine aminotransferase for 7 days following transplantation); (5) Follow-up information and outcomes at 90 and 180 days after LT.

The equations used to calculate the model scores are shown in the Supplementary File 1. Seven $L\text{-}GrAFT_7$ risk groups for were defined:[9,15] (1) Risk group 1 ($L\text{-}GrAFT_7$ score<-3.5); (2) Risk group 2 ($-3.5\leq L\text{-}GrAFT_7$ score<-2.5); (3) Risk group 3 ($-2.5\leq LGrAFT_7$ score<-1.5); (4) Risk group 4 ($-1.5\leq L\text{-}GrAFT_7$ score<-0.5); (5) Risk group 5 ($-0.5\leq L\text{-}GrAFT_7$ score<0.5); (6) Risk group 6 ($0.5\leq L\text{-}GrAFT_7$ score<1.5; and (7) Risk group 7 ($1.5\leq L\text{-}GrAFT_7$ score<7.5. Five $L\text{-}GrAFT_{10}$ risk groups were defined:[9,15] (1) Risk group 1 ($L\text{-}GrAFT_{10}$ score<-3.23); (2) Risk group 2 ($-3.23\leq L\text{-}GrAFT_{10}$ score<-1.18); (3) Risk group 3 ($-1.18\leq L\text{-}GrAFT_{10}$ score<-0.57); (4) Risk group 4 ($-0.57\leq L\text{-}GrAFT_{10}$ score <1.3); (5) Risk group 5 ($1.3\leq L\text{-}GrAFT_{10}$ score). Five EASE risk groups were defined:[10] (1) Risk group 1 (EASE score<-3.43); (2) Risk group 2 ($-3.43\leq$EASE score≤-1.26,; (3) Risk group 3 ($-1.25\leq$EASE score≤-0.75); (4) Risk group 4 ($-0.74\leq$EASE score≤-0.01); (5) Risk group 5: $0\leq$EASE score≤5). Five MEAF risk groups were defined:[7] (1) Risk group 1 ($0<$MEAF score≤2); (2) Risk group 2 ($2<$MEAF score≤5); (3) Risk group 3 ($5<$MEAF score≤6; (4) Risk group 4 ($6<$MEAF score≤8; (5) Risk group 5 ($8<$MEAF score≤10).

The study was reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (commonly known as STROBE) guidelines,[19] and was conducted in accord with the ethical guidelines of the Declaration of Helsinki and Istanbul and with the approval of the Independent Ethics committee for Clinical Research and Animal Trails of The First Affiliated Hospital of Sun Yat-sen University (No. [2022]560). Informed consent was waived because this was a retrospective study.

Statistical analysis

Continuous variables were reported as medians and interquartile range (IQR). Categorical variables were reported as numbers and percentage. Five models ($L\text{-}GrAFT_{10}$, $L\text{-}GrAFT_7$, EASE, MEAF and EAD) were calculated based on perioperative data. The Kaplan–Meier method was used to estimate the patient and graft survival rates at 90 and 180 days after LT. Receiver operating characteristics (ROC) curves were constructed to evaluate the models' ability to predict EAF. Areas under the ROC curve (AUROCs) were calculated, and compared using the Delong test.[20] In addition, to evaluate the ability of the models to differentiate survival risk, survival curves were constructed according to risk class in each model and compared using log rank tests. To identify underlying factors that influenced the ability of the models, ROC analysis was also done in subgroups stratified by pretransplant MELD score. DRI and graft types using the same methods as above. According to the cutoff point of $L\text{-}GrAFT_7=-1.5$,[15] overall patients were stratified into the $L\text{-}GrAFT_7$ high-risk group and low-risk group. Recipient, donor and operative risk factors were compared using univariate logistic regression. After excluding variables with potential multicollinearity, variables with p-values <0.1 were included in the multivariate logistic regression. As some cases had missing data for some variables, the analysis was based on the available information only. The statistical analysis was performed with IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) and R (version 4.2.0).

Results

A total of 1,167 liver transplants were performed during the study period. Of those, 221 cases were excluded because of recipient age younger than 18 years (33 cases), retransplantation (11 cases), combined transplantation (33 cases),

Table 1. Recipient, donor, and operative characteristics

Characteristics	Frequency or median (IQR)[a]
Recipient	
Age, years	51 (44–59)
Male, %	87.6
BMI	23.1 (21.0–24.9)
Diagnosis, %	
HBV-related cirrhosis	47.1
HCC	31.3
Alcoholic cirrhosis	4.2
Others	17.4
Pretransplantation	
Bilirubin in μmol/L	46.7 (20.2–210.6)
INR	1.36 (1.15–1.85)
Creatinine in μmol/L	73.0 (60.0–93.0)
Albumin in g/L	35.7 (32.0–40.0)
Lab MELD	12 (7–21)
RRT, %	1.8
Mechanical ventilation, %	1.5
Donor and operative	
Age, years	39 (24–47)
Male, %	76.5
The Chinese Classification of Deceased Organ Donation, %	
DBD	83.0
DCD	13.3
DBCD	3.7
DRI	1.60 (1.49–1.93)
Anhepatic phase in minutes	55 (45–66)
uPRBCs in U	5 (2–10)
CIT in hours	6.5 (4.6–8.2)
WIT in minutes[b]	6 (5–10)

[a]Continuous variables are medians and interquartile range; categorial variables are numbers and percentage; [b]Warm ischemia time was only calculated in DCD cases. BMI, body mass index; CIT, cold ischemia time; DBCD, donation after brain and cardiac death; DBD, donation after brain death; DCD, donation after cardiac death; DRI, donor risk index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR, interquartile range; MELD, model of end-stage liver disease; RRT, renal replacement therapy; uPRBCs, units of packed red blood cells; WIT, warm ischemia time.

living donor transplantation (1 cases), split LT (12 cases) and insufficient data (143 cases). The remaining 946 cases were included in the study.

The baseline data are shown in Table 1. Among the recipients, the median age was 51 years old and men accounted for 87.6%. As for the diagnosis of primary end-stage liver diseases, hepatitis B virus-related cirrhosis accounted for the largest proportion (47.1%) and was followed by hepatocellular carcinoma (31.3%). Alcoholic cirrhosis accounted for a small proportion (4.2%). The median laboratory MELD score of recipients was 12. Diabetes was present in 13.5% patients, and 12.2% cases had hypertension. Few cases need the renal replacement therapy and mechanical ventilation before transplantation (1.8% and 1.5%, respectively).

Regarding the donor characteristics, the median donor age was 39 years and 76.5% were men. The median DRI score was 1.60. According to the Chinese classification of deceased organ donation, the most frequent graft type was donation after brain death (83%) and donation after cardiac death accounted for 13.3%. The median CIT was 6.5 hours, and the median warm ischemia time was 6 minutes among the donor after cardiac death (DCD) cases. During the transplant operation, the median transfusion of red blood cells was five units. The median follow-up was 16.3 months, patient survival was 94.8% at 90 days and 93.0% at 180 days. Graft survival was 95.5% at 90 days and 93.7% 180 days.

Comparisons of L-GrAFT, EASE, MEAF, and EAD

Based on the ROC curves shown in Figure 1A, L-GrAFT$_7$ had an excellent AUROC of 0.85 (IQR 0.78–0.92) in all patients, which significantly outperformed MEAF (AUROC=0.78 [IQR 0.70–0.86] vs. L-GrAFT$_7$, p=0.044) and EAD (AUROC=0.78

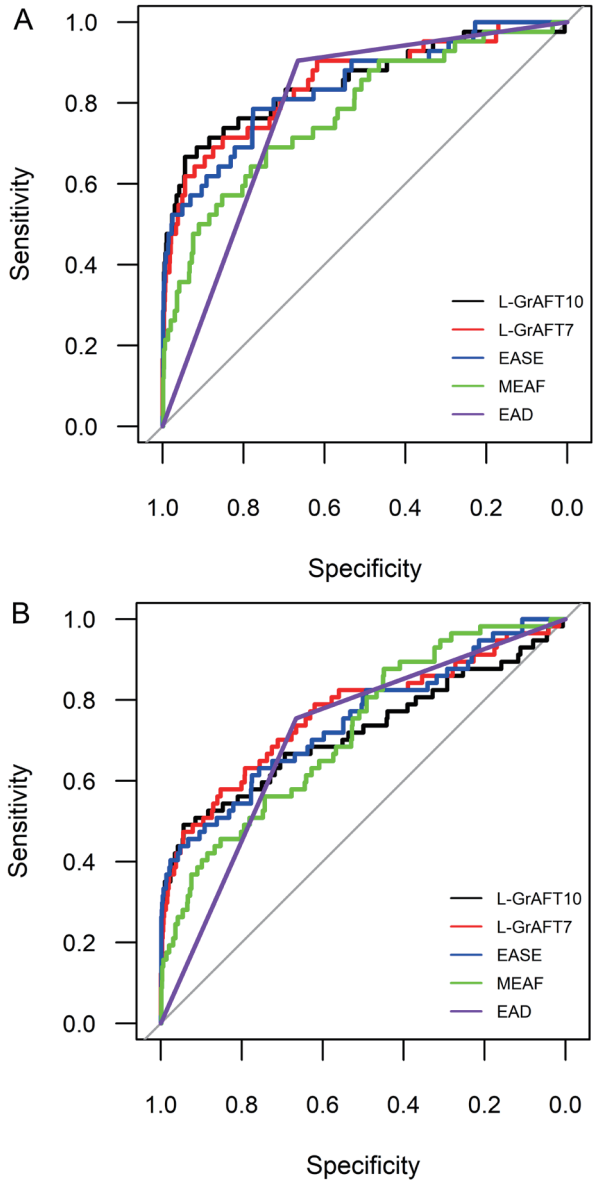

Fig. 1. ROC curves for the L-GrAFT$_{10}$, L-GrAFT$_{7}$, EASE, MEAF and EAD model. (A) Comparison for predicting 3-month graft survival; (B) Comparison for predicting 6-month graft survival. EAD, Early Allograft Dysfunction; EASE, the Early Allograft Failure Simplified Estimation score; L-GrAFT, the Liver Graft Assessment Following Transplantation risk model; MEAF, the model of early allograft function.

[IQR 0.74–0.83] vs. L-GrAFT$_{7}$, p=0.006) in predicting 90-day graft survival. L-GrAFT$_{10}$ also had a good AUROC of 0.85 (IQR 0.78–0.92), significantly superior to EAD (vs. L-GrAFT$_{10}$, p=0.024) but there was no statistical significance compared with MEAF (vs. L-GrAFT$_{10}$, p=0.090) in predicting 90-day graft survival. When it came to predicting 180-day graft survival (Fig. 1B), the comparisons among L-GrAFT$_{7}$, L-GrAFT$_{10}$ and MEAF, EAD failed to reach significance. There was no significant difference between L-GrAFT$_{10}$, L-GrAFT$_{7}$ and EASE (90 days, AUROC=0.84 [IQR 0.77–0.91]; 180 days, AUROC=0.75 [IQR 0.67–0.82]) in predicting 90- and 180-day graft survival.

In the subgroup analysis (Table 2), L-GrAFT$_{7}$ had a higher

Table 2. Subgroup ROC analysis of the L-GrAFT$_{7}$ model

Parameter	AUROC (95% CI)				*p*-value		
	L-GrAFT$_{7}$	EASE	MEAF	EAD	L-GrAFT$_{7}$ vs. EASE	L-GrAFT$_{7}$ vs. MEAF	L-GrAFT$_{7}$ vs. EAD
Overall (*n*=946)	0.85 (0.78–0.92)	0.84 (0.77–0.91)	0.78 (0.70–0.86)	0.78 (0.74–0.83)	0.64	0.044	0.006
Pre-LT MELD							
Above median (*n*=473)	0.83 (0.73–0.92)	0.80 (0.70–0.90)	0.77 (0.68–0.86)	0.76 (0.69–0.82)	0.47	0.20	0.024
Below median (*n*=473)	0.87 (0.76–0.98)	0.89 (0.81–0.97)	0.76 (0.61–0.91)	0.82 (0.75–0.88)	0.586	0.120	0.191
DRI							
Above median (*n*=473)	0.83 (0.74–0.93)	0.82 (0.72–0.92)	0.71 (0.59–0.82)	0.75 (0.68–0.82)	0.743	0.007	0.014
Below median (*n*=473)	0.87 (0.77–0.98)	0.86 (0.76–0.96)	0.87 (0.77–0.96)	0.83 (0.76–0.89)	0.416	0.918	0.169
Graft type							
DBD (*n*=785)	0.83 (0.75–0.92)	0.81 (0.72–0.90)	0.78 (0.69–0.86)	0.79 (0.73–0.85)	0.521	0.286	0.161
DCD (*n*=126)	0.92 (0.78–1.00)	0.92 (0.77–1.00)	0.81 (0.63–0.99)	0.72 (0.61–0.82)	0.776	0.051	<0.001
DBCD (*n*=35)	0.86 (0.61–1.00)	0.85 (0.65–1.00)	0.68 (0.24–1.00)	0.74 (0.65–0.83)	0.830	0.100	0.366

AUROC, area under the receiver operating characteristics curve; CI, confidence interval; DBCD, donation after brain and cardiac death; DBD, donation after brain death; DCD, donation after cardiac death; DRI, donor risk index; MELD, model of end-stage liver disease.

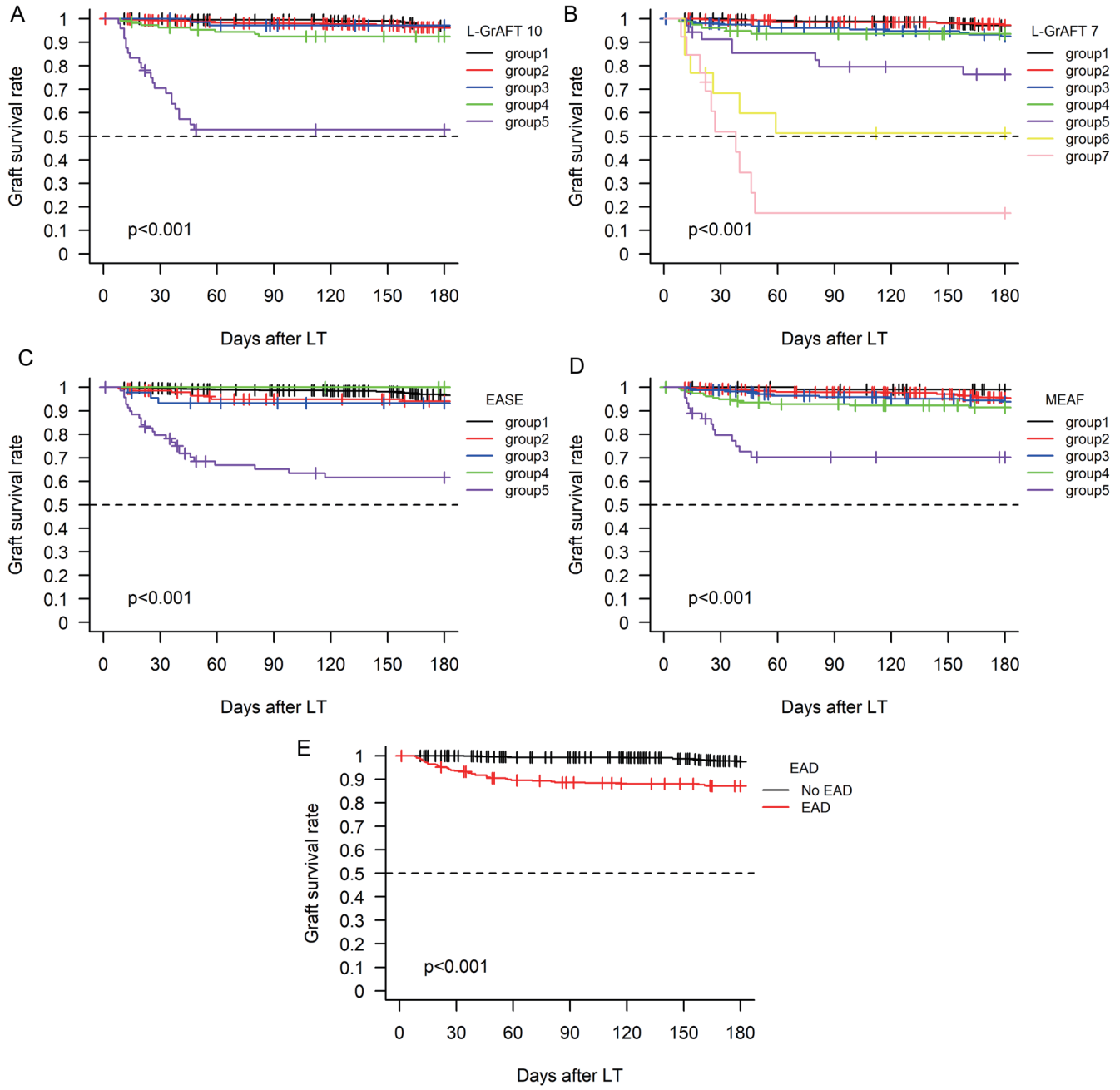

Fig. 2. Graft survival curves according to the L-GrAFT$_{10}$, L-GrAFT$_{7}$, EASE, MEAF, and EAD risk classes. (A) L-GrAFT$_{10}$; (B) L-GrAFT$_{7}$; (C) EASE; (D) MEAF; (E) EAD model. EAD, Early Allograft Dysfunction; EASE, the Early Allograft Failure Simplified Estimation score; L-GrAFT, the Liver Graft Assessment Following Transplantation risk model; LT, liver transplantation; MEAF, the model of early allograft function.

AUROC than MEAF and EAD in all subgroups. For recipients of high-risk grafts, L-GrAFT$_{7}$ maintained its superior ability in predicting 90-day graft survival. The Delong test[20] confirmed that L-GrAFT$_{7}$ significantly outperformed MEAF and EAD in the subgroup with a DRI above the median (L-GrAFT$_{7}$ vs. MEAF, p=0.007; L-GrAFT$_{7}$ vs. EAD, p=0.014). In the subgroup of DCD, L-GrAFT$_{7}$ outperformed EAD (p<0.001) but the comparison with MEAF failed to reach significance (p=0.051).

The Kaplan–Meier curves in Figure 2 showed that L-GrAFT$_{7}$ had a better ability to differentiate graft survival risk than EASE, MEAF, and EAD. Patients in risk groups 6 and 7 of L-GrAFT$_{7}$ or risk group 5 of L-GrAFT$_{10}$ had survival rates <0.5 at 6 months after LT.

Risk factors for the L-GrAFT$_{7}$ high-risk group

Based on the cutoff point of −1.5, 807 cases were classified as L-GrAFT$_{7}$ low risk and 139 were placed in high-risk groups. As shown in to Supplementary Table 1, L-GrAFT$_{7}$ the high-risk group had younger recipients (49 years of age

Table 3. Univariate and multivariate analysis of characteristics between L-GrAFT$_7$ high and low-risk groups

Characteristics	Univariate analysis	Multivariate analysis	
	***p*-value**	**Odds ratio (95% CI)**	***p*-value**
Recipient age	0.065		
Diagnosis			
HBV			
HCC	0.772		
Others	0.025		
Alcoholic	0.091		
Pre-LT bilirubin	< 0.001	1.002 (1.001–1.003)	< 0.001
Pre-LT INR	0.033		
DRI	0.044	1.459 (1.023–2.079)	0.037
uPRBCs	< 0.001	1.038 (1.018–1.058)	< 0.001

CI, confidence interval; DRI, donor risk index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; INR, international normalized ratio; LT, liver transplantation; uPRBCs, units of packed red blood cells.

[IQR 40–47] vs. 51 years of age [IQR 44–59], p=0.04), more serious end-stage liver diseases based on higher MELD scores (17 [IQR 8–27] vs. 12 [IQR 6–20], p<0.001), more DCD cases (20.1% vs. 12.1%, p=0.03), longer CIT (7.0 h [IQR 5.6–8.5] vs. 6.4 h [IQR 4.5–8.3], p=0.02) and more uPRBCs (8 units [IQR 4–14] vs. 5 units [IQR 2–9], p<0.001). Multivariate analysis found that pre-LT bilirubin level (OR=1.002, p<0.001), DRI (OR=1.459, p=0.037) and uPRBCs (OR=1.038, p<0.001) were independent risk factors for the high-risk group (Table 3).

Discussion

As an effective life-saving treatment of end-stage liver disease, LT has a great barrier of allograft shortage. To overcome this problem, the transplant community has allowed the use of marginal liver grafts, which result worse outcomes compared with standard donors.[4] Therefore, a tool to guide postoperative medical care, or help making decisions for early retransplantation is required. Translational studies to promote the strategies of machine perfusion need an accurate surrogate endpoint to assess postoperative graft function because of the difficulty in achieving sufficient sample sizes with high graft and patient survival rate.[8,15] The Chinese cohort in this study presented with different characteristics than those selected with existing algorithms (e.g. younger donors, lower pre-LT laboratory MELD, and a small proportion of those with pre-LT mechanical ventilation and/or renal replacement therapy).[9,10] However, we demonstrated that L-GrAFT$_7$ had an excellent ability to predict 3- and 6-month graft survival, significantly outperforming the MEAF and EAD models.

L-GrAFT$_7$ had a good AUROC of >0.80 for predicting 90-day graft survival, outperforming other models, which was consistent with a previous single-center result.[16] Compared with the MEAF and EAD models, L-GrAFT includes innovative kinetic algorithms that are likely the basis of its high accuracy. Aspartate aminotransferase, INR, serum bilirubin, and platelet count have been considered as predictors of adverse events and poor outcome.[21–24] Instead of focusing on the value of a specified postoperative day, the L-GrAFT$_7$ model takes their average and changing rate into account because the association between postoperative laboratory variables and survival rate does not follow the proportional hazards assumption.[9] Moreover, using similar algorithm, the EASE model also had an AUROC >0.80.[10] This study found no statistical significance between L-GrAFT$_7$ and EASE scores, which is consistent with the results reported in a German cohort by Moosburner *et al*.[25] The difference of the AUROCs in L-GrAFT$_7$ and L-GrAFT$_{10}$ was also small. However, only L-GrAFT can be calculated in the face of possible missing values,[26] and the missing values are mostly obtained between postoperative days 8–10 in clinical practice. Therefore, L-GrAFT$_7$ might be considered as a more feasible choice for assessing early allograft function.

As we considered L-GrAFT$_7$ to be an accurate predictor of postoperative graft survival, pre-LT bilirubin level, uPRBCs and DRI score were found to be independent risk factors of L-GrAFT$_7$ high-risk group by logistic regression, which emphasized the impact of recipient, operative, and donor factors on postoperative graft function, respectively. The organ allocation system based on the MELD score was established in 2002,[27] in which patients with the most severe end-stage liver diseases are prioritized to LT. Previous studies have demonstrated that the MELD system reduced mortality in those on the waiting list, while also causing worse post-LT outcomes.[14,28] It is not surprising that a high pre-LT bilirubin, which is a factor contributing to a high MELD score, was selected as one of the risk factors for the high-risk group. Moreover, with poor graft function, high bilirubin before LT may persist in the first postoperative week,[14] which leads to a higher risk score because L-GrAFT$_7$ includes the average bilirubin level as an indicator. Units of transfused packed red blood cells was associated with the high-risk group indicated by L-GrAFT$_7$, which is similar to the results reported by Avolio *et al*.[10] and Ramos *et al*.[29]

It should be highlighted that L-GrAFT$_7$ had superior discriminating ability in recipients receiving high-risk grafts with higher DRIs and in those who accepted DCD grafts. This was consistent with the result reported by Agopian *et al*.[15] As for donor characteristics, the DRI score was chosen to quantify the risk of graft failure from the donor site as it combines CIT, graft types, and other donor risk factors.[18] Although the difference of the DRI in low and high L-GrAFT$_7$ risk groups was small, and the clinical significance was questionable, multivariate regression still showed that a high DRI was an independent risk factor owing to the contributions of DCD grafts and longer CIT. Therefore, increasing risk indicated by a higher DRI graft indicated that L-GrAFT$_7$ discriminated

the risk of allograft failure in donors with higher risk, which fits the results of our subgroup analysis. Therefore, L-GrAFT$_7$ was a good clinical endpoint to estimate the graft failure risk helping in the decision in favor of early retransplantation. Furthermore, a continuous score is desired as an alternative endpoint for a machine perfusion trial in order to reach statistical power more easily.[30] Although the MEAF score was selected as primary endpoint by an ongoing trial of dual hypothermic oxygenated machine perfusion (ClinicalTrials.gov Identifier: NCT04812054), its accuracy needs testing according to this study and a previous validation by Jochmans *et al*.[8] L-GrAFT$_7$ had the potential to become an early surrogate to measure graft viability, as it is associated with graft quality. Another ongoing randomized controlled trial of hypothermic oxygenated machine perfusion (ClinicalTrials.gov Identifier: NCT03929523) has included it as the secondary endpoint to validate its practicality.

In a previous single-center study,[16] cases with early post-transplant vascular complications (< 14 days) were excluded due to the concern that hepatic arterial thrombosis and portal vein thrombosis are non-hepatogenic trigger risk factors of EAF. However, in a current study, we considered them as ones of the risk factors potentially leading to EAF, even though they were not strictly associated with ischemia-reperfusion injury, which was similar to the definition of the EASE study.[10] Therefore, we also included those cases in the analysis.

This study has some limitations. The first one is the retrospective design, where missing values are not avoidable. Second, the L-GrAFT$_7$ model needs laboratory data during 7 days post transplantation, hence it cannot predict allograft failure within the first 7 postoperative days. Actually, we excluded a few cases who died within 10 days post-transplant, and they represented an important status of EAF. Additional methods should be defined to complement with the L-GrAFT$_7$ model in the future. In addition, existing models were not developed in the perspective of retransplantation. Further studies are needed to estimate potential factors that might affect timely and successful retransplantation. Finally, our study included one high-volume center and two low-volume centers, which means that unbalanced center volume in this multicenter study might cause undesirable bias. A large multicenter international study with balanced center volume to develop a new definition of EAF is ongoing (ClinicalTrial.gov NCT05289609). Hopefully, a more reasonable study design will allow the development and validation of a new algorithm stronger than the existing models.[31]

Conclusions

In conclusion, this multicenter study showed that L-GrAFT$_7$ was a highly accurate tool for predicting postoperative 90-day allograft survival, which can be used as a clinical endpoint and help the decision making of early retransplantation for those who had a high risk of developing EAF. In addition, it has the potential to become a useful endpoint for transitional machine perfusion trials. Its feasibility might be evaluated by further well-designed clinical trials.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (SL, ZG, FD, QS), acquisition of data (SL, SC, QS, QL, FD), analysis and interpretation of data (SL, ZG, SC, ZJ, TW, WW, XY, YZ, JZ), drafting of the manuscript (SL), critical revision of the manuscript for important intellectual content (SC, ZG), administrative, technical or material support (ZG, XH, QS, FD), and study supervision (ZG, FD, QS, XH). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study was approved by the Independent Ethics Committee for Clinical Research and Animal Trails of The First Affiliated Hospital of Sun Yat-sen University (No. [2022]560). The requirement for patient informed consent was waived due to the nature of a retrospective study.

Data sharing statement

The datasets used in the study are available on reasonable request.

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