Original Article

Prediction of post-transplant graft survival by different definitions of early allograft dysfunction

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Background: The efficacy of early allograft dysfunction (EAD) definitions in predicting post-transplant graft survival in a Chinese population is still unclear.

Methods: A total of 607 orthotopic liver transplants (OLT) have been included in the current study. Model accuracy was evaluated using receiver operating characteristic (ROC) analysis. Risk factors for EAD was evaluated using univariable analysis and multivariable logistic regression model.

Results: The 3-, 6-, and 12-month patient/graft survival were 91.6%/91.4%, 91.1%/90%, and 87.5%/87.3%, respectively. MELDPOD5 had a superior discrimination of 3-month graft survival (C statistic, 0.83), compared with MEAF (C statistic, 0.77) and Olthoff criteria (C statistic, 0.72). Multivariate analysis of risk factors for EAD defined by MELDPOD5, showed that donor body mass index (P=0.001), donor risk index (P=0.006), intraoperative use of packed red blood cells (P=0.001), hypertension of recipient (P=0.004), and preoperative total bilirubin (P<0.001) were independent risk factors.

Conclusions: The results suggest that MLEDPOD5 is a better criterion of EAD for the Chinese population, which might serve as a surrogate end-point for graft survival in clinical study.

Keywords: Early allograft dysfunction (EAD); graft survival; patient survival

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Introduction

Orthotopic liver transplantation (OLT) is the standard treatment for end-stage liver disease (ESLD) (1-3). In the United States, the survival rate of transplant patients has increased year by year. Recently, in a multicenter clinical research, which included three US centers, 1-year

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and 5-year patient survival reached 90% and 77% (4). Early allograft dysfunction (EAD) was firstly proposed by Deschênes *et al.* (5) in 1998, which represents a state of the graft with marginal function in the early stage after OLT and reflected a set of transient clinical and laboratory test results of graft dysfunction (6). Ischemia-reperfusion injury (IRI) of graft is the leading cause of EAD (7). EAD might predict the survival status of patients and grafts after OLT (8-10). The criteria proposed by Olthoff and his colleagues is widely recognized (11). Nevertheless, the criteria, as a binary variable, is evaluated within seven days after surgery, making it difficult to evaluate the severity of the disease.

Alternatively, it has been shown that the Model for End-Stage Liver Disease score on postoperative day 5 (MELDPOD5), a continuous prognostic score for measuring EAD, is a reasonable predictor for 90-day graft failure (12-14). Moreover, Khandoga *et al.* (15) has proved that the MELD score might serve as a predictor for long-term outcome after OLT. Model for Early Allograft Function Scoring (MEAF) is another continuous prognostic score for EAD reported in 2015, and Jochmans *et al.* (16) has verified that MEAF is a more accurate predictor of graft loss. There was no consensus on which criteria is the best predictive model for post-transplant graft survival.

Here, we aimed to evaluate the incidence of EAD with distinct definitions and compare their prognostic performance in a large Chinese cohort. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-1012).

Methods

Patients

We performed a retrospective analysis of primary adult liver transplant recipients (>18 years of age) from January 2015 to December 2019. All OLTs were performed at the Organ Transplant Center of The First Affiliated Hospital of Sun Yat-sen University. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [No. (2020)336]. Individual consent for this retrospective analysis was waived.

The patients with the following criteria were excluded: (I) donor age less than 14 years; (II) living donors; (III) OLT for acute liver failure; (IV) the recipient of a split liver; (V) multivisceral transplantation; (VI) recipients diagnosed with vascular thrombosis during the first 7 days after OLT because vascular thrombosis during the first 7 days as a non-hepatogenic trigger can lead to elevated liver enzymes levels, resulting in abnormal liver function after surgery, which will interfere with statistical results (17,18); (VII) recipients whose follow-up was inadequate for assessing EAD. Data collection took place from July 15, 2020, to September 30, 2020. Follow-up database was closed on October 25, 2020. Data analysis was carried out from October 1, 2020, to November 10, 2020.

Calculation of EAD

The Olthoff criteria defined EAD based on any of the following factors: (I) total bilirubin level ≥10 mg/dL on postoperative day (POD) 7; (II) international normalized ratio (INR) ≥1.6 on POD7; (III) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level >2,000 IU/L within the first 7 days.

EAD was defined by the MELDPOD5 score >18.9 (12). The MELD score was calculated as follows: MLED score = 3.8*ln[bilirubin POD5 (mg/dL)] + 11.2*ln(INR POD5) + 9.6*ln[creatinine POD5 (mg/dL)] + 6.4*(etiology: 0 if cholestatic or alcoholic, 1 otherwise) (19).

MEAF was calculated according the following formula: MEAF = (score ALT + score INR + score bilirubin), where score ALT = 3.29/(1 + e^-1.9132[ln($ALT_{max.3POD}$) – 6.1723], score INR = 3.29/(1 + e^-6.8204(ln($INR_{max.3POD}$)-0.6658), score bilirubin = 3.4/(1 + e^-1.8005(ln($Bilirubin_{3POD}$) – 1.0607).

Risk factors associated with EAD

Potential risk factors related to donor, operation, recipient, and pretransplant status were included for analysis based on the previous reports (11,12,20,21). The selected variables were:

- Donor and operation characteristics [age, sex, blood type, height, body mass index (BMI), the Chinese Classification of Deceased Organ Donation, donor risk index (DRI), cold ischemia time, warm ischemia time, units of packed red blood cells used intraoperatively (uPRBCs)];
- Recipient characteristics [age, sex, blood type, height, weight, comorbidity (hypertension, diabetes mellitus, coronary artery disease), BMI];
- Pretransplant status [laboratory MELD score, Child-

Pugh score, creatinine, total bilirubin, international normalized ratio (INR), serum albumin, renal replacement therapy, mechanical ventilation].

Statistical analysis

Continuous variables were reported as median values and interquartile range (IQR), and the categorical variable as frequency (percentage). Graft failure was defined as death or need for retransplantation during the period of observation (11). Graft survival and patient survival were calculated using Kaplan-Meier method and compared using the log-rank test. Model accuracy was evaluated using receiver operating characteristic (ROC) analysis. The area under the receiver operating characteristic (AUROC) curve and C statistics were compared to evaluate the accuracy of the Olthoff criteria, MELDPOD5, and MEAF. The difference between AUROCs was calculated using the methods of DeLong *et al.* (in 1988) (22). Univariable analysis of risk factors associated with EAD was conducted using the Mann-Whitney U test for continuous variables and the χ^2-test for categorical variables. Risk factors with P values <0.05 in the univariable analysis were entered into the multivariable logistic regression model.

P values <0.05 were considered statistically significant. All statistical analysis was carried out using SPSS (version 24; IBM Crop., RRID: SCR_019096), MedCalc (version 19.5.3; MedCalc, RRID: SCR_015044), and GraphPad Prism (version 8.0.2; GraphPad Prism, RRID: SCR_002798).

Results

Patients overview

In total, 607 OLT has been included in the study population between January 2015 and December 2019. Patients who were excluded due to incomplete records accounted for 34 (*Figure 1*). The overview of recipient, donor, and operative characteristics are showed in *Table 1*.

Among the recipients, the median age was 50 years; 90.1% of recipients were male. The leading cause of liver diseases was hepatocellular carcinoma (HCC) (55.2%), with diabetes, hypertension, and coronary artery disease in 13.2%, 13.7%, and 4.0% of recipients. The median laboratory MELD score for all recipients before liver transplantation was 12, while 8 and 18 were for patients with HCC and the others; 2.1% of patients required renal replacement therapy, and 1.2% required mechanical ventilation.

The donor median age was 40 years, and 78.5% of the donors were male. Trauma was the primary cause of death, accounting for 47.8% donors. The donation after brain death (DBD) was the major source, accounting for 76.2%. The median DRI was 1.64 (1.41–2.07). The median CIT was 424 min (328–524 min).

In Figure S1, the 3-, 6-, and 12-month patient/graft survival were 91.6%/91.4%, 91.1%/90%, and 87.5%/87.3%, respectively. Retransplantation for only one patient occurred 14 days after primary transplantation due to primary nonfunction.

Incidence of EAD

A total of 294 patients were diagnosed with EAD (48.4%) according to the Olthoff criteria, 100 patients (16.5%) according to MELDPOD5, and only 36 patients (5.9%) with MEAF >8. Three definitions showed a great ability to distinguish between the EAD group and non-EAD group in 3-month, 6-month, and 12-month graft (*Figure 2*) or patient survival (Figure S2), with all P values <0.0001. In terms of different follow-up periods, all three definitions had the highest hazard ratio (log-rank) in 3-month follow-up and the lowest in 12-month follow-up regardless of graft or patient survival.

Analysis of EAD among three definitions

We plotted the AUROC curves to evaluate the predictive power of three definitions. As showed in *Figure 3* for AUROC of the graft survival, MELDPOD5 (C statistic, 0.83) was superior to the MEAF (C statistic, 0.77) and Olthoff criteria (C statistic, 0.72) with regard to 3-month graft survival. MELDPOD5 also had higher predictive power than the other two criteria of EAD in both 6-month and 12-month graft survival. Furthermore, concerning the 3-month, 6-month, and 12-month patient survival (Figure S3), MELDPOD5 performed better than the Olthoff criteria and MEAF. *Table 2* depicted the statistical significance of the difference between the AUCs of three criteria. There was only a significant difference between the Olthoff criteria and MELDPOD5, accounted for P=0.0007 in 3-month graft survival, P=0.0108 in 6-month graft survival, and P=0.0362 in 12-month graft survival. With respect to 3-month, 6-month, and 12-month patient survival, *Table 2* also showed a significant difference

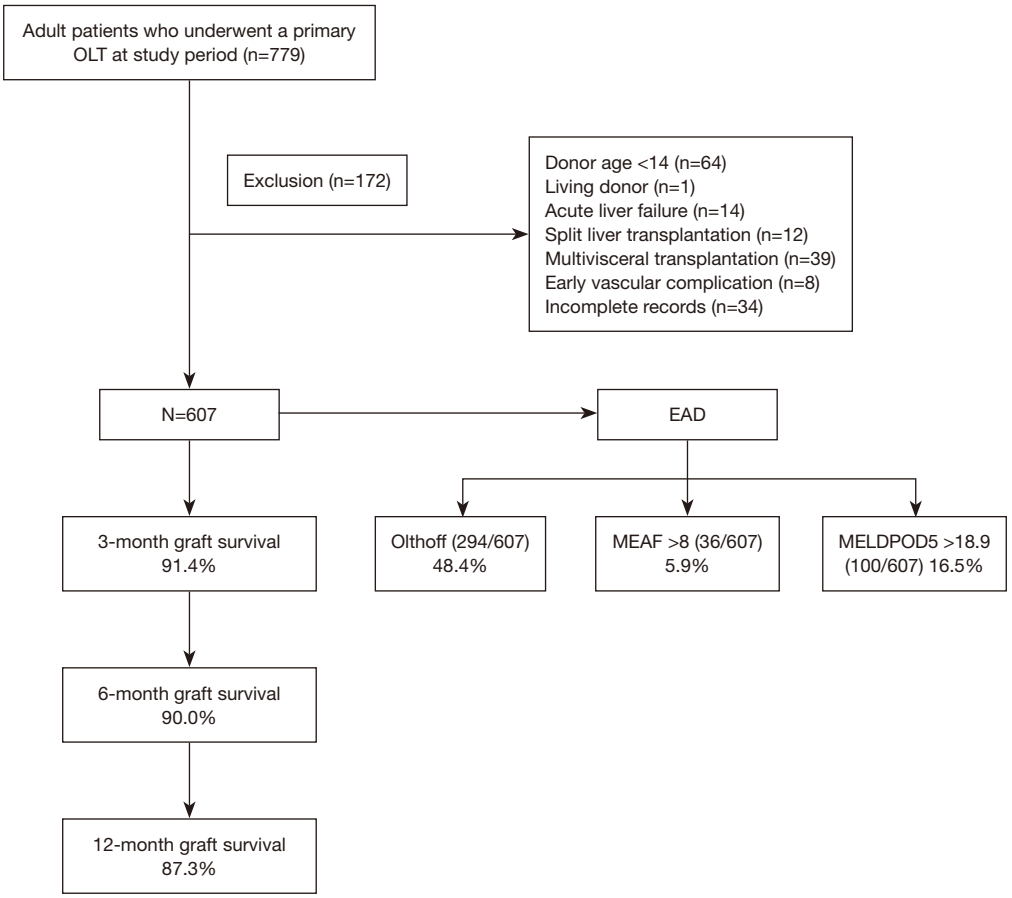

Figure 1 Orthotopic liver transplant recipients eligible for study inclusion. OLT, orthotopic liver transplantation; EAD, early allograft dysfunction; MEAF, Model for Early Allograft Function Scoring; MELDPOD5, Model for End-Stage Liver Disease score on Postoperative Day 5.

Table 1 Overview of 607 OLT cases included in the study

Variable	All OLT (n=607)
Donor	
Age, median (IQR), years	40 (27 to 48)
Male sex, (%)	78.5
Cause of death, %	
Trauma	47.8
CVA	37.6
HIE	6.3
Other	8.4
The Chinese Classification of Deceased Organ donation, %	
C-I (DBD)	76.2
C-II (DCD)	18.6

Table 1 (*continued*)

Table 1 (*continued*)

Variable	All OLT (n=607)
C-III (DBCD)	5.1
DRI, median (IQR)	1.64 (1.41 to 2.07)
Cold ischemia time, median (IQR), min	424 (328 to 524)
Warm ischemia time†, median (IQR), min	7 (5 to 10)
Recipient	
Age, median (IQR), years	50 (42 to 59)
Male sex, %	90.1
Diagnosis, %	
HCC	55.2
Hepatitis B virus-related cirrhosis	18.3
ACLF	11.7
Alcoholic cirrhosis	3.8
Cholestatic/autoimmune disease	2.5
Other	8.6
Comorbidity, %	
Hypertension	13.2
Diabetes mellitus	13.7
Coronary artery disease	4.0
Preoperative	
Laboratory MELD score (all), median (IQR)	12 (7 to 23)
Laboratory MELD score (HCC), median (IQR)	8 (5 to 14)
Laboratory MELD score (non-HCC), median (IQR)	18 (11 to 27)
Creatinine, median (IQR), μmol/L	73 (61 to 93)
Total bilirubin, median (IQR), mg/dL	2.8 (1.2 to 14.3)
INR, median (IQR)	1.38 (1.14 to 2.06)
Renal replacement therapy, %	2.1
Mechanical ventilation, %	1.2

Data of some variables were missing in some patients. The results reported here are based on patients with available information. †, warm ischemia time is defined as the time between withdrawal of therapy and start of cold flush of the organs in DCD or DBCD cases. OLT, orthotopic liver transplantation; IQR, interquartile range; CVA, cerebrovascular accident; HIE, hypoxic-ischemia encephalopathy; DBD, donation after death brain; DCD, donation after cardiac death; DBCD, donation after brain death followed cardiac death; DRI, donor risk index; HCC, hepatocellular carcinoma; ACLF, acute-on-chronic liver failure; MELD, the model of end-stage liver disease score.

between the Olthoff criteria and MELDPOD5, calculated as P=0.0011, P=0.0150, and P=0.0459. Therefore, MELDPOD5 might be the best criteria of EAD to predict both the graft and patient survival at 3-month, 6-month, and 12-month follow-ups.

The cutoff value for MELDPOD5 in our database was 18.2, which had the highest Youden index on the ROC curve, with sensitivity =0.691 and specificity =0.874 in 3-month graft survival (Table S1). Figure S4 showed that when the cutoff value was 18.2 instead of 18.9,

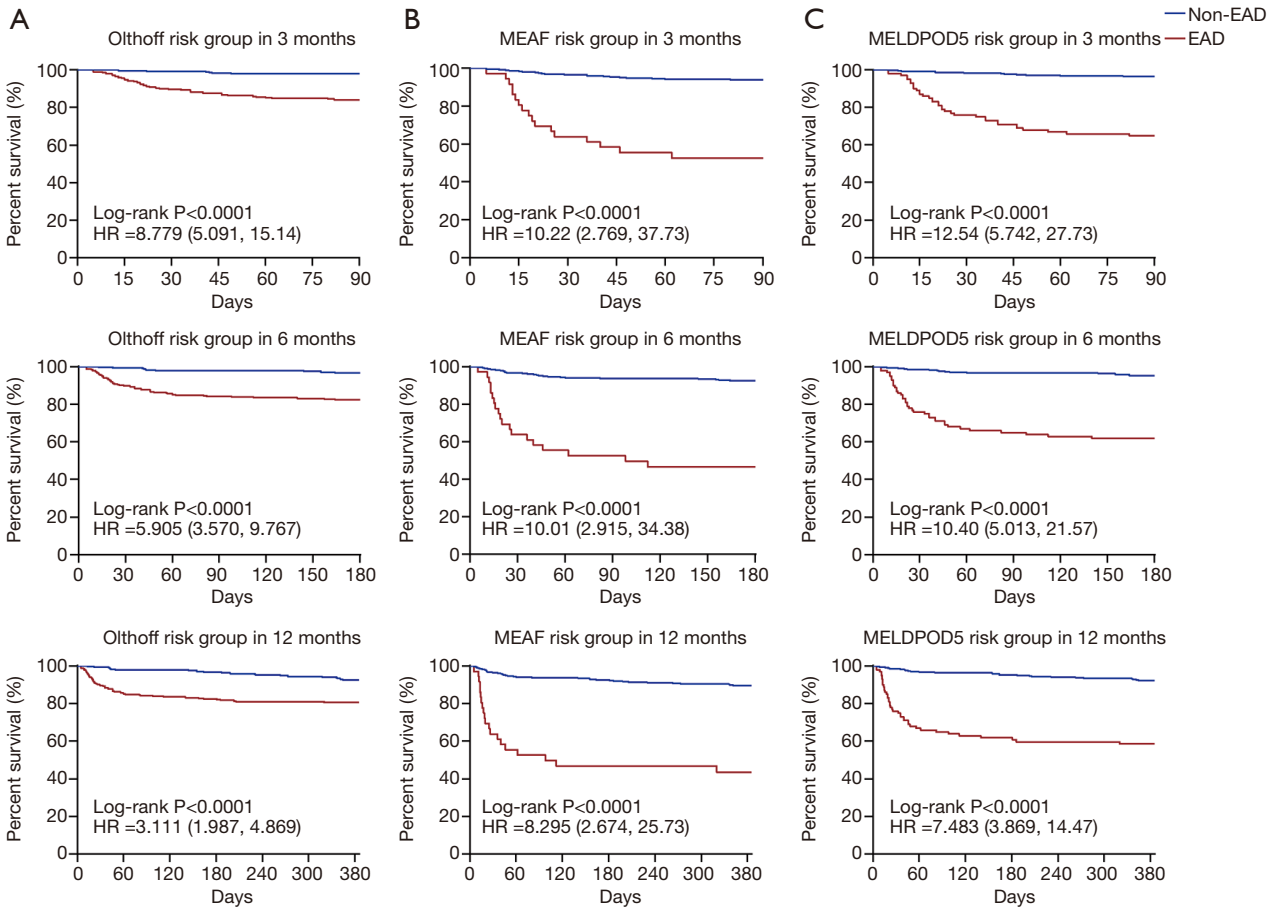

Figure 2 Comparison of Kaplan-Meier graft survival curves between three EAD definitions at 3-month, 6-month, and 12-month follow-up. (A) Olthoff risk group; (B) MEAF risk group was defined as MEAF score >8; (C) MELDPOD5 risk group was defined as MELDPOD5 >18.9. EAD, early allograft dysfunction; MEAF, Model for Early Allograft Function Scoring; MELDPOD5, Model for End-Stage Liver Disease score on Postoperative Day 5.

MELDPOD5 also maintained the distinguishing ability between The EAD and non-EAD recipients, with a P value <0.0001.

Analysis for risk factors associated with EAD

According to the comparison result of the predictive power of three criteria, we decided to select the MELDPOD5 as the criteria of EAD. Moreover, we identified all variables and calculated the univariate association with EAD (*Table 3*). Donor age (P=0.04), BMI (P<0.001), and DRI (P=0.01); cold ischemia time (P=0.02), and uPRBCs (P<0.001); hypertension of recipient (P=0.03); and laboratory MELD score (P<0.001), Child-Pugh score (P=0.01), creatinine (P=0.02), total bilirubin (P<0.001), INR (P=0.01) had a statistical association with EAD.

Variables with P<0.05 in the univariate analysis were entered into the multivariable logistic regression model (*Table 4*). Only donor BMI (OR 1.146, 95% CI: 1.055–1.244, P=0.001), DRI (OR 1.862, 95% CI: 1.198–2.894, P=0.006), uPRBCs (OR 1.045, 95% CI: 1.018–1.073, P=0.001), hypertension of recipient (OR 2.421, 95% CI: 1.325–4.423, P=0.004), and preoperative total bilirubin (OR 1.035, 95% CI: 1.018–1.052, P<0.001) were independent risk factors for EAD.

Postoperative analysis of transplant outcomes associated with EAD

As showed in the *Table 3*, there was a significant difference

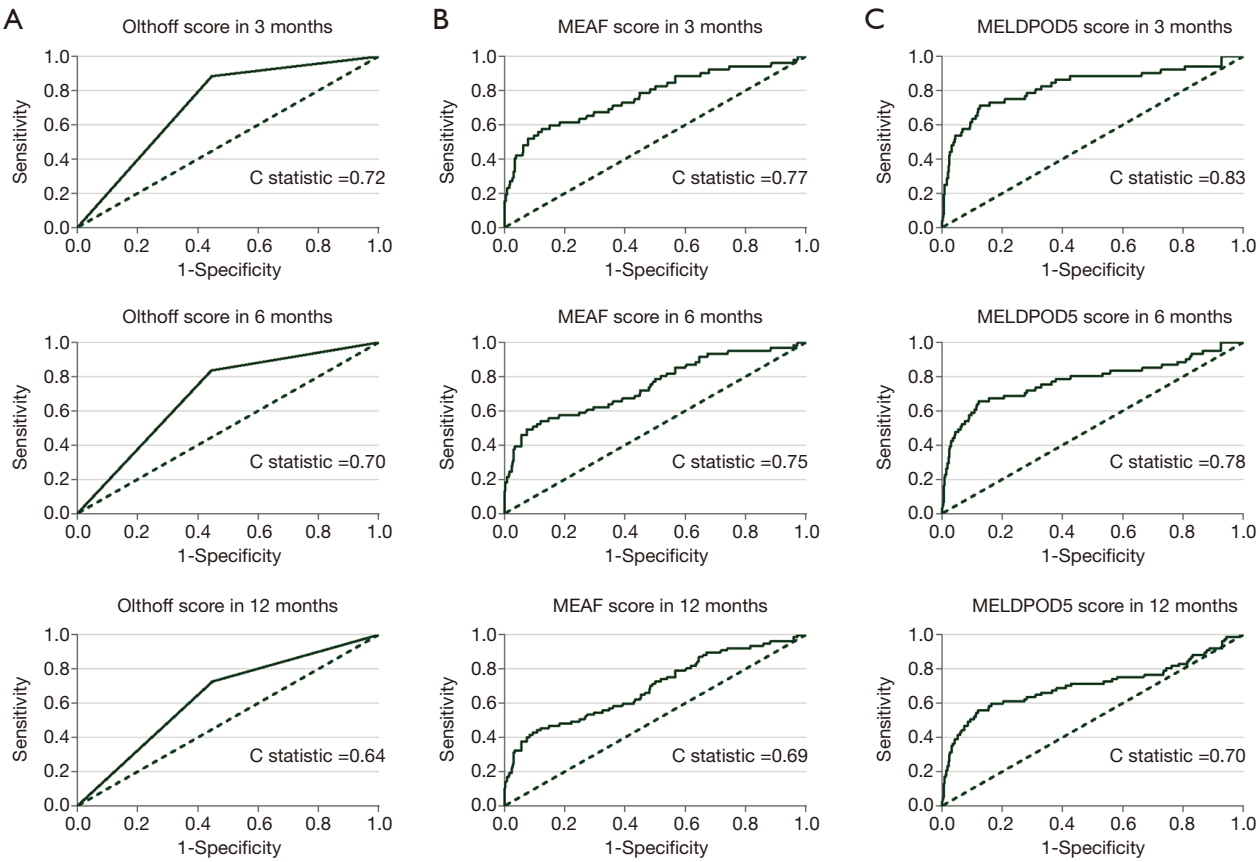

Figure 3 Comparison of the AUROC curve among three models of EAD to predict the graft survival at 3-month, 6-month, and 12-month follow-up. AUROC, area under the receiver operating characteristic; MEAF, Model for Early Allograft Function Scoring; MELDPOD5, Model for End-Stage Liver Disease score on Postoperative Day 5; EAD, early allograft dysfunction.

Table 2 Comparison of the AUROC Curves among three definitions of EAD

Prognosis	P value		
	Olthoff *vs.* MEAF	MEAF *vs.* MELDPOD5	MELDPOD5 *vs.* Olthoff
3-month graft survival	0.1521	0.0659	0.0007***
6-month graft survival	0.1002	0.2877	0.0108*
12-month graft survival	0.0537	0.6824	0.0362*
3-month patient survival	0.1909	0.0669	0.0011*
6-month patient survival	0.1269	0.2906	0.0150*
12-month patient survival	0.0683	0.6864	0.0459*

Comparison of AUROC curves was using DeLong *et al.* (in 1988) (22). *, P<0.05; ***, P<0.001. AUROC, the area under the receiver operating characteristic; EAD, early allograft dysfunction; MEAF, the Model for Early Allograft Function Scoring; MELDPOD5, the Model for End-Stage Liver Disease score on Postoperative Day 5.

Table 3 Univariable association in the MELDPOD5 model

Variable	Non-EAD (N=507)	EAD (N=100)	P value
Donor and operative			
Donor age, median (IQR), years	40 (26 to 47)	42 (34 to 49)	0.04*
Donor male sex, %	77.4	84.0	0.13
Donor blood type, %			0.40
O	38.7	41.0	
A	27.6	30.0	
B	26.6	20.0	
AB	7.1	8.0	
Donor height, median (IQR), cm	168 (160 to 170)	170 (162 to 172)	0.10
Donor BMI, median (IQR), kg/cm^2	22.2 (20.8 to 23.9)	23.7 (21.5 to 25.5)	<0.001***
The Chinese Classification of Deceased organ donation, %			0.50
C-I (DBD)	77.1	72.0	
C-II (DCD)	18.2	21.0	
C-III (DBCD)	4.7	7.0	
DRI, median (IQR)	1.60 (1.41 to 2.06)	1.80 (1.52 to 2.21)	0.01*
Perioperative			
Cold ischemia time, median (IQR), min	418 (324 to 514)	445 (355 to 572)	0.02*
Warm ischemia time†, median (IQR), min	7.5 (5 to 10)	6 (5 to 9)	0.10
uPRBCs, median (IQR), unit	5 (2 to 8)	8 (4 to 12)	<0.001***
Recipient			
Age, median (IQR), years	51 (42 to 59)	49 (42 to 56)	0.32
Male sex, %	89.7	92.0	0.48
Blood type, %			0.64
O	32.7	38.0	
A	28.8	26.0	
B	29.8	26.0	
AB	8.7	10.0	
ABO incompatibility, %	4.1	5	0.708
Height, median (IQR), cm	170 (165 to 172)	170 (165 to 172)	0.86
Weight, median (IQR), kg	66 (59 to 71)	68 (61 to 74)	0.09
Comorbidity			
Hypertension, %	11.8	20.0	0.03*
Diabetes mellitus, %	13.2	16.0	0.33
Coronary artery disease, %	3.7	5.0	0.57
BMI, median (IQR), kg/m^2	23.3 (20.9 to 24.9)	23.7 (22.0 to 25.7)	0.07

Table 3 (*continued*)

Table 3 (*continued*)

Variable	Non-EAD (N=507)	EAD (N=100)	P value
Pretransplant acuity			
Laboratory MELD score, median (IQR)	11 (6 to 21)	18 (10 to 29)	<0.001***
Child-Pugh score, median (IQR)	8 (7 to 10)	9 (7 to 11))	0.01*
Creatinine, median (IQR), μmol/L	72 (60 to 89)	77 (64 to 108)	0.02*
Total bilirubin, median (IQR), mg/dL	2.7 (1.2 to 11.8)	4.2 (1.7 to 24.8)	<0.001***
INR, median (IQR)	1.35 (1.12 to 2.03)	1.53 (1.17 to 2.16)	0.01*
Serum albumin, median (IQR), g/L	36.0 (32.6 to 40.5)	36.4 (32.0 to 41.0)	0.88
Renal replacement therapy, %	1.8	4.0	0.18
Mechanical ventilation, %	1.2	1.0	0.87
Postoperative evaluation			
Postoperative requirement of dialysis, %	1.6	26	<0.001***
ICU stay, median (IQR), h	37 (21 to 75)	123 (51 to 220)	<0.001***
Hospital stay, median (IQR), d	37 (25 to 52)	46 (29 to 66)	0.003

Data of some variables were missing in some patients. The results reported here are based on patients with available information. †, donor warm ischemia time is defined as the time between withdrawal of therapy and start of cold flush of the organs in DCD or DBCD cases. *, P<0.05; ***, P<0.001. IQR, interquartile range; BMI, body mass index; HIE, hypoxic-ischemia encephalopathy; DBD, donors after brain death; DCD, donation after cardiac death; DBCD, donation after brain death followed cardiac death; DRI, donor risk index; MELD, model of end-stage liver disease score; INR, international normalized ratio; uPRBCs, units of packed red blood cells; ICU, intensive care unit.

Table 4 Multivariate analysis for risk factors in MELDPOD5

Factors	Odd ratios	95% CI	P value
Donor BMI, median (IQR), kg	1.146	1.055, 1.244	0.001**
DRI, median (IQR)	1.862	1.198, 2.894	0.006**
uPRBCs, median (IQR), unit	1.045	1.018, 1.073	0.001**
Recipient hypertension	2.421	1.325, 4.423	0.004**
Preoperative total bilirubin, median (IQR), mg/dL	1.035	1.018, 1.052	<0.001***

**, P<0.01; ***, P<0.001. MELDPOD5, the Model for End-Stage Liver Disease score on Postoperative Day 5; IQR, interquartile range; DRI, donor risk index; uPRBC, packed red blood cells.

of postoperative requirement of dialysis between EAD (defined by MELDPOD5) and Non-EAD groups (OR 19.4, 95% CI: 8.767–43.111, P<0.001). Moreover, patients with EAD stayed longer in both ICU (123 *vs.* 37 hours, P<0.001) and hospital (46 *vs.* 37 days, P=0.003) than patients with non-EAD.

Discussion

This study is a single-center retrospective study to evaluate the predictive power of three EAD definitions for graft and patient survival in the short-term after surgery. Although the well-known criteria of EAD by Olthoff is the most recognized standard for EAD, it shows inferior ability to predict prognosis than several score standards proposed recently (12,21). As the continuous score, both MELDPOD5 and MEAF showed better predictive power than the Olthoff criteria in the current large Chinese cohort.

All the three criteria were established based on

retrospective studies. The main strength of Olthoff criteria lies in the multi-center clinical study, while the weakness lies in the criterion itself—a binary variable. As the continuous score validated by single-center, retrospective studies, both MELDPOD5 and MEAF are the formula conversion of several biochemical markers into numerical variables, which might better evaluate the severity of the patient's prognosis after OLT. Several studies have showed that the presence of EAD defined by the Olthoff criteria substantially affects graft and patient outcome (9,18,23). However, it has reported that EAD defined by the Olthoff criteria, which contains ALT and AST as indicators, is controversial in evaluating the prognosis of graft and patient (24). In the current study, all three criteria accurately distinguished the two groups of people in the Kaplan Meier survival curves—the EAD group and the non-EAD group. It is noteworthy that, according to the AUROC curves' comparison, MEALDPOD5 is superior to the Olthoff criteria in predicting the outcome.

In our country, the deceased organ donation system has been established since 2015. In addition, the proportion of patients with liver tumors was almost close to half of all recipients, which are different from those in the Western centers (12,14,16,21). Therefore, it is necessary to validate the criteria of EAD in Asian population. Compared with the original study (12), the preoperative MELD score (21.9 *vs.* 12), WIT (43.9 *vs.* 7 min), CIT (492 *vs.* 424 min) and DRI (1.69 *vs.* 1.64) indicates that the donor, recipient and operation factors might contribute to the decrease cutoff value of MELDPOD5 (18.9 *vs.* 18.2) in our study cohort. On the contrary, Khandoga *et al.* (15) in Germany proves that MELDPOD7 >29 had an excellent predictive power of 1-year graft survival, with the preoperative MELD score equal to 24.6 and CIT equal to 564 min. Therefore, the cutoff of 18.2 for MELDPOD5 might be more suitable for the Chinese population.

It is of great importance to analyze the risk factors of EAD to reduce the incidence of EAD. Bastos-Neves *et al.* (18) finds that donor overweight or grade I obesity shows an association with EAD. Similarly, in the current study, overweight (BMI >25 kg/m^2) donors in the EAD group accounted for 28.0%, much higher than 16.2% in the non-EAD group. DRI was first promoted by Feng *et al.* in 2005 to highlight the donor effect on transplant outcomes (25). Both DRI and multiplication product of MELD and DRI are significantly associated with patient survival after OLT (26). DRI seems to be not associated with EAD, as reported by the centers from United States (12) and Europe (14). However, in the current study, DRI is an independent risk factor for EAD.

uPRBCs has been reported to be strongly correlated with patient survival (27,28). In our study, high uPRBCs is associated with the higher risk of EAD. In addition, Ito *et al.* (7) demonstrates that the recipient hypertension contributes to the liver ischemia-reperfusion injury after OLT. And grade IV ischemia-reperfusion injury (IRI) is related to EAD (18). Both Pomposelli *et al.* (10) and Oweira *et al.* (29) prove that preoperative bilirubin is significantly associated with risk of EAD. Our study proved that hypertension and high levels of preoperative total bilirubin in the recipients contributes to the risk of EAD. Interestingly, preoperative hypertension of recipient became the independent risk factor for EAD for the first time.

ICU stay, hospital stay and postoperative requirement of dialysis in the EAD increased markedly, compared with the non-EAD groups. Wadei *et al.* has demonstrated that EAD is a risk factor for post-transplant acute kidney injury and end-stage renal disease (30). Furthermore, the liver function of the EAD patients recovers slower, resulting in patients requiring longer intensive care. Correspondingly, hospital stay and ICU time in the EAD patients would increase (21,23,31).

Conclusions

In summary, EAD indeed has predictive value for short-term prognosis in our center. EAD defined by the MELDPOD5 model might be a better criterion among the three assessed criteria, which help assess post-transplant patient outcomes. This criterion might serve as a better surrogate end-point for graft survival in clinical trial concerning liver machine perfusion. Though MELDPOD5 has showed extraordinary predictive power in Chinese and European single-center research, this might be generalizable to most transplant centers in different continents. The lack of Clavien-Dindo morbidity classification for recipients is also a limitation of our research and we intend to explore the clinical value of Clavien-Dindo morbidity classification in our center in the future. Finally, the differences in people from different ethnic and regions call for a global large-scale multi-center study to reach a consensus.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1012). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University [No. (2020)336] and individual consent for this retrospective analysis was waived.

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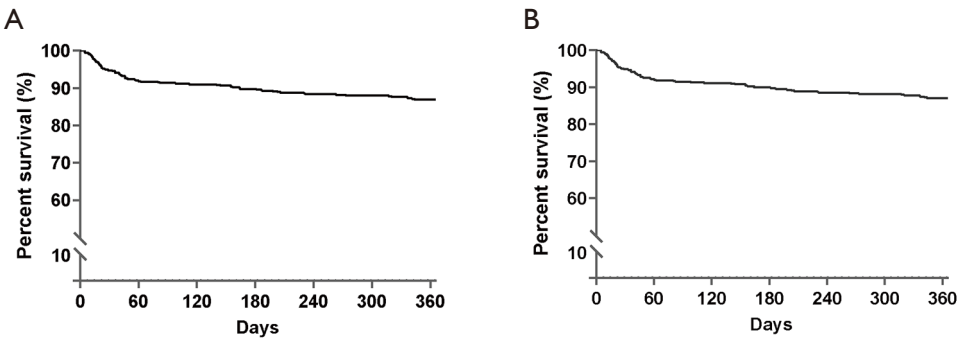

Figure S1 Kaplan-Meier survival curves of overall graft and patient in study period. Graft failure was defined as death or retransplantation. (A) Graft survival rate at 12-month follow-up; (B) overall patient survival rate at 12-month follow-up.

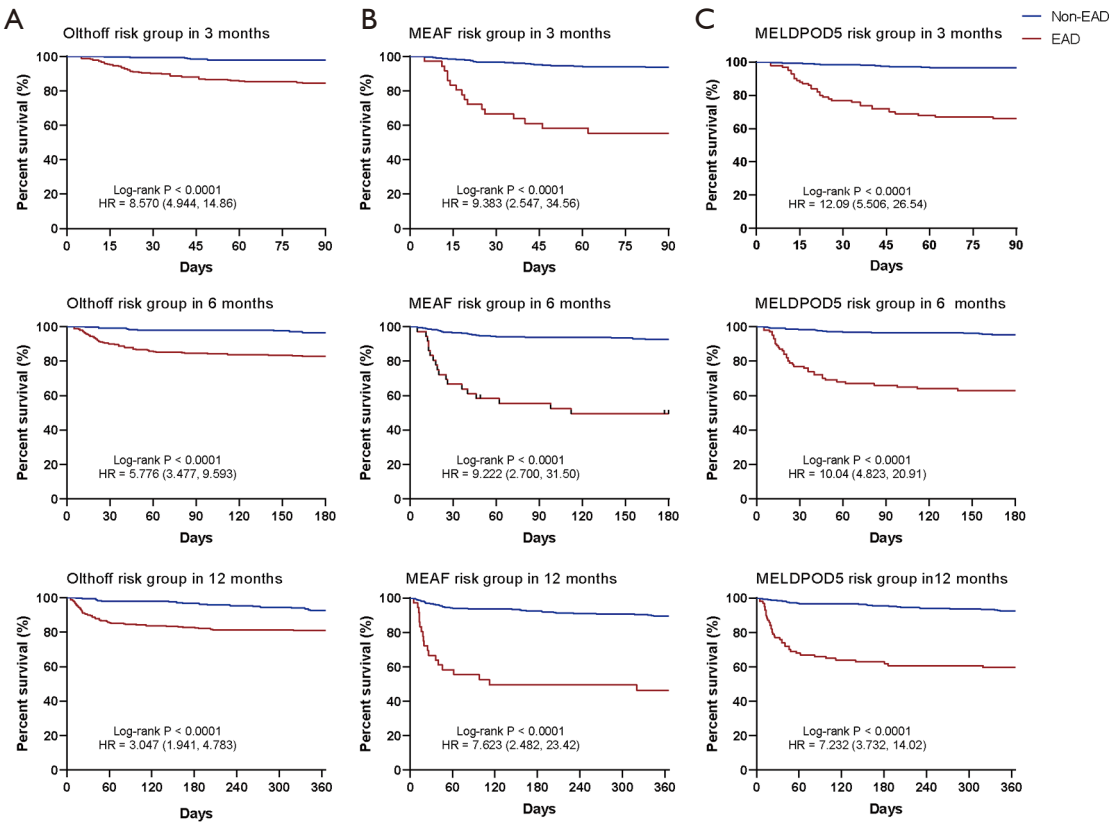

Figure S2 Comparison of Kaplan-Meier patient survival curves between three EAD definitions at 3-month, 6-month, and 12-month follow-up. (A) Olthoff risk group; (B) MEAF risk group was defined as MEAF >8; (C) MELDPOD5 risk group was defined as MELDPOD5 >18.9. MEAF, Model for Early Allograft Function Scoring; MELDPOD5, Model for End-Stage Liver Disease score on postoperative day 5; EAD, early allograft dysfunction.

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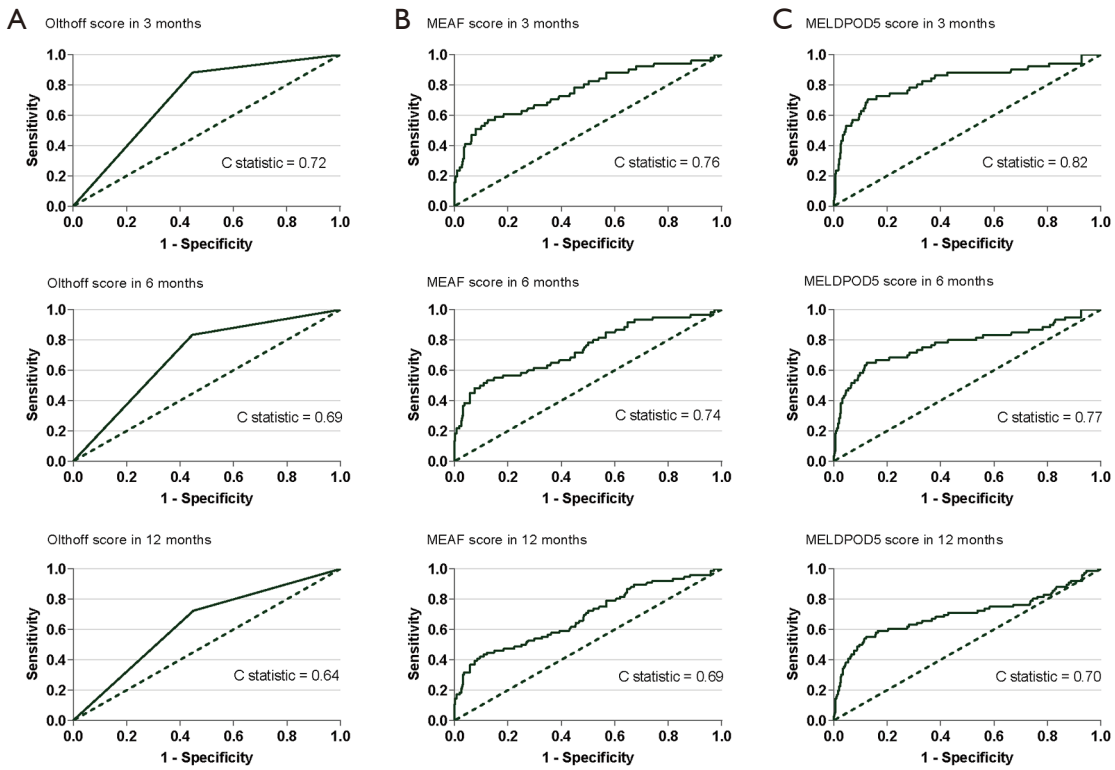

Figure S3 Comparison of the AUROC curve among three models of EAD to predict the patient survival at 3-month, 6-month, and 12-month follow-up. AUROC, area under the receiver operating characteristic; MEAF, Model for Early Allograft Function Scoring; MELDPOD5, Model for End-Stage Liver Disease score on Postoperative Day 5; EAD, early allograft dysfunction.

Table S1 The cutoff values of MELDPOD5 in different follow-ups

	Graft survival			Patient survival		
	3-month	6-month	12-month	3-month	6-month	12-month
Cutoff	18.2	18.2	18.2	18.2	18.2	18.2
Sensitivity	0.691	0.656	0.558	0.706	0.650	0.553
Specificity	0.874	0.877	0.879	0.872	0.876	0.878
Positive predictive value	0.340	0.372	0.402	0.336	0.339	0.393
Negative predictive value	0.968	0.958	0.932	0.970	0.962	0.932
Positive likelihood ratio	5.484	5.333	4.612	5.516	5.242	4.533
Negative likelihood ratio	0.354	0.392	0.503	0.337	0.400	0.509

MELDPOD5, the Model for End-Stage Liver Disease score on Postoperative Day 5.

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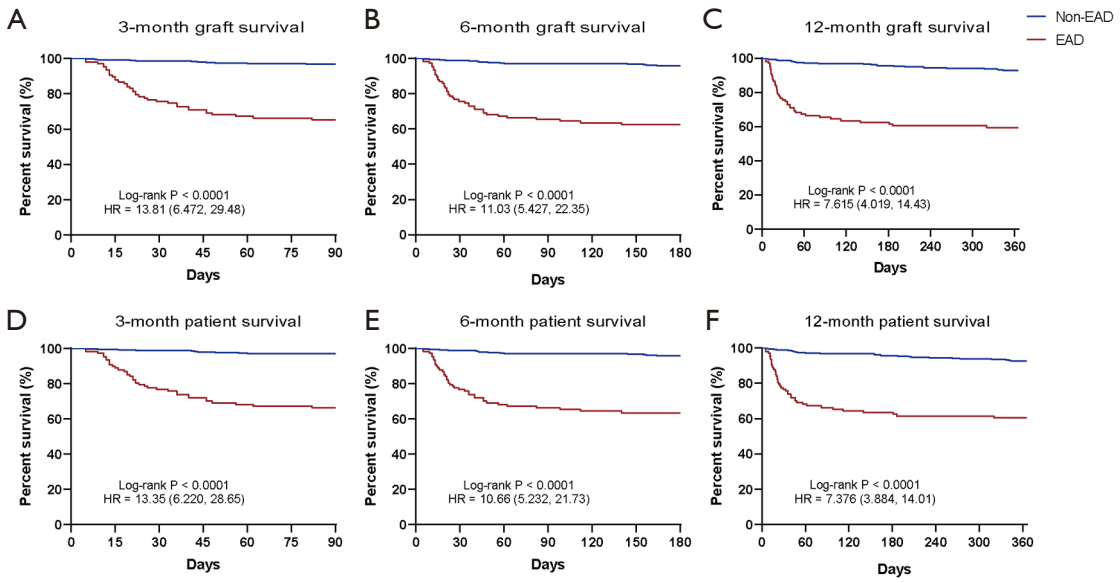

Figure S4 Kaplan-Meier survival curves of EAD defined by MELDPOD5 >18.2. Graft failure was defined as death or need for retransplantation during the period of observation. EAD, early allograft dysfunction; MELDPOD5, Model for End-Stage Liver Disease score on Postoperative Day 5.

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