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A new index predicts early allograft dysfunction following living donor liver transplantation: A propensity score analysis

Jiu-Lin Song, Jian Yang, Lu-Nan Yan, Jia-Yin Yang, Tian-Fu Wen, Bo Li, Yong Zeng, Hong Wu, Wen-Tao Wang, Ming-Qing Xu, Zhe-Yu Chen, Yong-Gang Wei, Li Jiang*

Liver Transplantation Center, Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan Province, China

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ABSTRACT

Objective/Aim: The aim of this study was to identify a new index to predict early allograft dysfunction following living donor liver transplantation.
Methods: The study enrolled 260 adult living donor liver transplantation recipients. Postoperative laboratory variables were assessed for their association with the prevalence of early allograft dysfunction using the inverse probability of treatment weighting and propensity-score matching (n = 93 pairs) analysis.
Results: Forty-seven recipients (18.1%) developed early allograft dysfunction. In multivariable analysis, the alanine aminotransferase and gamma-glutamyl transpeptidase levels on postoperative day 1 were independent predictors of early allograft dysfunction. The alanine aminotransferase to gamma-glutamyl transpeptidase ratio (AGR) was developed. All cases were divided into two groups (Group 1 [AGR ≥ 8.47, n = 103] and Group 2 [AGR < 8.47, n = 157]). AGR ≥ 8.47 (OR 10.345, 95%CI 4.502–23.772, $p < 0.001$), hepatorenal syndrome (OR 3.016, 95%CI 1.119–8.125, $p = 0.029$), and graft to recipient weight ratio <0.8% (OR 2.155, 95%CI 1.004–4.624, $p = 0.049$) were independent risk factors for early allograft dysfunction. The prevalence of early allograft dysfunction was higher in group 1 (after adjusting for inverse probability of treatment weighting [n = 39; 37.9% vs n = 8; 5.1%] and propensity-score matching [n = 33; 35.5% vs n = 2; 2.2%]) than that in group 2 ($p < 0.001$).
Conclusions: The postoperative AGR is a practical index for predicting early allograft dysfunction after living donor liver transplantation.

1. Introduction

Liver transplantation has become the curative treatment for end-stage liver disease, and the 5-year survival rate is more than 70% [1]. With the serious shortage of organs, the utilization of living donor liver transplantation (LDLT) has successfully expanded the donor pool [2,3]. Living donation can provide high-quality liver grafts with strict donor selection, but partial grafts might also cause hepatic insufficiency and failure after liver transplantation due to severe ischaemia/reperfusion (I/R) injury, liver regeneration impairment and small-for-size syndrome (SFSS) [4–6]. Therefore, an accurate preoperative evaluation of the graft availability and the timely postoperative identification of initial poor graft function are very crucial for LDLT.

Early allograft dysfunction (EAD) is a severe complication that is characterized by serum bilirubin ≥10 mg/mL on postoperative day (POD) 7, international normalized ratio (INR) ≥1.6 on POD7 or serum aminotransferase ≥2000 IU/mL in the first post-transplant week [7]. The occurrence of EAD is usually associated with progressive graft failure and related death [8]. Multiple previous studies have identified several different factors that precipitate graft dysfunction after liver transplant, including donor and recipient characteristics, intraoperative events and postoperative complications [9–11]. The early prediction of graft function following reperfusion is helpful for identifying recipients who may develop EAD or worse primary non-function (PNF) and benefit from timely retransplantation [12] or other treatments [13]. The aim of the present study was to determine the predictive ability of various postoperative laboratory values and develop a new, simple, and accurate index for predicting EAD.

* Corresponding author at: Liver Transplantation Center, Department of Liver Surgery, West China Hospital of Sichuan University, Chengdu 610041, Sichuan Province, China. Fax: +86 28 85422867.
E-mail address: jl339@126.com (L. Jiang).

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2. Methods

2.1. Study population

We analysed the records of consecutive patients who underwent LDLT between April 2002 and September 2015 in the West China Hospital Liver Transplantation Center. We included all recipients who were older than 18 years of age, and all recipients were followed up for at least 3 months. Before the analysis, all demographic, laboratory and clinical data were prospectively entered into the China Liver Transplantation Register (http://www.cltr.org/). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the West China Hospital of Sichuan University and with the Helsinki declaration. Written informed consent was obtained from all patients prior to surgery and was in accordance with the ethical guidelines of the Helsinki declaration.

2.2. Clinical variables

The baseline characteristics, laboratory variables and intraoperative data of both recipients and donors were collected from the China Liver Transplantation Register and presented in Tables 1 and 2. The preoperative and postoperative platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST), seral bilirubin, INR, gamma-glutamyl transpeptidase (GGT) and ALT – to – GGT ratio (AGR) were prospectively recorded daily from admission until POD7, weekly until postoperative week 4, and monthly until postoperative month 3. All recipients were divided into two groups according to the cut-off value of AGR on POD1 following LDLT. Additionally, the following significant variables of previous prediction models [14–16] were included as candidate risk factors for EAD: recipient age >60 years, fulminant hepatic failure, model for end-stage liver disease (MELD) score >25, encephalopathy, hepatorenal syndrome, dialysis before LT, donor age >40 years, donor anti-HBcAb positive, graft to recipient weight ratio (GRWR) <0.8%, and cold ischaemia time >6 h. The donor prescreening and selection, operative procedure and postoperative prescription were previously described [17].

2.3. Definition of outcome parameters

The primary outcome measure for liver allograft function was EAD, which was defined as the presence of one of the following situations [7]: serum bilirubin ≥10 mg/mL on POD7; INR ≥ 1.6 on POD7; and serum aminotransferase (ALT or AST) ≥2000 IU/mL within the first 7 postoperative days. PNF was defined as death or retransplantation within the first postoperative week with the exclusion of technical, immunological and infectious causes [10,18]. Severe postoperative complications were defined as grades III/IV according to the Clavien-Dindo classification [19]. Mortality was defined as any death occurring from the time of operation up to 90 days after transplantation.

2.4. Statistical analysis

Continuous data are presented as the mean ± standard deviation or median (interquartile range, IQR) and were compared by an independent sample Student t-test or Mann-Whitney *U* test. Categorical data are presented as the percentage and compared by the Chi-square test. Receiver operating characteristic (ROC) curve analysis was used to identify the ideal cut-off for laboratory variables to predict EAD. Multivariate logistic regression was performed to identify independent risk factors of EAD. Survivor curves were analysed using the Kaplan–Meier method and compared by the log-rank test. The outcome variables, including EAD, PNF, severe postoperative complication and mortality, were analysed using inverse probability of treatment weighting (IPTW) and propensity-score (PS) matching (n = 93 pairs).

To reduce the influence of confounding factors, we used IPTW [20] and PS matching methods to adjust the intergroup difference between different predictor groups. All variables shown in Table 2, without regard to outcome variables, were included in the multivariate logistic regression to obtain the propensity scores. The model calibration was evaluated by the Hansen–Bowers overall balance test ($\chi^2 = 10.07$; df = 26; $p = 0.998$). After all PS matching was complete, we compared all baseline characteristics between different predictor groups. The risk of the predictive variable for each outcome was evaluated using logistic regression in the crude, IPTW, and PS matching cohorts. All statistical analyses were performed using SPSS version 18 statistical software (SPSS Company, Chicago, IL, USA) or R software version 2.08. *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics and crude analysis

Between April 2002 and September 2015, 356 patients received LDLT in the West China Hospital Liver Transplantation Center. We excluded the recipients who were under 18 years of age (n = 75), had undergone retransplantation (n = 5), had acute vascular complications within one week postoperatively (n = 6) and lacked clinical data (n = 10). Eventually, a total of 260 recipients were enrolled in our study and followed until December 2015, and EAD occurred in 47 (18.1%) cases. The median follow-up was 16.4 months (range,

Table 1
Crude and multivariate analysis for factors associated with the presence of early allograft dysfunction (n = 260).

Variables	Crude			Multivariate		
	EAD (n = 47)	Non-EAD (n = 213)	*p* value	OR	95%CI	*p* value
Age (years)	41.9 ± 9.4	42.2 ± 8.7	0.818			
Male (%)	38 (80.9)	184 (86.4)	0.457			
Platelet (10^9/L)[a] [IQR]	40 (22–69)	60 (38–97)	0.002			
INR[a] [IQR]	1.99 (1.69–2.45)	1.67 (1.44–1.94)	<0.001	2.375	1.144–4.933	0.020
TB (μmol/L)[a] [IQR]	66.5 (46.2–132.8)	59.5 (40.1–90.1)	0.042			
Albumin (g/L)[a]	28.6 ± 7.6	32.1 ± 5.7	0.004	0.919	0.861–0.981	0.011
ALT (IU/L)[a] [IQR]	463 (206–1154)	282 (156.5–464)	<0.001	1.003	1.001–1.004	<0.001
AST (IU/L)[a] [IQR]	494 (246–1253)	314 (200–516)	0.002			
ALP (IU/L)[a] [IQR]	50 (38–67)	55 (44–74)	0.124			
GGT (IU/L)[a] [IQR]	29 (19–45)	49 (30–90)	<0.001	0.980	0.967–0.993	0.003
AGR[a] [IQR]	15.67 (9.20–32.76)	5.28 (2.50–10.18)	<0.001	Not available		

[a] All laboratory data were collected on the first post-operative day. EAD: early allograft dysfunction; IQR: inter quartile range; INR: international normalized ratio; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transpeptidase; and AGR: alanine aminotransferase to gamma-glutamyl transpeptidase ratio.

Table 2
Demographic and clinical variables between different alanine aminotransferase to gamma-glutamyl transpeptidase ratio groups on postoperative day 1 (n = 260).

Variables	Total (n = 260)	AGR ≥ 8.47 (n = 103)	AGR < 8.47 (n = 157)	*p* value
Recipient variables				
Preoperative variables				
Age (years)	42.2 ± 8.8	42.3 ± 9.1	42.1 ± 8.7	0.852
Male (%)	222 (85.4)	86 (83.5)	136 (86.6)	0.604
BMI (kg/m^2) [IQR]	22.1 (20.4–24.8)	22.7 (21.0–24.9)	21.8 (20.0–24.7)	0.054
Indications for LT				
Hepatitis B (%)	224 (86.2)	92 (89.3)	132 (84.1)	0.311
Hepatitis C (%)	5 (1.9)	1 (1.0)	4 (2.5)	0.651
Fulminant hepatic failure (%)	29 (11.2)	22 (21.4)	7 (4.5)	<0.001
Malignancy (%)	137 (52.7)	50 (48.5)	87 (55.4)	0.338
MELD score [IQR]	13 (9–20)	14 (9–24)	12 (8–17)	0.029
Child-Pugh (%)				
A	62 (23.8)	21 (20.4)	41 (26.1)	0.315
B	127 (48.8)	49 (47.6)	78 (49.7)	
C	71 (27.3)	33 (32.0)	38 (24.2)	
ASA PS classification (%)				
II	81 (31.2)	25 (24.3)	56 (35.7)	0.003
III	114 (43.8)	41 (39.8)	73 (46.5)	
IV	65 (25.0)	37 (35.9)	28 (17.8)	
Encephalopathy pre-LT (%)	27 (10.4)	17 (16.5)	10 (6.4)	0.016
Hepatorenal syndrome pre-LT (%)	24 (9.2)	17 (16.5)	7 (4.5)	0.002
Dialysis pre-LT (%)	7 (2.7)	5 (4.9)	2 (1.3)	0.117
laboratory data pre-LT				
Platelet (10^9/L) [IQR]	75 (40–121)	70 (38–110)	76 (43–134)	0.135
INR [IQR]	1.30 (1.11–1.75)	1.39 (1.15–1.91)	1.26 (1.10–1.60)	0.029
TB (μmol/L) [IQR]	36.2 (18.7–93.3)	42.8 (18.7–163.2)	30.6 (18.8–66.8)	0.086
Albumin (g/L)	34.3 ± 7.2	33.9 ± 7.0	34.6 ± 7.3	0.443
ALT (IU/L) [IQR]	45 (28–83)	42 (26–82)	47 (30–88)	0.375
AST (IU/L) [IQR]	59 (40–116)	61 (32–124)	59 (44–111)	0.363
GGT (IU/L) [IQR]	67 (35–151)	50 (28–81)	91 (40–203)	<0.001
Intraoperative variables				
Blood loss (mL) [IQR]	1000 (1000–2000)	1000 (1000–2000)	1000 (1000 −2000)	0.363
Blood transfusion				
PRBC (U) [IQR]	4.5 (0–9)	4.5 (0–9)	4.5 (0–9.5)	0.611
Fresh frozen plasma (mL) [IQR]	1000 (600–1650)	1050 (700–1850)	1000 (600–1650)	0.353
Platelet (U) [IQR]	0 (0–1)	0 (0–1)	0 (0–0)	0.494
Donor variables				
Age (years)	36.3 ± 10.2	36.1 ± 9.7	36.4 ± 10.56.7%instration(Yes/No)	0.793
Male (%)	150 (57.7)	59 (57.3)	91 (58.0)	>0.99
BMI (kg/m^2), [IQR]	23.0 (21.1–24.7)	22.8 (21.0–24.8)	23.1 (21.2–24.7)	0.530
Anti-HBcAb (+)	66 (25.4)	27 (26.2)	39 (24.8)	0.918
GRWR (%) [IQR]	0.91 (0.80–1.03)	0.89 (0.79–0.99)	0.92 (0.80–1.06)	0.238
Cold ischaemia time (min) [IQR]	198 (158–303)	203 (165–323)	196 (154–292)	0.086

AGR: alanine aminotransferase to gamma-glutamyl transpeptidase ratio; BMI: body mass index; IQR: inter quartile range; LT: liver transplantation; MELD: model for end-stage liver disease; ASA PS: American society of anesthesiologists physical status; INR: international normalized ratio; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; PRBC: packed red blood cell; Anti-HBcAb: anti-hepatitis B core antibody; and GRWR: graft to recipient weight ratio.

0–125 months). The crude analysis of laboratory data on POD1 is presented in Table 1. All cases were divided into two groups according to the AGR level on POD1 (Group 1 [AGR ≥8.47, n = 103] and Group 2 [AGR <8.47, n = 157]) based on the ROC curve.

The preoperative and intraoperative characteristics of both recipients and donors in the two groups are presented in Table 2. Recipients in group 1 were more likely to present with signs of fulminant hepatic failure (21.4% vs 4.5%, $p < 0.05$), encephalopathy (16.5% vs 6.4%, $p < 0.05$), and hepatorenal syndrome (16.5% vs 4.5%, $p < 0.05$) as well as to have higher MELD scores (14 [IQR, 9–24] vs 12 [IQR, 8–17], $p < 0.05$), American Society of Anesthesiologists Physical Status (ASA PS) classifications (II/III/IV [24.3%/39.8%/35.9% vs 35.7%/46.5%/17.8%], $p < 0.05$), and INR values (1.39 [IQR, 1.15–1.91] vs 1.26 [IQR, 1.10–1.60], $p < 0.05$) before operation than were recipients in group 2. Furthermore, recipients in group 1 had a lower serum GGT level (50 IU/mL [IQR, 28–81] vs 91 IU/mL [IQR, 40–203], $p < 0.05$) before transplantation than did those in group 2. To reduce confounding, all variables displayed in Table 2 were matched depending on the propensity sores. Table 3 lists the baseline characteristics of PS matching recipients (n = 93 pairs).

3.2. Definition and predictive performance of AGR on POD1 for EAD

The incidence of EAD was associated with the POD1 platelet count, INR, total bilirubin, albumin, ALT, AST, and GGT in crude analysis (Table 1). Subsequent multivariate analysis identified the INR, albumin, ALT and GGT on POD1 as independent predictors for EAD. However, the INR level within the first six postoperative days might still reflect the coagulative status of recipients at the time of transplantation instead of the graft function [7]. Furthermore, the serum albumin could easily be affected by perioperative albumin transfusion. Therefore, we chose the recipients' POD1 ALT and GGT values as the final EAD predictors. The variation trends of ALT and GGT before and after transplantation are presented in Fig. 1A and B. The ALT value had a positive impact on the EAD incidence (OR 1.003, 95% CI 1.001–1.004, $p < 0.05$), and the GGT value had a negative impact on the EAD incidence (OR 0.980, 95% CI 0.967–0.993, $p < 0.05$). To improve the prediction of these variables for EAD, a novel index of AGR was defined as the ALT (IU/mL)/GGT (IU/mL) ratio.

Table 3
Baseline characteristics of propensity scoring-matched recipients (n = 93 pairs).

Variables	Total (n = 186)	AGR ≥ 8.47 (n = 93)	AGR < 8.47 (n = 93)	*p* value
Recipient variables				
Preoperative variables				
Age (years)	42.5 ± 9.0	42.2 ± 9.3	42.8 ± 8.7	0.666
Male (%)	157 (84.4)	78 (83.9)	79 (84.9)	>0.99
BMI (kg/m^2) [IQR]	22.6 (20.8–25.0)	22.7 (21.0–24.9)	22.5 (20.4–25.5)	0.782
Indications for LT				
Hepatitis B (%)	168 (90.3)	82 (88.2)	86 (92.5)	0.457
Hepatitis C (%)	2 (1.1)	1 (1.1)	1 (1.1)	>0.99
Fulminant hepatic failure (%)	22 (11.8)	15 (16.1)	7 (7.5)	0.112
Malignancy (%)	103 (55.4)	49 (52.7)	54 (58.1)	0.555
MELD score [IQR]	13 (8–20)	14 (8–22)	12 (8–18)	0.414
Child-Pugh (%)				
A	47 (25.3)	21 (22.6)	26 (28.0)	0.686
B	88 (47.3)	45 (48.4)	43 (46.2)	
C	51 (27.4)	27 (29.0)	24 (25.8)	
ASA PS classification (%)				
II	55 (29.6)	25 (26.9)	30 (32.3)	0.629
III	78 (41.9)	39 (41.9)	39 (41.9)	
IV	53 (28.5)	29 (31.2)	24 (25.8)	
Encephalopathy pre-LT (%)	20 (10.8)	12 (12.9)	8 (8.6)	0.478
Hepatorenal syndrome pre-LT (%)	17 (9.1)	10 (10.8)	7 (7.5)	0.611
Dialysis pre-LT (%)	4 (2.2)	2 (2.2)	2 (2.2)	> 0.99
Laboratory data pre-LT				
Platelet (10^9/L) [IQR]	70 (38–110)	70 (38–111)	72 (35–108)	0.754
INR [IQR]	1.33 (1.12–1.79)	1.38 (1.14–1.84)	1.29 (1.11–1.78)	0.491
TB (μmol/L) [IQR]	35.2 (16.4–80.6)	37.6 (17.3–135.6)	30.5 (15.6–66.8)	0.255
Albumin (g/L)	34.4 ± 6.8	34.1 ± 7.3	34.7 ± 6.3	0.544
ALT (IU/L) [IQR]	42 (25–68)	42 (26–73)	41 (25–66)	0.834
AST (IU/L) [IQR]	53 (34–97)	56 (32–107)	52 (39–93)	0.749
GGT (IU/L) [IQR]	54 (30–92)	47 (28–79)	59 (35–106)	0.058
Intraoperative variables				
Blood loss (mL) [IQR]	1000 (1000–2000)	1000 (1000–2100)	1000 (1000–2000)	0.446
Blood transfusion				
Red blood cell (U) [IQR]	4.3 (0–9)	4 (0–8)	4.5 (0–9.4)	0.505
Fresh frozen plasma (mL) [IQR]	1000 (600–1800)	1000 (650–1725)	1000 (600–1800)	0.988
Platelet (U) [IQR]	0 (0–1)	0 (0–1)	0 (0–0.5)	0.440
Donor variables				
Age (years)	36.4 ± 10.3	36.1 ± 9.7	36.8 ± 10.8	0.638
Male (%)	106 (57.0)	53 (57.0)	53 (57.0)	>0.99
BMI (kg/m^2), [IQR]	23.3 (21.5–24.8)	23.0 (21.1–24.8)	23.4 (21.9–24.8)	0.355
Anti-HBcAb (+)	53 (28.5)	26 (28.0)	27 (29.0)	>0.99
GRWR (%) [IQR]	0.91 (0.79–1.02)	0.90 (0.80–1.00)	0.91 (0.79–1.09)	0.460
Cold ischaemia time (min) [IQR]	200 (160–311)	196 (162–307)	203 (156–321)	0.812

AGR: alanine aminotransferase to gamma-glutamyl transpeptidase ratio; BMI: body mass index; IQR: inter quartile range; LT: liver transplantation; MELD: model for end-stage liver disease; ASA PS: American society of anesthesiologists physical status; INR: international normalized ratio; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; PRBC: packed red blood cell; Anti-HBcAb: anti-hepatitis B core antibody; and GRWR: graft to recipient weight ratio.

An extreme increase in the AGR was observed during the first two days after operation, which was persistently decreased until 12 weeks in all cohorts (Fig. 1C). The area under the receiver operating characteristics (AUROC) for predicting EAD was higher when using POD1 AGR (0.809, 95% CI 0.736–0.882) than when using POD1 ALT alone (0.687, 95% CI 0.594–0.781, $p < 0.05$) and POD1 GGT alone (0.691, 95% CI 0.609–0.774, $p < 0.05$). Additionally, because the postoperative platelet count has been proposed as a predictor of the early postoperative outcome [21], we analysed the platelet count before and after transplantation (Fig. 1D). The AUROC of the POD1 platelet count (0.647, 95% CI 0.553–0.741, $p < 0.05$) was still lower than that of the AGR, but it was not significantly different from that of the ALT or GGT AUROC. For predicting EAD, the optimal AGR cut-off value was 8.47.

3.3. Risk factors for EAD

To identify the risk factors for the occurrence of EAD in LDLT recipients, 12 variables were analysed in Table 4. Univariate analysis suggested that fulminant hepatic failure (OR 2.760, 95% CI 1.118–6.409, $p = 0.018$), MELD score ≥ 25 (OR 3.341, 95% CI 1.569–7.114, $p = 0.002$), hepatorenal syndrome (OR 4.701, 95% CI 1.954–11.309, $p = 0.001$), POD1 AGR ≥ 8.47 (OR 11.350, 95% CI 5.023–25.645, $p < 0.001$), and POD1 platelet count $<43 \times 10^9$/L (OR 2.819, 95% CI 1.479–5.372, $p = 0.002$) were associated with the occurrence of EAD. Multivariate analysis demonstrated that POD1 AGR ≥ 8.47 (OR 10.345, 95% CI 4.502–23.772, $p < 0.001$), hepatorenal syndrome (OR 3.016, 95% CI 1.119–8.125, $p = 0.029$), and GRWR <0.8% (OR 2.155, 95% CI 1.004–4.624, $p = 0.049$) were independent risk factors for developing EAD after LDLT.

3.4. Association between AGR and postoperative outcomes

The association between AGR and postoperative outcomes was analysed in Table 5. The postoperative EAD and 90-day mortality were positively associated with a high POD1 AGR level in crude analysis and after adjusting for IPTW. However, after PS matching, only the occurrence of postoperative EAD was related to POD1 AGR, but the 90-day mortality was not found to be associated with POD1 AGR. Eventually, 18 deaths of recipients occurred in the 90 days

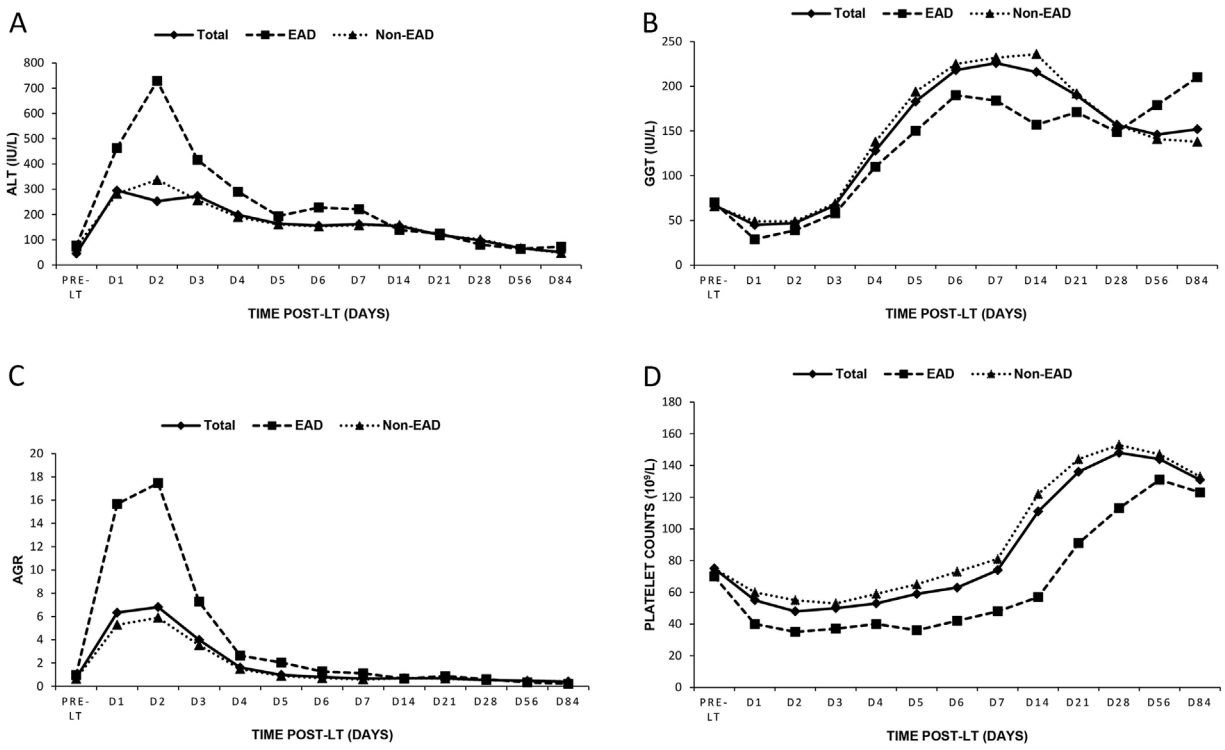

Fig. 1. Laboratory data before and after liver transplantation of total, early allograft dysfunction and non-early allograft dysfunction recipients. A, ALT levels; B, GGT levels; C, AGR index; and D, platelet counts. LT: liver transplantation; EAD: early allograft dysfunction; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase; and AGR: alanine aminotransferase to gamma-glutamyl transpeptidase ratio.

Table 4
Univariate and multivariate analyses of risk factors for early allograft dysfunction.

Clinical factor	Univariate			Multivariate		
	OR	95%CI	*p* value	OR	95%CI	*p* value
Recipient age >60	2.006	0.499–8.065	0.327			
Fulminant hepatic failure	2.760	1.118–6.409	0.018			
MELD Score >25	3.341	1.569–7.114	0.002			
Encephalopathy	2.094	0.856–5.125	0.105			
Hepatorenal syndrome	4.701	1.954–11.309	0.001	3.016	1.119–8.125	0.029
Dialysis pre-LT	3.562	0.770–16.483	0.104			
AGR ≥ 8.47	11.350	5.023–25.645	<0.001	10.345	4.502–23.772	<0.001
Platelet <43 ($\times 10^9$/L)	2.819	1.479–5.372	0.002			
Donor age >40	1.728	0.798–3.743	0.165			
Anti-HBcAb (+)	0.457	0.194–1.076	0.073			
GRWR <0.8%	1.922	0.987–3.741	0.055	2.155	1.004–4.624	0.049
Cold ischaemia time >6 h	1.375	0.626–3.019	0.428			

MELD: model for end-stage liver disease; LT: liver transplantation; AGR: alanine aminotransferase to gamma-glutamyl transpeptidase ratio; Anti-HBcAb: anti-hepatitis B core antibody; and GRWR: graft to recipient weight ratio.

Table 5
Postoperative outcomes adjusted by alanine aminotransferase to gamma-glutamyl transpeptidase ratio ≥ 8.47 on postoperative day 1.

Outcomes	Crude				Inverse probability of treatment weighting			Propensity score matching			
	Event/n	OR	95%CI	*p*	OR	95%CI	*p*	Event/n	OR	95%CI	*p*
EAD (%)	47/103	11.350	5.023–25.645	<0.001	10.341	4.378–24.427	<0.001	35/93	25.025	5.788–108.191	<0.001
PNF (%)	3/103	Not available		0.061	Not available		0.996	2/93	Not available		0.997
Grade III–IV (%)	69/103	1.146	0.655–2.006	0.633	0.763	0.432–1.348	0.763	50/93	1.000	0.523–1.912	>0.99
Mortality (%)	18/103	4.391	1.516–12.723	0.006	3.094	1.045–9.159	0.041	14/93	1.886	0.607–5.857	0.273

EAD: early allograft dysfunction and PNF: primary non-function.

following transplantation in the crude cohort. The causes of death were analysed in the Supplementary table and included allograft failure (n = 12, 4.6%), digestive bleeding (n = 2, 0.8%), surgical haemorrhage (n = 1, 0.4%), multiple organ dysfunction syndrome (MODS, n = 1, 0.4%), sepsis (n = 1, 0.4%), and acute rejection (n = 1, 0.4%). After PS matching, there were 14 deaths among the recipients. The causes of death included allograft failure (n = 9, 4.8%), digestive bleeding (n = 1, 0.5%), surgical haemorrhage (n = 1, 0.5%), MODS, (n = 1, 0.5%), sepsis (n = 1, 0.5%), and acute rejection (n = 1, 0.5%). Survival analyses with the Kaplan–Meier curve showed that recipients in group 1

had lower 1-, 3-, 5-, and 10-year overall survival rates (77.3%, 67.5%, 67.5%, and 63.8%, respectively) than did recipients in group 2 (87.6%, 76.1%, 74.5%, and 72.3%), but the difference was not statistically significant ($p = 0.058$). Additionally, recipients in group 1 exhibited lower 1-, 3-, 5-, and 10-year allograft survival rates (76.6%, 71.6%, 71.6%, and 67.7%) than did recipients in group 2 (87.6%, 83.1%, 81.6%, and 77.1%; $p = 0.019$). After PS matching, the difference in the 1-, 3-, 5-, and 10-year overall survival rates between group 1 (80.4%, 69.5%, 69.5%, and 64.8%) and group 2 (81.9%, 74.1%, 71.3%, and 71.3%) were not statistically significant ($p = 0.461$). However, group 1 also exhibited lower 1-, 3-, 5-, and 10-year allograft survival rates (78.7%, 73.2%, 73.2%, and 68.3% vs 88.3%, 85.5%, 85.5%, and 85.5%) than did group 2 ($p = 0.021$).

4. Discussion

EAD is a critical condition after liver transplantation, and it contributes to poor outcomes. Our current results show that 18.1% of the LDLT recipients developed EAD after transplantation, which is slightly lower than the 20–39.5% reported in previous studies [7–10,22]. This may benefit from more rigorous donor selection, superior allograft quality and a shorter ischaemia time in living donation over marginal or extended liver donations [22]. However, partial liver allografts may be insufficient for recipients' functional requirements, and the allografts may be injured by portal hyperperfusion [6,23], which also plays a critical role in early allograft loss in LDLT recipients. Moreover, the discrepancy in the morbidity for EAD may result in disagreement with the EAD criteria in early periods. In this study, we employed a recently validated simple clinical definition of EAD characterized by early high transaminase (for cytolysis), persistent cholestasis (for biotransformation) and prolonged coagulopathy (for synthesis) during the first week after transplantation, which was associated with allograft loss and death within the first 6 months in multicentre analysis [7].

The pathogenesis of EAD is often believed to be secondary to severe I/R injury after liver implantation, resulting in irreversible parenchymal and biliary liver damage mediated by oxidative stress and inflammatory response [4,24]. The eventual liver injury after reperfusion may not only reflect the duration of the ischaemic time, but it may also reflect the donor and recipient status (including the ages, primary disease severity, procurement process, and allograft quality), and intraoperative events. Previous studies have provided several predictive models to identify the recipients who have a high risk of initial allograft loss. Feng et al. [14] developed a quantitative donor risk index with seven donor characteristics to predict liver graft failure and help inform the process of organ acceptance. Furthermore, Rana et al. [15] devised the Survival Outcomes Following Liver Transplant score system, utilizing 18 factors (13 for recipients, 4 for donors, and 1 for the operation), to accurately predict the 3-month survival following liver transplantation. However, these preoperative predictive models are more practical for making organ acceptance decisions and optimizing donor/recipient matching rather than detecting EAD recipients ahead of time. Moreover, intraoperative biopsy detection is common in assessing the allograft quality and predicting allograft outcomes. Ali et al. [25] performed time-zero biopsies after complete revascularization and assessed the severity of the I/R injury with the presence of neutrophilic infiltration, cell apoptosis, and hepatocyte dropout to predict adverse clinical outcomes after liver transplantation. Further studies demonstrated that donor liver biopsy could affect either genomic [26] or metabolic [27] profiling signatures related to recipients undergoing EAD. Additionally, biopsy detection is complicated and uncommonly performed, and the results are usually delayed for early prediction requests.

Consequently, a quick and accurate predictive model based on parameters after reperfusion could be an ideal option to reflect graft injury resulting from both preoperative and intraoperative factors. Derangements in a variety of postoperative biochemical and haematological parameters within the first week after transplant have been used to identify recipients suffering from EAD [10], but previous studies have demonstrated that the association was not sufficiently strong to warrant early retransplantation. To the best of our knowledge, our current study was the first to employ a new simple biomarker index, AGR, to predict the initial graft outcome immediately after transplantation. In this study, we provided evidence showing that AGR $\geq$ 8.47 on POD1 (within 24 h) was associated with an almost 10-fold increased risk of EAD. Even after IPTW adjustment and PS matching, initial graft dysfunction was related to POD1 AGR in recipients undergoing LDLT. Furthermore, AGR $\geq$ 8.47 on POD1 was related to the 90-day mortality in the crude cohort and adjustment for the IPTW following LDLT; however, the significance was lost after PS matching. Furthermore, the allograft failure still caused more deaths for recipients in group 1 after PS matching. We selected the biomarkers within POD1 to detect postoperative EAD as early as possible.

Although the detailed mechanism of action by which high AGR has a positive effect on the initial graft outcome is unclear, studies have proposed that the postoperative ALT and GGT levels have a contradictory influence on early graft survival. Notably, ALT is an important pyridoxal enzyme in the intermediary metabolism of glucose and protein, catalysing the reversible transamination between alanine and 2-oxoglutarate to form pyruvate and glutamate [28]. Because it is predominantly found in hepatocytes, ALT has been used as a specific marker of liver injury. A significant elevation of the serum ALT activity is common in various chronic liver diseases and acute liver damage [29]. An explosive elevation in the postoperative peak ALT level has been reported to identify initial poor graft function after orthotopic liver transplantation. Ardite et al. [30] supposed that a peak serum ALT level more than 2500 IU/mL within the first 3 postoperative days could be identified as initial graft dysfunction. González et al. [31] identified the recipients with impaired graft function by progressive increase in the serum ALT level, absence of bile production and prothrombin inactivity. Although the serum ALT level on POD1 served as an endpoint of the EAD criteria if it was more than 2000 IU/mL, this situation was only observed in 3 recipients and had no impact on the results.

Furthermore, GGT is a membrane-bound enzyme that is essential for the synthesis of the antioxidant glutathione (GSH) [32]. An elevated serum GGT level usually indicated liver disease, such as biliary obstruction and alcohol consumption [33]. However, a recent study found that the serum GGT level is transiently increased in patients with good outcomes after partial hepatectomy [34]. Alkozai et al. [35] first reported that recipients with a transient elevation in the GGT level following liver transplant had a higher 90-day survival. The release of reactive oxygen species by activated Kupffer cells contributes to I/R injury of the liver allograft [36]. Experimental studies have demonstrated that endogenous GSH could defend against reperfusion injury caused by reactive oxygen species after prolonged warm ischaemia [37] and hypothermic preservation [38] in rat livers. Cellular GGT is a key enzyme in the gamma-glutamyl cycle that produces endogenous GSH. Additionally, Liu et al. [39] reported that hepatic ischaemia induced early elevation in the serum GGT, which peaked within 20 to 30 hours after the restoration of hepatic blood flow. As a result, Alkozai assumed that a transient increase in the GGT level after transplant may reflect the host compensatory mechanism against oxidative stress, which results from increased cell necrosis by damaging membrane lipids, redistributing membrane-bound and intracellular enzymes, and diminishing mitochondrial oxidative metabolism [35].

Another possible mechanism for EAD after liver transplantation is an impairment of liver regeneration, especially for LDLT with partial allograft. Eisenbach and colleagues [40] demonstrated that an initial increase in the GGT peak value was associated with a superior outcome after orthotopic liver transplant and assumed that an elevated GGT was related to rapid liver regeneration. Additionally, studies have suggested that platelets may contribute to liver regeneration after hepatic ischaemic injury via the platelet-derived serotonin/vascular endothelial growth factor pathway [41]. Lesurtel et al. [21] proposed a "60-5 criteria", namely, platelet counts less than 60×10^9/L on POD5, to predict early post-transplant survival after orthotopic liver transplantation. However, the association between thrombocytopenia on POD1 and EAD was negative in our study.

Additionally, small partial grafts and hyperperfusion, especially in cirrhotic patients with portal hypertension, usually triggered so-called SFSS, which resulted in poor recipient outcomes [6,42]. The suggested safe range of graft mass requirement is more than 0.8% of GRWR [2], and our study similarly found that GRWR less than 0.8% is a risk factor of EAD after adult-to-adult LDLT. Finally, hepatorenal syndrome prior to operation was a risk factor for EAD. Other authors have illustrated that hepatorenal syndrome and renal insufficiency pre-transplant are associated with a poor outcome following liver transplantation [10,43].

This study has several limitations. First, this is a retrospective observational study, and potential bias might interfere with the actual results. Although we tried to exclude selection bias via the IPTW method and PS matching, we cannot eliminate the impact of confounding factors. Second, this is a single centre analysis with a relatively small sample of patients undergoing LDLT. Third, the causality could not be determined due to the observational nature of this study. Therefore, further prospective large-scale multicentre studies will be needed to clarify the causality between the postoperative AGR and EAD after LDLT.

In conclusion, an AGR more than 8.47 on POD1 may predict the incidence of EAD after LDLT.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2017.06.007.

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