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The Lactate-to-Platelet Ratio: A Novel Predictor for Short-Term Early Allograft Failure After Liver Transplantation

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The Lactate-to-Platelet Ratio: A Novel Predictor for Short-Term Early Allograft Failure After Liver Transplantation

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ABSTRACT

Background. Early allograft dysfunction (EAD) is a criterion to evaluate initial graft dysfunction associated with inferior graft survival and postoperative complications after liver transplantation (LT). This study defined the lactate-to-platelet ratio (LPR) as lactate level immediately post-LT/platelet count on postoperative day 1 and evaluated its association with EAD and short-term graft failure.

Materials and methods. This study reviewed 434 deceased-donor LTs from individuals with confirmed brain death between January 2008 and December 2014. The area under the curve (AUC) was used to compare the predictive capacity for 3-month graft survival between EAD and the LPR. Along with LPR, the risk factors for 3-month graft failure were analyzed by multivariate analysis.

Results. EAD was reported in 127 patients (31%). The LPR in patients with EAD was significantly higher than that in patients without EAD (9.8 vs 5.9, $P < .001$). In the multivariate analysis, both the LPR (per 1.0 increase) and EAD were independent risk factors for 3-month graft failure (hazard ratio [HR] =1.03, $P = .03$; and HR = 9.14, $P = .001$). The comparison of the AUCs between the LPR and EAD showed no significant difference (0.79 vs 0.78, $P = .84$), whereas the combination of EAD and LPR had a better predictive capacity than EAD alone (0.86 vs 0.78, $P < .001$). The LPR showed an inverse relationship for predicting 3-month graft survival.

Conclusions. The LPR is a continuous parameter that enables prediction of initial graft function and estimation of the 3-month graft failure rate with the advantages of early availability and simple calculations.

THE success and durability of liver transplantation (LT) depends on the function of the liver graft. Initial graft dysfunction after LT presents the clinical phenotype of severe ischemia/reperfusion (I/R) injury secondary to a variety of recipient, donor, and perioperative factors. The parameters indicated for graft dysfunction reflect hepatocellular damage and synthetic impairment [1]. Currently, early allograft dysfunction (EAD) classification, defined by Olthoff et al [2] as a peak value of aminotransferase >2000 IU/mL during the first week after LT or an international normalized ratio of ≥1.6 and/or bilirubin ≥ of 10 mg/dL at day 7, is a widely accepted criterion for initial graft dysfunction, which results in inferior graft and patient survival, complications, and an increase in the use of medical resources. According to their report, the rate of graft loss was reported to be 26.1% for patients with EAD and 3.5% for patients without EAD; furthermore, 18.8% of patients with EAD died, whereas only 1.8% of recipients without EAD died. However, the EAD classification is an "all-or-nothing" criterion, and 7 days are still needed before diagnosis.

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Platelets are the smallest constituents in blood and contain 3 types of granules: alpha granules, dense granules, and lysosomal granules. Each granule contains growth factors such as hepatocyte growth factor, insulin-like growth factor−1, vascular endothelial growth factor, endothelial growth factor, and serotonin. Platelets have been traditionally recognized to have negative effects on the liver, such as under conditions of I/R injury and hepatitis [3−5]. However, recent studies have disclosed different roles of platelets in the liver. Platelets have been demonstrated to promote liver regeneration, ameliorate liver fibrosis, and protect hepatocytes by preventing apoptosis [6−8]. Specifically, in the LT field, platelets were suggested to enhance graft regeneration after living-donor LT [9], prevent biliary anastomotic stenosis [10], and improve graft survival after deceased-donor LT [11,12]. It was demonstrated that platelets accumulate in the liver graft immediately after LT and release growth factors from within, which enhances graft regeneration [13]. Lactate, a waste product of cellular metabolism, is mainly metabolized in the liver, and post-transplant serum lactate levels are considered a surrogate marker of early graft function [14]. Abnormally elevated lactate levels may indicate graft dysfunction. Recent studies have disclosed a relationship between perioperative lactate levels and short-term post-LT outcomes [14,15].

In this study, we developed a novel prognostic parameter, the lactate-to-platelet ratio (LPR), to define initial graft function that predicts short-term graft failure after LT. This study aimed to investigate the association of the LPR with EAD and assess whether the LPR could predict short-term graft failure after deceased-donor LT.

MATERIALS AND METHODS

Population

Between January 2008 and December 2014, 542 patients underwent deceased-donor LT at the Department of Transplant and Hepatobiliary Surgery, Henry Ford Hospital. Of these 542 patients, 48 underwent simultaneous organ transplants, 25 received a donation from cardiac death donors, 16 died intraoperatively, and 19 received LT under status 1A code (patient who had sudden-onset acute liver failure or had primary nonfunction of a transplanted liver within 7 days of transplantation); these patients were excluded from the analysis. A total of 434 recipients were finally enrolled in this study. The present study was approved by the Henry Ford Health System institutional review board, and the study was performed in accordance with the principles of the Declaration of Helsinki.

Definition of the LPR

The LPR was defined as "the lactate level immediately following LT divided by the platelet count on postoperative day (POD) 1." The lactate was obtained immediately after patients were admitted to the intensive care unit after transplantation. Lactate levels were used immediately after LT because we previously demonstrated that a high lactate level immediately after LT was a predictor of EAD and was strongly related to short-term graft loss [16]. The platelet count on POD 1 was used because the area under the curve (AUC) of the LPR for 3-month graft loss was the highest using the value recorded on POD 5 (Table 1). However, there was no remarkable difference between POD 1 and POD 5, and regarding the platelet count, obtaining a value rapidly after LT is clinically more important.

Outcome parameters

EAD was defined following the criteria described by Olthoff et al [2]. The survival outcomes following liver transplantation (SOFT) and balanced assessment of risk (BAR) scores were calculated according to the original articles [17,18]. Possible risk factors for 3-month graft failure were analyzed by univariate and multivariate analyses using Cox regression models. Warm ischemia time (WIT) and cold ischemia time (CIT) were equally divided into 3 groups (WIT, <34 minutes, 34-42 minutes, >42 minutes; CIT, <295 minutes, 295-372 minutes, >372 minutes). The AUC, net reclassification improvement (NRI), and integrated discrimination improvement (IDI) were used to compare the prediction abilities of EAD and the LPR for 3-month graft failure.

Statistical analysis

The results are presented as numbers and percentages. Continuous variables are expressed as medians and interquartile ranges, and groups were compared using unpaired *t* tests. Univariate and multivariate analyses, coefficient calculations, and operating cure analyses were performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) and SAS software version 9.4 (SAS Institute, Cary, NC, USA). Survival analysis was performed using the Kaplan-Meier method, and the difference was compared using the log-rank test. Variables that had $P < .10$ in the univariate analysis were included in the multivariate analysis. $P < .05$ was considered statistically significant.

RESULTS

Demographics

The median age at the time of LT was 58 years, and 278 patients were male (64%). The most common reason for LT was hepatitis C (49%, n = 211), followed by nonalcoholic steatohepatitis or cryptogenic (29%, n = 127). The median model for end-stage liver disease (MELD) scores, SOFT scores, and BAR scores were 22, 3, and 7, respectively. The median length of hospital stay was 10 days. Reoperation within 7 days occurred in 68 patients (15%). The 3-month and 1-year survival rates were 95% and 90%, respectively (Table 2).

Table 1. Combination of LPR: ROC Analysis for 3-Month Graft Loss

Platelet		Immediately post-LT	1 POD	3 POD	5 POD
Immediately Post-transplant	AUC	0.739	0.800	0.711	0.824
	P value	.048	.013	.080	.007

AUC, area under curve; LPR, lactate/platelet ratio; LT, liver transplantation; POD, postoperative day; ROC, receiver operating characteristic.

Table 2. Demographics (Total N = 434)

Recipient variables	
Age	58 (17-72)
Sex, male	278 (64%)
Ethnicity	
White	322 (74%)
African American	75 (17%)
Others	37 (9%)
Disease type	
Viral hepatitis C	212 (49%)
NASH/cryptogenic	127 (29%)
Hepatocellular carcinoma	31 (7%)
Cholestatic disease	33 (8%)
Others	31 (7%)
BMI (kg/m^2)	28.0 (16.9-67.0)
MELD score	22 (6-41)
SOFT score	3 (1-6.25)
BAR score	7 (4.5-11)
Diabetes mellitus	112 (26%)
Donor variables	
Age	44 (7-84)
Sex, male	242 (56%)
Ethnicity	
White	324(75%)
African American	89(21%)
Others	21 (4%)
Cause of death	
CVS	195 (45%)
Trauma	117 (27%)
Anorexia	109 (25%)
Others	10 (3%)
BMI (kg/m^2)	27.0 (15.1-60.6)
Location	
Local	371 (85%)
Regional	50 (12%)
National	10 (3%)
Steatosis >30%	7 (2%)
Surgical variables, intraoperative	
Warm ischemic time (min)	38 (19-92)
Cold ischemic time (min)	328 (140-699)
Estimated blood loss (ml)	1800 (100-26000)
Anhepatic time (min)	70.5 (28-179)
RBC transfusion, amount (units)	3 (0-48)
FFP transfusion, amount (units)	6 (0-57)
Platelet transfusion, amount (units)	0 (0-35)
Postoperative variables	
Length of stay after transplantation, days	10 (3-142)
Biliary complications within 1 y	138 (32%)
Rejection history within 1 y, yes	60 (14%)
Reoperation within 30 d, yes	102 (24%)

BAR, balanced assessment of risk; BMI, body mass index; CVS, cardiovascular system cause; FFP, fresh frozen plasma; MELD, model of end-stage liver disease; NASH, non-alcoholic steatohepatitis; RBC, red blood cell; SOFT, survival outcomes following liver transplantation.

EAD and the LPR

Of the 434 patients, 127 patients (31%) developed EAD. Patients with EAD showed significantly worse 3-month and 1-year graft survival than those without EAD (86% vs 99%, $P < .001$; 80% vs 94%, $P < .001$, Fig 1). The median LPR was 6.8 (3.8-12.8) in all the cohorts (Fig 2A), and the LPR in patients with EAD was significantly higher than that in patients without EAD (9.8 [3.0-16.6] vs 5.9 [1.9-10.1], $P < .001$, Fig 2B).

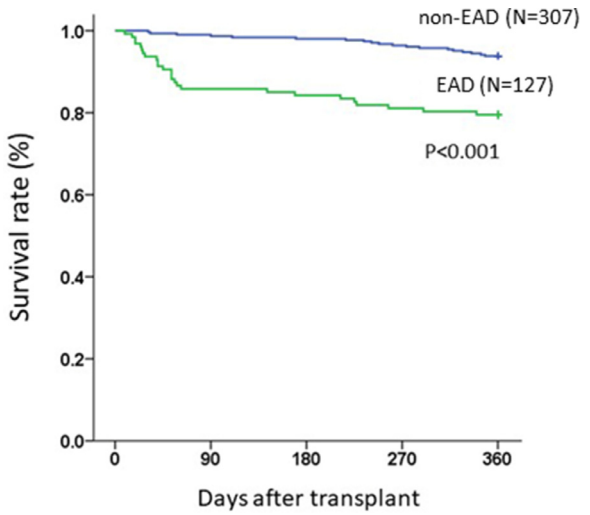

Fig 1. Graft survival rates in patients with or without EAD. Patients with EAD showed significantly worse 3-month and 1-year graft survival than those without EAD (3-month; 86% vs 99%, $P < .001$, 1-year; 80% vs 94%, $P < .001$). EAD, early allograft dysfunction; LPR; lactate-to-platelet ratio.

Univariate and multivariate analyses of EAD and the LPR for predicting 3-month graft failure

The univariate analysis revealed that male sex, body mass index >40 kg/m^2, dialysis before and during transplant, CIT >372 minutes, estimated blood loss (EBL) >2000 mL, red blood cell transfusion (per 1 unit increase), a high LPR (per 1.0 increase), and EAD were associated with 3-month graft failure ($P < .10$, Table 3). Since EBL and red blood cell transfusion were strongly related to each other (correlation coefficient $r = .76$), only EBL was included in the multivariate analysis.

The multivariate analysis revealed that male sex (hazard ratio [HR] =5.45, $P = .005$), dialysis before and during transplant (HR =3.83, $P = .04$), a high LPR (per 1.0 increase) (HR =1.03, $P = .03$), and EAD (HR =9.14, $P = .001$) were independent predictors of 3-month graft failure (Table 3).

AUCs, NRI values, and IDI values of the LPR, EAD classification, and their combination for 3-month graft failure

The AUCs of the SOFT score, BAR score, platelet count on POD 1, lactate immediately after LT, and LPR for 3-month graft failure were 0.62 ($P = .12$), 0.60 ($P = .37$), 0.66 ($P = .05$), 0.72 ($P < .001$), and 0.79 ($P < .001$), respectively. The LPR showed an inverse relationship, with the 3-month graft survival rate decreasing as the LPR increased (Fig 3A). Although the NRI had better predictive ability for EAD classification than did the LPR ($P < .001$, Table 4), comparison of the AUCs between LPR and EAD classification showed no

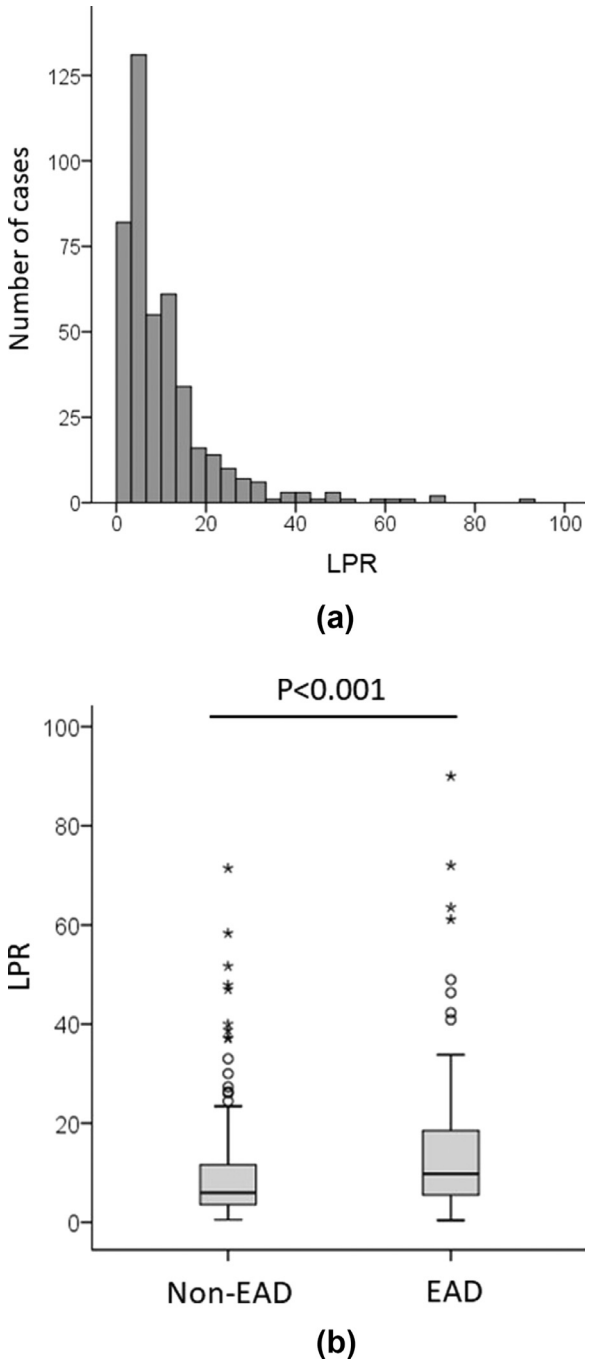

Fig 2. EAD and the LPR. (A) Distribution of the LPR. (B) Comparison of the LPR between patients with EAD and those without EAD. The median LPR was 6.8 (3.8-12.8) in all cohorts, and the LPR in patients with EAD was significantly higher than that in patients without EAD (9.8 [3.0-16.6] vs 5.9 [1.9-10.1], $P < .001$). EAD, early allograft dysfunction; LPR; lactate-to-platelet ratio.

significant differences between these 2 parameters (0.79 vs 0.78, $P = .84$, Table 4).

The AUCs of EAD classification alone and the combination of EAD classification and the LPR to predict 3-month graft failure were 0.78 and 0.86, respectively (Table 4). A direct comparison showed a statistically higher AUC for the combination of the EAD classification and LPR than for the EAD classification alone ($P < .001$). Furthermore, both the NRI ($P < .001$) and IDI ($P = .03$) showed significantly better predictive abilities with this combination than with the EAD classification alone (Table 4). Regardless of the presence of EAD, the LPR showed inverse relationships for predicting 3-month graft survival (Fig 3B).

DISCUSSION

The novelty of this study is that we developed the LPR, defined as "the lactate level immediately following LT divided by the platelet count on POD 1," as an early predictor for short-term graft failure after deceased-donor LT. The LPR enables the calculation of a valid 3-month graft survival rate, which is as accurate as the EAD classification. The LPR is a continuous parameter that enables us to interpret initial graft function and to calculate the 3-month graft failure rate with advantages of early availability and simple calculations.

Because of the increasing gap between supply and demand, marginal livers are used more for recipients with severe disease [19]. Initial graft dysfunction can occur in these situations and is related to longer intensive care unit and hospital stays, higher rates of complications, and increased mortality and graft loss. Numerous conditions, such as donor factors (eg, steatosis, prolonged CIT, cause of death, location), recipient factors (eg, diabetes, renal failure, infection), surgical factors (eg, prolonged WIT, blood loss, transfusions), and postoperative factors (eg, rejection, postoperative bleeding, bile leak), can affect early graft functions [19]. Although several scoring systems using preoperative parameters, such as the SOFT score, BAR score, D-MELD score and liver donor risk index, were developed to predict postoperative graft survival [17,20,21], they are mostly used for decision making regarding donor and recipient matching prior to transplant. In fact, the SOFT and BAR scores demonstrated low accuracies in our cohort. To conduct early medical intervention and decrease postoperative mortality and morbidity rates without wasting medical resources, an early and accurate parameter to judge initial graft dysfunction after LT is important. Although no universal definition for initial graft dysfunction exists, the EAD classification described by Oltoff et al [2] is currently one of the most widely accepted criteria used in the clinical field. Validity of the EAD classification has been established in previous studies, including our data [22,23]. However, there are still problems with this classification in that it takes 7 days before diagnosis and is an "all-or-nothing" binary criterion. Clinicians intuitively

Table 3. Univariate and Multivariate Analysis of Risk Factors for 3-Month Graft Loss

	Univariate Analysis			Multivariate Analysis		
	HR	CI	*P*	HR	CI	*P*
Recipient variables						
Age	1.00	0.95-1.04	0.78	-	-	-
Male, yes	3.17	1.33-7.56	0.01	5.45	1.65-18.01	0.005
Ethnicity, white	1.20	0.44-3.24	0.73	-	-	-
Disease type, hepatitis C	0.87	0.38-2.02	0.75	-	-	-
BMI 20-29	-	-	Reference	-	-	Reference
<20	1.99	0.25-15.89	0.52	-	-	-
30-40	2.10	0.83-5.32	0.12	-	-	-
40<	3.49	0.93-13.14	0.07	4.30	0.78-23.67	0.09
MELD score	1.95	0.79-4.78	0.15	-	-	-
Diabetes, pretransplant	1.12	0.40-3.19	0.83	-	-	-
Dialysis before and during transplant	2.86	0.93-8.76	0.07	3.83	1.04-14.17	0.04
Donor variables						
Donor age	1.01	0.98-1.04	0.57	-	-	-
Donor ethnicity, white	1.49	0.50-4.39	0.47	-	-	-
Donor cause of death, CVA	1.45	0.63-3.37	0.39	-	-	-
Donor local, yes	0.71	0.24-2.10	0.54	-	-	-
Steatosis >30%, yes	3.55	0.47-26.63	0.22	-	-	-
Surgical variables						
Warm ischemic time <34 min,	-	-	Reference	-	-	-
34-42 min	1.75	0.52-5.99	0.37	-	-	-
42 min <	2.66	0.83-8.48	0.10	-	-	-
Cold ischemic time <295 min,	-	-	Reference	-	-	-
295-372 min	1.64	0.39-6.84	0.50	-	-	-
372 min <	4.92	1.42-17.13	0.01	2.91	0.68-12.51	0.15
Anhepatic time >75 min, yes	2.11	0.86-5.15	0.10	-	-	-
Estimated blood loss >2000 mL	2.96	1.07-8.24	0.04	1.91	0.56-6.52	0.30
RBC transfusion, per 1 unit	1.07	1.02-1.12	0.008	-	-	-
Platelet transfusion, per 1 unit	1.02	0.94-1.10	0.65	-	-	-
Postoperative variables						
LPR (per 1 increase)	1.04	1.03-1.06	<0.001	1.03	1.00-1.05	0.03
EAD, yes	11.67	3.95-34.51	<0.001	9.14	2.42-34.47	0.001
Acute cellular rejection, yes	2.07	0.28-15.36	0.48	-	-	-
Biliary complications, yes	1.62	0.38-6.95	0.51	-	-	-

BMI, body mass index; CI, confidence interval; CVA, cardiovascular system cause; EAD, early allograft dysfunction; HR, hazard ratio; LPR, lactate/platelet ratio; MELD, model of end-stage liver disease; RBC, red blood cell.

understand that there is continuity between immediate graft function and primary nonfunction, and a score grading the extent of graft function after LT would allow clinicians to objectively assess graft dysfunction.

As a continuous parameter to understand initial graft function, the model of early allograft function was recently developed to understand the actual allograft function; this model comprises bilirubin, international normalized ratio, and alanine aminotransferase within 3 days post-transplant [24]. Model of early allograft function outperformed EAD as a predictor of transplant survival, either when used as a stand-alone parameter or when corrected for additional independent predictors of transplant survival [25]. However, this parameter also has some issues: the formula is not simple, and it still requires 3 days before a calculation can be completed. Another continuous parameter, the liver Graft Assessment Following Transplantation (L-GrAFT) risk score, enables risk estimation of 3-month graft failure post-LT [26]. The L-GrAFT model had an excellent C-statistic of 0.85, with a significantly superior discrimination for 3-month graft survival compared with that of the EAD classification. However, L-GrAFT needs 10 days before it can be calculated and is constituted by 7 factors, resulting in a complex formula.

We focused on the combination of lactate and platelets since the postoperative platelet counts and lactate level immediately following LT were related to post-transplant graft failure [11,12,14,15,27]. Postoperative lactate levels are dependent on I/R injury caused by, for example, prolonged ischemia times or anhepatic phase time, severe steatosis, and recipient infectious status under which lactate acidosis appears as early graft dysfunction [28]. Furthermore, recent studies have disclosed the relationship between perioperative lactate levels and short-term post-LT outcomes [16]. High lactate levels immediately post-transplant were related to major postoperative complications, longer length of intensive care unit stay, and higher rates of graft failure and mortality [14]. In addition, perioperative thrombocytopenia is related to poor graft regeneration, increases postoperative morbidity, and deteriorates graft and

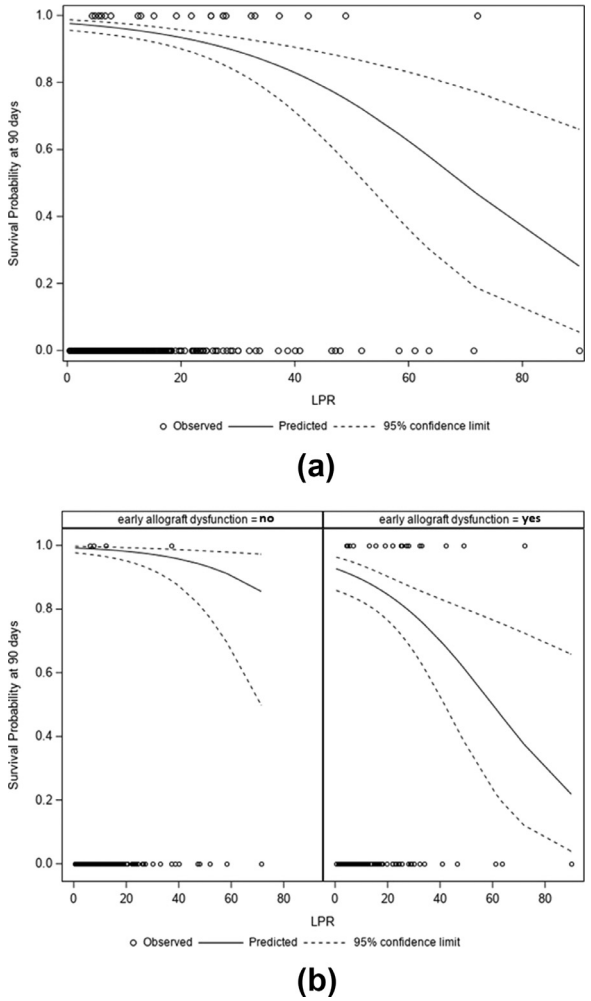

Fig 3. LPR and 3-month graft survival. (A) The LPR alone. The LPR showed an inverse relationship, and the 3-month graft survival rate decreased as the LPR increased. (B) Combination of the LPR and EAD. Regardless of the inclusion of EAD, the LPR showed inverse relationships for predicting 3-month graft survival. EAD, early allograft dysfunction; LPR; lactate-to-platelet ratio.

patient survival in both the short term and long term after LT [11,12,27]. In an animal model, we demonstrated that platelets accumulated in the liver graft immediately after LT, and the interaction of platelets with Kupffer cells at the liver graft induced the release of cytokines such as interleuken-6 and tumor necrosis factor−α from Kupffer cells and the secretion of growth factors such as insulin-like growth factor−1 and hepatocyte growth factor from platelets, both of which promoted hepatocyte proliferation at the liver graft without aggravating I/R injury [13]. Furthermore, insulin-like growth factor-1 and endothelial growth factor, which are found at high levels in platelets, were reported to protect the liver against I/R injury [29]. These studies explain how platelets can work as carriers of growth factors and result in platelet-induced hepatocyte proliferation and graft protection after LT.

Table 4. AUC, NRI, and IDI of LPR, EAD, and Their Combination for 3-Month Graft Survival

LPR vs EAD				
	LPR	EAD	Comparison (LPR vs EAD)	*P*
Cox & Snell R^2	0.039	0.062		
Nagelkerke R^2	0.118	0.187		
AUC	0.789	0.777	0.012 (−0.104 to 0.128)	.835
IDI (95% CI)			−0.015 (−0.063 to 0.033)	.545
NRI (95% CI)			−0.859 (−1.257 to −0.4606)	<.001
LPR+EAD vs EAD				
	LPR+EAD	EAD	Comparison (LPR+EAD vs EAD)	*P*
Cox & Snell R^2	0.083	0.062		
Nagelkerke R^2	0.250	0.187		
AUC	0.858	0.777	0.082 (0.039-0.124)	<.001
IDI (95% CI)			0.056 (0.005-0.106)	.032
NRI (95% CI)			0.797 (0.387-1.207)	<.001

AUC, area under the curve; CI, confidence interval; EAD, early allograft dysfunction; HR, hazard ratio; IDI, integrated discrimination improvement; LPR, lactate/platelet ratio; NRI, net reclassification improvement.

In our study, the higher LPR was a risk factor for predicting 3-months graft failure, which was independent from the amount of intraoperative hemorrhage by the multivariate analysis. This result demonstrated that LPR represents early graft function, not merely a result influenced by hemorrhage. The LPR showed a better predictive ability than either platelet count on POD 1 or lactate immediately post-LT alone and was as accurate as the EAD classification. When combined with the EAD classification, the LPR demonstrated better predictive ability for 3-month graft survival than the EAD classification alone, with a high AUC of over 0.85. These results suggest the practical usefulness of the LPR in the real clinical environment.

We emphasize the strengths and advantages of the LPR from the following 3 points. First, lactate level and platelet count are promptly available with minimal invasiveness to the patient, and the LPR can be calculated with a simple formula. Second, the EAD classification, a widely accepted criterion to predict poor graft function, has the limitation of requiring 7 days before diagnosis, which could miss the optimal timing for medical intervention. By contrast, the LPR is available 1 day after surgery, which can help clinicians implement early medical interventions to potentially prolong graft survival, such as N-acetyl cysteine, vitamin E, and prostaglandin E1, as needed [19]. Third, although the EAD classification is simply a binary classification that reflects early graft function, the LPR is a continuous parameter that enables us to estimate graft function and calculate the probability for 3-month graft survival post-LT.

We acknowledge several limitations of our study. First, the data are retrospective in nature with a small number of patients. In addition, we could not validate the utility of the LPR. Validation with prognosis prediction models in other cohorts is necessary. Second, the median MELD score for transplantation was lower than the median national score. Thus, the preoperative

general condition in our patients was better, and we might have obtained different results if we included patients with higher MELD scores. Third, we could not find any relationship of the LPR with mid- or long-term graft survival. We speculate that other factors, including rejection, infection, and de novo malignancy, could affect mid- or long-term graft survival more so than lactate levels and the platelet count immediately after posttransplantation. Despite these limitations, we emphasize the importance of the LPR in that it is one of the earliest predictors to estimate the short-term graft survival rate and understand allograft function, and it is as useful as the EAD classification.

CONCLUSIONS

The LPR is a continuous parameter that enables the prediction of 3-month graft failure with the advantages of early availability and simple calculations.

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