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Prediction of early allograft dysfunction using serum phosphorus level in living donor liver transplantation

Sang Hyun Hong,[1] Jung Ah Kwak,[1] Jin Yeong Jeon[2] and Chul Soo Park[1]

1 Department of Anaesthesiology and Pain Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
2 Department of Anaesthesiology and Pain Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Correspondence
Chul Soo Park MD, PhD, Department of Anaesthesiology and Pain Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 505 Banpo-dong, Seocho-gu, Seoul 137-701, Republic of Korea.
Tel.: 82 2 2258 2236;
fax: 82 2 537 1951;
e-mail: pcs6817@gmail.com

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Summary

Serum phosphorus is greatly affected by liver surgeries, but its change after liver transplantation has not yet been clarified. We investigated the predictive role of serum phosphorus for early allograft dysfunction (EAD) after living donor liver transplantation (LDLT). Perioperative factors, including serum phosphorus level, of 304 patients who underwent LDLT were retrospectively studied and compared between patients with and without EAD after LDLT. Potentially significant factors ($P < 0.15$) in univariate comparisons were subjected to multivariate logistic regression analysis to develop a prediction model for EAD. A total of 48 patients (15.8%) met the EAD criteria. Patients with EAD experienced more severe preoperative disease conditions, higher one-month mortality and more elevated serum phosphorus concentrations during the first week after surgery compared with patients without EAD ($P = 0.016$). Multivariate analysis showed that a serum phosphorus level ≥ 4.5 mg/dl on postoperative day 2 was an independent predictor of EAD occurrence after LDLT (relative risk: 2.36, 95% confidence interval [1.18–4.31], $P = 0.017$), together with a history of past abdominal surgery, emergency transplantation and preoperative continuous veno-venous haemodiafiltration. These data indicate that hyperphosphataemia during the immediate postoperative days could be utilized as a predictor of EAD after LDLT.

Introduction

Evaluating allograft dysfunction early after liver transplantation is clinically very important. A wide spectrum of 'allograft dysfunction' events has been introduced and used, including primary nonfunction, delayed nonfunction, initial poor function, initial nonfunction, primary graft failure and primary dysfunction [1]. Of these, initial poor function, also known as early allograft dysfunction (EAD), is a frequently adopted clinical endpoint and has been proven to be associated with graft loss and patient mortality [2,3].

Definitions of EAD have changed over the last two decades. EAD mainly referred to an abrupt postoperative elevation of serum aminotransferase levels prior to the model for end-stage liver disease (MELD) era [4–7]. In 1998, one of the first functional definitions of EAD using other indices of liver function (bilirubin levels and prothrombin time) and patient symptoms (evidence of encephalopathy) was established in a large multicentre trial [2,3]. The definitions of EAD used during the MELD era were simply variations of earlier definitions, incorporating aminotransferase levels, bilirubin levels, the international normalized ratio and other variables [8–10]. However, most previous studies were performed on patients undergoing deceased donor liver transplantation, and only a few reports included patients undergoing living donor liver transplantation (LDLT) [11,12].

Hypophosphataemia frequently develops after major liver resection [13,14]. Its pathogenesis remains poorly understood and has been hypothesized as being due either

to excessive use of phosphate by the regenerating liver or increased urinary losses of phosphate [15,16]. Changes in postoperative phosphorus levels in liver transplant recipients have not yet been reported except for those in children with fulminant hepatic failure who underwent liver transplantation [17], and the correlation with graft outcome has not been evaluated.

Early prediction of EAD using practical and reliable indicators is essential for prompt clinical intervention to improve graft and patient outcomes. In the present study, we investigated the postoperative changes in serum phosphorus levels and determined the existence of a relationship between serum phosphorus levels and EAD occurrence in LDLT recipients.

Patients and methods

We retrospectively collected the medical records of 309 adult patients (age $\geq$ 18 years) who underwent LDLT from January, 2007 to July, 2011 at Seoul St. Mary's Hospital. Perioperative donor and recipient data were retrieved from the hospital's electronic medical record system. The Institutional Review Board of the Seoul St. Mary's Hospital approved the present study and waived the requirement for written patient consent. No special exclusion criteria existed, but patient data with incomplete and missing variables were removed from the current study.

Perioperative patient management

Preoperative continuous veno-venous haemodiafiltration (CVVHDF) was instituted in recipients with severe hepatic encephalopathy as well as those with oliguria or anuria. Severe arterial hypoxia was managed with mechanical ventilation.

The LDLTs were performed using right hepatic lobes of donors using the piggyback technique without a veno-venous bypass. In every case, portal vein anastomosis was followed by hepatic artery anastomosis and bile duct reconstruction. A temporary portocaval shunt was applied when high portal vein pressure was diagnosed. All donor liver grafts were prepared with a histidine-tryptophan-ketoglutarate solution. Balanced anaesthesia was conducted using isoflurane, vecuronium (or atracurium) and opioids such as fentanyl or remifentanil. Intraoperative patient management was guided by the LDLT protocol of our hospital. Packed red blood cells (PRBCs) were administered to maintain a haematocrit between 25% and 30%. Fresh frozen plasma, cryoprecipitate and platelets were replaced to improve intraoperative coagulopathy under thromboelastography guidance. Vasopressors were administered when dangerous haemodynamic instabilities were indicated by invasive haemodynamic monitors. We used diuretics when oliguria continued despite adequate fluid resuscitation and vasopressor coverage. Calcium chloride was administered when serum calcium levels dropped below 80% of the normal lower limit. Sodium bicarbonate was indicated when the serum pH was lower than 7.15 in the presence of an adequate increase in minute ventilation. After completion of surgery, oral feeding was started on postoperative days 3–4. Total parenteral nutrition was not initiated unless a patient needed prolonged care with a mechanical ventilator. Intravenous phosphorus replacement was not performed during the early postoperative period. Immunosuppression was initiated by preoperative administration of an interleukin-2 receptor inhibitor (basiliximab). Intravenous methylprednisolone was injected before reperfusion of the liver graft, and oral calcineurin inhibitors (cyclosporine or tacrolimus), with or without mycophenolate mofetil, were administered from postoperative day 2.

EAD definition

The EAD was defined by the presence of one of the following after LDLT: a serum bilirubin level $\geq$ 10 mg/dl, an international normalized ratio (INR) $\geq$ 1.6 on postoperative day 7 and an alanine or aspartate aminotransferase level >2000 U/l within the first 7 days. This recently developed definition has been proven to be associated with graft loss and patient mortality, validating previously published data [3].

Serum phosphorus concentrations and related postoperative factors

Serum phosphorus concentration 1 day before surgery was determined and followed up until the seventh postoperative day. Serum calcium concentrations and transfused amounts of packed red blood cells (PRBCs) until the seventh postoperative day were also obtained. Daily urine output and serum creatinine concentration until the seventh postoperative day were investigated to evaluate perioperative renal function. The estimated glomerular filtration rate was calculated from serum creatinine concentration using the Modification of Diet in Renal Disease equation [18].

Preoperative recipient and donor factors

This data set included age, gender, body mass index (BMI), bone mineral density (BMD), causes of liver disease, MELD score, Child-Pugh-Turcotte (CPT) classification, accompanying systemic diseases other than liver disease (hypertension, diabetes and heart disease), symptoms of decompensated liver disease (ascites $\geq$ 1.0 l and hepatorenal syndrome), history of past abdominal surgery, variceal

bleeding and spontaneous bacterial peritonitis, preoperative CVVHDF and incidence of emergency transplantation. The laboratory tests included haematocrit, platelet count, creatinine, total bilirubin, prothrombin time, aspartate transaminase, alanine transaminase, albumin, sodium, potassium, magnesium, phosphorus and arterial gas analysis. Donor factors included age, gender, BMI, incidence of macrosteatosis of the graft liver $\geq 20\%$ and graft-to-recipient weight ratio <1.0%.

Intraoperative factors

Intraoperative variables included surgical time; units of transfused blood products; hourly urine output; use of vasopressors; drugs administered, including furosemide, sodium bicarbonate, calcium chloride and regular insulin; arterial pH, base excess; and lactate level. Intraoperative total change in arterial base excess and lactate level were also calculated.

Statistical data analysis

To compare patients with and without EAD, continuous data were analysed using the unpaired *t*-test or the Mann–Whitney *U*-test, and categorical data were compared using Pearson's chi-squared test or Fisher's exact test. The Shapiro–Wilk test was used to confirm normal distribution. Donor factors and preoperative and intraoperative recipient factors were compared between patients with and without EAD. Chronological changes in postoperative serum phosphorus concentrations and related factors were compared between patients with and without EAD using repeated-measures analysis of variance (ANOVA). An unpaired *t*-test with Bonferroni correction was performed for any significant difference over time or any significant interaction of the two groups to reveal differences between the two groups on each day. The predictive roles of individual factors for the occurrence of EAD were determined using univariate logistic regression. Perioperative factors that showed potential associations with EAD ($P < 0.15$) in the univariate logistic regression were selected for multivariate analysis. When multiple factors were significantly correlated, we chose the most significant factor from the clinical point of view. Before multivariate analysis, selected continuous variables were dichotomised at the median, quartile or clinically meaningful cut-off points.

We performed multivariate analysis using forward and backward stepwise logistic regression modelling processes with selected variables by univariate logistic regression. The sensitivity and unbiased estimate of the logistic model from multivariate analysis were evaluated using the area under a receiver operating characteristic (ROC) curve. Values are expressed as number (proportion) or the mean $\pm$ SD with relative risk (RR) and a 95% confidence interval (CI). $P < 0.05$ was deemed to indicate statistical significance. All statistical analyses were performed using SPSS 18.0 for Microsoft Windows (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 309 adult patients underwent LDLT at our medical centre. A total of five patients were excluded because of incomplete or missing data regarding EAD definition or serum phosphorus levels; thus, 304 patients were included in the present study. Of those, 48 patients (15.8%) met our EAD criteria. The mean timepoint for EAD occurrence was postoperative day 5.8 $\pm$ 1.5. Compared with non-EAD patients, EAD patients had a significantly higher mortality rate at 30 days (7/48 [14.6%] vs. 8/256 [3.1%]; $P = 0.001$) and stayed longer in the intensive care unit (10.9 $\pm$ 9.6 vs. 6.7 $\pm$ 2.2 days; $P = 0.004$).

Preoperatively, no difference was observed in the serum phosphorus level between EAD and non-EAD patients. Serum phosphorus concentrations started to increase from postoperative day 1 and reached their peaks on postoperative day 2 (Fig. 1). A significant difference in the chronological change in serum phosphorus concentrations between patients with and without EAD was observed over time until the seventh postoperative day ($P = 0.016$, repeated-measures ANOVA). *Post hoc* analysis showed that serum phosphorous levels on postoperative day 2 were significantly different between patients with and without EAD (4.28 $\pm$ 1.51 vs. 3.63 $\pm$ 1.22 mg/dl; $P = 0.006$, unpaired *t*-test with Bonferroni correction). Serum calcium concentrations were not significantly different over time between patients with and without EAD. Transfused amounts of PRBCs did not differ between the groups (Fig. 1) but showed a significant interaction with time ($P < 0.001$). Hourly urine output, serum creatinine concentration and estimated glomerular filtration rate were not significantly different between patients with and without EAD (Fig. 2). The numbers of patients who received CVVHDF after liver transplantation was not significantly different between patients with EAD (4[8.3%]) and those without EAD (13 [5.1%]).

Age, gender, body mass index and bone mineral density did not differ between recipients with and without EAD (Table 1). The most common reason for liver transplantation was hepatitis B virus-related liver disease; there was no intergroup difference. Liver disease was more severe in EAD than non-EAD patients, as indicated by the higher MELD scores of EAD patients. EAD patients had a higher incidence of past abdominal surgeries than did non-EAD patients. CVVHDF before liver transplantation was applied more frequently in EAD patients than non-EAD patients; however, the serum creatinine level and the incidence of

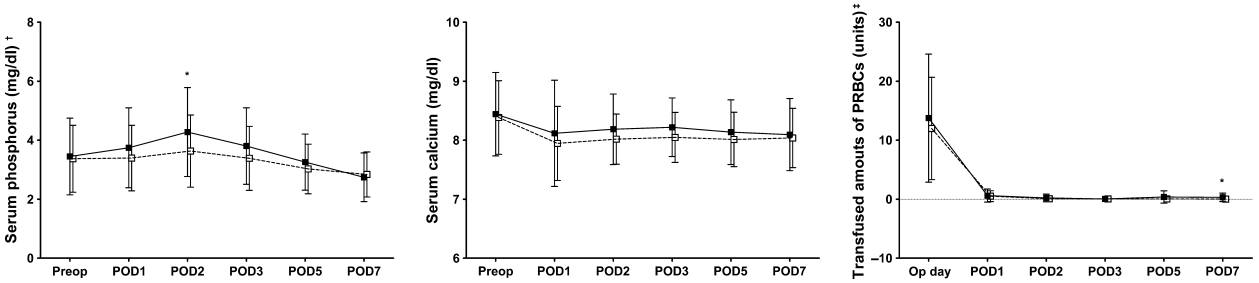

Figure 1 Comparison of changes in serum phosphorus, calcium concentrations and transfused amounts of packed red blood cells until postoperative day 7 between patients with early allograft dysfunction (■) and those without early allograft dysfunction (□) after living donor liver transplantation. Error bars represent the standard deviation. $*P < 0.05$ between the two groups on the respective postoperative day, $^{\dagger}P < 0.05$ between the two groups over time, and $^{\ddagger}P < 0.05$ for the interaction between the two groups by time. PRBCs, packed red blood cells; Preop, preoperative day; POD, postoperative day; Op day, day of operation.

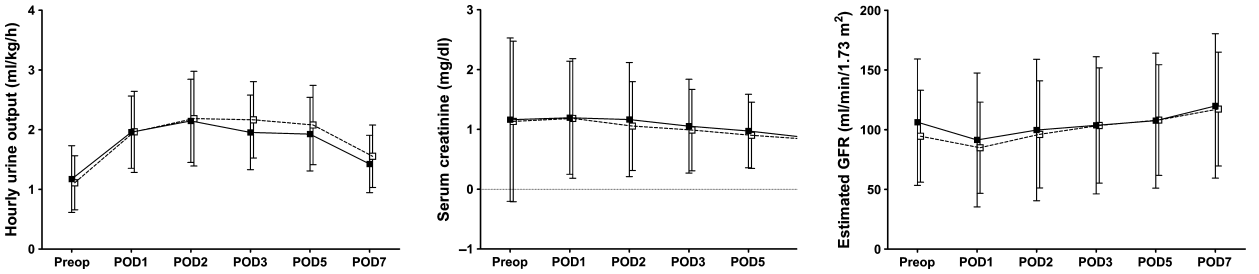

Figure 2 Comparison of changes in hourly urine output, serum creatinine concentration and estimated glomerular filtration rate until postoperative day 7 between patients with early allograft dysfunction (■) and those without early allograft dysfunction (□) after living donor liver transplantation. Error bars represent the standard deviation. No differences were observed between the two groups over time. Preop, preoperative day; POD, postoperative day; GFR, glomerular filtration rate.

hepatorenal syndrome in EAD and non-EAD patients were not different. Emergency liver transplantations were performed more frequently in EAD patients than non-EAD patients. According to preoperative laboratory results, EAD patients exhibited higher total bilirubin levels than non-EAD patients.

Donor-related factors in both groups are shown in Table 2. The incidence of a graft-to-recipient weight ratio (GRWR) <1.0 was higher in patients with EAD than in patients without EAD; however, no other donor factors, including graft liver steatosis, were associated with EAD after LDLT.

Intraoperatively, patients with and without EAD did not differ in terms of surgical time, quantities of transfused red blood cells and fresh frozen plasma, hourly urine output and use of vasopressors (Table 3). The quantity of drugs administered intraoperatively and the degree of metabolic acidosis were not different between the two groups.

Table 4 lists all binary, continuous variables and postoperative serum phosphorus levels that were entered into the multivariate analysis. Stepwise multivariate logistic regression analysis identified four independent predictors for EAD occurrence after LDLT: postoperative phosphorus level on day 2, previous abdominal surgery, emergency surgery and preoperative CVVHDF (Table 5). A serum phosphorus level ≥ 4.5 mmol/l on postoperative day 2 was independently associated with a more than two times greater relative risk of EAD in LDLT recipients. The area under the ROC curve indicated that this model had a clinically suitable accuracy to predict EAD after LDLT ($P < 0.001$).

Discussion

We examined postoperative serum phosphorus concentrations for the first time in patients undergoing adult liver transplant surgery and demonstrated that hyperphosphataemia on postoperative day 2 was independently associated with EAD occurrence. Patients with a serum phosphorus level ≥ 4.5 mg/dl on postoperative day 2 had a 2.36-fold greater risk of developing EAD compared with those without hyperphosphataemia.

The EAD definition used in the present study included the serum bilirubin level and internal normalized ratio on

Table 1. Preoperative factor comparison between patients with and without early allograft dysfunction after living donor liver transplantation.

	Early allograft dysfunction		
	No (n = 256)	Yes (n = 48)	P
Age (years)	49.9 ± 9.9	46.2 ± 12.3	0.051
Gender (M/F)	230/99	56/23	0.865
Body mass index (kg/m2)	23.9 ± 3.1	24.7 ± 3.04	0.129
Bone mineral density (T-score)	−2.3 ± 1.2	−2.8 ± 1.7	0.222
Aetiology of liver disease			0.303
Hepatitis B virus	69 (27.0%)	17 (35.4%)	
Hepatocellular carcinoma	24 (9.4%)	2 (4.2%)	
Hepatitis B virus, hepatocellular carcinoma	65 (25.4%)	9 (18.8%)	
Alcoholic	43 (16.8%)	6 (12.5%)	
Hepatitis C virus	9 (3.5%)	1 (2.1%)	
Acute fulminant failure	26 (10.2%)	5 (10.4%)	
Others	20 (7.8%)	8 (16.7%)	
Model for end-stage liver disease score (pts)	16.6 ± 10.4	19.9 ± 8.7	0.039
Child-Pugh-Turcotte classification			0.200
A	64 (24.8%)	7 (14.6%)	
B	76 (29.7%)	13 (27.1%)	
C	116 (45.3%)	28 (56.4%)	
Accompanying systemic disease			
Hypertension	35 (13.7%)	5 (10.4%)	0.534
Diabetes	67 (26.3%)	9 (18.8%)	0.270
Heart disease	7 (2.8%)	0 (0.0%)	0.509
Past abdominal surgery	45 (17.6%)	15 (31.3%)	0.030
Ascites ≥ 1 l	105 (41.0%)	21 (43.8%)	0.724
Hepatorenal syndrome	27 (10.5%)	5 (10.4%)	0.978
History of variceal bleeding	52 (20.4%)	10 (20.8%)	0.945
History of spontaneous bacterial peritonitis	22 (8.6%)	5 (10.4%)	0.690
Preoperative CVVHDF	21 (8.2%)	12 (25.0%)	0.001
Emergency transplantation	48 (18.8%)	19 (39.6%)	0.001
Preoperative laboratory findings			
Haematocrit (g/dl)	30.3 ± 6.2	28.5 ± 5.6	0.071
Platelet count (μl)	71 600 ± 52 400	74 700 ± 50 800	0.708
Creatinine (mg/dl)	1.13 ± 1.34	1.16 ± 1.37	0.876
Total bilirubin (mg/dl)	2.6 (1.2–8.9)	13.7 (2.1–26.2)	0.001
Prothrombin time (INR)	1.72 ± 0.79	1.96 ± 0.84	0.060
Aspartate transaminase (U/l)	50 (34–87)	56 (37–144)	0.226
Alanine transaminase (U/l)	33 (23–59)	30 (25–95)	0.512
Albumin (g/dl)	3.1 ± 0.5	3.1 ± 0.5	0.922
Sodium (mEq/l)	138.0 ± 5.2	138.3 ± 6.1	0.756
Potassium (mEq/l)	4.0 ± 0.6	4.0 ± 0.6	0.750
Magnesium (mEq/l)	1.96 ± 0.51	2.00 ± 0.33	0.612
Phosphorus (mg/dl)	3.37 ± 1.14	3.45 ± 1.30	0.693
Arterial gas analysis			
pH	7.441 ± 0.461	7.443 ± 0.508	0.728
PaO_2/FiO_2	499.0 ± 124.2	493.6 ± 114.6	0.850

Values are expressed as the mean ± SD, number (proportion) or median (interquartile range).
CVVHDF, continuous veno-venous haemodiafiltration; INR, international normalized ratio; PaO_2/FiO_2, ratio of arterial oxygen tension to fractional inspired oxygen.

postoperative day 7 and the alanine or aspartate aminotransferase level within the first 7 postoperative days [3]. This recently developed definition of EAD has been associated with graft loss and patient mortality and has been validated by data published previously. The incidence of EAD in a study of patients undergoing deceased donor liver transplantation was 23.2%, which is similar to the report prior to the MELD era [2]. In our study, the EAD incidence was 15.8%, which was lower than that reported in the previous studies. Superior graft and recipient

Table 2. Donor-related factor comparison between patients with and without early allograft dysfunction after living donor liver transplantation.

	Early allograft dysfunction		
	No (n = 256)	Yes (n = 48)	P
Age (years)	33.3 ± 11.3	35.6 ± 11.5	0.208
Gender (M/F)	172/84	35/13	0.435
Body mass index (kg/m^2)	23.6 ± 2.9	22.8 ± 2.6	0.091
Macrosteatosis of the liver graft ≥20%	10 (3.9%)	1 (2.1%)	0.554
Graft-to-recipient weight ratio <1.0%	23 (9.0%)	9 (18.8)	0.023

Values are expressed as the mean ± SD or number (proportion).

Table 3. Intraoperative factor comparison between patients with and without early allograft dysfunction after living donor liver transplantation.

	Early allograft dysfunction		
	No (n = 256)	Yes (n = 48)	P
Surgical time (min)	559 ± 101	547 ± 118	0.499
Transfusion (units)			
Packed red blood cells	11.7 ± 8.6	13.5 ± 10.9	0.202
Fresh frozen plasma	11.3 ± 8.3	13.3 ± 11.2	0.154
Hourly urine output (ml/kg/h)	2.1 ± 1.4	1.9 ± 1.3	0.550
Use of vasopressors			0.665
None	24 (9.3%)	3 (6.3%)	
Dopamine or dobutamine infusion	72 (28.2%)	12 (25.0%)	
Noradrenaline or phenylephrine infusion	160 (62.5%)	33 (68.8%)	
Administered drugs			
Furosemide (mg)	15 (5–30)	10 (0–30)	0.462
Calcium chloride (mg)	600 (150–1350)	540 (210–1313)	0.899
Sodium bicarbonate (mEq)	40 (0–140)	55 (0–160)	0.571
Regular insulin (units)	25 (10–50)	20 (3–50)	0.235
Last arterial pH	7.314 (0.068)	7.321 (0.080)	0.490
Base excess (mmol/l)			
At the start of surgery	−0.57 ± 3.72	−0.71 ± 4.26	0.817
At the end of surgery	−6.77 ± 3.58	−6.11 ± 4.60	0.273
Intraoperative change	−6.39 ± 4.12	−5.70 ± 4.65	0.307
Lactate level (mmol/l)			
At the start of surgery	2.28 ± 1.73	2.83 ± 2.32	0.059
At the end of surgery	6.03 ± 3.28	6.69 ± 3.75	0.221
Intraoperative change	3.85 ± 3.22	4.01 ± 3.68	0.763

Values are expressed as the mean ± SD, number (proportion) or median (interquartile range).

conditions in LDLT over deceased donor liver transplantation seem to have lowered the EAD incidence. However, regardless of any reduction in incidence, EAD patients experienced a mortality rate more than four times that of non-EAD patients within the 30 days after LDLT in this study. The impact of EAD on the immediate postoperative outcome was obviously noteworthy, although the long-term outcome was not evaluated.

Table 4. Individual assessment of potentially predictive perioperative factors and serum phosphorus for early allograft dysfunction by univariate logistic regression.

Risk factors or diagnostic predictors	Relative risk	95% CI	P
Binary variables			
Graft-to-recipient weight ratio <1.0%	2.63	1.11–6.19	0.027
Past abdominal operation	2.12	1.06–4.23	0.033
Preoperative CVVHD	3.73	1.69–8.23	0.001
Emergency operation	2.84	1.47–5.48	0.002
Continuous variables			
Donor's body mass index (kg/m^2)	0.91	0.81–1.02	0.092
Recipient's age (years)	0.97	0.94–1.00	0.024
Recipient's body mass index (kg/m^2)	1.08	0.98–1.19	0.130
Model for end-stage liver disease score (pts)	1.03	1.00–1.06	0.042
Haematocrit (g/dl)	0.95	0.90–1.00	0.070
Total bilirubin (mg/dl)	1.05	1.02–1.07	<0.001
Prothrombin time (INR)	1.35	0.98–1.87	0.070
Lactate level at the start of surgery (mmol/l)	1.14	0.99–1.32	0.067
Postoperative serum phosphorus level (mg/dl)			
level on POD 1	1.28	0.99–1.66	0.057
level on POD 2	1.41	0.13–1.75	0.002
level on POD 3	1.34	1.05–1.71	0.021
level on POD 5	1.35	0.96–1.91	0.088

CVVHDF, continuous veno-venous haemodiafiltration; INR, international normalized ratio; POD, postoperative day.

Table 5. Independent predictors of early allograft dysfunction after living donor liver transplantation through multivariate logistic regression model.

	Relative risk	95% CI	P
Phosphorus level on postoperative day 2 ≥ 4.5 mg/dl	2.36	1.17–4.79	0.017
Past abdominal operation	2.44	1.18–5.06	0.017
Emergency operation	2.44	1.14–5.26	0.037
Preoperative CVVHDF	2.46	1.00–6.17	0.050
Area under receiver operating characteristic curve: 0.712		0.632–0.793	<0.001

CVVHDF, continuous veno-venous haemodiafiltration.

Postoperative changes in phosphorus levels in LDLT recipients are quite different from those in healthy donors undergoing hepatectomy. Phosphorus levels in the healthy donors decreased from postoperative day 1, reached a nadir on day 3 and recovered thereafter [13]. Conversely, phosphorus levels in recipients in our study increased from

day 1, peaked on day 2 and decreased from day 3 (Fig. 1). The mechanism underlying these differences is unclear. However, ischaemia/reperfusion injury of the liver graft may explain the differences of postoperative changes in phosphorus levels between LDLT donors and recipients. Specifically, donor livers undergo only hepatectomy, whereas liver grafts have to endure an additional ischaemic period and become reperfused. Thus, donor livers may begin to regenerate and utilize phosphorus vigorously as soon as the surgical insults cease. In contrast, liver grafts undergo a degree of graft dysfunction during the early postoperative period until the damage from ischaemia/reperfusion injury disappears, which could delay phosphorus utilization. On the other hand, many recent reports have shown an association between hypophosphataemia with the increased urinary phosphorus loss caused by liver regeneration [15,16]. However, the evaluation of postoperative serum creatinine concentration and estimated glomerular filtration rate in our study indicates that postoperative renal function did not markedly worsen during the early postoperative period. Therefore, our results indicate that postoperative increases in phosphorus concentrations in LDLT recipients appear to be more closely associated with delayed consumption of phosphorus rather than decreased urinary phosphorus excretion.

The difference in postoperative phosphorus concentrations between patients with and without EAD could be also explained by ischaemia/reperfusion injury, which is believed to be the mechanism underlying EAD [1]. A patient who receives more severe liver injury from graft reperfusion might not have sufficient hepatocyte reserve to effect regeneration, not utilize phosphorus vigorously, and, thus, show higher phosphorus level [19]. However, several factors should be considered for this assumption to be reasonable. First, the effect of transfused PRBCs on postoperative phosphorus level should be considered because we used stored red blood cell units containing a CPDA-1 preservative. Although there was a time interaction between the two groups, transfusion amounts of PRBCs on any particular day did not differ according to EAD occurrence until postoperative day 7. Therefore, PRBC transfusion did not cause the difference in postoperative phosphorus concentrations between patients with and without EAD. Serum calcium concentrations also affect serum phosphorus concentrations, but we could not identify a difference between patients with and without EAD. Last, postoperative renal condition should be considered because it plays a critical role in clearing serum phosphorus from the body. Renal functional indices during the early postoperative period in the present study, such as hourly urine output, creatinine concentration and estimated glomerular filtration rate, indicated that the difference in postoperative phosphorus concentrations between patients with and without EAD was not caused by the difference in urinary phosphorus excretion. The CVVHDF before liver transplantation was applied more frequently in patients with EAD than in those without; however, the incidences of application of postoperative CVVHDF between EAD and non-EAD patients were also not different. Because we did not determine whether CVVHDF was applied for renal or hepatic support or both, application of CVVHDF did not necessarily mean renal dysfunction. Daily urinary excretion of phosphorus from a 24-h urine collection or fractional excretion of phosphorus from spot urine collection for urinary phosphorus and creatinine should be evaluated for a more precise analysis, but were not available in our study.

Our predictive model included previous abdominal surgery, emergency transplantation and preoperative application of CVVHDF as independent risk factors for EAD occurrence other than postoperative hyperphosphataemia. Renal complications in patients with end-stage liver disease can be reversible after successful liver transplantation [20], and did not result in any significant post-transplant differences according to EAD development in the present study. However, severe preoperative renal or hepatic dysfunction requiring CVVHDF seems to have a strong association with postoperative graft dysfunction.

Some of the putative risk factors proposed in previous reports were not identified in the multivariate analysis in our study. The preoperative MELD score was found to be a risk factor for development of EAD in multivariate analysis in a recent report concerning EAD [3]. This was also demonstrated in a study during the pre-MELD era, in which components of the MELD score—pretransplant bilirubin and prothrombin time—were found to be independently associated with EAD [2]. In contrast, whether the MELD score correlates with patient outcome after liver transplantation remains controversial [21–23]. Considering that the occurrence of EAD is closely associated with patient outcome, further studies are necessary to evaluate the relationship between the MELD score and EAD. Generally, the selection of a graft with a GRWR >0.8% (and preferably >1.0%) has been recommended to improve graft survival and prevent postoperative graft dysfunction [24,25]. In our study, a GRWR <1.0% was associated with EAD occurrence after LDLT in the univariate, but not multivariate, analyses. If GRWR had been dichotomised at 0.8%, it would have resulted in a higher odds ratio for EAD after LDLT. However, because very few recipients received grafts with a GRWR <0.8% in our study, we decided to dichotomise GRWR into $\geq$ 1.0% and <1.0%. Recipient age was inversely associated with EAD in univariate analysis in our study. It is controversial whether increasing recipient age has an influence on outcome after liver transplant surgery [26]. Although recipient age has been associated with poorer graft outcome in some studies [27,28], our data did

not support this notion. Interestingly, in a recent study of LDLT recipients older than 60 years, recipient age did not affect LDLT outcome when patients with a MELD score <20 received grafts from consanguineous donors [29]. Cold ischaemic time was stated to be a risk factor for graft dysfunction in previous reports [2,9], but was not addressed in our study. LDLT has a relatively short and uniform ischaemic time compared with deceased donor liver transplantation, so we assumed that the influence of ischaemic time would be insufficient to cause a noticeable intergroup difference.

The present study has several limitations associated with its retrospective design. First, intraoperative administration of drugs or fluid solutions that have possible effects on the phosphorus level was not guided under specific rules, although we observed a guideline in our centre described in the 'Patients and Methods' section. Second, it was impossible to consider all possible risk factors in one model, although nearly 60 perioperative variables were included in the analysis. Phosphorus-related factors such as parathyroid hormone and vitamin D levels as well as graft-related factors such as cold ischaemic time and the occurrence of postreperfusion syndrome were not included in our analyses because of insufficient or incorrect data. Third, we could not determine the exact cause of early postoperative hyperphosphataemia because of the design of the present study.

In conclusion, patients with EAD had higher serum phosphorus levels than did non-EAD patients during the period immediately following LDLT. Hyperphosphataemia on postoperative day 2 could be an early indicator of EAD occurrence after LDLT. A further prospective study needs to be conducted to reveal in detail the causes of hyperphosphataemia after liver transplantation.

Authorship

SHH: wrote the paper. JAK: collected the data. JYJ: performed data analyses. CSP: designed research/study, analysed data and wrote paper.

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