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Influence of oxygen content immediately after graft reperfusion on occurrence of postoperative acute kidney injury in living donor liver transplantation

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Abstract

Acute kidney injury (AKI) is a common complication after living donor liver transplantation (LDLT). In this study, we investigated perioperative factors, including oxygen content, related to the postoperative development of AKI after LDLT. The perioperative data of 334 patients were reviewed retrospectively. We identified the postoperative development of AKI based on the Acute Kidney Injury Network criteria. Perioperative variables, including oxygen content, were compared between patients with and without AKI. Potentially significant variables in a univariate analysis were evaluated by multivariate analysis. Postoperative AKI developed in 76 patients (22.7%). Univariate analysis revealed that preoperative factors (body mass index [BMI], diabetes mellitus, C-reactive protein) and intraoperative factors (severe postreperfusion syndrome, packed red blood cell transfusion, furosemide, and oxygen content at the anhepatic phase, 5 minutes and 1 hour after graft reperfusion, and at peritoneal closure) of recipients were significant. The multivariate analysis showed that oxygen content 5 minutes after graft reperfusion, BMI, and furosemide administration were independently associated with postoperative AKI. In conclusion, postoperative AKI was independently associated with oxygen content 5 minutes after graft reperfusion, BMI, and furosemide administration. Meticulous ventilator care and transfusion should be required to maintain sufficient oxygen content immediately after graft reperfusion in patients who undergo LDLT.

Abbreviations: AKI = acute kidney injury, AUC = area under the receiver operating characteristic curve, CTP = Child–Turcotte–Pugh, INR = international normalized ratio, MELD = model for end-stage liver disease, PT = prothrombin time.

Keywords: acute kidney injury, blood gas analysis, liver transplantation

1. Introduction

Acute kidney injury (AKI) is a common complication after orthotopic liver transplantation (LT) and is associated with poor graft outcomes and patient mortality and morbidity. The incidence of AKI after orthotopic LT is 17.0% to 95.0% because diverse definitions of AKI have been applied in this setting.[1] The causes of postoperative AKI are multifactorial, including hepatic decompensation of recipients, poor donor graft quality, blood product transfusions, and nephrotoxic drug administration.[2–5]

To date, the development of AKI after living donor liver transplantation (LDLT) has not been sufficiently studied. The incidence of AKI after LDLT has been reported to be 29.0% to 63.1%.[6–8] As partial liver grafts are transplanted during LDLT, persistent portal hypertension and a hyperdynamic condition in recipients owing to a small-for-size graft can contribute to the occurrence of AKI after LDLT. Additionally, other causes, such as hypovolemia, high model for end-stage liver disease (MELD) score, and preoperative renal dysfunction, play independent roles in the development of postoperative AKI in patients who have undergone LDLT.[3,6,9]

The kidney is susceptible to low arterial oxygenation.[10,11] This poor arterial oxygenation disrupts kidney autoregulation, resulting in insufficient perfusion.[12] These observations indicate the close relationship between arterial oxygenation and kidney function.

The purpose of the present study was to investigate the modifiable perioperative factors, including oxygen content, related to the development of AKI.

2. Patients and methods

2.1. Study population

The preoperative, intraoperative, and postoperative data of 430 adult LDLT recipients and donors (age ≥18 years, respectively) between March 2009 and February 2016 at St. Mary's Hospital (Seoul, South Korea) were retrospectively analyzed using the hospital electronic medical records system. Exclusions of incomplete or deficient data in critical values were performed in the present analysis. The present study was approved by the institutional review board of Seoul St. Mary's Hospital Ethics

Editor: Emmanuel Melloul.

The authors report no conflicts of interest.

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Medicine (2017) 96:31(e7626)

Received: 15 March 2017 / Received in final form: 6 July 2017 / Accepted: 10 July 2017

http://dx.doi.org/10.1097/MD.0000000000007626

Committee. Because of the retrospective study design, informed consent was waived.

2.2. Surgery and perioperative patient management

Details of the operative procedures and anesthetic management in LDLT are described elsewhere.[13] In summary, the right hepatic lobe from the donor was transplanted into the recipient using the piggyback technique; venovenous bypass was not adopted. The liver grafts were preserved in a histidine-tryptophan-ketoglutarate solution (Custodiol; Dr. Franz Köhler Chemie, Bensheim, Germany). After reconstructing the hepatic vessels (hepatic vein, portal vein, and hepatic artery, successively), adequacy of hepatic inflow and outflow was confirmed by Doppler ultrasonography (USG).

Anesthetic agents, including desflurane, cisatracurium (or rocuronium), and remifentanil (or fentanyl), were applied for balanced anesthesia. Hemodynamic instability was corrected by adequate fluid resuscitation and infusion of a vasopressor under invasive hemodynamic monitoring. Diuretics were administered to correct oliguria with stable systemic hemodynamics, volume overload, or electrolyte imbalance, based on clinical determinations of anesthesiologists.

Immunosuppression was started after LDLT using a triple-drug regimen (i.e., tacrolimus or cyclosporine, mycophenolate mofetil, and prednisolone). Because of the nephrotoxicity of calcineurin inhibitors (i.e., tacrolimus or cyclosporine),[8] administration of the immunosuppressant was begun under meticulous monitoring of kidney function.

2.3. Determination of postoperative AKI

We applied the Acute Kidney Injury Network (AKIN) criteria to diagnose the development of postoperative AKI in patients who had undergone LDLT. The AKIN criteria were summarized as follows: stage I, increase in serum creatinine (sCr) $\geq$0.3 mg/dL or 150% to 200% from baseline within 48 hours, or urine output $<$0.5 mL/kg/h for $\geq$6 hours; stage II, increase in sCr $>$200% to 300% from baseline within 48 hours, or urine output $<$0.5 mL/kg/h for $\geq$12 hours; stage III, increase sCr $>$300% from baseline or $\geq$4.0 mg/dL with an acute increase of at least 0.5 mg/dL within 48 hours, or urine output $<$0.3 mL/kg/h for $\geq$24 hours or anuria $\geq$12 hours.[14]

The AKIN classification has reliable sensitivity and specificity to predict the prognosis of recipients undergoing LT compared with the Risk, Injury, Failure, Loss, and End-Stage Renal Failure (RIFLE) and the Kidney Disease Improving Global Outcomes (KDIGO) classifications.[15]

The study population was classified into the AKI and non-AKI groups. The AKI group included patients with kidney dysfunction after LDLT based on the AKIN criteria, and the non-AKI group included the other patients with normal kidney function within 48 hours after LDLT.

2.4. Postoperative clinical outcomes

Postoperative outcomes included intensive care unit (ICU) and hospital stays, duration of mechanical ventilation after LDLT, and incidences of fast-track extubation in the operating room (OR), reintubation and infection in the ICU, reoperation, in-hospital mortality, early graft dysfunction, nonfunctional primary graft, and liver size on postoperative day (POD) 7.

Early extubation was performed in the OR when recipients became alert and fully responsive immediately after surgery and met the following criteria for fast-track extubation: hemodynamic stability; normoxia; normothermia; sufficient spontaneous tidal volume (5–8 ml/kg); respiratory rate $<$ 20 breaths/min; adequate minute ventilation; and positive gag reflex.[16–18] After fast-tracked extubation in the OR, oxygen was applied in the ICU via a face mask to maintain oxygen saturation (SaO_2) $>$ 94%.[19]

2.5. Perioperative recipient and donor factors

Preoperative factors included age, sex, body mass index (BMI), etiology of liver disease, severity of hepatic decompensation, comorbidity, and laboratory variables. Intraoperative factors were surgical time, incidence of severe postreperfusion syndrome (PRS), mean hemodynamic parameter values during surgery, amount of blood products transfused, drug administration, such as furosemide, and mean level of brain natriuretic peptide.

Severe PRS was defined as a reduction in MBP by $>$30% from baseline during the anhepatic phase, hemodynamically unstable arrhythmia, the need for potent rescue drugs, or prolonged ($>$30 minutes) or recurrent (reappearing within 30 minutes after graft reperfusion) hyperfibrinolysis.[20]

Arterial blood gases (ABG) were analyzed 5 times during surgery: at the preanhepatic phase, immediately after anesthetic induction; at the anhepatic phase, when the hepatic venous anastomosis was begun; at the neohepatic phase, 5 minutes and 1 hour after graft reperfusion; and at closure of the peritoneum. Arterial blood samples were collected with no stasis and gas bubbles into heparin-coated syringes (BD Preset, Plymouth, UK), and measured as point-of-care testing using an ABL800 FLEX blood gas analyzer (Radiometer, Brønshøj, Denmark). Arterial oxygen content was calculated by: (O_2 carried by hemoglobin) + (O_2 dissolved in blood) = $(1.34 \times \text{hemoglobin} \times SaO_2 \times 0.01) + (0.0031 \times PaO_2)$. SaO_2 (%) and PaO_2 (mmHg) stand for the percentage saturation of hemoglobin with oxygen and the partial pressure of oxygen, respectively. The normal range of arterial oxygen content is 17 to 20 ml/dL in a clinical setting.[21]

Donor factors included age, sex, graft-recipient weight ratio (GRWR), graft steatosis, and graft ischemic time.

2.6. Statistical analysis

The perioperative factors were compared between the AKI and non-AKI groups using Student *t* test or the Mann–Whitney *U* test and χ^2 test. The Shapiro–Wilk test was applied to determine the normality of the continuous data distributions. Intraoperative changes in oxygen content were analyzed by repeated measures analysis of variance and compared between groups by the Bonferroni post-hoc test. The Kruskal-Wallis test was used to determine whether there was a significant difference in oxygen content at 5 minutes after graft reperfusion according to the severity of postoperative AKI and the subgroups were compared by the Bonferroni post-hoc test. The perioperative variables that influenced the occurrence of postoperative AKI were assessed using univariate and multivariate logistic regression analyses. Potentially significant variables ($P < 0.1$) in the univariate analysis were chosen for a multivariate analysis. When multiple perioperative variables were correlated with each other, the variables with the most clinical association were selected. The values are presented as means ± standard deviations, median and interquartile range, number and proportion, or odd ratio (95% confidence interval [CI]). All tests were 2-sided, and a *P* value $<$.05 was considered significant. Statistical analyses were conducted through SPSS for Windows ver. 19.0 (SPSS Inc.,

Chicago, IL) and MEDCALC for Windows ver. 11.0 software (MedCalc Software, Mariakerke, Belgium).

3. Results

Ninety-six patients were excluded in the present study because of preoperative kidney injury (n = 50), hepatorenal syndrome (n = 31), or missing intraoperative vital parameters (n = 10) or postoperative sCr data (n = 5). Eventually, data of 334 patients were analyzed in our study. The study population was principally male (68.8%); median age was 53.0 (48.0–59.0) years, and median BMI was 24.1 (22.0–26.5) kg/m^2. The indications for LDLT were liver cirrhosis (51.1%) and hepatocellular carcinoma (48.9%). The hepatitis B virus (60.8%) was the most common liver disease etiology, followed by alcohol abuse (16.5%), hepatitis C virus (8.1%), drug-related or autoimmune hepatitis (5.7%), hepatitis A virus (1.2%), and cryptogenic findings (7.8%). Median MELD score was 12.0 (8.0–18.0) points. Comorbid diseases were diabetes mellitus (22.7%) and systemic hypertension (17.0%). Seventy-six patients (22.7%) developed AKI immediately after LDLT. According to the AKIN criteria, AKI severity was stage I in 52 patients (15.5%), stage II in 16 (4.8%), and stage III in 8 (2.4%).

Demographic findings of the AKI and non-AKI groups are compared in Table 1. Among preoperative factors, the BMI of recipients was significantly different between the groups. Diabetes mellitus was significantly more common in the AKI group than in the non-AKI group. Hepatic dysfunction evaluated by the MELD score was higher in patients with AKI than in those without it. However, the incidences of complications related to hepatic decompensation, such as encephalopathy (West Haven criteria grades III and IV), variceal hemorrhage, and ascites (>1 L), did not differ between the groups. In terms of the laboratory findings, C-reactive protein level was higher in the AKI group than in the non-AKI group. Sodium level was lower in patients with AKI than in those without it, whereas sCr level was comparable between recipients with and without postoperative AKI. Among intraoperative factors, the incidence of severe PRS was higher in the AKI group than in the non-AKI group. PRBCs and fresh frozen plasma were transfused more frequently in patients with postoperative AKI than in those without postoperative AKI. Total amount of crystalloid and colloids, strong vasopressor (i.e., epinephrine or norepinephrine) uses, and mean serum lactate level were not different between both groups. Hourly urine output was less in the AKI group than in the non-AKI group. Furosemide was administered more frequently in the AKI group than in the non-AKI group. Donor and graft quality-related factors did not differ between the groups. The average tacrolimus trough level within POD 7 was comparable between the groups.

In Figure 1, the differences of oxygen content between the AKI and non-AKI groups are depicted during LDLT. Each level of oxygen content (non-AKI group vs. the AKI group; mL/dL) was followed: 14.7 (12.5–17.3) versus 13.9 (12.4–15.9) in the preanhepatic phase ($P = .101$); 14.5 (12.9–16.2) versus 13.5 (12.2–15.2) in the anhepatic phase ($P = .015$); 14.0 (12.5–15.4) versus 13.4 (12.1–14.3) at 5 minutes after graft reperfusion ($P = .004$); 13.8 (12.4–15.2) versus 12.9 (12.0–14.6) at 1 hour after graft reperfusion ($P = .011$); and 14.6 (13.1–15.8) versus 13.7 (12.5–15.4) at peritoneal closure ($P = .019$). After Bonferroni post hoc correction, the oxygen content at 5 minutes after graft reperfusion was significantly different between patients with and without postoperative AKI in LDLT. In Table 2, the hemoglobin, PaO_2, and SaO_2 were presented at the times that the ABGs were drawn.

In Figure 2, the differences in oxygen content at 5 minutes after graft reperfusion are presented according to postoperative AKI stage. The oxygen content (mL/dL) of the non-AKI group was highest at 14.0 (12.5–15.4), followed by AKI stage I (13.4 [12.2–14.5]) and AKI stage II or III (13.4 [11.9–13.9]). The oxygen content of recipients with AKI stage I and stage II or III was significantly lower than that of those without AKI ($P = .032$, non-AKI vs. AKI stage I; $P = .015$, non-AKI vs. AKI stage II or III).

The relationships between perioperative factors and postoperative AKI were investigated using logistic regression analysis in patients who underwent LDLT (Table 3). Univariate analysis showed that preoperative BMI of the recipients, history of diabetes mellitus, C-reactive protein level, severe PRS, total PRBC transfusion, total furosemide infusion, and oxygen content in the anhepatic phase, 5 minutes, and 1 hour after graft reperfusion and at peritoneal closure were significant predictors of developing postoperative AKI. The multivariate analysis revealed that oxygen content 5 minutes after graft reperfusion, high BMI of the recipients, and total furosemide administration were independently associated with developing postoperative AKI. The predictive model combining the oxygen content at 5 minutes after graft reperfusion, preoperative BMI of recipients, and total frusemide administration was significantly associated with postoperative AKI development, but was moderately foreseeable according to the area under the receiver-operating characteristic curve (0.723; 95% CI: 0.671–0.771; sensitivity: 57.9%; specificity: 78.6%; $P = .0001$).

The in-hospital outcomes are described in Table 4. Recipients with postoperative AKI stayed longer in the ICU and hospital and were more difficult to wean from mechanical ventilation than those without postoperative AKI. The success rate of early extubation in the OR was higher in the non-AKI group than in the AKI group, but the reintubation rates were comparable between the groups. No differences between the groups in graft size or liver dysfunction rate were detected on POD 7.

4. Discussion

In the present study, the main finding is that arterial oxygen content 5 minutes after graft reperfusion is a significant determinant of the occurrence of early postoperative AKI, in combination with preoperative BMI of recipients and intraoperative furosemide dose, in LDLT. The incidence of AKI after LDLT was 22.8% in our study.

Our results suggest a lower incidence of postoperative AKI than that of a previous study, which reported a 60.5% incidence in patients who underwent LDLT. Overexposure to a calcineurin inhibitor (CNI) is an important determinant of developing postoperative AKI in these patients.[8] According to the LDLT protocol of our transplantation center, CNIs, such as tacrolimus or cyclosporine, which are immunosuppressants, are administered to patients after the recognition of normal kidney function because CNI-induced nephrotoxicity is one of most common causes of developing post-LT AKI.[22] This may be one of the explanations for the low AKI incidence in our study.

Factors associated with AKI have been investigated in LT settings. Hilmi et al reported that predisposing factors for AKI after LT are female sex, severe obesity (>100 kg), low Child–Turcotte–Pugh (CPT) score, and history of diabetes mellitus.[2] Leithead et al[5] found that hepatic ischemia-reperfusion injury, which was assessed by peak perioperative

Table 1

Demographic findings in recipients and donors with/without postoperative AKI.

Group	Non-AKI	AKI	
N	258	76	*P*
Preoperative findings			
Age, y	52.2 ± 9.6	52.6 ± 8.0	.707
Sex (male)	79 (30.6%)	25 (32.9%)	.707
Body mass index, kg/m^2	24.2 ± 3.4	25.3 ± 4.3	.038
Etiology of liver disease			.806
Alcohol	41 (15.9%)	14 (18.4%)	
Hepatitis A virus	3 (1.2%)	1 (1.3%)	
Hepatitis B virus	154 (59.7%)	49 (64.5%)	
Hepatitis C virus	22 (8.5%)	5 (6.6%)	
Drug and autoimmune hepatitis	16 (6.2%)	3 (3.9%)	
Cryptogenic hepatitis	22 (8.5%)	4 (5.3%)	
Comorbidity			
Diabetes mellitus	51 (19.8%)	25 (32.9%)	.016
Systemic hypertension	42 (16.3%)	15 (19.7%)	.481
Model for end-stage liver disease score (pts)	12.0 (8.0–18.0)	14.5 (9.0–21.0)	.026
Complications of liver disease			
Severe encephalopathy	15 (5.8%)	8 (10.5%)	.157
Variceal hemorrhage	61 (23.6%)	19 (25.0%)	.821
Ascites (>1 L)	99 (38.4%)	38 (50.0%)	.070
Laboratory findings			
Hemoglobin, g/dL	10.4 (8.6–12.3)	10.1 (8.8–11.3)	.312
Sodium, mEq/L	140.0 (136.0–142.0)	137.5 (134.0–141.8)	.012
C-reactive protein, mg/L	0.2 (0.1–0.8)	0.4 (0.1–1.2)	.004
Creatinine, mg/dL	0.8 (0.6–1.0)	0.8 (0.6–1.1)	.738
Intraoperative findings			
Duration of surgery, min	528.6 ± 97.8	536.5 ± 102.2	.540
Strong vasopressor uses	130 (50.4%)	32 (42.1%)	.194
Severe postreperfusion syndrome	45 (17.6%)	23 (30.3%)	.016
Average of vital sign during whole surgery			
Mean blood pressure, mmHg	77.6 ± 8.7	77.7 ± 8.8	.949
Heart rate, beats/min	87.3 ± 13.3	89.1 ± 14.9	.308
Central venous pressure, mmHg	9.8 ± 2.7	9.9 ± 3.3	.967
Cardiac index, L/min/m^2	4.1 (3.7–4.9)	4.3 (3.6–5.0)	.585
SVRI, dynes-sec/cm^5/m^2	1294.9 ± 371.2	1234.9 ± 206.5	.307
Stroke volume variation (%)	6.9 (5.1–9.2)	7.3 (6.2–10.0)	.133
Blood product transfusion, U			
Packed red blood cell	6.0 (3.0–12.0)	10.0 (6.3–15.0)	.000
Platelet count	0.00 (0.00–6.00)	1.5 (0.0–6.0)	.310
Fresh frozen plasma	7.0 (4.0–10.0)	8.0 (5.0–10.8)	.013
Cryoprecipitate	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.065
Total crystalloid infusion, mL	5075.0 (3600.0–6700.0)	5135.0 (3875.0–6522.5)	.147
Total colloid infusion, mL	700.0 (39.0–1100.0)	500.0 (0.0–1000.0)	.500
Hourly urine output, mL/kg/h	1.6 (0.9–2.3)	0.9 (0.5–1.5)	.000
Furosemide administration, mg	5.0 (0.0–20.0)	20.0 (5.0–40.0)	.000
Mean serum potassium, mEq/L	3.8 (3.5–4.1)	3.9 (3.4–4.4)	.492
Mean serum ionized calcium, mmol/L	1.1 (1.0–1.1)	1.1 (1.0–1.1)	.806
Mean serum lactate, mmol/L	4.4 (3.4–5.9)	4.1 (3.4–5.3)	.278
Mean brain natriuretic peptide, pg/mL	71.2 (36.0–165.6)	87.9 (52.1–151.3)	.280
Donor findings			
Age, y	31.0 (25.0–41.0)	35.0 (23.5–48.0)	.291
Sex (male)	104 (40.3%)	29 (38.2%)	.803
Graft-recipient-weight ratio	1.1 (0.9–1.4)	1.1 (1.0–1.5)	.306
Steatosis (%)	5.0 (0.0–5.0)	3.0 (0.0–5.0)	.322
Graft ischemic time, min	92.0 (68.8–118.0)	95.5 (74.3–118.8)	.325
Postoperative findings			
Average of tacrolimus trough level, ng/mL	4.7 (2.8–7.5)	4.0 (2.3–6.1)	.091

Values are expressed as number (proportion), mean ± SD or median (interquartile range). AKI = acute kidney injury, SVRI = systemic vascular resistance index.

serum AST, was independently related to the occurrence of AKI in patients who underwent LT. The independent variables for developing AKI in association with graft quality after LT are longer warm ischemic time, donation after circulatory death, old donor age (≥60 years), and high donor BMI (≥30 kg/m^2).[4] Patients who receive an ABO-incompatible LT have a higher incidence of AKI than those with an ABO-compatible one. Additionally, a lower hemoglobin level and longer surgery

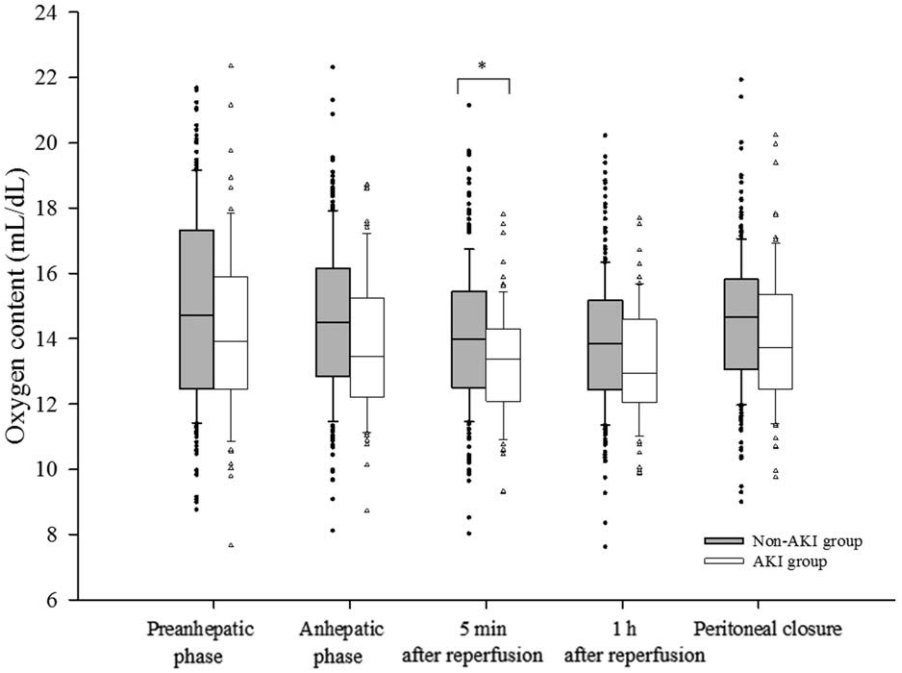

Figure 1. Comparison of the oxygen content between recipients with/without postoperative acute kidney injury (AKI) during living donor liver transplantation. The box plots show the median (line in the middle of the box), interquartile range (box), 10th and 90th percentiles (whiskers), and outliers (dots). *$P = .004$, non-AKI group vs. AKI group by Bonferroni post hoc test.

duration are linked to AKI in patients who have undergone an ABO-incompatible LT.[23] Another study found a significant association between graft recipient weight ratio (<0.8) and early postoperative renal dysfunction, MELD score, and preoperative renal dysfunction in patients who underwent LDLT.[3] The present study demonstrated that oxygen content 5 minutes after graft reperfusion was an independent determinant of AKI after LDLT. This is the first study to detect a relationship between intraoperative arterial oxygenation and the development of early postoperative AKI in the LDLT setting. Other significant determinants in our study were high BMI of the recipient and furosemide administration, which were identified in previous studies.

Bert et al[12] suggested that kidney autoregulation was maintained in response to acute hypoperfusion in an animal study. However, the protective mechanism against acute hypoperfusion was not achieved under the concomitant hypoxic condition, and renal perfusion pressure decreased. Brabrand et al demonstrated that global hypoxia modifies overall and regional

Table 2

Comparison of hemoglobin, PaO_2, and SaO_2 in patients with/without postoperative AKI.

Group	Non-AKI	AKI	
N	258	76	*P*
Hemoglobin, g/dL			
Preanhepatic phase	10.3 (8.6–12.1)	9.8 (8.6–11.2)	.117
Anhepatic phase	10.1 (8.9–11.3)	9.3 (8.4–10.7)	.015
5 min after reperfusion	9.7 (8.7–10.9)	9.2 (8.5–9.9)	.004
1 h after reperfusion	9.6 (8.6–10.6)	9.0 (8.4–10.0)	.018
Peritoneal closure	10.2 (9.2–11.1)	9.6 (8.7–10.7)	.028
PaO_2, mmHg			
Preanhepatic phase	183.5 (136.0–215.8)	169.0 (128.3–202.3)	.139
Anhepatic phase	199.0 (167.5–231.5)	189.0 (161.0–224.0)	.140
5 min after reperfusion	205.0 (173.0–236.5)	202.0 (167.0–230.0)	.865
1 h after reperfusion	201.0 (171.3–229.0)	195.0 (173.0–228.0)	.648
Peritoneal closure	182.0 (148.0–215.0)	177.0 (147.3–208.0)	.872
SaO_2 (%)			
Preanhepatic phase	99.4 (98.8–99.8)	99.3 (98.8–99.8)	.417
Anhepatic phase	99.4 (98.9–99.7)	99.5 (99.0–99.7)	.435
5 min after reperfusion	99.3 (98.9–99.6)	99.4 (99.0–99.6)	.334
1 h after reperfusion	99.3 (98.9–99.5)	99.4 (99.1–99.6)	.123
Peritoneal closure	99.2 (98.9–99.5)	99.4 (98.9–99.6)	.349

Values are expressed as median (interquartile range). AKI = acute kidney injury, PaO_2 = arterial oxygen partial pressure, SaO_2 = arterial oxygen saturation.

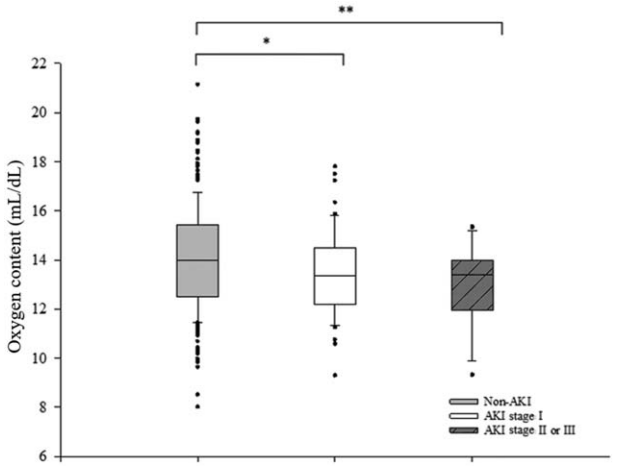

Figure 2. Comparison of oxygen contents at 5 minutes after graft reperfusion according to the severity of postoperative acute kidney injury (AKI) in living donor liver transplantation. The box plots show the median (line in the middle of the box), interquartile range (box), 10th and 90th percentiles (whiskers), and outliers (dots). *$P = .032$, non-AKI vs. AKI stage I; **$P = .015$, non-AKI vs. AKI stage II or III by Bonferroni post hoc test.

Table 3

Univariate and multivariate logistic regression analyses of the relationships between perioperative factors and postoperative acute kidney injury in patients who underwent living donor liver transplantation.

	Univariate analysis			Multivariate analysis		
	β	Relative risk (95% CI)	*P*	β	Relative risk (95% CI)	*P*
Preoperative factors						
Body mass index, kg/m^2	0.084	1.087 (1.014–1.166)	.019	0.093	1.097 (1.020–1.180)	.012
Diabetes mellitus	0.688	1.990 (1.127–3.512)	.018			
MELD score (pts)	0.029	1.029 (0.999–1.060)	.056			
C-reactive protein, mg/L	0.223	1.250 (1.068–1.463)	.005			
Intraoperative factors						
Severe postreperfusion syndrome	0.710	2.035 (1.133–3.655)	.017			
Total PRBC transfusion, U	0.040	1.041 (1.012–1.071)	.005			
Total FFP transfusion, U	0.034	1.034 (0.999–1.071)	.059			
Furosemide administration, mg	0.017	1.017 (1.008–1.026)	.000	0.017	1.018 (1.008–1.027)	.000
Oxygen content, mL/dL						
Preanhepatic phase	−0.088	0.916 (0.836–1.004)	.061			
Anhepatic phase	−0.135	0.874 (0.779–0.980)	.021			
5 min after graft reperfusion	−0.196	0.822 (0.722–0.937)	.003	−0.183	0.833 (0.725–0.956)	.009
1 h after graft reperfusion	−0.175	0.840 (0.732–0.963)	.013			
Peritoneal closure	−0.132	0.877 (0.771–0.996)	.044			

CI = confidence interval, FFP = fresh frozen plasma, MELD = model for end-stage liver disease, PRBC = packed red blood cell.

renal perfusion using contrast-enhanced USG in an experimental setting. Renal vasoconstriction occurred under the hypoxic condition, overall renal perfusion was reduced, and regional perfusion changed. Blood volume decreased predominantly in the renal cortex, whereas blood flow velocity decreased in the renal medulla.[24] In our study, low oxygen content 5 minutes after liver graft reperfusion was a significant determinant related to AKI after LDLT. Additionally, the incidence of severe PRS was significantly higher in the AKI group than that in the non-AKI group. Given these findings, we speculate that arterial hypoxia, which is representative of low oxygen content, disturbs kidney autoregulation and induces acute kidney damage. Furthermore, severe systemic hypotension immediately after liver graft reperfusion reinforces the arterial hypoxic effect on kidney injury in patients who have undergone LDLT.

From the anatomical point of view, the kidney can show a notable disparity between oxygen blood supply and tissue oxygenation. Oxygen tension in kidney tissues is lower in animal studies than might be expected even under fluent blood flow to the kidney. This results from parallel alignment of preglomerular arterial vessels and postglomerular venous vessels, allowing oxygen to bypass the renal capillaries via diffusional shunting of oxygen (i.e., renal arterial-venous oxygen shunting). This confined renal tissue oxygenation is thought to make the kidney vulnerable to hypoxia and low arterial oxygenation, which could be a major cause of AKI in a clinical setting.[10,11] Some clinical studies have suggested that extreme hemodilution during cardiopulmonary bypass is a major determinant related to AKI after cardiac surgery because a low hematocrit causes disturbance between oxygen supply and demand, particularly in the renal

Table 4

Postoperative outcomes in recipients with/without postoperative AKI.

Group	Non-AKI	AKI	
N	258	76	*P*
Intensive care unit stay, days	7.0 (5.0–7.0)	7.0 (6.0–8.0)	.000
Hospital stay, days	23.0 (21.0–31.0)	28.0 (22.0–39.0)	.004
Fast-track extubation	138 (53.5%)	27 (35.5%)	.005
Mechanical ventilation, min	0.0 (0.0–653.3)	256.0 (0.0–772.5)	.008
Reintubation in ICU	14 (5.4%)	6 (7.9%)	.417
Infection in ICU	25 (9.7%)	12 (15.8%)	.136
Reoperation	16 (6.2%)	5 (6.6%)	1.000
In hospital mortality	22 (8.5%)	10 (13.2%)	.228
Liver dysfunction on postoperative day 7			
Early allograft dysfunction	54 (20.9%)	16 (21.1%)	.981
Primary graft nonfunction	44 (17.1%)	8 (10.5%)	.168
Absolute liver volume, mL			
Preoperative day	818.3 (731.5–993.0)	879.9 (744.5–1030.0)	.240
Postoperative day 7	1158.8 (1026.2–1260.0)	1178.1 (1034.9–1407.9)	.119
Relative liver volume (%)			
Standard liver volume, mL	1524.2 (1369.8–1635.3)	1579.7 (1398.0–1694.6)	.050
Preoperative day	54.8 (47.5–66.9)	56.2 (47.2–69.5)	.703
Postoperative day 7	75.5 (67.9–85.8)	78.6 (67.5–91.4)	.421

Values are expressed as number (proportion), mean ± standard deviation or median (interquartile range). AKI = acute kidney injury, ICU = intensive care unit.

medullary segment.[12,25] PO_2 was shown to decrease in the renal segments after injecting contrast medium in an animal study. The low PO_2 was linked to reduced renal function, which may account for contrast medium-related AKI.[26] Patients with septic AKI have worse outcomes than those with the nonseptic equivalent. Poor pulmonary function associated with low arterial oxygenation is a critical cause of septic AKI.[27] Given these observations, it is very feasible that intraoperative hypoxia could develop postoperatively into AKI and that oxygen-related parameters, such as hemoglobin and PO_2, could be associated with the development of AKI.

Regarding the relationship between hepatic decompensation and arterial oxygenation, one study suggested that arterial hypoxemia (PaO_2 $\leq$70 mmHg) develops predominantly in patients with end-stage liver disease. Arterial hypoxemia is closely related to low pulmonary vascular resistance, high alveolar-arterial oxygen gradient (A-a oxygen gradient), high hepatic venous pressure gradient, and severe CPT class.[28] Researchers in another study measured pulmonary gas exchange (PaO_2 and A-a oxygen gradient) and carbon monoxide diffusion capacity. They estimated intrapulmonary shunt in LT candidates and compared the values before and after LT. The results showed that these pulmonary factors improved after LT. In particular, intrapulmonary shunting was an important factor in abnormal oxygen uptake in transplant candidates.[29] Patients with liver cirrhosis have decreased oxygen binding capacity by hemoglobin, as the level of 2,3-diphosphoglycerate in erythrocytes increases in patients with liver cirrhosis.[30] Therefore, hemoglobin level may not directly reflect arterial oxygenation in patients with liver cirrhosis. Another option to directly access arterial oxygenation is needed.

In patients with end-stage liver disease, hyperdynamic circulation is manifested in patients with end-stage liver disease as elevated cardiac output and heart rate, and reduced systemic vascular resistance with normal or decreased MAP.[31] Although overall splanchnic vascular resistance decreases, no decrease in vascular resistance is demonstrated in whole vascular beds[32] including the kidneys.[33] Renal vasoconstriction is caused by effective hypovolemia and neurohormonal activation in patients with cirrhosis.[34] Central blood volume does not increase effectively in response to volume infusion despite elevated cardiac output in patients with advanced cirrhosis, indicating that increased cardiac output is not directly associated with effective volume status in patients with liver cirrhosis but is affected by an imbalance in endogenous vasoconstrictors and vasodilators in regional vascular beds.[35] Therefore, the direct effect of cardiac output on oxygen delivery and renal hemodynamics may be diminished in patients with liver cirrhosis. This is why we focused on oxygen content instead of oxygen delivery, which is affected by systemic circulatory parameters, even though the CI, heart rate, systemic vascular resistance index, stroke volume variation, mean blood pressure, and serum brain natriuretic peptide did not differ between the groups.

Furosemide is a loop diuretic that is often applied to improve urine output in patients with AKI in clinical settings. The administration of high-dose furosemide converts oliguric to nonoliguric AKI, but this practice can induce harmful oxidative stress on the kidneys.[36] Furosemide does not decrease the risk of renal replacement therapy or patient mortality when applied as a preventive or curative drug in patients with AKI. In particular, a high dose of furosemide is closely associated with renal toxicity.[37] Our study demonstrated that patients with AKI were administered a higher dose of furosemide than those without AKI. We speculate that the renal toxicity of furosemide can aggravate severe oxidative stress secondary to ischemic-reperfusion injury[38] in patients who have undergone LDLT.

A previous study suggested that high preoperative BMI is an independent determinant associated with early postoperative AKI in patients who have undergone LT.[39] This association was also consistent with a survey by Hilmi et al and explained by metabolic syndrome and multiple organ injuries.[2,40] We ignored the effect of ascites volume on BMI in our study population because the incidence of severe ascites (>1 L) did not differ significantly between the groups.

Several limitations of our study should be mentioned. First, the substantial effect of renal arterial oxygen supply on the development of AKI was not evaluated, as renal arterial oxygenation and flow were not measured directly by intraoperative cannulation or Doppler USG of the renal artery. Second, sCr is the most practical indicator and is used commonly to assess renal function in clinical settings, but the sCr has some limitations because its levels are influenced by muscle mass, age, and nutrient status. In particular, because patients with cirrhosis have reduced sCr synthesis owing to decreased muscle mass,[41] this could affect the development of AKI. Third, 5 ABG samples during the entire liver transplant surgery maybe insufficient to accurately assess the oxygen content as the timing for blood loss may vary between different LDLT cases. Finally, because this was a retrospective study, some critical parameters were inevitably missed during data collection. However, the present study also provided some new findings. This is the first study to identify an association between low arterial oxygen content immediately after graft reperfusion and the development of early postoperative AKI in patients who have undergone LDLT. A randomized control study is required to examine the optimal arterial oxygen content range after graft reperfusion to prevent the development of early postoperative AKI in patients who have undergone LDLT.

In conclusion, we showed that arterial oxygen content 5 minutes after graft reperfusion, preoperative BMI, and furosemide doses were independent predictors of the development of early postoperative AKI in patients who underwent LDLT in the present study. Patients with early postoperative AKI showed poorer postoperative outcomes requiring prolonged ICU care than those without it. Therefore, meticulous ventilator care and cautious PRBC transfusions during the immediate postreperfusion period should be provided to reduce the development of AKI after LDLT.

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