BMJ Open Predictive role of vitamin B₁₂ in acute kidney injury in living donor liver transplantation: a propensity score matching analysis

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ABSTRACT

Objectives We examine the association between vitamin B₁₂ level and risk for acute kidney injury (AKI) in patients undergoing living donor liver transplantation (LDLT).

Design Retrospective observational cohort study.

Setting University hospital, from January 2009 to December 2018.

Participants A total of 591 patients who underwent elective LDLT were analysed in this study. Those with a preoperative history of kidney dysfunction, vitamin B₁₂ supplementation due to alcoholism, low vitamin B₁₂ (<200 pg/mL) or missing laboratory data were excluded.

Primary and secondary outcome measures The population was classified into AKI and non-AKI groups according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, and associations between perioperative factors and AKI were analysed. After 1:1 propensity score (PS) matching, the association between high vitamin B₁₂ (>900 pg/mL) and postoperative AKI was evaluated.

Results Preoperative vitamin B₁₂ was higher in the AKI group. Potentially significant perioperative factors from univariate analyses were entered into multivariate analyses, including preoperative factors (vitamin B₁₂, diabetes), intraoperative factors (hourly urine output) and donor graft fatty change in LDLT patients. PS matching analyses with adjustment using PS revealed that high serum vitamin B₁₂ (>900 pg/mL) was associated with risk for AKI, and the risk was 2.8-fold higher in patients with high vitamin B₁₂ than in those with normal vitamin B₁₂. Higher vitamin B₁₂ was also related to a higher AKI stage. In addition, inflammatory factors (C reactive protein, white blood cells and albumin) were associated with vitamin B₁₂ level.

Conclusions Our study may improve the accuracy of predicting postoperative AKI by introducing preoperative vitamin B₁₂ into risk assessments for patients undergoing LDLT.

INTRODUCTION

Living donor liver transplantation (LDLT) is an important treatment for patients with end-stage liver disease (ESLD), but postoperative complications may lead to mortality and morbidity. Many factors affect the development of acute kidney injury (AKI) after

Strengths and limitations of this study

- This is the first analysis of the association between high vitamin B₁₂ and morbidity after liver transplantation.
- One-to-one propensity score (PS) matching was performed to correct for confounder imbalance between the normal vitamin B₁₂ group and high vitamin B₁₂ group.
- Our study could improve the accuracy of predicting postoperative acute kidney injury (AKI) by introducing preoperative vitamin B₁₂ into risk assessments for patients undergoing living donor liver transplantation.
- Further research is needed to identify the mechanism behind the relationship between vitamin B₁₂ level and risk for AKI.
- We analysed only liver transplants from living donors, and there are important differences between liver transplants from living donors and those from deceased donors.
- Additional studies are required to validate the predictive role of vitamin B₁₂ in liver transplantation from deceased donors.

liver transplantation (LT) in patients with ESLD, including older donor age, male sex, model for end-stage liver disease (MELD) score, body mass index (BMI), chronic kidney disease (CKD) and diabetes mellitus (DM).^{1–4} Preoperative systemic inflammation is related to an increased risk for AKI after surgery. Systemic inflammatory markers such as C reactive protein (CRP) and albumin are associated with postoperative AKI in non-cardiac surgery.⁵ In addition, proinflammatory markers such as interleukin (IL)-6 are associated with AKI after LDLT.⁶ Many studies have reported that AKI negatively affects postoperative outcomes, resulting in a prolonged hospital stay, early graft dysfunction, infection and poor patient survival.^{7,8} Therefore,

the risk for AKI should be evaluated before surgery, in particular in patients undergoing LDLT.

There are several definitions of AKI, including Risk, Injury, Failure, Loss and End-stage renal disease (RIFLE) as well as Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) criteria.⁹ We determined AKI using the KDIGO definition based on a study by Tsai *et al* showing that the KDIGO definition provides better prognostic ability than the RIFLE or AKIN definitions.¹⁰

Vitamin B₁₂ is an essential nutrient that is not created in the body and may be deficient in patients with malnutrition or medical conditions such as Wernicke-Korsakoff syndrome.^{11 12} Although there have been numerous studies on vitamin deficiency, including vitamin B₁₂ deficiency, few studies have focused on patients with high vitamin B₁₂ and the association between preoperative vitamin B₁₂ and postoperative AKI in LDLT patients. However, the importance of high vitamin B₁₂ in the clinical setting has recently emerged.^{13 14} High vitamin B₁₂ is related to hepatic disease, haematological disorders such as leukaemia and polycythemia vera¹⁵ and renal impairment.^{11 16} There have also been reports of an association between high vitamin B₁₂ and systemic inflammation, in particular CRP.^{17 18} In studies of intensive care unit (ICU) patients, elevated vitamin B₁₂ was associated with mortality^{19 20} and length of hospital stay.¹⁴

We investigated the association between high serum vitamin B₁₂ and the development of AKI after LDLT. Here, we propose a prognostic model to identify patients at high risk for AKI and compare postoperative outcomes between non-AKI and AKI groups.

PATIENTS AND METHODS

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Study population

Data from 591 adult patients (age >19 years) undergoing elective LDLT between January 2009 and December 2018 at Seoul St. Mary's Hospital were retrospectively collected with the electronic medical record system. Exclusion criteria included a preoperative history of kidney dysfunction (eg, dialysis, chronic kidney disease (<60 mL/min/1.73 m²), hepatorenal syndrome), a history of vitamin B₁₂ supplementation due to alcoholics, low vitamin B₁₂ (<200 pg/mL) and missing laboratory data. Based on the exclusion criteria, 112 patients were excluded. In total, 479 adult patients were analysed, and 198 patients were matched after 1:1 propensity score (PS) matching.

Living donor liver transplantation

Surgery and anaesthesia were consistently provided by expert transplant surgeons and anesthesiologists,

respectively. The surgical procedure and anaesthetic management were described in detail in our previous studies.²¹ Briefly, the piggyback surgical technique was performed using the right liver lobe with reconstruction of the middle hepatic vein. Vascular anastomoses of hepatic, portal vein and hepatic artery and bile duct anastomoses were performed, and hepatic vascular flow (such as portal venous flow and hepatic arterial resistive index) was checked with Doppler ultrasonography (Prosound SSD-5000; Hitachi Aloka Medical, Tokyo, Japan). Splenectomy, splenic artery ligation or portacaval shunting were performed as required.

Balanced anaesthesia was supplied with proper haemodynamic management (mean arterial pressure (MBP) ≥65 mm Hg and central venous pressure (CVP) ≤10 mm Hg) under multiple haemodynamic monitoring. Based on transfusion guidelines,²² packed red blood cells (PRBC) were transfused to reach a hematocrit ≥25%, and coagulation factors (fresh frozen plasma (FFP), single donor platelet and cryoprecipitate) were also transfused based on laboratory findings or thromboelastography.

Severe postreperfusion syndrome (PRS) was defined as follows: unstable vital signs (MBP ≥30% or hypotensive duration ≥5 min), fatal arrhythmia (asystole or ventricular tachycardia), use of rescue vasopressors (epinephrine or norepinephrine), continuing or reoccurring fibrinolysis or a requirement for antifibrinolytic drug treatment.²³

An immunosuppression regimen (calcineurin inhibitor, mycophenolate mofetil and prednisolone) was administered according to our hospital's LDLT protocol. The trough level of tacrolimus was preserved between 7 and 10 ng/mL for the first month after surgery and tapered to 5–7 ng/mL thereafter. We compared the serum calcineurin inhibitor level (table 1) between patients with and those without AKI, and there was no significant difference.

Methylprednisolone was administered immediately before graft reperfusion and then gradually tapered. MMF was withdrawn at 3–6 months after surgery. Basiliximab was given prior to surgery and on postoperative day (POD) 4. Immunosuppressants were gradually adjusted and tapered after LDLT.

Patients with a malnutrition condition were under an oral supplement diet provided by experienced nutritionists.

Criteria for acute kidney injury

AKI was determined clinically by KDIGO classification as follows: stage 1, increase in serum creatinine (SCr) ≥0.3 mg/dL (in 48 hours) or 1.5–1.9 times baseline (in 7 days) or urine output <0.5 mL/kg/hour for 6–12 hours; stage 2, 2.0–2.9 times by baseline SCr or urine output <0.5 mL/kg/hour for ≥12 hours; stage 3, 3.0 or more times baseline SCr, increase in SCr ≥4.0 mg/dL, beginning of renal replacement therapy regardless of previous KDIGO stage or urine output <0.3 mL/kg/hour for ≥24 hours. Based on these definitions, AKI was classified as stage 1, stage 2 or stage 3. For the comparison of vitamin B₁₂ by stage, we collapsed stages 2 and 3 into one

Table 1 Comparison of preoperative and intraoperative recipient and donor factors between the non-AKI and AKI groups

Group	Non-AKI	AKI	P value
n	364	115	
Preoperative recipient factors			
Age (years)	54 (48–59)	52 (47–59)	0.379
Sex (male)	247 (67.9%)	84 (73%)	0.294
Body mass index (kg/m ²)	24.12 (22.08–26.47)	25.13 (22.64–27.9)	0.013
Nephrotoxic drug exposure	31 (8.5%)	13 (11.3%)	0.367
Calcineurin inhibitor level	7.3 (6.6–8.8)	7.4 (6.2–9.4)	0.554
Aetiology of end- stage liver disease			0.199
Alcohol	66 (18.1%)	30 (26.1%)	
Hepatitis A	5 (1.4%)	4 (3.5%)	
Hepatitis B	219 (60.2%)	59 (51.3%)	
Hepatitis C	30 (8.2%)	7 (6.1%)	
Autoimmune	10 (2.7%)	1 (0.9%)	
Drug and toxin	5 (1.4%)	2 (1.7%)	
Cryptogenic	29 (8.0%)	12 (10.4%)	
Comorbidity			
Diabetes mellitus	86 (23.6%)	39 (33.9%)	0.029
Hypertension	68 (18.7%)	26 (22.6%)	0.355
MELD score (point)	13 (8–22)	19 (12–29)	<0.001
Hepatic decompensation			
Encephalopathy (West- Haven criteria I or II)	23 (6.3%)	9 (7.8%)	0.572
Varix	89 (24.5%)	35 (30.4%)	0.202
Ascites	167 (46.9%)	67 (58.3%)	0.021
Cardiac function			
Ejection fraction (%)	64.54 (62–67)	64.54 (61–67.3)	0.542
Diastolic dysfunction	171 (47%)	53 (46.1%)	0.867
Laboratory variables			
Haemoglobin (g/L)	98.8 (83.8–116.7)	93.7 (81.3–109.3)	0.085
WBC count (×10 ⁹ /L)	4.06 (2.61–6.12)	4.14 (3.06–7.73)	0.129
Albumin (g/dL)	3.0 (2.7–3.5)	2.9 (2.6–3.3)	0.022
Platelet count (×10 ⁹ /L)	64 (47–104.75)	56 (39–76)	0.002
Vitamin B ₁₂ (pg/mL)	1152.68 (691.73–2238.24)	1954.25 (1085.48–3380.34)	<0.001
Sodium (mEq/L)	139 (135–142)	138 (135–141)	0.256
Potassium (mEq/L)	4.0 (3.7–4.3)	4.0 (3.7–4.3)	0.711
Calcium (mg/dL)	8.4 (8.0–8.8)	8.4 (7.8–8.69)	0.218
Glucose (mg/dL)	137.75 (91–186)	111 (93.75–138)	0.411
Creatinine (mg/dL)	0.82 (0.67–1.09)	0.91 (0.66–1.3)	0.18
Ammonia (µg/dL)	94 (64.25–151.75)	104 (69–149)	0.713
Intraoperative recipient factors			
Surgical duration (min)	509.50 (455–579.5)	515 (465–585)	0.337
Post reperfusion syndrome	185 (50.8%)	67 (58.3%)	0.164
Average vital signs			
MBP (mm Hg)	76.33 (70.75–83.67)	76 (67.91–81.41)	0.041
HR (beats/min)	88 (79.25–96.5)	88.5 (83–100.25)	0.047

Continued

Table 1 Continued

Group	Non-AKI	AKI	P value
CVP (mm Hg)	9 (7.5–10.5)	9 (8–10.25)	0.946
Mean lactate (mmol/L)	3.6 (2.86–4.65)	3.75 (2.75–5.05)	0.675
Blood product transfused (unit)			
Packed red blood cells	7 (3–13)	10 (7–16)	<0.001
Fresh frozen plasma	6 (4–10)	10 (7–14)	<0.001
Platelet concentrate	5 (0–10)	6 (0–12)	0.033
Hourly fluid infusion (mL/kg/hour)	9.43 (6.72–12.71)	9.6 (6.3–13.02)	0.748
Hourly urine output (mL/kg/hour)	1.37 (0.73–2.18)	0.87 (0.51–1.4)	<0.001
Donor graft factors			
Age (years)	34 (25.25–41)	34 (27–41)	0.448
Sex (male)	236 (64.8%)	84 (73%)	0.103
GRWR (%)	1.25 (1.06–1.61)	1.33 (1.05–1.95)	0.118
Graft ischaemic time (min)	107.5 (73–182.82)	171 (96–182.82)	<0.001
Fatty change (%)	4.6 (0–5)	4.6 (0–5)	0.475

Values are medians (IQR) or frequencies (percentage).

AKI, acute kidney injury; CVP, central venous pressure; GRWR, graft recipient weight ratio; HR, heart rate; MBP, mean blood pressure; MELD, model for end-stage liver disease; WBC, white blood cell.

group (stage 2–3). We divided the study population into non-AKI and AKI groups to evaluate the risk for AKI (see online supplemental additional file 1).

Measurement of serum vitamin B₁₂

As a part of preoperative patient assessment, laboratory variables, including vitamin B₁₂, were measured for all patients scheduled for LDLT. All laboratory variables were measured with venous or arterial blood samples (Clot Activator Tube; BD Vacutainer, Becton, Dickinson, Franklin, New Jersey, USA) collected the day before surgery and processed on an automated chemistry analyser (Hitachi 7600; Hitachi, Tokyo, Japan). If multiple tests were performed on a single day, the results of the test closest to the time of surgery were used in the study.

Perioperative recipient and donor graft factors

Preoperative recipient factors included age, sex, BMI, aetiology for LDLT, comorbidity (eg, diabetes mellitus or hypertension), MELD score, hepatic decompensation (eg, encephalopathy (West-Haven grade I or II),²⁴ varix and ascites), transthoracic echocardiography (ejection fraction and diastolic dysfunction)²⁵ and laboratory variables (white blood cell (WBC) count, albumin, platelet count, sodium, potassium, calcium, glucose, creatinine ammonia). Intraoperative recipient factors included surgical duration, PRS,²⁶ average vital signs (MBP, heart rate (HR) and CVP), mean lactate, amount of blood product transfused (PRBC, FFP, platelet concentrate), hourly fluid infusion and urine output. Donor graft factors included age, sex, graft recipient weight ratio, graft ischaemic time and donor graft fatty change.

Postoperative outcomes included total length of hospital and ICU stay, infection (eg, pneumonia or sepsis), early allograft dysfunction (EAD) and overall patient mortality.

Clinical postoperative outcomes

Clinical postoperative outcomes included duration of ICU stay and hospital stay, incidence of infection, EAD and overall mortality. EAD was defined as the presence of one or more of the following: total bilirubin ≥ 10 mg/dL or international normalised ratio ≥ 1.6 on postoperative day 7 and aspartate transaminase or alanine transaminase ≥ 2000 IU/mL during the first week.²⁷

Statistical analyses

We compared perioperative recipient and donor graft factors between the non-AKI and AKI groups using the Mann-Whitney U test and the χ^2 test or Fisher's exact test, as appropriate. The association between the perioperative factors and AKI was analysed with univariate and multivariate logistic regression. Potentially significant factors ($p < 0.1$) in the univariate analyses were entered into forward and backward multivariate logistic analyses. When multiple perioperative variables were intercorrelated, the most clinically relevant factors were retained in the analyses. The predictive accuracy of the models was evaluated with the area under the receiver operating characteristic curve (AUROC). In addition, 1:1 PS matching was used to correct the imbalance in confounders between the normal vitamin B₁₂ group and high vitamin B₁₂ group. After matching, we compared perioperative recipient and donor graft factors using the Mann-Whitney U test and the χ^2 test or Fisher's exact test, as appropriate. The association between high vitamin B₁₂ (>900 pg/mL) and postoperative AKI was evaluated with multivariate logistic regression.

analyses with PS adjustment, and ORs with 95% CIs were calculated. Continuous data are presented as medians and IQRs, and categorical data are presented as frequencies and proportions. Correlations between inflammatory factors and vitamin B₁₂ level were evaluated with Spearman's method.

In all analyses, $p < 0.05$ was taken to indicate statistical significance. Statistical analyses were performed with SPSS for Windows (V.24; IBM, Chicago, Illinois, USA), R V.2.10.1 (R Foundation for Statistical Computing, Vienna, Austria) and MedCalc for Windows (V.11.0; MedCalc, Ostend, Belgium).

RESULTS

Baseline characteristics of the study population

The population of the study was largely male (69.1%), and the median (IQR) age and BMI were 53 (48–59) years and 24.3 (22.2–26.8) kg/m². The aetiology for LDLT was as follows: hepatitis B (58%), alcoholic hepatitis (20%), hepatitis C (7.7%), autoimmune hepatitis (2.3%), hepatitis A (1.9%), drug and toxic hepatitis (1.5%) and cryptogenic hepatitis (8.6%). The median (IQR) MELD score and ejection fraction were 14^{9–24} and 64.5 (62–67). The prevalence of hypertension, diabetes, encephalopathy, varix and ascites was 19.6% ($n=94$), 26.1% ($n=125$), 6.7% ($n=32$), 25.9% ($n=124$) and 48.9% ($n=234$), respectively.

Comparison of preoperative and intraoperative factors between the non-AKI and AKI groups

Preoperative BMI, DM, MELD, ascites and vitamin B₁₂ were higher in the AKI group than in the non-AKI group. Preoperative albumin and platelet count were higher in the non-AKI group than in the AKI group (table 1). Intraoperative mean HR, amount of blood product transfused and graft ischaemic time were higher in the AKI group than in the non-AKI group. Intraoperative mean blood pressure and hourly urine output were higher in the non-AKI group than in the AKI group. The prevalence of patients with exposure to nephrotoxic drugs such as non-steroidal anti-inflammatory drugs, aminoglycosides, ACE inhibitors, angiotensin II receptor blockers and diuretics was similar in the AKI and non-AKI groups ($p=0.367$).

Associations between preoperative and intraoperative factors and postoperative development of AKI

According to results of the univariate logistic regression (table 2), preoperative factors (BMI, DM, MELD, ascites, haemoglobin, WBC count, platelet count, vitamin B₁₂) and intraoperative factors (mean HR, PRC, FFP, hourly urine output, graft ischaemic time, donor graft fatty change) were potentially significant.

Multivariate logistic regression (table 2) revealed that vitamin B₁₂ (continuous data) was significantly associated with AKI as well as the incidence of diabetes mellitus, hourly urine output and donor graft fatty change (area under the curve (AUC): 0.718, 95% CI: 0.669 to 0.767, sensitivity: 68.7%, specificity: 66.5%, $p < 0.001$ in the predictive model). The probability of patients with high vitamin B₁₂ (>900 pg/dL) developing AKI was about threefold higher than that of

patients with normal vitamin B₁₂ (200–900 pg/dL; OR: 2.955, 95% CI: 1.669 to 5.232, $p < 0.001$; online supplemental additional file 2). Multivariate logistic regression analysis without vitamin B₁₂ (see online supplemental additional file 3) showed an area under the ROC curve of 0.695 (figure 1).

Comparison of preoperative and intraoperative recipient and donor graft factors before and after PS matching

There were significant differences between the groups in preoperative factors (ascites, haemoglobin, WBC count, platelet count, sodium), intraoperative factors (PRC, FFP, hourly urine output) and donor graft parameters (sex; table 3). After PS matching, there were no significant differences between the groups.

Proportions of PS-matched patients with normal kidney function, mild AKI and moderate-to-severe AKI according to vitamin B₁₂ level

The overall incidence of AKI was higher in patients with high vitamin B₁₂ levels than in those with normal vitamin B₁₂ levels. The severity of kidney injury, according to the KDIGO stage, was more aggravated in the high vitamin B₁₂ group than in the normal vitamin B₁₂ group (table 4 and online supplemental additional file 4).

Comparison of vitamin B₁₂ level by AKI stage in PS-matched patients

Patients with a higher AKI stage exhibited higher median and IQR values of vitamin B₁₂ (figure 2). Median (IQR) vitamin B₁₂ levels were 841.3 (671.3–1282.1), 1373.5 (741.5–1954.3) and 1566.8 (724.9–3525.8) for stages 0, 1 and 2–3, respectively.

Correlation between high vitamin B₁₂ and postoperative AKI in PS-matched patients

High vitamin B₁₂ was associated with the development of AKI in the entire study population and in PS-matched patients (table 5). After PS adjustment, high vitamin B₁₂ remained an independent factor related to AKI ($p=0.008$).

Figure 1 Comparison of area under the curve (AUC)-receiver operating characteristic (ROC) of multiple logistic regressions models with or without inclusion of vitamin B₁₂.

Table 2 Associations between preoperative and intraoperative recipient and donor factors and postoperative development of AKI

	Univariate analyses				Multivariate analyses			
	β	OR	95% CI	P value	β	OR	95% CI	P value
Preoperative recipient factors								
Age (years)	−0.009	0.991	0.969 to 1.014	0.457				
Sex (male vs female)	−0.250	0.779	0.488 to 1.243	0.295				
Body mass index (kg/m ²)	0.077	1.08	1.023 to 1.140	0.005				
Nephrotoxic drug exposure	0.314	1.369	0.690 to 2.715	0.368				
Calcineurin inhibitor level	0.083	1.087	0.959 to 1.232	0.192				
Comorbidity								
Diabetes mellitus	0.506	1.659	1.052 to 2.616	0.029	0.547	1.728	1.068 to 2.795	0.026
Hypertension	0.24	1.272	0.763 to 2.118	0.356				
MELD score (point)	0.041	1.041	1.022 to 1.062	<0.001				
Hepatic decompensation								
Encephalopathy (West-Haven criteria I or II)	0.23	1.259	0.565 to 2.804	0.573				
Varix	0.301	1.352	0.850 to 2.149	0.202				
Ascites	0.499	1.647	1.077 to 2.516	0.021				
Cardiac function								
Ejection fraction (%)	0.02	1.02	0.974 to 1.069	0.392				
Diastolic dysfunction	−0.036	0.965	0.634 to 1.469	0.867				
Laboratory variables								
Haemoglobin (g/L)	−0.086	0.918	0.831 to 1.013	0.09				
White blood cell count (×10 ⁹ /L)	0.034	1.034	0.995 to 1.076	0.092				
Albumin (g/dL)	0.037	1.038	0.985 to 1.094	0.165				
Platelet count (×10 ⁹ /L)	−0.006	0.994	0.989 to 0.998	0.009				
Vitamin B ₁₂ (pg/mL; continuous)	0	1	1.000 to 1.000	0.001	<0.001	1	1.000 to 1.000	0.003
Sodium (mEq/L)	−0.017	0.983	0.946 to 1.022	0.385				
Potassium (mEq/L)	−0.080	0.923	0.651 to 1.309	0.654				
Calcium (mg/dL)	−0.194	0.824	0.617 to 1.099	0.187				
Glucose (mg/dL)	0.001	1.001	0.997 to 1.004	0.78				
Creatinine (mg/dL)	0.049	1.05	0.886 to 1.245	0.573				
Ammonia (µg/dL)	0	1	0.998 to 1.003	0.795				
Intraoperative recipient factors								
Surgical duration (min)	0.001	1.001	0.999 to 1.003	0.333				
Postreperfusion syndrome	0.301	1.351	0.884 to 2.063	0.165				
Average vital signs								
MBP (mm Hg)	−0.004	0.996	0.988 to 1.004	0.337				
HR (beats/min)	0.015	1.015	0.999 to 1.031	0.059				
CVP (mm Hg)	0.006	1.006	0.932 to 1.086	0.882				
Mean lactate (mmol/L)	0.056	1.061	0.977 to 1.152	0.161				
Blood product transfused (unit)								
Packed red blood cells	0.033	1.034	1.011 to 1.057	0.003				
Fresh frozen plasma	0.041	1.042	1.014 to 1.071	0.003				
Platelet concentrate	−0.003	0.997	0.983 to 1.011	0.655				

Continued

Table 2 Continued

	Univariate analyses				Multivariate analyses			
	β	OR	95% CI	P value	β	OR	95% CI	P value
Hourly fluid infusion (mL/kg/hour)	0.01	1.097	0.992 to 1.028	0.295				
Hourly urine output (mL/kg/hour)	-0.503	0.605	0.474 to 0.771	<0.001	-0.446	0.64	0.499 to 0.821	<0.001
Donor graft factors								
Age (years)	0.006	1.006	0.987 to 1.025	0.543				
Sex (male)	-0.385	0.68	0.428 to 1.083	0.104				
GRWR (%)	0.081	1.084	0.983 to 1.196	0.107				
Graft ischaemic time (min)	0.001	1.001	1.000 to 1.002	0.03				
Fatty change (%)	0.028	1.028	0.999 to 1.058	0.055	0.031	1.032	1.001 to 1.064	0.045

AKI, acute kidney injury; CVP, central venous pressure; GRWR, graft recipient weight ratio; HR, heart rate; MBP, mean blood pressure; MELD, model for end-stage liver disease.

Analysis using alternative cut-offs for high vitamin B₁₂

Patients were divided into low and high vitamin B₁₂ level groups using 1300pg/mL as an alternative cut-off value for AKI development (AUC: 0.659, 95% CI: 0.519 to 0.623, sensitivity: 71.3%, specificity: 51.14%, $p < 0.001$). After PS matching with adjustment for the PS (table 6), a high serum vitamin B₁₂ level (>1300pg/mL) was also associated with a risk for AKI, and the risk was 3.2-fold higher in patients with high vitamin B₁₂ levels than in those with normal vitamin B₁₂ levels.

Correlations between vitamin B₁₂ level and inflammatory markers in PS-matched patients

Vitamin B₁₂ level was significantly associated with inflammatory markers, including CRP, WBC and albumin, in PS-matched patients ($p < 0.001$, $p = 0.005$ and $p = 0.002$, respectively).

Figure 2 Comparison of serum vitamin B₁₂ by acute kidney injury (AKI) stage in patients undergoing living donor liver transplantation (LDLT). The box plots show the median (line in the middle of the box), IQR (box) and 5th and 95th percentiles (whiskers). * $P < 0.05$ compared with normal kidney function.

Comparison of postoperative outcomes

Among all patients, postoperative AKI was associated with mortality, EAD and infection ($p = 0.005$, $p = 0.001$ and $p = 0.029$, respectively). In addition, AKI was associated with length of ICU stay and hospital stay ($p = 0.001$ and $p = 0.002$, respectively).

Among PS-matched patients, there were no significant differences in complications, including ICU stay, hospital stay, infection, graft rejection, EAD or mortality (table 7).

DISCUSSION

The main findings of our study are that preoperative factors (diabetes, vitamin B₁₂), intraoperative factors (hourly urine output) and donor factors (donor graft fatty change percentage) are associated with postoperative AKI in LDLT patients. Among PS-matched patients, high serum vitamin B₁₂ (>900pg/mL) with adjustment using PS was associated with risk for AKI, and the risk was 2.8-fold higher in patients with high vitamin B₁₂ than in those with normal vitamin B₁₂. The level of vitamin B₁₂ and the proportion of patients with high vitamin B₁₂ increased significantly according to the severity of AKI.

AKI is a common postoperative complication, and the incidence of AKI after LT ranges from 17% to 90%.^{12 28} Its pathogenesis may include inflammation, hypotension and perioperative nephrotoxin usage.²⁹⁻³¹ Aggravation of the systemic inflammatory response is an important contributor to the development of AKI.³² CRP may also act as a pathogenic mediator in the development of AKI.³³ Tang *et al* indicated that CRP promotes AKI by impairing G1/S-dependent tubular epithelial cell regeneration.³³ Sergio *et al* found that tubular epithelial cells interact with circulating inflammatory mediators, such as tumour necrosis factor alpha and IL-6, which are related to AKI.³⁴ Han *et al* showed that leukocytosis, a clinical sign of inflammation, is associated with the risk for AKI in critically ill patients.³⁵ Postoperative AKI is an important risk factor

Table 3 Comparison of preoperative and intraoperative recipient and donor graft factors before and after PS matching

Group	Before propensity score matched analysis					After propensity score matched analysis						
	Normal vitamin B ₁₂		High vitamin B ₁₂		P value	SD	Normal vitamin B ₁₂		High vitamin B ₁₂		P value	SD
	N	156	323	High vitamin B ₁₂			99	99				
Preoperative factors												
Age (years)		54 (49–59)	52 (47–59)	0.084	–0.126	55 (50–60)	54 (48–60)	0.395	–0.105			
Sex (male)		116 (74.4%)	215 (66.6%)	0.084	–0.165	70 (70.7%)	67 (67.7%)	0.644	–0.064			
Body mass index (kg/m ²)		23.9 (22.3–26.0)	24.4 (22.2–27)	0.146	0.164	24.2 (22.7–26.2)	24.2 (21.9–26.5)	0.695	–0.049			
Nephrotoxic drug exposure		17 (10.9%)	27 (8.4%)	0.367	–0.092	11 (11.1%)	13 (13.1%)	0.663	0.073			
Calcineurin inhibitor level		7.4 (6.5–8.7)	7.3 (5.8–8.9)	0.95	0.051	7.5 (6.7–8.8)	7.3 (6.5–9.2)	0.879	0.016			
Diabetes		38 (24.4%)	87 (26.9%)	0.547	0.058	29 (29.3%)	26 (26.3%)	0.634	–0.068			
Hypertension		34 (21.8%)	60 (18.6%)	0.406	–0.083	24 (24.2%)	22 (22.2%)	0.736	–0.052			
MELD		14.5 (9–25)	14 (9–23)	0.39	0.983	10 (8–14)	12 (9–15)	0.073	0.185			
Encephalopathy		5 (3.2%)	27 (8.4%)	0.034	0.186	4 (4.0%)	7 (7.1%)	0.352	0.109			
Varix		40 (25.6%)	84 (26%)	0.932	0.008	28 (28.3%)	25 (25.3%)	0.63	–0.069			
Ascites		49 (31.4%)	185 (57.3%)	<0.001	0.522	39 (39.4%)	39 (39.4%)	1	0			
Ejection fraction		64 (62–67)	64.54 (62–67)	0.74	0.045	64.5 (62–67)	64.5 (62–67)	0.851	0.026			
Diastolic dysfunction		80 (51.3%)	144 (44.6%)	0.168	–0.135	48 (48.5%)	47 (47.5%)	0.887	–0.02			
Laboratory variables												
Haemoglobin (g/L)		108 (91–124)	92 (80–108)	<0.001	–0.609	100 (85–120)	101 (87–118)	0.82	0.007			
White blood cell count (×10 ⁹ /L)		3.4 (2.4–5.0)	4.5 (3.0–7.7)	<0.001	0.4	3.3 (2.4–5.0)	3.9 (2.8–5.7)	0.121	0.189			
Albumin (g/dL)		3.3 (2.8–3.8)	2.9 (2.6–3.3)	<0.001	0.034	3.1 (2.7–3.8)	3.0 (2.7–3.4)	0.072	0.101			
Platelet count (×10 ⁹ /L)		72 (52.3–119.8)	57 (41–85)	<0.001	–0.335	64 (51–103)	67 (46–105)	0.988	0.12			
Sodium (mEq/L)		141 (138–142)	138 (134–141)	<0.001	–0.462	140 (136–142)	140 (135–141)	0.1	–0.142			
Potassium (mEq/L)		4 (3.7–4.2)	4 (3.6–4.4)	0.864	0.05	4 (3.7–4.2)	4.1 (3.8–4.4)	0.396	–0.001			
Calcium (mEq/L)		8.4 (8.1–8.8)	8.4 (7.9–8.8)	0.339	0.043	8.4 (7.9–8.8)	8.3 (7.9–8.7)	0.47	–0.02			
Glucose (mg/dL)		103 (91–126)	110 (92–142)	0.027	0.203	107 (89–130)	106 (93–126)	0.999	–0.113			
Creatinine (mg/dL)		0.84 (0.69–0.96)	0.85 (0.65–1.31)	0.14	0.238	0.84 (0.68–1.06)	0.78 (0.63–1.02)	0.423	0.147			
Lactate (mg/dL)		3.7 (3.0–4.6)	3.6 (2.8–4.9)	0.567	–0.017	3.6 (3.0–4.6)	3.6 (2.7–4.9)	0.432	–0.034			
Ammonia		90 (65–140.75)	98 (66–155)	0.485	0.032	96 (66–145)	97 (61–145)	0.91	–0.084			
Intraoperative factors												
Total surgery duration (min)		513 (455–593)	510 (460–570)	0.699	–0.108	510 (450–575)	500 (455–585)	0.9	0.01			
Severe PRS (class >1)		76 (48.7%)	176 (54.5%)	0.236	0.116	49 (49.5%)	44 (44.4%)	0.476	0.101			
Average of vital signs												
MBP (mm Hg)		76.9 (71.5–84.3)	76 (69.4–82.4)	0.053	0.058	76.9 (71.6–84.3)	76 (71–84)	0.401	–0.005			
HR (beats/min)		85.8 (77.8–95)	88 (80.8–97.3)	0.019	0.192	87 (80–97.3)	88 (79.5–96.0)	0.69	0.033			
CVP (mm Hg)		9 (7.5–10.5)	9 (7.5–10.5)	0.522	0.124	9 (7.5–10.5)	9 (7.5–10.8)	0.889	0.06			

Continued

Table 3 Continued

Group	Before propensity score matched analysis				After propensity score matched analysis			
	Normal vitamin B ₁₂		High vitamin B ₁₂		Normal vitamin B ₁₂		High vitamin B ₁₂	
	N	156	323	P value	SD	99	99	P value
Blood product transfusion (unit)								
Packed red blood cells		5 (2–12)	9 (5–15)	<0.001	0.349	5 (3–1)	4 (6–11)	0.313
Fresh frozen plasma		5 (3–7)	9 (5–13)	<0.001	0.496	5 (3–9)	7 (4–10)	0.046
Platelet concentrate		0 (0–6)	6 (0–12)	<0.001	0.219	4 (0–6)	5 (0–12)	0.307
Hourly fluid infusion (mL/kg/hour)		9.6 (7.2–11.5)	9.4 (6.5–13.1)	0.551	0.12	9.2 (6.4–12.7)	10.1 (8.2–13.1)	0.485
Hourly urine output (mL/kg/hour)		1.7 (0.9–2.5)	1.1 (0.5–1.8)	<0.001	–0.564	1.7 (0.8–2.3)	1.3 (0.8–2.3)	0.184
Donor-graft factors								
Age (years)		31 (25–41)	34 (17–41)	0.229	0.068	34 (25–42)	32 (25–41)	0.653
Sex (male)		64 (40.3%)	95 (29.4%)	0.011	–0.254	39 (39.4%)	40 (40.4%)	0.891
GRWR (%)		1.2 (1.1–1.6)	1.3 (1.0–1.8)	0.361	0.035	1.3 (1.1–1.6)	1.3 (1.1–1.7)	0.767
Graft ischaemic time (min)		102.5 (60–182.8)	127 (83–182.8)	0.003	0.093	104 (64–182.8)	106 (73–182.8)	0.46
Fatty change (%)		3.8 (0–5)	4.6 (1–5)	0.397	0.176	5 (1–5)	4.6 (1–5)	0.179

Values are expressed as medians (IQR) or numbers (%).

CVP, central venous pressure; GRWR, graft recipient weight ratio; HR, heart rate; MBP, mean blood pressure; MELD, model for end-stage liver disease; PRS, postreperfusion syndrome.

Table 4 Comparison of proportions in PS-matched patients by normal kidney function, mild AKI and moderate-to-severe AKI according to vitamin B₁₂ level

Group	Normal vitamin B ₁₂ (200–900 pg/mL)	High vitamin B ₁₂ (>900 pg/mL)	P value
n	99	99	0.015
Normal kidney function	88 (88.9%)	72 (72.7%)	
Mild AKI (stage 1)	8 (8.1%)	19 (19.2%)	
Moderate-to-severe AKI (stage 2/3)	3 (3.0%)	8 (8.1%)	

Values are frequencies (percentage).

AKI, acute kidney injury; PS, propensity score.

associated with morbidity and mortality after LDLT.^{36–38}

Therefore, it is important to predict the development of postoperative AKI in patients undergoing major surgery, in particular LDLT. In our study, the AKI group had a higher incidence of EAD and infection, longer ICU and hospital stays, and worse overall patient survival than the non-AKI group.

Vitamin B₁₂ is a water-soluble vitamin that plays an important role in maintaining cell function, blood cell formation and homocysteine metabolism.¹¹ Serum vitamin B₁₂ is usually maintained within the range of 200–900 pg/mL.^{16 39 40} Although vitamin B₁₂ deficiency is a well-known pathological condition that can cause haematological and neurological disorders or coronary artery disease,⁴¹ high vitamin B₁₂ (>900 pg/mL) is also associated with systemic inflammatory response syndrome and impaired hepatic and/or renal function.^{15 41} In critically ill or elderly patients, high vitamin B₁₂ is significantly related to increased morbidity and mortality.^{19 20 41–43} Because it is stored mainly in the liver, vitamin B₁₂ increases with the severity of hepatic injury.^{15 44} In patients with cirrhosis, high vitamin B₁₂ is associated with mortality. In patients with acute-on-chronic liver failure, high vitamin B₁₂ is correlated with the severity of hepatic disease and with mortality.⁴⁵ Serum vitamin B₁₂ increases with Child-Pugh score in patients with viral hepatitis and is an independent predictor of patient survival.⁴⁶

High vitamin B₁₂ is related to impaired kidney function due to impaired clearance of transcobalamin, the transporter of vitamin B₁₂.^{11 13 15 16} In addition, because vitamin B₁₂ uptake by mononuclear cells decreases in patients with end-stage renal disease, high vitamin B₁₂ is found in such patients.^{11 47} Although the role of vitamin B₁₂ in AKI is unclear, elevated vitamin B₁₂ is significantly associated with the severity of inflammation and may serve as a blood marker for AKI. This result is supported by previous studies showing an association between elevated vitamin B₁₂ levels and systemic inflammation. A study by Corcoran *et al* indicated that elevated vitamin B₁₂ is correlated with higher levels of CRP in ICU patients.¹⁷ Similarly, Philippe *et al* found that elevated vitamin B₁₂ is related to CRP in patients with cancer.¹⁸ Vitamin B₁₂ toxicity may also be

Table 5 Associations between high vitamin B₁₂ and postoperative AKI in the entire study population and in PS-matched patients

	β	OR	95% CI	P value
Entire patient population (n=479)				
High vitamin B ₁₂ (vs normal vitamin B ₁₂) adjusted for PS	0.750	2.117	1.099 to 4.076	0.025
PS-matched patients (n=198)				
High vitamin B ₁₂ (vs normal vitamin B ₁₂) adjusted for PS	1.060	2.888	1.320 to 6.315	0.008

AKI, acute kidney injury; PS, propensity score.

related to renal injury. In a multicentre study by House *et al*, high doses of B vitamins containing vitamin B₁₂ (1 mg/day) decreased GFR in patients with diabetic nephropathy.⁴⁸ In that study, serum B vitamins were very high in the B vitamin group. The authors suggested that the accumulation of folate and vitamin B₁₂ due to reduced renal function can result in vitamin toxicity. One study examined the use of folic acid and B vitamins to decrease homocysteine levels in vascular disease (HOPE-2) and found that high-dose B vitamin supplements did not affect renal dysfunction.⁴⁹ However, mean serum vitamin B₁₂ was within the normal range in the supplement group. In our study, mean serum vitamin B₁₂ in the AKI group was >2000 pg/mL, which suggests an association between vitamin B₁₂ toxicity and the development of renal injury.

In the current study, diabetes was a preoperative risk factor for the development of postoperative AKI. Although the mechanism behind the development of AKI in diabetic kidney remains unknown, some reports indicate that diabetic kidneys lack proper recovery of renal perfusion after ischaemia. In those studies, higher apoptosis of proximal tubular cells and delayed reperfusion in cortex were suggested as possible causes of renal ischaemia reperfusion injury in diabetic kidneys.^{50 51}

Table 6 Association of high vitamin B₁₂ levels with postoperative AKI development, using 1300 pg/mL as the cut-off value, in the entire and PS-matched patients

	β	OR	95% CI	P value
In all patients (n=479)				
High vitamin B ₁₂ (vs normal vitamin B ₁₂) adjusted for PS	1.198	3.313	2.104 to 5.218	<0.001
In the PS-matched patients (n=190)				
High vitamin B ₁₂ (vs normal vitamin B ₁₂) adjusted for PS	1.164	3.204	1.554 to 6.605	0.002

AKI, acute kidney injury; PS, propensity score.

Table 7 Comparison of postoperative outcomes between the normal vitamin B₁₂ group and high vitamin B₁₂ group in PS-matched patients

Group	Normal vitamin B ₁₂ (200–900 pg/mL)	High vitamin B ₁₂ (>900 pg/mL)	P value
n	99	99	
ICU stay (days)	7 (5–7)	7 (5–7)	0.653
Hospital stay (days)	23 (21–31)	26 (21–34)	0.202
Infection	7 (7.1%)	5 (5.1%)	0.551
Graft rejection	16 (16.2%)	19 (19.2%)	0.576
Early allograft dysfunction	9 (9.1%)	9 (9.1%)	1.000
Overall patient mortality	12 (12.1%)	13 (13.1%)	0.831

Values are medians (IQR) or frequencies (percentage). ICU, intensive care unit; PS, propensity score.

Decreased hourly urine output during surgery was independently associated with postoperative AKI in the current study. Decreased urine output usually indicates hypotension or hypovolemia, which are related to decreased perfusion to the afferent arteriole of the glomerulus.⁵² Mizota *et al* reported that intraoperative oliguria was significantly associated with increased risk for postoperative AKI in patients undergoing major abdominal surgery.⁵³

Graft steatosis is a risk factor for postoperative morbidity and mortality. Marsman *et al* reported that the use of liver grafts containing up to 30% fat is associated with lower patient and graft survival.⁵⁴ Steatosis of liver graft is also associated with EAD and AKI.⁸ Multivariate analyses in the present study showed that donor graft fat content was associated with the development of AKI after liver transplantation. In addition, more EAD occurred in the AKI group than in the non-AKI group.

Our study has several limitations. First, although confounder imbalance was corrected between the normal vitamin B₁₂ group and high vitamin B₁₂ group after PS matching, hidden biases due to the retrospective study design may have been present. Second, the mechanism underlying the association between high serum vitamin B₁₂ and postoperative AKI is still unknown. Although vitamin B₁₂ is associated with systemic inflammation, further studies are required to identify the specific pathways of the effects of vitamin B₁₂ on renal injury. Further research on vitamin B₁₂ toxicity in the kidney is also needed. Third, there are important differences between liver transplants from living donors and those from deceased donors. In previous studies, liver grafts from deceased donors were more than twice as strongly associated with postoperative AKI than grafts from living donors.⁵⁵ Therefore, the association between vitamin B₁₂ and AKI may differ according to the graft donor. Additional studies are required to

validate the predictive role of vitamin B₁₂ in LT from living donors and from deceased donors.

CONCLUSION

AKI, a common postoperative complication in patients undergoing liver transplantation, is associated with patient morbidity and mortality. Thus, the risk for AKI should be evaluated before liver transplantation. Our results may increase the accuracy of risk stratification of postoperative AKI by introducing vitamin B₁₂ as a risk factor for patients undergoing LDLT. Predictive models of AKI that include preoperative vitamin B₁₂ and other perioperative factors (eg, diabetes, intraoperative hourly urine output, graft steatosis) will help predict AKI and enable early management of patients.

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