Predictive role of vitamin B$_{12}$ 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 B$_{12}$ 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 B$_{12}$ supplementation due to alcoholism, low vitamin B$_{12}$ (<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 B$_{12}$ (>900 pg/mL) and postoperative AKI was evaluated.

Results Preoperative vitamin B$_{12}$ was higher in the AKI group. Potentially significant perioperative factors from univariate analyses were entered into multivariate analyses, including preoperative factors (vitamin B$_{12}$, 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 B$_{12}$ (>900 pg/mL) was associated with risk for AKI, and the risk was 2.8-fold higher in patients with high vitamin B$_{12}$ than in those with normal vitamin B$_{12}$. Higher vitamin B$_{12}$ was also related to a higher AKI stage. In addition, inflammatory factors (C reactive protein, white blood cells and albumin) were associated with vitamin B$_{12}$ level.

Conclusions Our study may improve the accuracy of predicting postoperative AKI by introducing preoperative vitamin B$_{12}$ 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 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). 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. In addition, proinflammatory markers such as interleukin (IL)-6 are associated with AKI after LDLT. Many studies have reported that AKI negatively affects postoperative outcomes, resulting in a prolonged hospital stay, early graft dysfunction, infection and poor patient survival. 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. 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. Vitamin $B_{12}$ 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. Although there have been numerous studies on vitamin deficiency, including vitamin $B_{12}$ deficiency, few studies have focused on patients with high vitamin $B_{12}$ and the association between preoperative vitamin $B_{12}$ and postoperative AKI in LDLT patients. However, the importance of high vitamin $B_{12}$ in the clinical setting has recently emerged. High vitamin $B_{12}$ is related to hepatic disease, haematological disorders such as leukaemia and polycythemia vera and renal impairment. There have also been reports of an association between high vitamin $B_{12}$ and systemic inflammation, in particular CRP. In studies of intensive care unit (ICU) patients, elevated vitamin $B_{12}$ was associated with mortality and length of hospital stay.

We investigated the association between high serum vitamin $B_{12}$ 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 vitamin $B_{12}$ supplementation due to alcoholics, platelet and cryoprecipitate) were also transfused based on laboratory findings or thromboelastography.

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

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) $\geq 0.3\text{mg/dL}$ (in 48 hours) or 1.5–1.9 times baseline (in 7 days) or urine output $<0.5\text{mg/dL}$ for 6–12 hours; stage 2, 2.0–2.9 times by baseline SCr or urine output $<0.5\text{mg/dL}$ for $\geq 12$ hours; stage 3, 3.0 or more times baseline SCr, increase in SCr $\geq 4.0\text{mg/dL}$, beginning of renal replacement therapy regardless of previous KDIGO stage or urine output $<0.3\text{mg/dL}$ for $\geq 24$ hours. Based on these definitions, AKI was classified as stage 1, stage 2 or stage 3. For the comparison of vitamin $B_{12}$ by stage, we collapsed stages 2 and 3 into one respectively. The surgical procedure and anaesthetic management were described in detail in our previous studies. 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) $\geq 65\text{mm Hg}$ and central venous pressure (CVP) $\leq 10\text{mm Hg}$) under multiple haemodynamic monitoring. Based on transfusion guidelines, packed red blood cells (PRBC) were transfused to reach a hematocrit $\geq 25\%$, and coagulation factors (fresh frozen plasma (FFP), single donor platelet and cryoprecipitate) were also transfused based on laboratory findings or thromboelastography.

Living donor liver transplantation

Surgery and anaesthesia were consistently provided by expert transplant surgeons and anesthesiologists.
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/m²)              | 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 (×10⁹/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 (×10⁹/L)              | 64 (47–104.75) | 56 (39–76) | 0.002     |
| Vitamin B₁₂ (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
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), varix and ascites), transthoracic echocardiography (ejection fraction and diastolic dysfunction) and laboratory variables (white blood cell (WBC) count, albumin, platelet count, sodium, potassium, calcium, glucose, creatinine, ammonia). Intraoperative recipient factors included surgical duration, PRS, 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 \( \geq 10 \text{ mg/dL} \) or international normalised ratio \( \geq 1.6 \) on postoperative day 7 and aspartate transaminase or alanine transaminase \( \geq 2000 \text{ IU/mL} \) during the first week.

**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 \( \chi^2 \) 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 \( \chi^2 \) 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

| 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  |

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.

Table 1
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 $B_{12}$ 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 149–24 and 64.5 (62–67). The prevalence of patients with exposure to nephrotoxic drugs such as non-steroidal anti-inflammatory drugs, blockers and diuretics was similar in the AKI and non-AKI groups.

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

Preoperative BMI, DM, MELD, ascites and vitamin $B_{12}$ 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 $B_{12}$) 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 $B_{12}$ (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 $B_{12}$ (>900 pg/dL) developing AKI was about threefold higher than that of patients with normal vitamin $B_{12}$ (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 $B_{12}$ (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 $B_{12}$ level

The overall incidence of AKI was higher in patients with high vitamin $B_{12}$ levels than in those with normal vitamin $B_{12}$ levels. The severity of kidney injury, according to the KDIGO stage, was more aggravated in the high vitamin $B_{12}$ group than in the normal vitamin $B_{12}$ group (table 4 and online supplemental additional file 4).

Comparison of vitamin $B_{12}$ level by AKI stage in PS-matched patients

Patients with a higher AKI stage exhibited higher median and IQR values of vitamin $B_{12}$ (figure 2). Median (IQR) vitamin $B_{12}$ 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 $B_{12}$ and postoperative AKI in PS-matched patients

High vitamin $B_{12}$ was associated with the development of AKI in the entire study population and in PS-matched patients (table 5). After PS adjustment, high vitamin $B_{12}$ remained an independent factor related to AKI (p=0.008).
Table 2  Associations between preoperative and intraoperative recipient and donor factors and postoperative development of AKI

| Preoperative recipient factors | Univariate analyses | Multivariate analyses |
|-------------------------------|---------------------|----------------------|
|                               | β       | OR   | 95% CI   | P value | β       | OR   | 95% CI   | P value |
| 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/m²)       | 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        | 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 (×10⁹/L)       | -0.006  | 0.994 | 0.989 to 0.998 | 0.009   |          |       |          |         |
| Vitamin B₁₂ (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 | Univariate analyses | Multivariate analyses |
|---------------------------------|---------------------|----------------------|
| 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
Analysis using alternative cut-offs for high vitamin B₁₂

Patients were divided into low and high vitamin B₁₂ level groups using 1300 pg/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 (>1300 pg/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).

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 (>900 pg/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 levels.

AKI is a common postoperative complication, and the incidence of AKI after LT ranges from 17% to 90%. Its pathogenesis may include inflammation, hypotension and perioperative nephrotoxin usage. Aggravation of the systemic inflammatory response is an important contributor to the development of AKI. CRP may also act as a pathogenic mediator in the development of AKI. Tang et al indicated that CRP promotes AKI by impairing G1/S-dependent tubular epithelial cell regeneration. 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. Han et al showed that leukocytosis, a clinical sign of inflammation, is associated with the risk for AKI in critically ill patients. 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<sub>12</sub> | High vitamin B<sub>12</sub> | Normal vitamin B<sub>12</sub> | High vitamin B<sub>12</sub> |
|                           | P value | SD | P value | SD |
| Preoperative factors      |          |     |          |     |
| Age (years)               | 54 (49–59) | 52 (47–59) | 0.084 | −0.126 |
| Sex (male)                | 116 (74.4%) | 215 (66.6%) | 0.084 | −0.165 |
| Body mass index (kg/m<sup>2</sup>) | 23.9 (22.3–26.0) | 24.4 (22.2–27) | 0.146 | 0.164 |
| Nephrotoxic drug exposure | 17 (10.9%) | 27 (8.4%) | 0.367 | −0.092 |
| Calcineurin inhibitor level | 7.4 (6.5–8.7) | 7.3 (5.8–8.9) | 0.95 | 0.051 |
| Diabetes                  | 38 (24.4%) | 87 (26.9%) | 0.547 | 0.058 |
| Hypertension              | 34 (21.8%) | 60 (18.6%) | 0.406 | −0.083 |
| MELD                      | 14.5 (9–25) | 14 (9–23) | 0.39 | 0.983 |
| Encephalopathy            | 5 (3.2%) | 27 (8.4%) | 0.034 | 0.186 |
| Varix                     | 40 (25.6%) | 84 (26%) | 0.932 | 0.008 |
| Ascites                   | 49 (31.4%) | 185 (57.3%) | <0.001 | 0.522 |
| Ejection fraction         | 64 (62–67) | 64.5 (62–67) | 0.74 | 0.045 |
| Diastolic dysfunction     | 80 (51.3%) | 144 (44.6%) | 0.168 | −0.135 |
| Laboratory variables      |          |     |          |     |
| Haemoglobin (g/L)         | 108 (81–124) | 92 (80–108) | <0.001 | −0.609 |
| White blood cell count (<10<sup>9</sup>/L) | 3.4 (2.4–5.0) | 4.5 (3.0–7.7) | <0.001 | 0.4 |
| Albumin (g/dL)            | 3.3 (2.8–3.8) | 2.9 (2.6–3.3) | <0.001 | 0.034 |
| Platelet count (<10<sup>12</sup>/L) | 72 (52.3–119.8) | 57 (41–85) | <0.001 | −0.335 |
| Sodium (mEq/L)            | 141 (138–142) | 138 (134–141) | <0.001 | −0.462 |
| Potassium (mEq/L)         | 4 (3.7–4.2) | 4 (3.6–4.4) | 0.864 | 0.05 |
| Calcium (mEq/L)           | 8.4 (8.1–8.8) | 8.4 (7.9–8.8) | 0.339 | 0.043 |
| Glucose (mg/dL)           | 103 (81–126) | 110 (92–124) | 0.027 | 0.203 |
| Creatinine (mg/dL)        | 0.84 (0.69–0.96) | 0.85 (0.65–1.31) | 0.14 | 0.238 |
| Lactate (mg/dL)           | 3.7 (3.0–4.6) | 3.6 (2.8–4.9) | 0.567 | −0.017 |
| Ammonia                   | 90 (65–140.75) | 98 (66–155) | 0.485 | 0.032 |
| Intraoperative factors    |          |     |          |     |
| Total surgery duration (min) | 513 (455–593) | 510 (460–570) | 0.699 | −0.108 |
| Severe PRS (class >1)     | 76 (48.7%) | 176 (54.5%) | 0.236 | 0.116 |
| Average of vital signs    |          |     |          |     |
| MBP (mm Hg)               | 76.9 (71.5–84.3) | 76 (69.4–82.4) | 0.053 | 0.058 |
| HR (beats/min)            | 85.8 (77.8–95) | 88 (80.8–97.3) | 0.019 | 0.192 |
| CVP (mm Hg)               | 9 (7.5–10.5) | 9 (7.5–10.5) | 0.522 | 0.124 |
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 B\textsubscript{12} is a water-soluble vitamin that plays an important role in maintaining cell function, blood cell formation and homocysteine metabolism. 11 Serum vitamin B\textsubscript{12} is usually maintained within the range of 200–900 pg/mL. 16 39 40 Although vitamin B\textsubscript{12} deficiency is a well-known pathological condition that can cause haematological and neurological disorders or coronary artery disease, 41 high vitamin B\textsubscript{12} (>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 B\textsubscript{12} is significantly related to increased morbidity and mortality. 19 20 41–43 Because it is stored mainly in the liver, vitamin B\textsubscript{12} increases with the severity of hepatic injury. 15 44 In patients with cirrhosis, high vitamin B\textsubscript{12} is associated with mortality. 45 Serum vitamin B\textsubscript{12} increases with Child-Pugh score in patients with viral hepatitis and is an independent predictor of patient survival. 46

High vitamin B\textsubscript{12} is related to impaired kidney function due to impaired clearance of transcobalamin, the transporter of vitamin B\textsubscript{12}. 11 13 15 16 In addition, because vitamin B\textsubscript{12} uptake by mononuclear cells decreases in patients with end-stage renal disease, high vitamin B\textsubscript{12} is found in such patients. 11 47 Although the role of vitamin B\textsubscript{12} in AKI is unclear, elevated vitamin B\textsubscript{12} 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 B\textsubscript{12} levels and systemic inflammation. A study by Corcoran et al indicated that elevated vitamin B\textsubscript{12} is correlated with higher levels of CRP in ICU patients. 17 Similarly, Philippe et al found that elevated vitamin B\textsubscript{12} is related to CRP in patients with cancer. 18 Vitamin B\textsubscript{12} toxicity may also be

| Group                  | Normal vitamin B\textsubscript{12} (200–900 pg/mL) | High vitamin B\textsubscript{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  | 3 (3.0%)                                         | 8 (8.1%)                                      |         |

Values are frequencies (percentage). 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

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

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### Table 5

| Group | β | OR  | 95% CI | P value |
|-------|---|-----|--------|---------|
| Entire patient population (n=479) | 0.750 | 2.117 | 1.099 to 4.076 | 0.025 |
| PS-matched patients (n=198) | 1.060 | 2.888 | 1.320 to 6.315 | 0.008 |

AKI, acute kidney injury; PS, propensity score.

### Table 6

| Group | β | OR  | 95% CI | P value |
|-------|---|-----|--------|---------|
| High vitamin B₁₂ (vs normal vitamin B₁₂) | 1.198 | 3.313 | 2.104 to 5.218 | <0.001 |
| High vitamin B₁₂ (vs normal vitamin B₁₂) | 1.164 | 3.204 | 1.554 to 6.605 | 0.002 |

AKI, acute kidney injury; PS, propensity score.
validate the predictive role of vitamin B$_{12}$ 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 B$_{12}$ as a risk factor for patients undergoing LDLT. Predictive models of AKI that include preoperative vitamin B$_{12}$ and other perioperative factors (e.g., diabetes, intraoperative hourly urine output, graft steatosis) will help predict AKI and enable early management of patients.

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