BMJ Open

Predictive role of vitamin B_{12} in acute kidney injury in living donor liver transplantation: a propensity score matching analysis

Jaesik Park ,[1] Jung Hee Choi,[1] Ho Joong Choi,[2] Sang Hyun Hong ,[1] Chul Soo Park,[1] Jong Ho Choi,[1] Min Suk Chae [1]

To cite: Park J, Choi JH, Choi HJ, *et al*. Predictive role of vitamin B_{12} in acute kidney injury in living donor liver transplantation: a propensity score matching analysis. *BMJ Open* 2020;**10**:e038990. doi:10.1136/bmjopen-2020-038990

► Prepublication history and additional materials for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-038990).

Received 31 March 2020
Revised 22 September 2020
Accepted 12 October 2020

[1]Anesthesiology and Pain Medicine, Catholic University of Korea College of Medicine, Seoul, The Republic of Korea
[2]Surgery, Catholic University of Korea College of Medicine, Seoul, The Republic of Korea

Correspondence to
Dr Min Suk Chae;
shscms@gmail.com

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.

Strengths and limitations of this study

- ► This is the first analysis of the association between high vitamin B_{12} and morbidity after liver transplantation.
- ► One-to-one propensity score (PS) matching was performed to correct for confounder imbalance between the normal vitamin B_{12} group and high vitamin B_{12} group.
- ► Our study could improve the accuracy of predicting postoperative acute kidney injury (AKI) by introducing preoperative vitamin B_{12} into risk assessments for patients undergoing living donor liver transplantation.
- ► Further research is needed to identify the mechanism behind the relationship between vitamin B_{12} 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 B_{12} in liver transplantation from deceased donors.

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).[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 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.[11 12] 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.[13 14] High vitamin B_{12} is related to hepatic disease, haematological disorders such as leukaemia and polycythemia vera[15] and renal impairment.[11 16] There have also been reports of an association between high vitamin B_{12} and systemic inflammation, in particular CRP.[17 18] In studies of intensive care unit (ICU) patients, elevated vitamin B_{12} was associated with mortality[19 20] and length of hospital stay.[14]

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 kidney dysfunction (eg, dialysis, chronic kidney disease (<60 mL/min/1.73 m^2), hepatorenal syndrome), a history of vitamin B_{12} supplementation due to alcoholics, low vitamin B_{12} (<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 B_{12} 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 B_{12}

As a part of preoperative patient assessment, laboratory variables, including vitamin B_{12}, 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 B_{12} group and high vitamin B_{12} 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 B_{12} (>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 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/m^2. 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 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).

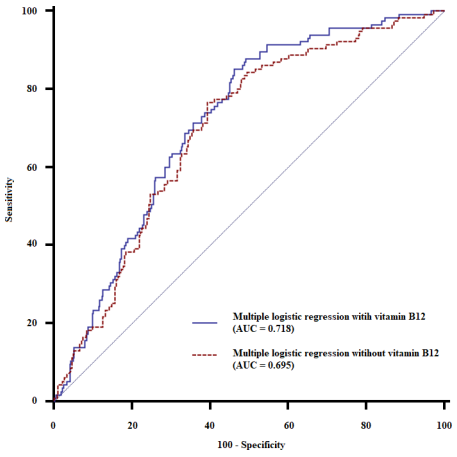

Figure 1 Comparison of area under the curve (AUC)-receiver operating characteristic (ROC) of multiple logistic regressions models with or without inclusion of vitamin B_{12}.

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 B_{12}

Patients were divided into low and high vitamin B_{12} 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 B_{12} 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 B_{12} levels than in those with normal vitamin B_{12} levels.

Correlations between vitamin B_{12} level and inflammatory markers in PS-matched patients

Vitamin B_{12} 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).

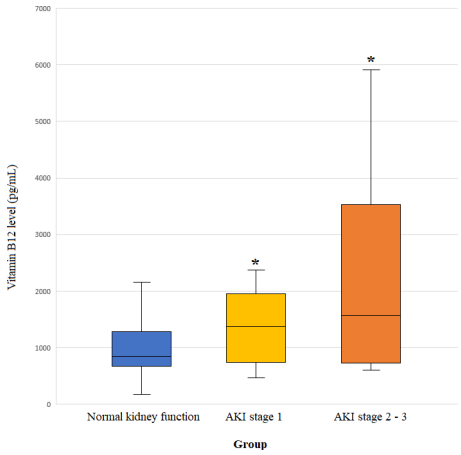

Figure 2 Comparison of serum vitamin B_{12} by acute kidney injury (AKI) stage in patients undergoing living donor liver transplantation (LDLT). The box plots show the median (line in the middle of the box), IQR (box) and 5th and 95th percentiles (whiskers). *P<0.05 compared with normal kidney function.

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 B_{12}), 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 B_{12} (>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 B_{12} than in those with normal vitamin B_{12}. The level of vitamin B_{12} and the proportion of patients with high vitamin B_{12} 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

	Before propensity score matched analysis				After propensity score matched analysis			
Group	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	SD
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	SD
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	0.025
Fresh frozen plasma	5 (3–7)	9 (5–13)	<0.001	0.496	5 (3–9)	7 (4–10)	0.046	0.124
Platelet concentrate	0 (0–6)	6 (0–12)	<0.001	0.219	4 (0–6)	5 (0–12)	0.307	0.092
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	0.086
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	−0.124
Donor-graft factors								
Age (years)	31 (25–41)	34 (17–41)	0.229	0.068	34 (25–42)	32 (25–41)	0.653	−0.061
Sex (male)	64 (40.3%)	95 (29.4%)	0.011	−0.254	39 (39.4%)	40 (40.4%)	0.891	0.022
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	−0.06
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	−0.01
Fatty change (%)	3.8 (0–5)	4.6 (1–5)	0.397	0.176	5 (1–5)	4.6 (1–5)	0.179	−0.091

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 B_{12} 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 B_{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_{12} is usually maintained within the range of 200–900 pg/mL.[16 39 40] Although vitamin B_{12} deficiency is a well-known pathological condition that can cause haematological and neurological disorders or coronary artery disease,[41] high vitamin B_{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_{12} is significantly related to increased morbidity and mortality.[19 20 41–43] Because it is stored mainly in the liver, vitamin B_{12} increases with the severity of hepatic injury.[15 44] In patients with cirrhosis, high vitamin B_{12} is associated with mortality. In patients with acute-on-chronic liver failure, high vitamin B_{12} is correlated with the severity of hepatic disease and with mortality.[45] Serum vitamin B_{12} increases with Child-Pugh score in patients with viral hepatitis and is an independent predictor of patient survival.[46]

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

Table 5 Associations between high vitamin B_{12} 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 B_{12} (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 B_{12} 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 B_{12} was within the normal range in the supplement group. In our study, mean serum vitamin B_{12} in the AKI group was >2000 pg/mL, which suggests an association between vitamin B_{12} 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 B_{12} 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 B_{12} group and high vitamin B_{12} 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 B_{12} group and high vitamin B_{12} 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 B_{12} and postoperative AKI is still unknown. Although vitamin B_{12} is associated with systemic inflammation, further studies are required to identify the specific pathways of the effects of vitamin B_{12} on renal injury. Further research on vitamin B_{12} 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 B_{12} and AKI may differ according to the graft donor. Additional studies are required to

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 (eg, diabetes, intraoperative hourly urine output, graft steatosis) will help predict AKI and enable early management of patients.

Acknowledgements The authors would like to thank Eunju Choi, Hyeji An and Hyunsook Yoo (Anesthesia Nursing Unit, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea) for their support and dedication.

Contributors JP and MSC were responsible for the study concept and design. JP wrote the manuscript. JP, JHC, HJC, SHH, CSP, JHC and MSC participated in the collection and interpretation of the data. All authors approved the final version of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The institutional review board of Seoul St. Mary's Hospital Ethics Committee approved this study for LDLT recipients (KC19RESI0214), and it was performed according to the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Jaesik Park http://orcid.org/0000-0001-5472-9567
Sang Hyun Hong http://orcid.org/0000-0002-7091-8963
Min Suk Chae http://orcid.org/0000-0002-1426-4651

REFERENCES

1 Rymarz A, Serwacki M, Rutkowski M, *et al*. Prevalence and predictors of acute renal injury in liver transplant recipients. *Transplant Proc* 2009;41:3123–5.
2 Wiesen P, Massion PB, Joris J, *et al*. Incidence and risk factors for early renal dysfunction after liver transplantation. *World J Transplant* 2016;6:220–32.
3 Cabezuelo JB, Ramírez P, Ríos A, *et al*. Risk factors of acute renal failure after liver transplantation. *Kidney Int* 2006;69:1073–80.
4 Abdel-Khalek EE, Alrefaey AK, Yassen AM, *et al*. Renal dysfunction after living-donor liver transplantation: experience with 500 cases. *J Transplant* 2018;2018:5910372
5 Murashima M, Nishimoto M, Kokubu M, *et al*. Inflammation as a predictor of acute kidney injury and mediator of higher mortality after acute kidney injury in non-cardiac surgery. *Sci Rep* 2019;9:20260.
6 Chae MS, Kim Y, Chung HS, *et al*. Predictive role of serum cytokine profiles in acute kidney injury after living donor liver transplantation. *Mediators Inflamm* 2018;2018:8256193
7 Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, *et al*. Cost and mortality associated with postoperative acute kidney injury. *Ann Surg* 2015;261:1207–14.
8 Wadei HM, Lee DD, Croome KP, *et al*. Early allograft dysfunction after liver transplantation is associated with short- and long-term kidney function impairment. *Am J Transplant* 2016;16:850–9.
9 Machado MN, Nakazone MA, Maia LN. Acute kidney injury based on KDIGO (kidney disease improving global outcomes) criteria in patients with elevated baseline serum creatinine undergoing cardiac surgery. *Rev Bras Cir Cardiovasc* 2014;29:299–307.
10 Tsai T-Y, Chien H, Tsai F-C, *et al*. Comparison of RIFLE, AKIN, and KDIGO classifications for assessing prognosis of patients on extracorporeal membrane oxygenation. *J Formos Med Assoc* 2017;116:844–51.
11 Capelli I, Cianciolo G, Gasperoni L, *et al*. Folic acid and vitamin B12 administration in CKD, why not? *Nutrients* 2019;11
12 Shimomura T, Mori E, Hirono N, *et al*. Development of Wernicke-Korsakoff syndrome after long intervals following gastrectomy. *Arch Neurol* 1998;55:1242–5.
13 Jammal M, Deneuville T, Mario N, *et al*. [High plasmatic concentration of vitamin B12: an indicator of hepatic diseases or tumors]. *Rev Med Interne* 2013;34:337–41.
14 Cappello S, Cereda E, Rondanelli M, *et al*. Elevated plasma vitamin B12 concentrations are independent predictors of in-hospital mortality in adult patients at nutritional risk. *Nutrients* 2016;9
15 Andrès E, Serraj K, Zhu J, *et al*. The pathophysiology of elevated vitamin B12 in clinical practice. *QJM* 2013;106:505–15.
16 Carmel R, Vasireddy H, Aurangzeb I, *et al*. High serum cobalamin levels in the clinical setting-clinical associations and holo-transcobalamin changes. *Clin Lab Haematol* 2001;23:365–71.
17 Corcoran TB, O'Neill MP, Webb SAR, *et al*. Inflammation, vitamin deficiencies and organ failure in critically ill patients. *Anaesth Intensive Care* 2009;37:740–7.
18 Geissbühler P, Mermillod B, Rapin CH. Elevated serum vitamin B12 levels associated with CRP as a predictive factor of mortality in palliative care cancer patients: a prospective study over five years. *J Pain Symptom Manage* 2000;20:93–103.
19 Moraes RB, Friedman G, Wawrzeniak IC, *et al*. Vitamin D deficiency is independently associated with mortality among critically ill patients. *Clinics* 2015;70:326–32.
20 Sviri S, Khalaila R, Daher S, *et al*. Increased vitamin B12 levels are associated with mortality in critically ill medical patients. *Clin Nutr* 2012;31:53–9.
21 Chae MS, Moon KU, Jung J-Y, *et al*. Perioperative loss of psoas muscle is associated with patient survival in living donor liver transplantation. *Liver Transpl* 2018;24:623–33.
22 American Society of Anesthesiologists Task Force on Perioperative Blood M. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task force on perioperative blood management. *Anesthesiology* 2015;122:241–75.
23 Hilmi I, Horton CN, Planinsic RM, *et al*. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. *Liver Transpl* 2008;14:504–8.
24 Cash WJ, McConville P, McDermott E, *et al*. Current concepts in the assessment and treatment of hepatic encephalopathy. *QJM* 2010;103:9–16.
25 Park J, Lee J, Kwon A, *et al*. The 2016 ASE/EACVI recommendations may be able to more accurately identify patients at risk for diastolic dysfunction in living donor liver transplantation. *PLoS One* 2019;14:e0215603.
26 Höroldt BS, Burattin M, Gunson BK, *et al*. Does the Banff rejection activity index predict outcome in patients with early acute cellular rejection following liver transplantation? *Liver Transpl* 2006;12:1144–51.
27 Olthoff KM, Kulik L, Samstein B, *et al*. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl* 2010;16:943–9.

28 Barri YM, Sanchez EQ, Jennings LW, *et al*. Acute kidney injury following liver transplantation: definition and outcome. *Liver Transpl* 2009;15:475–83.
29 Bell S, Ross VC, Zealley KA, *et al*. Management of post-operative acute kidney injury. *QJM* 2017;110:695–700.
30 Gameiro J, Fonseca JA, Neves M, *et al*. Acute kidney injury in major abdominal surgery: incidence, risk factors, pathogenesis and outcomes. *Ann Intensive Care* 2018;8:22.
31 Park JT. Postoperative acute kidney injury. *Korean J Anesthesiol* 2017;70:258–66.
32 Cantaluppi V, Quercia AD, Dellepiane S, *et al*. Interaction between systemic inflammation and renal tubular epithelial cells. *Nephrol Dial Transplant* 2014;29:2004–11.
33 Tang Y, Huang XR, Lv J, *et al*. C-reactive protein promotes acute kidney injury by impairing G1/S-dependent tubular epithelium cell regeneration. *Clin Sci* 2014;126:645–59.
34 Dellepiane S, Marengo M, Cantaluppi V. Detrimental cross-talk between sepsis and acute kidney injury: new pathogenic mechanisms, early biomarkers and targeted therapies. *Crit Care* 2016;20:61.
35 Han SS, Ahn SY, Ryu J, *et al*. U-shape relationship of white blood cells with acute kidney injury and mortality in critically ill patients. *Tohoku J Exp Med* 2014;232:177–85.
36 Rahman S, Davidson BR, Mallett SV. Early acute kidney injury after liver transplantation: predisposing factors and clinical implications. *World J Hepatol* 2017;9:823–32.
37 Thongprayoon C, Kaewput W, Thamcharoen N, *et al*. Incidence and impact of acute kidney injury after liver transplantation: a meta-analysis. *J Clin Med* 2019;8
38 de Haan JE, Hoorn EJ, de Geus HRH. Acute kidney injury after liver transplantation: recent insights and future perspectives. *Best Pract Res Clin Gastroenterol* 2017;31:161–9.
39 Trimarchi H, Forrester M, Schropp J, *et al*. Low initial vitamin B12 levels in Helicobacter pylori-positive patients on chronic hemodialysis. *Nephron Clin Pract* 2004;96:c28–32.
40 Al-Khamis FA. Serum vitamin B12 and thyroid hormone levels in Saudi patients with multiple sclerosis. *J Family Community Med* 2016;23:151–4.
41 Romain M, Sviri S, Linton DM, *et al*. The role of vitamin B12 in the critically ill-a review. *Anaesth Intensive Care* 2016;44:447–52.
42 Salles N, Herrmann F, Sakbani K, *et al*. High vitamin B12 level: a strong predictor of mortality in elderly inpatients. *J Am Geriatr Soc* 2005;53:917–8.
43 Tal S, Shavit Y, Stern F, *et al*. Association between vitamin B12 levels and mortality in hospitalized older adults. *J Am Geriatr Soc* 2010;58:523–6.
44 Stevenson TD, Beard MF. Serum vitamin B12 content in liver disease. *N Engl J Med* 1959;260:206–10.
45 Dou J, Xu W, Ye B, *et al*. Serum vitamin B12 levels as indicators of disease severity and mortality of patients with acute-on-chronic liver failure. *Clin Chim Acta* 2012;413:1809–12.
46 Sugihara T, Koda M, Okamoto T, *et al*. Falsely elevated serum vitamin B12 levels were associated with the severity and prognosis of chronic viral liver disease. *Yonago Acta Med* 2017;60:31–9.
47 Obeid R, Kuhlmann M, Kirsch C-M, *et al*. Cellular uptake of vitamin B12 in patients with chronic renal failure. *Nephron Clin Pract* 2005;99:c42–8.
48 House AA, Eliasziw M, Cattran DC, *et al*. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. *JAMA* 2010;303:1603–9.
49 Lonn E, Yusuf S, Arnold MJ, *et al*. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567–77.
50 Patschan D, Müller GA. Acute kidney injury in diabetes mellitus. *Int J Nephrol* 2016;2016:6232909
51 Habib SL. Diabetes and renal tubular cell apoptosis. *World J Diabetes* 2013;4:27–30.
52 Chenitz KB, Lane-Fall MB. Decreased urine output and acute kidney injury in the postanesthesia care unit. *Anesthesiol Clin* 2012;30:513–26.
53 Mizota T, Yamamoto Y, Hamada M, *et al*. Intraoperative oliguria predicts acute kidney injury after major abdominal surgery. *Br J Anaesth* 2017;119:1127–34.
54 Marsman WA, Wiesner RH, Rodriguez L, *et al*. Use of fatty donor liver is associated with diminished early patient and graft survival. *Transplantation* 1996;62:1246–51.
55 Hilmi IA, Damian D, Al-Khafaji A, *et al*. Acute kidney injury after orthotopic liver transplantation using living donor versus deceased donor grafts: a propensity score-matched analysis. *Liver Transpl* 2015;21:1179–85.