Perioperative risk factors for acute kidney injury after liver resection surgery: an historical cohort study

Facteurs de risque périopératoires de lésion rénale aiguë après résection hépatique: une étude de cohorte historique

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Abstract

Purpose This study aimed to identify the incidence and risk factors for acute kidney injury (AKI) after liver resection surgery and to clarify the relationship between postoperative AKI and outcome.

Methods We conducted a historical cohort study of patients who underwent liver resection surgery with sevoflurane anesthesia from January 2004 to October 2011. Acute kidney injury was diagnosed based on the Acute Kidney Injury Network classification within 72 hr after the surgery. Patient data, surgical and anesthetic

data, and laboratory data were extracted manually from the patients' electronic charts. Multivariable logistic regression analysis was used to identify perioperative risk factors for postoperative AKI.

Results Acute kidney injury was diagnosed in 78 of 642 patients (12.1%; 95% confidence interval [CI]: 9.7 to 14.9). Multivariable analysis showed an independent association between postoperative AKI and preoperative estimated glomerular filtration rate (adjusted odds ratio [aOR] 0.74; 95% CI: 0.64 to 0.85), preoperative hypertension (aOR 2.10; 95% CI: 1.11 to 3.97), and intraoperative red blood cell transfusion (aOR 1.04; 95% CI: 1.01 to 1.07). Development of AKI within 72 hr after liver resection surgery was associated with increased hospital mortality, prolonged length of stay, and increased rates of mechanical ventilation, reintubation, and renal replacement therapy.

Conclusion Perioperative risk factors for AKI after liver resection surgery are similar to those established for other surgical procedures. Further studies are needed to establish causality and to determine whether interventions on modifiable risk factors can reduce the incidence of postoperative AKI and improve patient outcome. This study was registered at the University Hospital Medical Information Network (UMIN) Center (UMIN 000008089).

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Résumé

Objectif Cette étude visait à identifier l'incidence et les facteurs de risque de lésion rénale aiguë (LRA) après résection hépatique et à clarifier les rapports entre les LRA postopératoires et l'évolution des patients.

Méthodes Nous avons effectué une étude de cohorte historique de patients qui avaient subi une chirurgie de résection hépatique sous anesthésie au sévoflurane entre

janvier 2004 et octobre 2011. La lésion rénale aiguë a été diagnostiquée en se basant sur la classification du Acute Kidney Injury Network dans les 72 heures suivant l'intervention. Les données des patients, les données chirurgicales, anesthésiques et de laboratoire ont été extraites manuellement des dossiers électroniques des patients. Une analyse de régression logistique multifactorielle a servi à l'identification des facteurs de risque périopératoires de la LRA postopératoire.

Résultats Une lésion rénale aiguë a été diagnostiquée chez 78 des 642 patients (12,1 %; intervalle de confiance à 95 % [IC]: 9,7 à 14,9). L'analyse multifactorielle a montré une association indépendante entre la LRA postopératoire et le taux de filtration glomérulaire estimé (rapport de cotes ajusté [aOR] 0,74; IC à 95 %: 0,64 à 0,85), hypertension préopératoire (aOR 2,10; IC à 95 %: 1,11 à 3,97), et transfusion de globules rouges peropératoire (aOR 1,04; IC à 95 %: 1,01 à 1,07). L'apparition d'une LRA dans les 72 heures suivant la résection hépatique a été associée à une augmentation de la mortalité en cours d'hospitalisation, un allongement de la durée de séjour, et à des taux plus élevés de ventilation mécanique, de réintubation et de traitement de remplacement rénal.

Conclusion Les facteurs de risque périopératoires de LRA après résection hépatique sont semblables à ceux déterminés pour les autres procédures chirurgicales. D'autres études sont nécessaires pour en établir la causalité et pour déterminer si des interventions sur des facteurs de risque modifiables peuvent réduire l'incidence des LRA postopératoires, et améliorer l'évolution des patients. Cette étude a été enregistrée auprès du Centre du réseau d'information de l'hôpital universitaire (UMIN - University Hospital Medical Information Network) sous le numéro: UMIN 000008089.

Postoperative acute kidney injury (AKI) accounts for 18–47% of all hospital-acquired AKI.^{1,2} It has been shown to be associated with prolonged hospital stay^{3–5} and increased morbidity and mortality^{3,4,6–10} after both cardiac^{3,6,7,9} and non-cardiac surgery.^{4,5,7,8,10} Beyond in-hospital complications, postoperative AKI has been shown to decrease long-term survival, even after full recovery of renal function.¹¹ Thus, identification of patient and procedural risk factors may therefore allow for improvements in long-term outcome by affecting changes in perioperative management and disease prevention.

Liver resection surgery is one of the major abdominal surgical procedures, and although rare, the procedure can be associated with massive bleeding.¹² If hypovolemia due to excessive blood loss persists and a reduction in oxygen delivery is not corrected, the renal medulla may be susceptible

to ischemic acute tubular necrosis,¹³ and as a result, patients may suffer from AKI. Furthermore, red blood cell transfusion has been shown to be one of the risk factors for postoperative AKI.⁹ Although patients who undergo liver resection surgery seem to be at risk of postoperative AKI, partly because of the possibility of bleeding, there is limited information on either the incidence of and risk factors for postoperative AKI or the relationship between AKI and outcome.¹⁴

The definition of AKI has evolved over the last decade. An early definition of AKI (Risk, Injury, Failure, Loss, and End-stage renal disease [RIFLE]) was published in 2004 at the Second International Consensus Conference of the Acute Dialysis Quality Initiative.¹⁵ A modified version of the classification was proposed by the Acute Kidney Injury Network (AKIN) in 2007 in order to address a perceived lack of sensitivity of the RIFLE criteria.¹⁶ The objectives of the present study were threefold: 1) to estimate the incidence of AKI (as defined by AKIN within 72 hr) after liver resection surgery, 2) to identify pre- and intraoperative risk factors for AKI, and 3) to clarify the relationship between postoperative AKI and outcome.

Methods

This report is based on our single-centre historical cohort study of patients who underwent liver resection surgery from January 2004 to October 2011.

The study was approved by the Clinical Research Ethics Board at Tokyo Medical and Dental University (No. 1134; December 2011), and the need for informed consent was waived.

Patient data, surgical and anesthetic data, as well as laboratory data were manually abstracted from the patients' electronic charts. The data collected included: age, sex, height, body weight, body mass index, American Society of Anesthesiologists (ASA) physical status, history of chronic kidney disease, hypertension, ischemic heart disease, atrial fibrillation, cerebrovascular disease, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, liver cirrhosis, and peripheral vascular disease. We also recorded preoperative use of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), statins, steroids, or diuretics. The surgical and anesthetic factors recorded were: surgical procedure, emergency or elective surgery, thoracic epidural, maintenance anesthetic agent, duration of anesthesia and surgery, volume and type of intraoperative fluids administered (crystalloid, colloid), and lowest systolic blood pressure during anesthesia. Major liver resection surgery was defined as resection of at least three Couinaud liver segments. Colloid solutions

used during the study period consisted of 6% hydroxyethyl starch (HES) 70/0.5 (Hespander®; Fresenius Kabi, Tokyo, Japan) and 5% albumin. Intraoperative transfusions of red blood cells, fresh frozen plasma, or platelets were recorded. One unit of each blood component was derived from 200 mL of whole blood. Laboratory values, including hemoglobin, serum creatinine concentration, albumin, total bilirubin, and transaminase enzymes, were obtained from the electronic charts.

Definitions and outcome

Acute kidney injury was identified based on AKIN creatinine criteria,¹⁶ defined as an abrupt (within a 48-hr period) increase in either absolute serum creatinine (sCr) of $\geq 0.3 \text{ mg}\cdot\text{dL}^{-1}$ or a percentage increase in sCr of $\geq 50\%$ (1.5-fold from baseline). Data on urine output were not used for diagnosis as the information was inconsistently charted depending on the site of postoperative recovery. To identify the influence of perioperative interventions on the occurrence of AKI, we distinguished between early (within 72 hr) and late (≥ 72 hr) AKI. Unless otherwise specified in this manuscript, “AKI” refers to occurrences within 72 hr postoperatively. The preoperative glomerular filtration rate (GFR) was estimated from the formula developed for Japanese adult patients and adjusted for each 1.73 m^2 of body surface area: estimated GFR (eGFR) ($\text{mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^2$) = $194 \times \text{sCr} (\text{mg}\cdot\text{dL}^{-1})^{(-1.094)} \times \text{Age} (\text{yr})^{(-0.287)} \times 0.739$ (if female).¹⁷ Chronic kidney disease was defined as a baseline eGFR of $\leq 60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^2$.

Outcome variables included postoperative mechanical ventilation, reintubation, renal replacement therapy (RRT), length of hospital stay, and in-hospital mortality. Postoperative mechanical ventilation was defined as any extension of ventilatory support past the operating room, whether as continuation of intraoperative care or support for postoperative respiratory failure.

As the purpose of this study was to determine the risk factors for postoperative AKI, our sample size was determined to help ensure stability of our final multivariable model. To avoid overfitting our final outcome model, no less than eight outcome events would be required per covariate of interest.¹⁸ Thus, to fit a model with nine covariates at maximum, we would require approximately 70 outcome events. Based on an estimated AKI incidence of 11%, which we determined in a chart review of 100 patients after liver resection surgery (unpublished), we calculated that we would need to include approximately 640 patients.

Statistical analysis

Continuous variables were summarized as median [25th, 75th percentiles] or mean (SD). Categorical variables were

summarized as frequency (percent). Hospital length of stay was compared between the two groups using the Wilcoxon rank-sum test. Categorical clinical outcomes were compared using Fisher’s exact test.

Multivariable logistic regression was used to model the relationship between postoperative AKI (as defined by AKIN developing within 72 hr) and perioperative risk factors. Factors that were selected *a priori* based on their potential association with postoperative AKI were: age, sex, hemoglobin concentration, serum albumin concentration, chronic renal failure (low eGFR), hypertension, ACE inhibitors or ARB use, red blood cell transfusion, and duration of surgery. Pairwise correlations for all predictor variables were estimated. To avoid multicollinearity, two or more highly correlated predictor variables ($r > 0.8$) were not included in the multivariable analysis model simultaneously. Finally, the assumption of linearity in the log odds for each continuous predictor was assessed in two ways. First, the linear relationship was confirmed by visual inspection using the graphs - with the logit of the probability of the outcome (AKI) on the vertical axis and the continuous variables (age, hemoglobin, eGFR, units of red blood cell transfusion, and duration of surgery) on the horizontal axis. Each continuous predictor was categorized, and the log odds of the outcome was plotted against the midpoint of each category. Second, univariable logistic regression analysis was performed in each of the nine variables, and the likelihood ratio Chi square test was performed.

All reported *P* values are two sided. Statistical analyses were conducted using STATA version 12 (StataCorp, College Station, TX, USA).

Results

During January 2004 to October 2011, 695 patients who underwent liver resection surgery were identified for this study. Fifty-three patients were excluded, leaving 642 patients in the final analysis (Figure). Indications for surgery were: hepatocellular carcinoma in 445 patients (69.3%), metastatic liver tumour in 78 patients (12.1%), cholangiocarcinoma in 68 patients (10.6%), and gallbladder cancer in 17 patients (2.6%). The majority of patients (84%) were ASA physical status II.

Acute kidney injury based on AKIN criteria occurred in 78 patients (12.1%) (95% confidence interval [CI]: 9.7 to 14.9) within the first 72 hr, and the patients were deemed as AKIN stage 1 ($n = 63$), stage 2 ($n = 13$), or stage 3 ($n = 2$). At least three Couinaud liver segments were resected in 230 cases (36%), and they were classified as major liver resection surgery. A small difference in the incidence of AKI was observed between patients with major liver resection vs patients with non-major liver resection (13.9%

Figure Flow chart outlining the inclusion and exclusion criteria used in the study

vs 11.2%, respectively); however, this difference was not statistically significant (mean difference 2.7%; 95% CI: −2.4 to 8.5; $P = 0.31$).

Patients who developed AKI were older and more likely to be male; they also had a higher ASA class, lower preoperative hemoglobin concentration, higher sCr, lower eGFR, and lower serum albumin concentration. Acute kidney injury patients were more likely to have chronic kidney disease and hypertension than non-AKI patients. Additionally, AKI patients were more likely to be taking ARB preoperatively (Table 1). Neither antifibrinolytic agents nor nephrotoxic antibiotics were administered intraoperatively during the study period.

The average (SD) peak sCr within 72 hr after surgery was 1.5 (0.5) $\text{mg}\cdot\text{dL}^{-1}$ in AKI patients and 0.8 (0.2) $\text{mg}\cdot\text{dL}^{-1}$ in non-AKI patients. Final sCr before discharge remained high in AKI patients compared with non-AKI patients [1.3 (0.9) $\text{mg}\cdot\text{dL}^{-1}$ vs 0.8 (0.5) $\text{mg}\cdot\text{dL}^{-1}$, respectively]. Descriptive statistics for the intraoperative variables are presented in Table 2. Acute kidney injury patients experienced greater blood loss than non-AKI patients and were more likely to receive red blood cells, fresh frozen plasma, and platelets. Major resection was more common in AKI patients and they had longer durations of surgery and anesthesia than non-AKI patients. The association between AKI and each of the nine risk factors was statistically significant in the univariable analyses (Table 3). Since no pair of continuous variables was highly correlated ($r > 0.8$), all nine variables were incorporated into the multivariable logistic regression analysis (full model). No nested model was used in the present study. Multivariable analysis revealed that low eGFR, hypertension, and red blood cell transfusion were independently associated with postoperative AKI (Table 4).

Perioperative AKI was associated with significantly increased rates of postoperative mechanical ventilation, reintubation, RRT, and hospital mortality. Hospital stays were significantly longer in AKI patients than in non-AKI patients (Table 5). Three patients in the non-AKI group who required postoperative RRT reached the AKIN creatinine criteria on the fifth, 14th, and 35th postoperative days, respectively (late AKI). All required tracheal reintubation and mechanical ventilation, and two died during hospitalization.

Discussion

We have assessed the incidence and risk factors for postoperative AKI in patients undergoing liver resection surgery with sevoflurane anesthesia during 2004–2011. Acute kidney injury, as defined by the AKIN criteria, occurred in 12.1% of liver resection surgeries within the first 72 hr. The variables in our study that were independently associated with AKI after liver resection surgery were: preoperative low eGFR, preoperative hypertension, and intraoperative red blood cell transfusion. Acute kidney injury was associated with increased hospital mortality, prolonged length of stay, and increased rates of mechanical ventilation, reintubation, and RRT.

The incidence of postoperative AKI in the present study (12.1%) was slightly lower than that in the study by Slankamenac *et al.*¹⁴ (15.1%). In their study, which was based on the RIFLE criteria, the authors investigated the incidence of postoperative AKI occurring in 569 patients within 48 hr after liver resection surgery. The difference in incidence may simply reflect sample to sample variability. The observed higher incidence in the Slankamenac *et al.* study than in our study could be real and may be explained in part by a higher percentage of major liver resection surgeries (57% vs 36%, respectively) and a higher incidence of red blood cell transfusions ($> 50\%$ vs 33%, respectively). The difference in incidence could also be due to the different definitions for AKI used in the two studies. The data available in this study did not allow us to calculate the incidence using the RIFLE criteria. Other studies have shown a similar incidence of AKI regardless of the diagnostic criteria,¹⁹ while the incidence of AKI was higher according to the RIFLE criteria in critically ill patients.²⁰

The incidence of postoperative AKI in most other non-cardiac surgical settings was lower than in the present study, e.g., joint arthroplasty (0.6–1.8%),^{21,22} bariatric surgery (5.8%),²³ lung resection surgery (5.9–6.8%),^{24,25} and colorectal surgery (7.4%).²⁶ A higher incidence of AKI after liver resection surgery among non-cardiac surgery

Table 1 Preoperative patient characteristics by status of AKI

	All patients (<i>n</i> = 642)	AKI patients (<i>n</i> = 78)	Non-AKI patients (<i>n</i> = 564)
Median age, yr [IQR]	67 [60-74]	70 [63-76]	67 [59-73]
Female sex, <i>n</i> (%)	179 (28)	14 (18)	165 (29)
Median height, cm [IQR]	162 [155-168]	163 [156-169]	162 [155-168]
Median body weight, kg [IQR]	60 [53-68]	62 [53-71]	60 [53-68]
Median BMI, kg·m ² [IQR]	23.2 [21.1-25.2]	23.3 [21.3-25.7]	23.2 [21.1-25.1]
ASA classification, <i>n</i> (%)			
I	34 (5)	0 (0)	34 (6)
II	542 (84)	66 (85)	476 (84)
III	66 (10)	12 (15)	54 (10)
IV	0 (0)	0 (0)	0 (0)
V	0 (0)	0 (0)	0 (0)
Baseline laboratory values			
Median hemoglobin, g·dL ⁻¹ [IQR]	13.0 [11.6-14.1]	12.7 [11.0-13.6]	13.0 [11.7-14.2]
Median platelet count, μ L ⁻¹ [IQR]	16.5 [11.9-21.2]	17.2 [11.8-23.8]	16.4 [11.9-20.9]
Median creatinine, mg·dL ⁻¹ [IQR]	0.8 [0.6-0.9]	0.9 [0.8-1.1]	0.7 [0.6-0.9]
eGFR, mL·min ⁻¹ ·1.73 m ² [IQR]	75.0 [63.3-88.1]	63.5 [50.2-77.2]	76.3 [65.4-88.5]
Median albumin, g·dL ⁻¹ [IQR]	4.0 [3.7-4.3]	3.9 [3.5-4.2]	4.1 [3.7-4.3]
Median total bilirubin, mg·dL ⁻¹ [IQR]	0.8 [0.6-1.0]	0.8 [0.5-1.0]	0.8 [0.6-1.0]
Median GOT, IU·L ⁻¹ [IQR]	35 [25-56]	46 [27-57]	34 [25-56]
Median GPT, IU·L ⁻¹ [IQR]	31 [20-52]	31 [22-53]	31 [19-52]
Median ICG 15 min, % [IQR]	14.3 [9.2-20.8]	14.8 [10.6-21.2]	14.2 [9.1-20.8]
Comorbidities, <i>n</i> (%)			
Chronic kidney disease	124 (19)	32 (41)	92 (16)
Hypertension	310 (48)	54 (69)	256 (45)
Ischemic heart disease	36 (6)	7 (9)	29 (5)
Atrial fibrillation	28 (4)	5 (6)	23 (4)
Cerebrovascular disease	40 (6)	7 (9)	33 (6)
Diabetes mellitus			
No diabetes	512 (80)	55 (71)	457 (81)
Oral medication	72 (11)	14 (18)	58 (10)
Insulin therapy	58 (9)	9 (12)	49 (9)
Hyperlipidemia	49 (8)	7 (9)	42 (7)
COPD	64 (10)	8 (10)	56 (10)
Liver cirrhosis	93 (14)	16 (21)	77 (14)
Peripheral vascular disease	14 (2)	3 (4)	11 (2)
Preoperative medications, <i>n</i> (%)			
NSAIDs	19 (3)	3 (4)	16 (3)
ACE inhibitors	40 (6)	7 (9)	33 (6)
ARB	116 (18)	22 (28)	94 (17)
Statin	32 (5)	6 (8)	26 (5)
Steroid	4 (1)	1 (1)	3 (1)
Diuretics	52 (8)	7 (9)	45 (8)

ACE = angiotensin-converting enzyme; AKI = acute kidney injury; ARB = angiotensin II receptor blockers; ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; ICG = indocyanine green; IQR = interquartile range; NSAIDs = nonsteroidal anti-inflammatory drugs

patients may be the result of larger amounts of blood loss and need for blood transfusion. In fact, the mean estimated blood loss²¹ and the percentage of patients who needed red blood cell transfusion²³⁻²⁵ were much lower in the abovementioned surgeries than in the present study. We assumed that both red blood cell transfusion and large amounts of blood loss could be risk factors for AKI; however, because both variables were highly correlated ($r > 0.92$; $P < 0.0001$), only transfusion was included in the final multivariable analysis model to avoid multicollinearity.

Both preoperative low renal function and hypertension have been shown to be risk factors for postoperative AKI in various surgical settings.^{21,24,27} Although the relationships between red blood cell transfusion and postoperative AKI are not fully understood, there are several mechanisms that may be taken into account. First, because of a deficiency in 2,3-biphosphoglycerate (also called 2,3-diphosphoglycerate) in stored donated blood, oxygen unloading from hemoglobin could have been impaired. Second, because of less deformability of stored red blood cells, they may have obstructed smaller capillaries and led to impairment of oxygen delivery to tissues.²⁸ Furthermore, since transfused red blood cells have a shortened lifespan, they may have caused hemolysis and led to an increase in circulating free iron. Since free iron is a highly potent contributor to oxidative stress, an increased level of free plasma iron may have played an important role in causing postoperative AKI in transfused patients.²⁹ Other mechanisms behind the transfusion-related

AKI might include loss of the ability to generate nitric oxide, increased adhesiveness to vascular endothelium, release of procoagulant phospholipids, and accumulation of pro-inflammatory phospholipids.^{28,30-33}

Among the patients who required red blood cell transfusion, there may have been intraoperative hypovolemia associated with a large amount of blood loss, although volume status was monitored only in some of our patients by using filling pressure (e.g., central venous pressure [CVP]) and/or dynamic indicators to predict fluid responsiveness (e.g., stroke volume variation). Because of the combination of low blood flow and the high metabolic demand of the medulla relative to the cortex, acute tubular necrosis is considered the commonest cause of postoperative AKI and is primarily a result of hypoxic damage to the medulla.³⁴ If hypovolemia continues, the medulla may become more vulnerable to hypoxic damage.

Intraoperative fluid management, including the type (crystalloid or colloid) and amount of fluid was at the discretion of the anesthesiologists during the study period. Although it has been shown that low CVP during liver resection surgery may help minimize blood loss and mortality,³⁵ it is not clear whether it would have lowered the incidence of AKI, as renal perfusion pressure can be lower during relative hypovolemia. Further studies are required to prove this hypothesis.

Angiotensin II receptor blockers have been shown to be one of independent risk factors for postoperative AKI in some surgical settings, including one of our previous

Table 2 Intraoperative variables by status of AKI

	All patients ($n = 642$)	AKI patients ($n = 78$)	Non-AKI patients ($n = 564$)
Adjuvant epidural, n (%)	544 (85)	61 (78)	483 (86)
Lowest median SBP, mmHg [IQR]	78 [70-80]	75 [70-80]	78 [70-80]
EBL, median mL [IQR]	1,310 [611-2,410]	2,170 [1,068-3,364]	1,200 [571-2,239]
Intraoperative fluids			
Median crystalloid, mL [IQR]	4,400 [3,250-5,870]	4,540 [3,450-6,650]	4,350 [3,220-5,730]
Received HES, n (%)	123 (19)	16 (21)	107 (19)
Median albumin, mL [IQR]	500 [0-500]	500 [200-1000]	500 [0-500]
Received RBCs, n (%)	214 (33)	44 (56)	170 (30)
Units of RBCs, median [IQR]	0 [0-4]	2 [0-6]	0 [0-2]
Received FFP, n (%)	226 (35)	42 (54)	184 (33)
Units of FFPs, median [IQR]	0 [0-4]	3 [0-10]	0 [0-4]
Received platelets, n (%)	74 (12)	18 (23)	56 (10)
Surgical procedure			
Major resection *, n (%)	230 (36)	32 (41)	198 (35)
Duration of surgery, median min [IQR]	300 [236-384]	340 [250-421]	297 [234-377]
Duration of anesthesia, median min [IQR]	364 [299-449]	393 [313-493]	360 [295-444]

AKI = acute kidney injury; EBL = estimated blood loss; FFP = fresh frozen plasma; HES = hydroxyethyl starch; IQR = interquartile range; RBCs = red blood cells; SBP = systolic blood pressure

* Defined as a resection of at least 3 Couinaud liver segments

Table 3 Univariable logistic regression analysis of potential predictors of postoperative AKI

Variable	OR	95% CI	P value
Age in years (per 10 yr)	1.41	1.10 to 1.81	0.006
Female	0.53	0.29 to 0.97	0.039
Preoperative hemoglobin (g·dL ⁻¹)	0.85	0.74 to 0.97	0.017
Preoperative albumin (g·dL ⁻¹)	0.59	0.37 to 0.97	0.036
eGFR (per 10 mL·min ⁻¹ ·1.73 m ²)	0.69	0.60 to 0.79	< 0.001
Hypertension	2.71	1.63 to 4.50	< 0.001
Angiotensin II receptor blocker	1.96	1.14 to 3.37	0.014
Red blood cell transfusion (per unit) ^a	1.05	1.03 to 1.08	< 0.001
Duration of surgery (per 10 min)	1.03	1.01 to 1.04	0.004

AKI = acute kidney injury; CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio unadjusted

^a One unit of each blood component was derived from 200 mL of whole blood

studies.²⁴ They are considered to decrease the glomerular capillary pressure and the GFR by reducing the resistance of the efferent arterioles. Angiotensin II receptor blockers were not independently associated with AKI in the present study, which may be partly explained by the relationship with other risk factors (e.g., hypertension).

Although the percentage of patients receiving tracheal reintubation and postoperative mechanical ventilation was significantly higher in the AKI group, we were not able to identify the cause and effect relationship between those adverse events and AKI partly because of the slow response of sCr to impaired renal function. While mechanical ventilation may influence renal function through hemodynamic and biohumoral effects, blood gas disturbances, and biotrauma, AKI may cause acute lung injury through volume overload, increased pulmonary vascular permeability, induction of oxidative stress, and apoptosis.³⁶ Further information on kidney-lung crosstalk and early detectable biomarkers of AKI and respiratory insufficiency may be needed to clarify the pathophysiology of pulmonary and renal interaction.

Although some HES solutions were withdrawn from clinical use in many countries, it seems unlikely that

Table 4 Multivariable logistic regression analysis of potential predictors of postoperative AKI

Variable	aOR	95% CI	P value
Age in years (per 10 yr)	1.02	0.76 to 1.37	0.897
Female	0.53	0.28 to 1.03	0.060
Preoperative hemoglobin (g·dL ⁻¹)	0.91	0.76 to 1.09	0.287
Preoperative albumin (g·dL ⁻¹)	0.71	0.37 to 1.36	0.303
eGFR (per 10 mL·min ⁻¹ ·1.73 m ²)	0.74	0.64 to 0.85	< 0.001
Hypertension	2.10	1.11 to 3.97	0.022
Angiotensin II receptor blocker	1.07	0.56 to 2.04	0.847
Red blood cell transfusion (per unit) ^a	1.04	1.01 to 1.07	0.004
Duration of surgery (per 10 min)	1.01	0.99 to 1.04	0.261

AKI = acute kidney injury; aOR = odds ratio adjusted; CI = confidence interval; eGFR = estimated glomerular filtration rate

^a One unit of each blood component was derived from 200 mL of whole blood

postoperative AKI was attributed to HES in the present study, as studies are lacking that show significant relationships between this low-molecular-weight HES and perioperative kidney dysfunction. Furthermore, a recent study by Endo *et al.* showed that intraoperative 6% HES 70/0.5 was not related to postoperative AKI in patients with major intraoperative blood loss.³⁷ Because only a small number of studies have investigated the effects of this HES solution on postoperative renal function, further studies are needed to confirm that it is safe and does not contribute to AKI. The results of our study may not be extrapolated to the clinical situations where other HES solutions are used.

We had two reasons for using the cut-off point of 72 hr. First, our primary aim was to identify risk factors for AKI that were directly related to perioperative interventions. Second, we did not want to miss the patients whose sCr slowly increased beyond the time frame of 48 hr after the surgery. Even though sCr is used in the standard criteria for AKI, it is not necessarily a sensitive marker to detect impaired kidney function.³⁸ We excluded patients who died within three days following surgery because patients with impaired kidney function who died before sCr reached the AKIN criteria (i.e., within 72 hr) would automatically

Table 5 Postoperative clinical outcomes by status of AKI

	All patients (n = 642)	AKI patients (n = 78)	Non-AKI patients (n = 564)	Difference (95% CI)	P value
Mechanical ventilation, n (%)	130 (20)	30 (38)	100 (18)	20 (9 to 31)	< 0.0001
Reintubation, n (%)	33 (5.1)	8 (10.3)	25 (4.4)	5.8 (0.5 to 14.6)	0.049
Renal replacement therapy, n (%)	7 (1.1)	4 (5.1)	3 (0.5)	4.6 (1.3 to 11.9)	0.005
Hospital days, median [IQR]	19 [15-30]	26.5 [16-45]	19 [14-29]	12 (7 to 18)	0.0001
Hospital mortality, n (%)	24 (3.7)	11 (14.1)	13 (2.3)	11.8 (5.5 to 21.3)	< 0.0001

AKI = acute kidney injury; CI = confidence interval; IQR = interquartile range

be classified into the non-AKI group. Although we focused on AKI within 72 hr after liver resection surgery, it does not mean that late AKI should be taken lightly. As was seen in the present study, late AKI can also be associated with poor outcome.

We chose to include only patients who received sevoflurane anesthesia. Although sevoflurane is widely accepted and considered safe, even in patients with chronic kidney disease,³⁹ it has been shown that sevoflurane anesthesia increases serum fluoride concentration along with urinary excretion of N-acetyl- β -(D)-glucosaminidase (NAG), a sensitive biomarker of renal tubular damage.⁴⁰ Considering that the increase in NAG⁴⁰ may suggest that patients given sevoflurane anesthesia are at a higher risk for AKI and that the majority of patients in our hospital received sevoflurane anesthesia during the study period, we decided to exclude patients given desflurane or total intravenous anesthesia.

There are several additional limitations to the present study that need to be addressed. First, although multivariable logistic analysis showed that red blood cell transfusion was independently associated with postoperative AKI, we were not able to identify if transfusion itself contributed to AKI as stated above. The conditions that necessitated transfusion, e.g., hypovolemia and anemia, may have played an important role in causing AKI. Second, we were not able to evaluate the effects of a low CVP strategy on the occurrence of AKI, since CVP was monitored and recorded only in some patients. Because of the nature of the retrospective study, we were also not able to look into the number of patients in whom measures were taken to reduce the CVP. Third, although arterial blood pressure was monitored continuously in most of the liver resection surgeries, it was recorded on the anesthesia chart in only 2.5 to five-minute intervals. Thus, because of the intermittent blood pressure recordings, we could not evaluate the duration of hypotension in each patient or address the exact stage when blood pressure was at its lowest. Furthermore, as with all observational research, residual or unmeasured confounders may be an alternate explanation for our results. Finally, generalizability is limited to centres with patient and surgical profiles similar to our own.

In conclusion, postoperative AKI based on AKIN criteria occurred in 12.1% of patients after liver resection surgery. Low preoperative renal function, hypertension, and red blood cell transfusion were independently associated with postoperative AKI. Postoperative AKI was closely related to postoperative mechanical ventilation, reintubation, RRT, prolonged hospital stay, and hospital mortality. Further studies are needed to establish causality and to determine whether interventions on modifiable risk factors can reduce the incidence of postoperative AKI and improve patient outcome.

Conflicts of interest None declared.

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