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Early Acute Kidney Injury Associated with Liver Transplantation: A Retrospective Case-Control Study

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Background: A retrospective case-control study was carried out to assess the occurrence of acute kidney injury (AKI) in liver transplantation (LT) recipients and its related risk factors.

Material/Methods: The study enrolled 131 patients undergoing LT from December 2017 to June 2019 at Beijing Tsinghua Chang Gung Hospital, China. AKI and its classification were defined according to KDIGO guidelines. We collected patients' demographic characteristics and perioperative parameters, and identified independent risk factors of AKI by multivariate logistic regression analysis.

Results: We included 122 patients in analysis. AKI occurred in 52 (42.6%) patients (22.1% stage I, 8.2% stage II, and 12.3% stage III). AKI was notably associated with 12 factors: sex, body mass index (BMI), hepatic etiology, MELD score, ascites, prothrombin time (PT), international normalized ratio of prothrombin time (INR), preoperative total bilirubin (TBIL), operative time, total fluid intake, fresh frozen plasma (FFP), and estimated blood loss (EBL) ($P<0.05$). The factors independently associated with AKI were BMI (adjusted odds ratio: 0.605, 95% confidence interval: 0.425–0.859; $P=0.005$) and intraoperative FFP infusion (adjusted odds ratio: 0.998, 95% confidence interval: 0.995–1.000; $P=0.047$). Compared with the non-AKI group, the AKI group showed higher likelihood of renal replacement therapy (RRT), and longer ICU and hospital stays, higher in-hospital mortality, and higher hospitalization costs ($P<0.05$).

Conclusions: There is a high risk of AKI in patients undergoing LT. BMI and intraoperative FFP infusion are factors independently correlated with AKI. AKI can result in extended hospital stays and higher hospitalization expenses.

MeSH Keywords: Acute Kidney Injury • Incidence • Liver Transplantation • Risk Factors

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Background

Liver transplantation (LT) is a common method for treating end-stage liver disease. Acute kidney injury (AKI) has attracted much attention as a complication after LT, with an incidence ranging between 5% and 95% in different studies [1–3]. Several perioperative risk factors may be associated with AKI following LT, including advanced age, high body weight, prolonged operation duration, and high intraoperative blood loss [4,5]. AKI development in LT patients may lead to unfavorable outcomes, including prolonged hospital and intensive care unit (ICU) stay, as well as increased mortality [6,7].

In this study, we assessed the morbidity of AKI in LT patients and evaluated the associated risk factors, which may improve the early detection of patients with high risk and subsequent perioperative management to prevent or mitigate negative outcomes of AKI.

Material and Methods

This was a single-center, retrospective, case-control study of 131 consecutive adults (≥18 years of age) undergoing LT between February 2018 and June 2019 at Beijing Tsinghua Chang Gung Hospital. All patients underwent combined intravenous-inhalation anesthesia with uniform medication management. A flow diagram of patients throughout the study is presented in Figure 1. AKI and its classification were defined on the basis of Kidney Disease Improving Global Outcomes (KDIGO) guidelines: an increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h or an increase in serum creatinine to ≥1.5 times baseline within the previous 7 days pre-operatively [8,9]. AKI severity was assessed using the KDIGO criterion [10]: increase in creatinine at 24 h after LT compared to baseline. Postoperative renal status was categorized as follows: no AKI (<1.5-fold increase in creatinine), stage I (1.5–2-fold increase), stage II (2–3-fold rise), and stage III (>3-fold rise or the commencement of RRT).

Data collection

Data for the following variables were obtained from patients' medical records: patient characteristics (age, sex, BMI, diabetes, hypertension, hepatic etiology, MELD score, and ascites); preoperative laboratory test results (serum creatinine, prothrombin activity, PT, INR, TBIL, albumin); operative variables (operation duration, total fluid intake, crystal liquid, HES, 5% albumin, RBC, FFP, EBL, urine output, and anhepatic phase); and postoperative course (postoperative RRT, ICU and hospital stay duration, in-hospital mortality, and hospitalization expense).

Statistical analysis

All data were analyzed using SPSS 22.0. Normally distributed measurement data are presented as mean and SD (x±SD) and were analyzed using the *t* test. Skewed measurement data are presented as median (interquartile ranges, IQR) and analyzed using the Mann-Whitney U test. Categorical variables are described as numbers (percentage) and were analyzed using the Pearson chi-square test or Fisher's exact test. In logistic regression, univariate and multivariate analyses were used

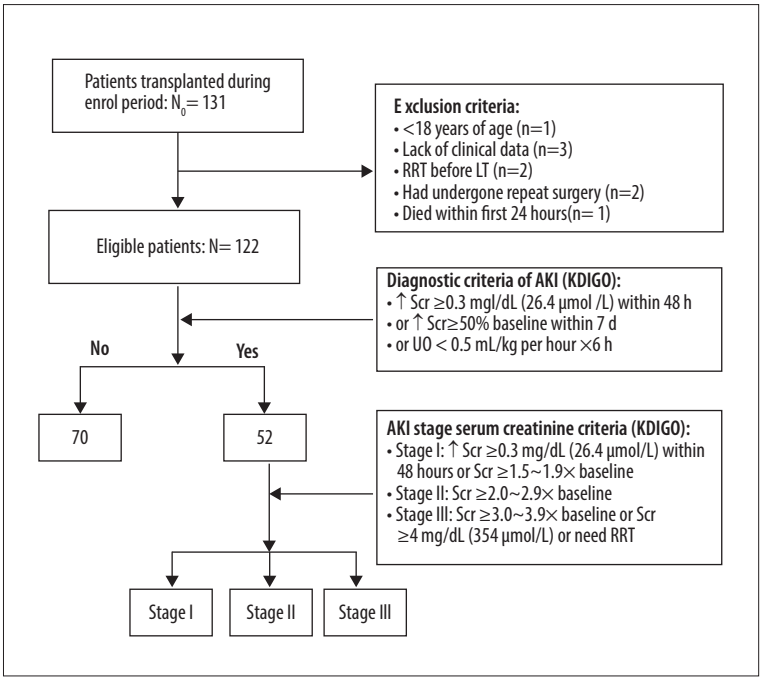

Figure 1. Study profile.

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Table 1. Patient characteristics.

Variable	All patients (n=122)	AKI (n=52)	Non-AKI (n=70)	P value
Age ($\bar{\chi}$±SD, yr)	50.66±11.19	53.02±10.96	48.90±11.11	0.873
Male/Female [n (%)]	97(79.9)/25(20.1)	37(71.2)/15(28.8)	60(85.7)/10(14.3)	**0.049**
BMI ($\bar{\chi}$±SD, kg/m^2)	23.56±3.67	23.90±4.2	23.31±3.2	**0.005**
Diabetes [n (%)]	10 (8.2)	4 (7.7)	6 (8.6)	0.861
Hypertension [n (%)]	12 (9.8)	6 (11.5)	6 (8.6)	0.586
Etiology				
Hepatic malignancy [n (%)]	60 (49.1)	22 (42.3)	38 (54.3)	0.191
Viral hepatitis [n (%)]	28 (22.9)	16 (30.8)	12 (17.1)	0.077
Alcoholics [n (%)]	15 (12.3)	6 (11.5)	9 (12.9)	0.826
Hepatic echinococcosis [n (%)]	6 (4.9)	0	6 (8.6)	**0.034**
Autoimmune hepatitis [n (%)]	7 (5.7)	3 (5.8)	4 (5.7)	0.99
Others [n (%)]	6 (4.9)	5 (9.6)	1 (1.4)	0.402
MELD score [M (IQR)]	12.95 (8.39–21.11)	19.12 (11.77–21.82)	10.10 (7.26–16.1)	**<0.001**
Hepatorenal syndrome [n (%)]	9 (7.4)	5 (9.6)	4 (5.7)	0.415
Ascites [n (%)]	56 (45.9)	29 (55.8)	27 (38.6)	**0.035**

Values are presented as mean±standard deviation, median (IQR), or number (%). BMI – body mass index; MELD score – model for end-stage liver disease (MELD) score.

for assessing the independent risk factors for AKI. $P<0.05$ was considered statistically significant.

Results

Participants

A total of 131 adult recipients underwent LT during our enrollment period (Figure 1). Nine patients were excluded (1 due to age <18 years, 3 due to lack of clinical data, 2 due to receiving RRT before LT, 2 due to undergoing repeat surgery, and 1 due to death within first 24 h after transplantation). Finally, 122 patients were included in the study, and their biochemical data were analyzed.

Incidence of early AKI following LT

Of the 122 patients included in the study, AKI occurred in 52 (42.6%) patients according to the KDIGO criteria (stage I, 22.1%; stage II, 8.2%; and stage III, 12.3%). Most early AKI cases after LT were stage I.

Risk factors for early AKI following LT

Patient characteristic data of the 122 eligible patients are presented in Table 1. The factors affecting postoperative AKI in univariate analysis were as follows: sex, BMI, hepatic etiology, MELD score, and ascites. Results of univariate analysis of pre- and intraoperative data are shown in Tables 2–4. The following factors were correlated with AKI: preoperative prothrombin time (PT), international normalized ratio of prothrombin time (INR), preoperative total bilirubin (TBIL), operative time, total fluid intake, fresh frozen plasma (FFP) requirement, and estimated blood loss (EBL) ($P<0.05$).

Effect of early AKI on patient outcomes

Compared with the non-AKI group, the AKI group patients were significantly more likely to have received RRT, had longer postoperative ICU and hospital stays, higher in-hospital mortality, and higher hospitalization costs ($P<0.05$) (Table 4).

Multivariate logistic regression analysis showed that BMI (adjusted odds ratio: 0.605, 95% confidence interval: 0.425–0.859; $P=0.005$) and FFP (adjusted odds ratio: 0.998, 95% confidence interval: 0.995–1.000; $P=0.047$) were independently correlated with AKI (Table 5).

Discussion

AKI is common in LT recipients, and its incidence varies in previous studies with different diagnostic criteria [11,12].

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Table 2. Preoperative laboratory data.

Variable	All patients (n=122)	AKI (n=52)	Non-AKI (n=70)	P value
Serum creatinine [M (IQR), μmol/L]	70 (53.7–84.45)	68.85 (50.98–94.1)	70.95 (60.0–84.45)	0.387
Prothrombin activity ($\bar{\chi}$±SD,%)	57.93±28.06	46.85±26.93	66.16±26.14	0.907
Prothrombin time [M (IQR), s]	15 (12.9–20)	17.9 (14.65–23.7)	13.7 (12.6–16.8)	**<0.001**
International normalized ratio of prothrombin time [M (IQR)]	1.35 (1.12–1.81)	1.51 (1.25–1.98)	1.23 (1.07–1.49)	**0.001**
Total bilirubin [M (IQR), μmol/L]	34.43 (17.6–164.85)	95.25 (27.19–376)	22.45 (15.65–72.6)	**<0.001**
Albumin [M (IQR), g/L]	35.3 (32.42–40)	34.95 (32.2–39.35)	35.8 (32.5–41.05)	0.199

Values are presented as mean±standard deviation, median (IQR), or number (%).

Table 3. Intraoperative factors.

Variable	All patients (n=122)	AKI (n=52)	Non-AKI (n=70)	P value
Operation duration [M (IQR), h]	9.0 (7.8–11.44)	9.75 (8.5–12.5)	8.5 (7.71–10.02)	**<0.001**
Total fluid intake ($\bar{\chi}$±SD, ml)	7721.89±1699.73	8237.40±1926.99	7338.93±1404.52	**0.002**
Crystal liquid ($\bar{\chi}$±SD, ml)	4221.97±1634.47	4634.71±1696.37	3915.36±1527.76	0.46
HES [M (IQR), ml]	0 (0–1000)	100 (0–1000)	0 (0–925)	0.899
5% albumin ($\bar{\chi}$±SD, ml)	2865.57±1279.59	2989.42±1263.68	2773.57±1292.61	0.572
RBC ($\bar{\chi}$±SD, U)	7.28±5.74	10.02±6.42	5.24±4.18	0.051
FFP [M (IQR), ml]	700 (400–1000)	900 (600–1200)	400 (0–800)	**<0.001**
EBL [M (IQR), ml]	1000 (750–1700)	1500 (800–2750)	850 (600–1500)	**0.005**
Urine ($\bar{\chi}$±SD, ml)	2133.61±1277.13	1851.7±1196.3	2343.0±1303.10	0.936
Anhepatic phase [M (IQR), min]	75 (58–102)	78 (69–110.25)	73.5 (57.75–102)	0.379

Values are presented as mean±standard deviation, median (IQR), or number (%). EBL – estimated blood loss; RBC – red blood cells; FFP – fresh frozen plasma; Cryo – cryoprecipitate; PLT – platelet.

Table 4. Postoperative outcomes.

Variable	All patients (n=122)	AKI (n=50)	Non-AKI (n=72)	P value
RRT [n (%)]	14 (11.5)	12 (23.1)	2 (2.9)	**<0.001**
ICU days [M (IQR), d]	3 (2–4)	4 (2–8.75)	2.5 (2–4)	**0.001**
Postoperative hospital stays [M (IQR), d]	20 (15–30.75)	25.5 (15.75–48.75)	19 (15–25)	**0.002**
Death [n (%)]	3 (2.5%)	3 (5.8)	0 (0)	**0.038**
Hospitalization expense [M (IQR), ¥]	253234.9 (208128.9–309904.9)	309857.2 (263951.6–393104.1)	226702.3 (205127.6–265889.9)	**<0.001**

Values are presented as mean±standard deviation, median (IQR), or number (%). ICU – Intensive Care Unit; RRT – renal replacement therapy.

Table 5. Logistic regression analysis of patients with and without AKI.

	B	P	OR	95% CI
BMI (kg/m^2)	–0.503	0.005	0.605	0.425–0.859
Intraoperative FFP infusion (ml)	–0.002	0.047	0.998	0.995–1.000

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In the present study, we chose to use the traditional definition of kidney injury, evaluated using changes in serum creatinine. Serum creatinine is a more reliable and valid indicator to assess renal function, although, alone, it cannot fully reflect GFR [7].

In this study, a retrospective case-control study involving 122 LT recipients was carried out to determine the incidence of AKI and its relevant risk factors. The occurrence of early postoperative AKI was 42.6% based on the KDIGO guidelines, and most early AKI after LT was in AKI stage I/II (71.2%); these results are similar to previously reported trends. Therefore, it is necessary to increase efforts to prevent AKI after LT, especially in the early postoperative period. Patients who develop AKI following surgery should be actively treated to restore renal function to normal levels as soon as possible to avoid persistent AKI, further deterioration of renal function, and increased risk of other postoperative adverse events.

Our univariate analysis showed that 12 factors affect postoperative AKI, which is similar to previous studies [4,13–15]. Among these factors, MELD score and other components of MELD such as TBIL and INR are associated with AKI development, suggesting that the severity of preoperative liver disease, as reflected by MELD score, is associated with AKI following LT [16,17]. Surprisingly, no significant correlation between preoperative serum creatinine levels and AKI occurrence after LT was noted in our study, perhaps because patients with severe liver disease show reduced serum creatinine due to factors such as malnutrition and muscle atrophy. It is less reliable to estimate renal function using serum creatinine for patients with liver disease. In addition, prolonged PT and ascites are correlated with postoperative AKI, and these are also indicators of primary liver function before surgery [18–20]. Therefore, for patients with severe liver disease prior to surgery, the transplant itself may herald the increased risk of postoperative AKI. However, in this study, AKI incidence was lower in patients with hepatic echinococcosis. The kidney function of the patient may be impaired by the immune response caused by hepatic echinococcosis. However, the detection of serum creatinine does not reflect the slight kidney damage caused by hepatic echinococcosis due to the strong compensatory ability of the kidneys. It may require further research by accumulating additional cases to elucidate this finding. EBL appears to be another sign of surgical complications or intraoperative adverse events. In addition, hemodynamic instability or anemia caused by heavy bleeding may reduce oxygen delivery to the kidney, eventually leading to kidney damage.

BMI is a common indicator used to evaluate the body's metabolism, which may play an important role in AKI. Patients with high BMI are at an increased potential risk of severe metabolic syndrome and associated comorbidities (e.g., hypertension and cardio- and cerebrovascular diseases), glomerular hypertrophy, mesangial hyperplasia, and postoperative infection [21]. These changes can affect kidney function, even though no apparent changes under normal conditions before LT are seen. In our study, patients with higher BMI were more likely to develop AKI after LT. However, the predictive value of BMI remains controversial [22,23] because weight and BMI of patients may be confounded by the ascites and fluid overload that can occur in patients preparing for LT [24,25]. The predictive effects of BMI on AKI following LT may simply reflect the severity of liver disease and/or renal function. The present study also investigated whether infusion of FFP is involved in the AKI. Kalisvaart et al. found that FFP requirement during LT was the best predictor of post-transplant AKI [26]. In this study, FFP requirement was independently associated with AKI, which is consistent with previous research. This may be because patients often experience significant blood loss during LT due to coagulopathy and portal hypertension. In addition, coagulopathy and fibrinolysis reflect severe hepatic ischemia/reperfusion injury and early impaired graft function [27,28].

AKI was remarkably associated with higher likelihood of receiving RRT, prolonged postoperative ICU and hospital stays, and increased hospitalization costs. As demonstrated in our study, AKI following LT was also associated with higher mortality. These results indicate the complexity of the postoperative course in patients undergoing LT, although this finding is merely an association and does not imply a causal relationship.

Our study has some limitations. First, this was a single-center, retrospective, observational study with a relatively small number of cases, which may reduce the generalizability of our results. Second, there were restrictions on access to data; for example, since preoperative urine output was not recorded in our database, the true renal function status of patients with severe liver disease could not be reported.

Conclusions

In conclusion, the incidence of early AKI following LT, specifically AKI stage I/II, is high in our hospital. BMI and intraoperative FFP infusion are independently associated with AKI development. AKI is significantly associated with prolonged hospitalization and increased hospitalization costs. In the future, prospective trial validation, preferably in a multicenter study with a large cohort, is required.

Conflicts of interest

None.

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