Chronic severe hepatitis and preoperative creatinine are independent risk factors for acute kidney injury after liver transplantation

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Background: Orthotopic liver transplantation (OLT) offers the highest chance of cure in comparison with all other treatment for liver tumors and other end stage liver disease. However, the complications caused by liver transplantation significantly affect its therapeutic effect, and acute kidney injury (AKI) is one of the most common of these. It is, therefore, necessary to identify the risk factors of AKI after liver transplantation.

Methods: A single-center, retrospective study of patients receiving liver transplantation at the Beijing Chao-Yang Hospital between January 2015 to January 2019 was conducted.

Patients were divided into a normal control group and AKI group based on their previous medical history. Preoperative and intraoperative indicators including preoperative creatinine, uric acid, and the intraoperative input of protein were then recorded.

Results: A total of 419 patients were enrolled into the study. The control group consisted of 336 patients while 83 patients formed an AKI group based on the grading criteria of AKI. There were significant differences in chronic severe hepatitis (P=0.001), liver cancer (P=0.044), intraoperative input of sodium bicarbonate (P=0.019), input of red blood cell suspension (P=0.004), the input of blood plasma (P=0.043), intraoperative urine output (P=0.006), and preoperative creatinine (P=0.041) between the control and AKI group. Multivariate analysis indicated that chronic severe hepatitis (OR: 2.872; P=0.003) and preoperative creatinine (OR: 1.083; P=0.011) were independent risk factors for AKI in patients receiving liver transplantation.

Conclusions: Chronic severe hepatitis and preoperative creatinine may be potential risk factors for the occurrence of AKI after liver transplantation.

Keywords: Acute kidney injury (AKI); liver transplantation; risk factors; creatinine

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Introduction

Orthotopic liver transplantation (OLT) offers the highest chance of cure in comparison with all other treatments including drug treatment and radiation therapy for the treatment of liver tumors and other end stage liver diseases (1). In general, patients who fail to respond to conservative treatment and may die within 6–12 months should be considered for OLT. As its availability increases in both developed and developing countries, OLT is being regarded as a standard therapy for early liver cancer (1,2), however, the complications caused by OLT significantly impact on its treatment effect. Acute kidney injury (AKI) is

Table 1 Characteristics of patients receiving OLT

	Gender		AKI				Living status	
	Male	Female	Normal	Stage I	Stage II	Stage III	Survival	Death
N	349	70	336	46	22	15	403	16
Percentage (%)	83.3	16.7	80.2	11.0	5.3	3.6	96.2	3.8

a common complication following OLT, with an incidence of between 12% and 95% (3,4), and has been reported to increase the mortality of recipients after OLT (5,6).

While acute kidney disease usually occurs when kidney damage is present for less than 3 months, AKI can occur over as little as 7 days (7). Usually leading to a longer recovery time and a heavier economic burden for patients (8), AKI has been identified as an independent risk factor for death, especially in critically ill patients (9). The etiology of AKI after OLT is related to multiple factors, including renal ischemia, the influence of immunosuppressive drugs, and the general condition of patients (10,11). Research evaluating OLT prior to 2015 is limited (12-14). Thus, it is necessary to identify the risk factors of AKI after OLT.

This study compared several preoperative and intraoperative factors in both a control and AKI group, with the aim of determining risk factors for the occurrence of AKI after OLT.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7680).

Methods

Study design

A single-center, retrospective study of patients receiving OLT in the Beijing Chao-Yang Hospital from January 2015 to January 2019 was conducted. The study was approved by the Beijing Chao-Yang Hospital Ethics Committee was conducted in accordance with the provisions of the Declaration of Helsinki (as revised in 2013). Medical records were collected with the consent of the patients involved.

Exclusion criteria: patients under 14 years of age were excluded from the study; those who had undergone kidney transplantation, and those who had incomplete laboratory data. The age, gender, and medical history of the following conditions were recorded; HBV cirrhosis, alcoholic cirrhosis, chronic severe hepatitis, liver cancer, congenital liver disease, liver failure, hepatitis B surface antigen, hepatitis C antibody, hypertension, diabetes, ascites, hepatorenal syndrome, upper gastrointestinal bleeding, liver coma, preoperative lung infections, and input of blood coagulation factor.

Perioperative levels of creatinine, uric acid, urea and urine specific gravity were recorded and intraoperative measures of protein input, Ringer's solution, sodium bicarbonate, intraoperative blood loss, input of red blood cell suspension and blood plasma, intraoperative urine output, operation time and intraoperative no-liver time.

Patients

Of the 419 patients, 349 were male and 70 female, and the average age was 47.74±11.34. At time of writing, 403 (96.2%) patients had survived, and 16 (3.8%) patients were deceased. According to AKI grading criteria, there were 336 (80.2%) normal patients and 83 (19.9%) AKI patients (*Table 1*).

Definition of AKI

The Kidney Disease Improving Global Outcomes (KDIGO) criteria defines AKI as an abnormal rise of the serum creatinine after OLT (7). Moreover, the staging of AKI in patients receiving OLT is defined as (7) stage I: rise of ≥26 μmol/L or 0.3 mg/dL within 48 h or 50–99% Cr rise from baseline within 7 days; stage II: 100–199% Cr rise from baseline within 7 days; stage III: ≥200% Cr rise from baseline within 7 days or (current) Cr ≥354 μmol/L, with either: rise of ≥26 μmol/L or 0.3 mg/dL within 48 h or ≥50% Cr rise from baseline within 7 days or any requirement for renal replacement therapy. The specific number of patients in different stages is listed in *Table 1*. Among the AKI patients, 46 patients were in stage I, 22 were in stage II, and 15 were in stage III.

Statistical analysis

The data was analyzed using SPSS 19.0 (IBM). Quantitative data were expressed as mean ± standard deviation or median

Table 2 Comparison of characteristics between patients with and without AKI

	Control (n=336)	AKI (n=83)	t (χ^2/z)	P
Age (years)	47.80±11.73	47.48±9.68	0.229	0.819
Gender			0.139	0.710
Male	281	68		
Female	55	15		
HBV cirrhosis	245	60	0.013	0.908
Alcoholic cirrhosis	12	6	2.166	0.141
Chronic severe hepatitis	38	21	10.770	0.001
Liver cancer	175	33	4.044	0.044
Congenital liver disease	6	1	0.137	0.712
Liver failure	13	5	0.752	0.386
Hepatitis B surface antigen	256	664	0.031	0.860
Hepatitis C antibody	25	3	1.562	0.211
Hypertension	24	5	0.129	0.719
Diabetes	16	3	0.202	0.653
Ascites	227	56	0.000	0.988
Hepatorenal syndrome	13	3	0.012	0.914
Upper gastrointestinal bleeding	68	18	0.086	0.770
Liver coma	32	9	0.131	0.717
Preoperative lung infections	23	5	0.072	0.788
Input of blood coagulation factor	60	18	0.644	0.422

(interquartile range). Qualitative data were expressed as rates or composition ratios. Comparisons of normally distributed data between groups were analyzed by the *t*-test. Comparisons of non-normally distributed data between groups were analyzed by the rank-sum test. The categorical data were expressed as n (%), and comparison of the two groups was examined by Pearson χ^2 test or Fisher's exact test. Multivariate analysis was performed using a logistic multiple regression model, and risk factors were used to predict the occurrence of AKI using a ROC curve. P<0.05 was considered statistically significant. If the odds ratio (OR) of a factor is greater than 1, then this factor is a risk factor for the disease.

Results

Comparison of characteristics between patients with and without AKI

A total of 419 patients were involved in this study. When the characteristics of the control group and the AKI group were compared (*Table 2*), no significant difference was found in age (P=0.819) and gender (P=0.710) between the two.

A history of chronic severe hepatitis was significantly different (11.31% in control *vs.* 25.30% in AKI; P=0.001) between the groups, as was liver cancer (52.08% in control *vs.* 39.76% in AKI; P=0.044), while there were no difference between the groups in the status of HBV cirrhosis (P=0.908), alcoholic cirrhosis (P=0.141), congenital liver disease (P=0.712), liver failure (P=0.386), hepatitis B surface antigen (P=0.860), and hepatitis C antibody (P=0.211).

There were also no significant differences in the two groups between patients with a history of other diseases, including hypertension (P=0.719), diabetes (P=0.653), ascites (P=0.988), hepatorenal syndrome (P=0.914), upper gastrointestinal bleeding (P=0.770), liver coma (P=0.717), preoperative lung infections (P=0.788), and input of blood coagulation factor (P=0.422).

Table 3 Comparison of preoperative and intraoperative indicators between patients with and without AKI

	Control (n=336)	AKI (n=83)	t (χ^2/z)	P
Preoperative creatinine (μmol/L)	64.0 (50.0–75.0)	70.2 (53.0–79.3)	2.049	0.041
Preoperative uric acid (μmol/L)	224.60±148.77	236.18±161.97	0.624	0.533
Preoperative urea (μmol/L)	5.04 (3.74–7.33)	5.05 (3.66–6.68)	0.007	0.995
Preoperative urine specific gravity (μmol/L)	0.59±0.51	0.50±0.51	1.366	0.173
Intraoperative input of protein (μmol/L)	2,478.94±1,219.59	2,493.90±1,127.53	0.101	0.920
Intraoperative input of Ringer's solution (μmol/L)	500 (500–1,000)	500 (500–1,000)	0.887	0.375
Intraoperative input of sodium bicarbonate (μmol/L)	353.37±224.04	458.11±600.63	2.364	0.019
Intraoperative blood loss (mL)	2,287.92±1,987.82	1,732.06±70.10	1.721	0.086
Input of red blood cell suspension (μmol/L)	1,628.99±1,386.97	2,137.35±1,543.81	2.922	0.004
Input of blood plasma (μmol/L)	1,274.40±812.44	2,137.34±1,543.81	2.027	0.043
Intraoperative urine output (μmol/L)	2,022.62±879.15	1,732.06±740.10	2.777	0.006
Operation time (h)	9.80±2.69	10.14±2.18	1.060	0.290
Intraoperative no-liver time (min)	69.09±28.09	75.23±34.51	1.699	0.090
Living status			6.002	0.014
Survival	327	76		
Death	9	7		

Comparison of preoperative and intraoperative indicators

A comparison of preoperative and intraoperative indicators is shown in *Table 3*. Preoperative indicators including uric acid (P=0.533), urea (P=0.995) and urine specific gravity (P=0.173) showed no difference whereas preoperative creatinine was significantly higher in the AKI group in comparison to the control group (P=0.041).

Intraoperative indicators including the input of protein, input of Ringer's solution, blood loss, operation time, and no-liver time were not different in patients with and without AKI. However, the intraoperative input of sodium bicarbonate (P=0.019), input of red blood cell suspension (P=0.004), and input of blood plasma (P=0.043) were significantly higher in the AKI group, which may be related to the significantly decreased intraoperative urine output (P=0.006) in that group compared with the control group. Importantly, the living status was significantly different (P=0.014), as 327 (97.32%) patients survived in the control group while 76 (91.57%) survived in the AKI group.

Evaluation of risk factors for AKI in patients receiving OLT

A multivariate analysis was formed to identify risk factors for AKI in patients receiving OLT (*Table 4*). Chronic severe hepatitis (OR: 2.872; 95% CI: 1.429–5.772; P=0.003) and preoperative creatinine (OR: 1.083; 95% CI: 1.071–1.096; P=0.011) were independent risk factors for AKI in patients receiving OLT.

Other factors were not significant, including the intraoperative input of sodium bicarbonate (P=0.169), input of red blood cell suspension (P=0.076), the input of blood plasma (P=0.979), intraoperative blood loss (P=0.172), and intraoperative no-liver time (P=0.641). Although the P-value was less than 0.05 in the hypothesis test regarding the correlation between intraoperative urine output and AKI, the OR value was equal to 1, suggesting that this was not a risk factor.

Predictive value of factors for AKI occurrence

The predictive value of factors for AKI occurrence was studied by drawing ROC curves (*Figure 1*). As shown in *Table 5*, four significant predictors were found, including preoperative creatinine (AUC =0.577; P=0.031), intraoperative urine output (AUC =0.591; P=0.011), input of red blood cell suspension (AUC =0.611; P=0.002), and intraoperative blood loss (AUC =0.572; P=0.042).

Discussion

As a common complication following OLT, AKI is associated with a poor prognosis and sometimes death.

Table 4 Multivariate analysis of AKI in patients receiving OLT

	χ^2	P value	OR	95% CI	
				Lower	Upper
Chronic severe hepatitis	8.773	0.003	2.872	1.429	5.772
Preoperative creatinine	6.429	0.011	1.083	1.071	1.096
Intraoperative input of sodium bicarbonate	1.894	0.169	1.001	1.000	1.002
Input of red blood cell suspension	3.158	0.076	1.000	1.000	1.001
Input of blood plasma	0.001	0.979	1.000	1.000	1.000
Intraoperative urine output	4.937	0.026	1.000	0.999	1.000

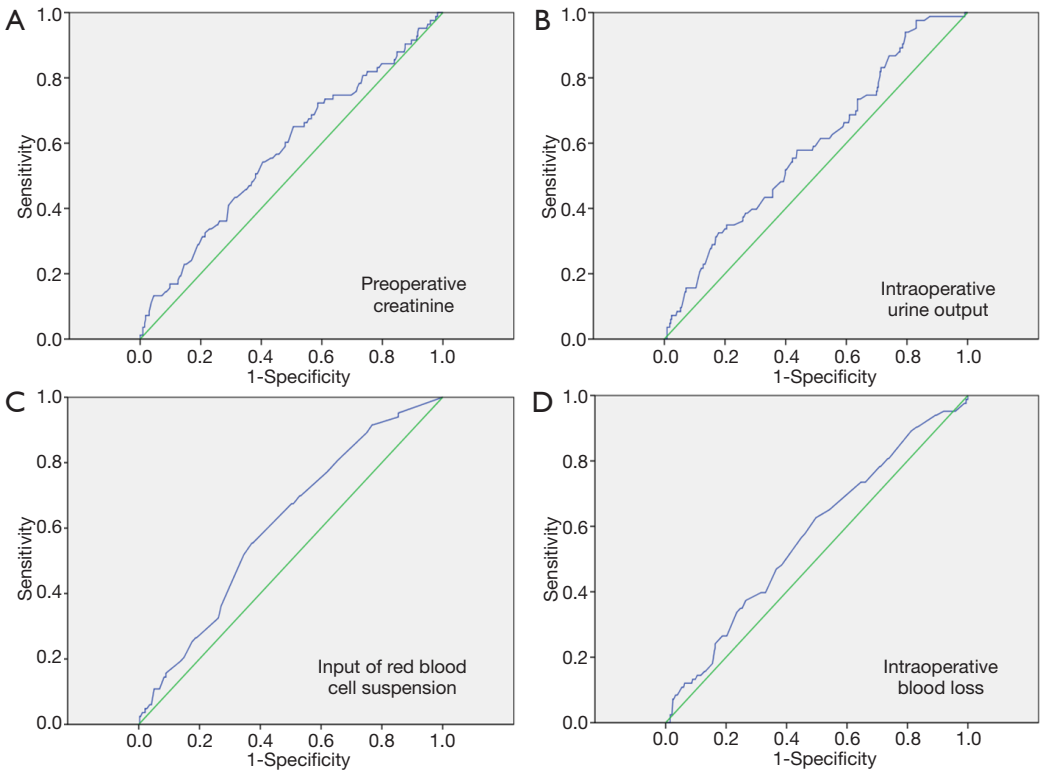

Figure 1 Predictive value of (A) preoperative creatinine (P=0.031), (B) intraoperative urine output (P=0.011), (C) input of red blood cell suspension (P=0.002), and (D) intraoperative blood loss (P=0.042) for AKI occurrence.

The incidence rate of AKI in patients receiving OLT in this study was 19.8%, which is lower than that seen in previous studies. Cabezuelo *et al.* reported the postoperative, first-month overall incidence of acute renal failure following OLT was 48% (15) while Sirivatanauksorn *et al.* found an even higher incidence rate of 71.6% during the first week (16). The use of newly announced criteria of the Kidney Disease Improving Global Outcomes (KDIGO) may account for the lower rate seen in our study.

Although more than half of the AKI patients in this study were in the less severe stage 1 of the disease, there was a higher incidence of death in that group in comparison to the control group. To assess the severity of liver disease, the Model for End-stage Liver Disease (MELD) classification has been put forward. Some doctors have related higher MELD score and Child-Pugh grade with AKI after OLT (17).

Confirming results seen in other studies, in comparison to the control group, the AKI group in this study had a

Table 5 Predictive value of factors for AKI occurrence by ROC curves

Predictors	ROC curves			
	Cut-off value	AUC	95% CI	P value
Preoperative creatinine (μmol/L)	145.7	0.577	0.506–0.647	0.031
Intraoperative urine output (μmol/L)	272.5	0.591	0.523–0.658	0.011
Input of red blood cell suspension (μmol/L)	1725	0.611	0.546–0.675	0.002
Intraoperative blood loss (mL)	1650	0.572	0.504–0.640	0.042

higher incidence of chronic severe hepatitis and this was found to be an independent risk factor for AKI in patients receiving OLT. This suggests that patients with chronic severe hepatitis and poor condition should receive special attention and care after surgery.

Supporting the results of Zongyi *et al.* (18), our results also show that preoperative creatinine is an independent risk factor for AKI and shows moderate predictive ability. In their multicenter study of 5074 patients, the average preoperative serum creatinine of the AKI group was 85 (64–136), significantly higher than that of the control group of 74.6 (56.2–110) and their multivariate analysis showed preoperative serum creatinine (>354 μmol/L) was a risk factor (OR: 1.352; 95% CI: 1.181–1.763; P<0.001). The relatively high preoperative serum creatinine may result from the unavoidable whole body ischemia occurring during OLT (8,19). To prioritize the blood supply to other important organs, a transitory insufficient supply to the kidney may occur, causing tubular necrosis (20). This study is limited by its single-center, retrospective design and only moderate number of participants. Multi-center, prospective studies with larger cohorts are required to confirm the results.

Conclusions

In summary, chronic severe hepatitis and high preoperative creatinine levels may be potential risk factors for the occurrence of AKI after OLT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-7680

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The clinical study was approved by the Ethics Committee of Beijing Chao-Yang Hospital and was conducted in accordance with the provisions of the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all participants before enrolment.

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