Original Article

Optimal timing of initiating CRRT in patients with acute kidney injury after liver transplantation

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Background: Acute kidney injury (AKI) is a frequent complication after liver transplantation (LT), and is associated with high mortality. Continuous renal replacement therapy (CRRT) is an important treatment for AKI, but the optimal time for initiation is still controversial. The purpose of this study was to investigate the prognostic effect of initial CRRT treatment time.

Methods: We retrospectively reviewed the clinical data of 173 recipients undergoing LT from January 2018 to March 2019. AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. All patients receiving CRRT were divided into early and late group according to urine output. Prognosis was compared between the two groups.

Results: A total of 48 (27.8%) patients were identified with AKI, 23 (13.3%) of whom received CRRT. According to urine output, 13 (56.5%) patients were in early group and 10 (43.5%) patients in late group. AKI was associated with longer intensive care unit (ICU) and hospital stay, increased post-operative 90-day mortality and the incidence of early allograft dysfunction (EAD). Patients in late CRRT group had a longer ICU stay {median, IQR, 183.5 [92.25–336.75] *vs.* 139 [94–240] hours, P=0.043} and hospital stay {median, IQR, 38.5 [17.5–62.75] *vs.* 35 [17–38] days, P=0.019} than patients in early CRRT group, respectively. The rate of severe infection was significantly higher in the late CRRT group than in the early CRRT group (80.0% *vs.* 30.8%, P=0.026).

Conclusions: AKI was associated with longer length of ICU and hospital stay, poor short-term mortality and functional recovery of transplanted organ. Early initiation of CRRT could reduce the severe infection and length of ICU and hospital stay.

Keywords: Continuous renal replacement therapy (CRRT); acute kidney injury (AKI); liver transplantation (LT)

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Introduction

Acute kidney injury (AKI) is one of the main postoperative complications after liver transplantation (LT), and is associated with increased morbidity and mortality (1). The incidence of AKI and severe AKI requiring continuous renal replacement therapy (CRRT) were 40.7% and 7.7%, respectively (1). Post-LT AKI is associated with an increased short-term mortality rate and graft dysfunction (2,3). Post-LT AKI is caused by multifactorial origin with recipient, graft, perioperative, and postoperative

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factors (4). There is increasing evidence that increased model for end-stage liver disease (MELD) score, diabetes mellitus (DM), hypertension, obesity, intraoperative blood loss and transfusion of blood products, postoperative immunosuppression therapy are risk factors (5).

In order to standardize the definition and classification of AKI, the Risk, Injury, Failure, Loss and End-stage (RIFLE) definitions, the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) criteria were put forward successively (6-8). Although most patients eventually recover after an episode of AKI, many patients invaded their renal reserve or did not return to baseline renal function. And severe AKI requires CRRT, however, there is a lack of consensus on several aspects of CRRT, especially the optimal initiation timing (9). Indeed, despite the large amount of evidence available, it still represents an unsolved problem (10). Especially, there is no report about the optimal initiation timing of CRRT for AKI after LT.

Thus, we aim to estimate the incidence of post-LT AKI in our center and to evaluate its impact on patient outcomes. For severe post-LT AKI patients receiving CRRT treatment, we focus on the effect of the timing of initiation of CRRT on prognosis. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2352).

Methods

Patients who underwent LT between January 2018 to March 2019 at The First Affiliated Hospital, Sun Yat-Sen University (Guangzhou, China) were included. Patients with chronic kidney disease or receiving preoperative CRRT or kidney transplantation before were excluded. Eventually 173 patients were included in this study. Immunosuppressive therapy for all patients after LT was individualized therapy, and immunosuppressive agents were adjusted based on drug blood concentrations.

Recipient data extracted from the medical records included age and gender, model of end-stage liver disease (MELD) score, HBV infection status, previous history of hypertension, DM, previous liver disease, hepatic encephalopathy. For donors, age and gender, body mass index (BMI), donor status (DCD or DBD), cold ischemia time, Pathology of donor liver, serum Na^+ and total bilirubin. From the intraoperative period, we recorded: blood loss, volume of blood transfusion, duration of surgery and anhepatic period. Postoperative indicators included: Urine volume, serum creatinine, primary nonfunction (PNF), early allograft dysfunction (EAD), days of intensive care unit (ICU) and overall in-hospital stay, 30 and 90 day mortality rates, as well as follow-up time.

AKI was defined according to KDIGO criteria by serum creatinine and urine output (8). They were categorized as patients with AKI or not. We defined the initiation timing of CRRT based on urine output (during the 24 h prior to CRRT initiation) (11), urine output (UO) criteria were defined as "early" when UO during the 24h prior to CRRT was >0.05 mL/kg/h and as "late" when UO was <0.05 mL/kg/h.

Fisher's exact test or chi-square test was used for comparisons of categorical data. Student's *t*-test and the Mann-Whitney U test were used for the comparisons of continuous variables, according to their distribution, as appropriate. Effects of parameters to estimate AKI were evaluated with multivariate logistic regression models.

All statistical analyses were performed using SPSS version 19.0 statistical software (SPSS, Chicago, IL, USA). Values of $P<0.05$ were considered to indicate statistical significance.

All organs come from voluntary donation from citizens, no executed prisoner (even with his/her consent) was involved. The study was approved by the Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University (Approval No. (2020) 343) and in accordance with the Declaration of Istanbul. All protocols conformed to the ethical guidelines of the Helsinki Declaration (as revised in 2013).

Results

Of the 173 eligible patients, 158 patients (91.33%) were men. The mean age ± SD was 50.88±9.43 years. Hepatocellular carcinoma (HCC) was the most common etiologic factor (53.18%). One hundred and forty-nine patients (86.13%) were hepatitis B positive. the median model of end-stage liver disease (MELD) score prior to LT was 14 (IQR, 9–20.75). There were 14 diabetic patients (8.09%), and 7 patients (4.05%) presented hypertension before LT (*Table 1*).

Among the 173 patients, 48 (27.75%) developed AKI after LT. *Table 1* shows the risk factors for AKI. Of the 48 AKI patients, 23 received RRT treatment. According to the definition of the initial time of "early" and "late" RRT, 13 patients were divided into the early group and 10 patients into the late group. The clinical differences were compared

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Table 1 Patient demographic and perioperative data

Variables	AKI (n=48)	Non-AKI (n=125)	P value
Preoperative variables			
Age, mean (SD), year	51.69 (9.53)	50.32 (10.23)	0.424
Male, n (%)	43 (89.58)	115 (92.0)	0.563
BMI, mean (SD)	23.23 (2.24)	22.18 (2.46)	0.269
HBV, n (%)	38 (79.17)	111 (88.8)	0.139
MELD score, median (IR)	18 (11.25–25.75)	12.5 (9–19.25)	0.239
Etiologic factors			0.291
HCC, n (%)	22 (45.83)	70 (56.0)	
Hepatitis B cirrhosis, n (%)	10 (20.83)	30 (24.0)	
Alcoholic cirrhosis, n (%)	4 (8.33)	3 (2.4)	
hepatic failure, n (%)	11 (22.92)	18 (14.4)	
Other, n (%)	1 (2.08)	4 (3.2)	
Diabetes, n (%)	5 (10.42)	9 (7.2)	0.537
Hypertension, n (%)	3 (6.25)	4 (3.2)	0.398
Hepatic encephalopathy, n (%)	4 (8.33)	1 (0.8)	0.021
Donor graft			
Age, mean (SD), year	41.4 (8.38)	34.15 (12.81)	0.238
Male, n (%)	40 (83.33)	88 (70.4)	0.121
DBD, n (%)	48 (100.0)	124 (99.2)	0.723
DCD, n (%)	0 (0)	1 (0.8)	
Total bilirubin, median (IR), μmol/L	18.9 (12.35–34)	22.8 (13.25–33.75)	0.921
Na^+, median (IR), $mmol \cdot L^{-1}$	148 (140.5–158)	148 (141.75–156)	0.969
Cold ischemia time, median (IR), min	415 (352.5–477.75)	323 (67.5–388.5)	0.217
Steatosis in donor liver			0.144
0, n (%)	29 (60.42)	85 (68.0)	
1, n (%)	16 (33.33)	33 (26.4)	
2, n (%)	3 (6.25)	2 (1.6)	
3, n (%)	0 (0)	5 (4.0)	
Intraoperative			
Operation time, median (IR), min	442.5 (393–505.25)	452.5 (386.75–520)	0.217
Piggyback, n (%)	30 (62.5)	72 (57.6)	0.341
Anhepatic phase, median (IR), min	52 (41.5–65)	49 [40–59]	0.446
Blood loss, median (IR), mL	2,500 (1,950–5,175)	1,500 (800–2,500)	<0.001
RBC transfusion, median (IR), unit	7.5 (3.75–12)	9 [2–7]	<0.001
Plasma transfusion, median (IR), mL	1,750 (1,200–2,575)	1,400 (1,000–1,950)	<0.001
Cryoprecipitate transfusion, median (IR), unit	0 (0–0)	0 (0–0)	0.022
Platelet transfusion, median (IR), unit	1 (0–1)	0 (0–1)	0.023

AKI, acute kidney injury; SD, standard deviation; n, number; IR, interquartile range; BMI, body mass index; MELD, model of end-stage liver disease; HCC, hepatocellular carcinoma; DBD, donors after brain death; DCD, donors after cardiocirculatory death; RBC, red blood cells.

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Table 2 Patient demographic and perioperative data between early group and late group

Variables	Early (n=13)	Late (n=10)	P value
Preoperative variables			
Age, mean (SD), year	48.27 (8.81)	49.44 (10.82)	0.687
Male, n (%)	11 (84.62)	9 (90.00)	0.704
BMI, mean (SD)	23.34 (2.50)	22.73 (2.27)	0.548
HBV, n (%)	11 (84.62)	8 (80.00)	0.772
MELD score, median (IR)	23.50 (14.25–26.00)	18.00 (10.00–29.00)	0.946
Etiologic factors			0.806
HCC, n (%)	5 (38.46)	4 (40.0)	
Hepatitis B cirrhosis, n (%)	3 (23.08)	2 (20.0)	
Alcoholic cirrhosis, n (%)	1 (7.69)	1 (10.0)	
hepatic failure, n (%)	4 (30.77)	2 (20.0)	
Other, n (%)	0 (0)	1 (10.0)	
Diabetes, n (%)	2 (15.38)	1 (10.0)	0.704
Hypertension, n (%)	1 (7.69)	0 (0)	0.370
hepatic encephalopathy, n (%)	3 (23.08)	1 (10.0)	0.459
Donor graft			
Age, mean (SD), year	37.08 (11.00)	44 (6.75)	0.151
Male, n (%)	10 (76.92)	8 (80.0)	0.859
DBD, n (%)	13 (100.0)	10 (100.0)	
DCD, n (%)	0 (0)	0 (0)	
Total bilirubin, median (IR), μmol/L	23.6 (12.08–43.15)	18.6 (15.5–25.6)	0.730
Na^+, median (IR), $mmol \cdot L^{-1}$	145.5 (139.75–161)	145 [143–156]	0.850
Cold ischemia time, median (IR), min	377 (337–412.5)	430 [420–477]	0.363
Steatosis in donor liver			0.840
0, n (%)	8 (61.54)	7 (70.0)	
1, n (%)	4 (30.77)	2 (20.0)	
2, n (%)	1 (7.69)	1 (10.0)	
3, n (%)	0 (0)	0 (0)	
Intraoperative			
Operation time, median (IR), min	435 (420–504.75)	505 [440–660]	0.069
Piggyback, n (%)	8 (61.54)	6 (60.0)	0.940
Anhepatic phase, median (IR), min	43.5 (38–55.25)	46 [38–69]	0.372
Blood loss, median (IR), mL	3,000 (2,000–6,350)	5,000 [1,200–10,000]	0.498
RBC transfusion, median (IR), unit	6 (4.13–9.13)	4 [4–21]	0.206
Plasma transfusion, median (IR), mL	2,200 (1,500–3,050)	2,200 (1,750–6,150)	0.141
Cryoprecipitate transfusion, median (IR), unit	0 (0–0)	0 (0–0)	0.517
Platelet transfusion, median (IR), unit	1 (0–1.25)	1 (0–2)	0.697

AKI, acute kidney injury; SD, standard deviation; n, number; IR, interquartile range; BMI, body mass index; MELD, model of end-stage liver disease; HCC, hepatocellular carcinoma; DBD, donors after brain death; DCD, donors after cardiocirculatory death; RBC, red blood cells.

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between early and late group (*Table 2*). The following factors were AKI predictors: preoperative encephalopathy, high MELD score, intraoperative bleeding volume, Blood transfusion volume, long operation time and cold ischemia time. In the multivariate analysis, independent risk factors for AKI were: intraoperative bleeding volume (OR =1, 95% CI: 1.000–1.001) and plasma transfusion (OR =1, 95% CI: 1.000–1.001) (*Table 3*).

AKI patients had a longer ICU stay, 85 hours (range, 21.5–196.5) *vs.* 28.6 hours (range, 15–42), P<0.001, as well as longer overall hospital stay, 24.5 days (range, 17–40) *vs.* 20 days (range, 15–29) (P=0.003), than non-AKI patients, respectively. There were 10 patients (20.83%) and 13 patients (27.08%) died within 30 days and 90 days in the AKI group, while 2 patients (1.6%) and 2 patients (1.6%) died in the non-AKI group. EAD occurred in 25 patients (52.08%) in AKI group and 27 patients (21.6%) in non-AKI group. Primary nonfunction (PNF) occurred in 8 patients (16.67%) in AKI group and 0 patients (0 %) in non-AKI group (*Table 4*).

The 30-day mortality was 23.08% in the early group, 40% in the late group. The 90-day mortality was 30.77% in the early group, 50% in the late group. The patients in late group had a longer ICU stay, 183.5 hours (range, 92.25–336.75) *vs.* 139 hours (range, 94–240), P=0.043, as well as longer overall hospital stay, 38.5 days (range, 17.5–62.75) *vs.* 35 days (range, 17–38), (P=0.019) than early group patients, respectively. EAD occurred in 9 patients (69.23%) in early group and 8 patients (80%) in late group. Primary non-function (PNF) occurred in 1 patient (7.69%) in early group and 4 patients (40%) in late group. There were 8 patients with severe infection in late group and 4 patients in early group (P=0.026) (*Table 5*).

Table 3 Independent predictors of AKI after liver transplantation based on multivariate logistic regression

Variables	OR (95% CI)	P
Anhepatic phase	1.007 (0.984–1.030)	0.563
Cold ischemia time	1.002 (1.000–1.004)	0.097
Hepatic encephalopathy	0.160 (0.012–2.187)	0.170
Operation time	0.996 (0.990–1.001)	0.137
Blood loss	1.000 (1.000–1.001)	0.001
RBC transfusion	1.000 (0.999–1.000)	0.339
Plasma transfusion	1.000 (1.000–1.001)	0.032
Cryoprecipitate transfusion	0.994 (0.930–1.064)	0.869

RBC, red blood cells.

Discussion

LT is the most effective treatment for end-stage liver disease. AKI is a common complication following LT, the incidence ranging from 26.3% to 75.6% in recipients, this disparity is largely due to non-uniform definitions of AKI (12-14). In 2012, KDIGO revised AKI classification merged the AKIN and RIFLE criteria by including both an increase of serum creatinine by ≥26 μmol/L within 48 h as well as an increase to ≥1.5 times baseline within 7 days as threshold for diagnosis of AKI (8). So far, few studies have used KDIGO criteria to evaluate post-LT AKI. The present study used the KDIGO criterion to define and classify AKI, and the incidence of post-LT AKI was 27.75%.

Several risk factors for post-LT AKI have been identified in varying populations. It is likely that post-LT is of

Table 4 Comparison of clinical outcomes between AKI group and non-AKI group

Variables	AKI (n=48)	Non-AKI (n=125)	P value
Length of ICU stay, median (IR), h	85 (21.5–196.5)	28.6 [15–42]	<0.001
Length of hospital stay, median (IR), day	24.5 [17–40]	20 [15–29]	0.003
30-day mortality, n (%)	10 (20.83)	2 (1.6)	<0.001
90-day mortality, n (%)	13 (27.08)	2 (1.6)	<0.001
PNF, n (%)	8 (16.67)	0 (0)	<0.001
EAD, n (%)	25 (52.08)	27 (21.6)	<0.001
Acute rejection, n (%)	1 (2.08)	10 (8.0)	0.138

AKI, acute kidney injury; h, hour; ICU, intensive care unit; PNF, primary nonfunction; EAD, early allograft dysfunction; IR, interquartile range.

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Table 5 Comparison of clinical outcomes between early group and late group

Variables	Early (n=13)	Late (n=10)	P value
Length of ICU stay, median (IR), h	139 (94–240)	183.5 (92.25–336.75)	0.043
Length of hospital stay, median (IR), day	35 (17–38)	38.5 (17.5–62.75)	0.019
30-day mortality, n (%)	3 (23.08)	4 (40.0)	0.337
90-day mortality, n (%)	4 (30.76)	5 (50.0)	0.306
PNF, n (%)	1 (7.69)	4 (40.0)	0.089
EAD, n (%)	9 (69.23)	8 (80.0)	0.463
Severe infection, n (%)	4 (30.76)	8 (80.0)	0.026

ICU, intensive care unit; h, hour; PNF, primary nonfunction; EAD, early allograft dysfunction; IR, interquartile range.

multifactorial origin with recipient, graft, perioperative and postoperative factors contributing to its development. Recipient factors included high MELD-scores, pretransplant SCr and BMI (15,16). Intraoperative factors, such as inferior portal vein clamping, intraoperative blood loss and blood transfusion, cold and warm ischemia time, and operation time contributes to AKI occurrence (17). Furthermore, perioperative hyperglycaemia has been suggested as a risk factor for AKI (18). Risk factors for AKI in the post-transplant period included nephrotoxic drugs use, mainly calcineurin inhibitors, and hypoalbuminemia (17,19). In our study, Logistic multivariate analysis suggested that intraoperative bleeding volume and plasma transfusion were risk factors for AKI.

Due to the absence of effective pharmacological treatment, the treatment of AKI patients mainly depends on the management of hemodynamics and volume status, the correction of electrolyte and acid-base disturbances, the provision of adequate nutrition and the adjustment of drug doses. For less severe AKI patients, conservative treatment can be considered as the treatment option. For patients with sustained, severe renal failure, CRRT can be used to treat volume overload, hyperkalemia, acidosis and symptoms of uraemia waiting for the recovery of renal function (20). 20% of AKI patients require CRRT approximately (21). Although survival rates have improved over the past two decades even though the dialysis rate requiring AKI has increased (22), many problems still remain in the optimal administration of CRRT for AKI. Apart from the therapy mode, treatment dose and type of anticoagulation, the initiation timing of treatment is considered an important determinant of the outcome of critically ill patients receiving CRRT (23). The KDIGO AKI guideline is widely accepted and recommend the initiation CRRT without delay in case of life-threatening complications (24). Until recently, only few small RCTs and some observational and cohort studies examining timing of initiation of CRRT, some of which showed beneficial effects of "early" CRRT (25). However, there has been no clear consensus on how to define "timing" relative to the initiation of CRRT in AKI, different definitions of "early" and "late" initial timing of CRRT might have biased the results. Basis of definitions in published studies include urine output, creatinine, urea, time from AKI development and hospital or ICU admission (26,27). In addition, the terms "early" and "late" are relative and what may represent early CRRT in one case could be late in another (28). In our study, we defined "early" and "late" based on urine output, which were defined as "early" when UO during the 24 h prior to CRRT was >0.05 mL/kg/h and as "late" when UO was <0.05 mL/kg/h (11). Timing based on urine output seems to be a more physiological than hospital or ICU admission. Recently, several systematic review and meta-analyses exploring initiation timing of and outcome have been published. The study by Zou *et al.* (29) strongly supported early initiation, based on the outcomes of 28-day mortality, ICU length of stay, and hospital length of stay. However, there was no difference in survival, ICU or hospital length of stay between early and late CRRT in the studies of Bhatt and Wierstra (26,30). There are a few studies on the application of CRRT in post-LT AKI, but no studies on the prognosis of the initiation timing. According to our study, late initiation of CRRT can prolong ICU and hospital length of stay, and also increase the risk of infection.

This paper had several limitations. This was a retrospective, single-center study with a small number of patients and the short period of time. Thus, there is clearly a requirement for a prospective large scale trial to further

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understand CRRT for LT-associated AKI in the future.

In conclusion, AKI is a frequent complication of LT, which is associated with higher mortality and longer ICU and hospital stay. The more intraoperative bleeding volume and plasma transfusion are risk factors of post-LT AKI. Late initiation of CRRT can prolong ICU and hospital length of stay, and also increase the risk of infection.

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Footnote

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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 study protocol conforms to the ethical guidelines of the Declaration of Helsinki (as revised in 2013) as reflected in a priori approval by the institutional ethics committee [Approval No. (2020) 343]. Because of the retrospective nature, the requirement of informed consent was waived.

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