Characteristics of Acute Kidney Injury and Its Impact on Outcome in Patients With Acute-On-Chronic Liver Failure

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Abstract

Objective: Acute kidney injury (AKI) is a common and life-threatening complication of liver failure. However, the characteristics of AKI and its impact on prognosis in patients with acute-on-chronic liver failure (ACLF) are limited.

Methods: 574 ACLF patients were evaluated retrospectively. AKI was defined by criteria proposed by International Club of Ascites (ICA) and divided into community-acquired and hospital-acquired AKI (CA-AKI and HA-AKI). The difference between CA-AKI and HA-AKI, factors associated with development into and recovered from AKI periods, and its impact on prognosis in ACLF patients were evaluated.

Results: Among 574 patients, 217(37.8%) patients had AKI, CA-AKI and HA-AKI were 56 (25.8%) and 161 (74.2%) respectively. Independent risk factors of AKI occurrence were age, gastrointestinal (GI) bleeding, bacterial infections, albumin (ALB), total bilirubin (TBIL), blood urea nitrogen (BUN) and prothrombin time (PTs). The AUROC of the model in internal and external validations were 0.747 and 0.759, respectively. Among 217 AKI patients, 81(37.3%), 96(44.2%) and 40(18.4%) patients were with ICA-AKI stage progression, regression and fluctuated in-situ, respectively. The 90-day mortality of patients with AKI was 55.3% (CA-AKI 58.9% and HA-AKI 54.0%) higher than non-AKI patients 21.6%. The 90-day mortality of patients with progression of AKI was 88.9%, followed by patients with fluctuated in-situ 40% and regression of AKI 33.3%. Independent predictors of 90-day mortality in ACLF patients were GI bleeding, hepatic encephalopathy (HE), TBIL, INR, progression of AKI.

Conclusions: AKI can increase the 90-day mortality significantly in ACLF patients. TBIL, INR, GI bleeding, HE, progression of AKI are independent risk factors affecting 90-day mortality in ACLF patients.

Trial registration: Chinese clinical trials registry: ChiCTR1900021539.

Introduction

Acute-on-chronic liver failure (ACLF) is an acute deterioration of liver function within a short period under acute precipitating insult, which manifests as multiple organ failure and high 28 and 90-day mortality [1, 2]. Acute kidney injury (AKI), which is the most common complication of ACLF, is characterized by a sudden decline in renal function [3]. Patients with liver disease are prone to intravascular volume depletion secondary to gastrointestinal bleeding, and tend to be susceptible to usage of diuretic and aminoglycosides. Most importantly, because of the hyperdynamic circulatory state, patients with cirrhosis are highly susceptible to renal events associated with a further decrease in effective arterial blood volume [4].

A previous study showed that among 1032 patients with ACLF who had underlying cirrhosis, 11.7% had AKI at admission (community-acquired), and 30.9% developed AKI during hospitalization (hospital-acquired) [5]. AKI is an early stage disease, and exacerbation of the initial kidney injury can eventually progress to irreversible damage to kidney function [6, 7]. Approximately 2/3 of AKI episodes in patients with cirrhosis are functional or volume-responsive and reversible [8]. However, patients with even mild renal impairment (peak AKI stage 1) had significantly higher 90-day mortality than those without any renal impairment [4, 9]. Moreover, patients who completely recovered renal function at the end of AKI episodes also had a much higher 90-day mortality than those who had never suffered from AKI [10]. However, knowledge of the characteristics of AKI and its impact on the prognosis of patients with ACLF is limited.
This study aimed to investigate the characteristics of AKI in ACLF patients. We compared community-acquired and hospital-acquired AKI (CA-AKI and HA-AKI, respectively) patients and evaluated the risk factors associated with development of and recovery from AKI. The effect of AKI on the prognosis of patients with ACLF was also evaluated. Furthermore, we constructed a visual nomogram and online calculator for predicting the development of AKI based on a model. This may be used by physicians to determine the occurrence of AKI and to minimize poor prognosis.

**Patients And Methods**

**Study participants**

A flowchart explaining the patient selection process is shown in Fig. 1. The data of 574 patients with ACLF admitted to Tianjin Third Central Hospital between June 2006 and May 2019 were analyzed retrospectively. ACLF was defined according to the APAPL criteria: acute deterioration of liver function manifesting as jaundice [total bilirubin (TBIL) ≥ 5mg/dL or ≥ 85umol/L] and coagulopathy with international normalized ratio of prothrombin time (INR) ≥ 1.5 or prothrombin activity (PTA) ≤ 40%, complicated with ascites and/or hepatic encephalopathy noted within 4 weeks in a patient with previously diagnosed or undiagnosed chronic liver disease [11]. Patients who were discharged alive from hospital were followed at least 3 months by telephone. Exclusion criteria were as follows: age < 18 or age > 70 years old, with hepatic and non-hepatic neoplasia, chronic kidney disease under hemodialysis treatment before admission, previous kidney or liver transplant, clinically estimated life expectancy < 3 days.

This retrospective study was approved by the Ethics Committee of Tianjin Third Central Hospital, Beijing You’an Hospital Affiliated to Capital Medical University and the Fifth Medical Center of PLA General Hospital and conducted according to the principles of the Declaration of Helsinki. Approved No. of ethic committee: SZX-IRB-SOP-016(F)-002-01. This trial was registered in the Chinese clinical trials registry: ChiCTR1900021539. We obtained written informed consent from all patients or their legal guardian.

**Data collection**

Baseline population characteristics (age, sex, concomitant disease, and etiology of chronic liver disease) and clinical data (complications of chronic liver disease, laboratory parameters, and other parameters) were collected or calculated from the electronic medical records of patients. The estimated glomerular filtration rate (eGFR) was derived from MDRD equation [12]. The Model for End-Stage Liver Disease (MELD) = 3.78 × ln [bilirubin (mg/dL) + 11.2 × ln (INR) + 9.57 × ln [creatinine (mg/dL)] + 6.43. MELD-Na score = MELD + 1.59 × (135 – Na⁺). Hepatic encephalopathy (HE) was defined and graded by the West Haven criteria. Definitions of bacterial infections were depicted as well as in reference 13 [13].

According to the International Club of Ascites (ICA) criteria, the definition of AKI is an absolute increase in serum creatinine (sCr) of ≥ 0.3 mg/dL from baseline within 48 hours or a percent increase of sCr ≥ 50% from baseline within the prior 7 days [3] and then classified it into stage 1, 2, and 3 [3]. Progression of AKI was considered as ICA-AKI stage progressed to a higher stage and/or need for renal replacement therapy (RRT). Regression of AKI was considered as ICA-AKI stage regressed to a lower stage. Fluctuated in-situ of AKI was considered as AKI stage neither progression nor regression during hospitalization. Initial ICA-AKI stage was
defined by the AKI stage at the time of first fulfillment of the ICA-AKI criteria. Peak ICA-AKI stage was defined by the highest AKI stage reached during hospitalization.

The baseline sCr value is as a stable sCr that is available within the previous 3 months. In patients with more than one value within the previous 3 months, the value closest to admission time to the hospital was used. When sCr measurement has never been done, the sCr on admission was used as baseline [3]. Community-acquired AKI were patients diagnosed with AKI on admission. Hospital-acquired AKI were patients which without AKI on admission and developed AKI during the hospitalization [14].

**Statistical analysis**

Continuous variables were described by mean ± SD, while categorical variables were expressed by frequency (percentage). Differences between groups continuous variables were compared with Mann-Whitney test or two-tailed t test, categorical variables were compared with fisher exact test or chi-square test. Missing values of several variables were included in the descriptive analysis but were removed from the logistic regression analyses.

Statistically significant factors and the clinical correlates of AKI were transferred to stepwise multivariate binary logistic regression model: Forward: LR, selected variables (P ≤ 0.05); Eliminating variables (P > 0.05), to identify the independent factors, OR and construct the predictive model. The model was evaluated by the Hosmer-Lemeshow test to appraise the goodness of fit and visualized by nomogram through package “rms” and “ggplot2” in R. Harrells concordance index (C-index) and the area under the Receiver Operator Characteristic (AUROC) curve were used as metric to quantify the nomogram performance in training and validation cohort. The calibration curves were established by randomly booting 1000 times in training and validation groups respectively to further assess the accuracy of the nomogram.

Finally, Kaplan-Meier survival curves were used to discriminate the relationship between the model and 90-day survival probability through packed “survival” and “survminer” in R and assessed by log-rank test. All data were analyzed by SPSS.24 and R software (version 4.0.5).

**Results**

**Baseline characteristics of eligible patients**

The mean age of the 574 patients was 51.1 ± 12.2, and 434 (75.6%) were male. The most common etiology of liver disease was hepatitis B virus (HBV) infection (51.7%). The complications of ACLF on admission were as follows: hepatic encephalopathy (n = 54), ascites (n = 300), GI bleeding (n = 114), bacterial infections (n = 100), and AKI (n = 217).

Among the 574 patients with ACLF, 217 (37.8%) had AKI, and 132 (60.8%), 58 (26.7%), and 27 (12.4%) patients met ICA-AKI stages 1, 2, and 3, respectively. Compared with non-AKI patients, patients with AKI tended to be older and more frequently had GI bleeding and bacterial infections (P < 0.05). Moreover, compared with non-AKI patients, AKI patients tended to have a higher heart rate, WBC count, total bilirubin (TBIL), INR, blood urea nitrogen (BUN), admission sCr, serum potassium, CTP, MELD, and MELD-Na scores, and lower albumin, eGFR and serum sodium values (P < 0.05) (Table 1).
Table 1
Comparison of characteristics between patients with and without AKI, CA-AKI and HA-AKI

| Variables                          | Non-AKI (N=357) | AKI (N=217) | P-value | AKI (N=56) | AKI (N=161) | P-value |
|------------------------------------|-----------------|-------------|---------|------------|-------------|---------|
| **Age (years)**                    | 49.6±11.9       | 53.6±12.1   | <0.001  | 54.1±11.8  | 53.5±12.2   | 0.728   |
| **Male-n (%)**                     | 265(74.2)       | 169(77.9)   | 0.323   | 45(80.4)   | 124(77.0)   | 0.604   |
| **Death-n(%)**                     | 77(21.6)        | 120(55.3)   | <0.001  | 33(58.9)   | 87(54.0)    | 0.0526  |
| Hypertension-n(%)                  | 42(11.8)        | 41(18.9)    | 0.019   | 10(17.9)   | 31(19.3)    | 0.818   |
| Diabetes mellitus-n(%)             | 56(9.8)         | 43(19.8)    | 0.204   | 10(17.9)   | 33(20.5)    | 0.669   |
| **Baseline Cr(umol/L)**            | 60.5±18.4       | 84.9±49.1   | <0.001  | 128.2±70.8 | 69.9±25.5   | <0.001  |
| **Baseline eGFR(ml/min/1.73m^2)**  | 134.6±43.1      | 109.5±61.1  | <0.001  | 73.4±45.6  | 122.0±60.9  | <0.001  |
| **Peak Cr(umol/L)**                | -               | 214.2±139.9 |         | 276.4±158.8| 192.6±126.1 | <0.001  |
| **Etiology of liver disease-n (%)**|                 |             | 0.013   |            |             | 0.793   |
| Hepatitis B                        | 195(54.6)       | 102(47.0)   |         | 25(44.6)   | 77(47.8)    |         |
| Alcohol                            | 92(25.8)        | 81(37.3)    |         | 23(41.1)   | 58(36.0)    |         |
| Other causes                       | 70(19.6)        | 34(15.7)    |         | 8(14.3)    | 26(16.1)    |         |
| **Complications at admission-n (%)**|               |             |         |            |             |         |
| Ascites                            | 182(51.0)       | 118(54.4)   | 0.429   | 30(53.6)   | 88(54.7)    | 0.888   |
| HE                                 | 32(9.0)         | 22(10.1)    | 0.640   | 7(12.5)    | 15(9.3)     | 0.497   |
| Gl bleeding                        | 51(14.3)        | 63(29.0)    | <0.001  | 19(33.9)   | 44(27.3)    | 0.349   |
| Bacterial infection                | 46(12.9)        | 54(24.9)    | <0.001  | 11(19.6)   | 43(26.7)    | 0.292   |
| **Admission parameters**           |                 |             |         |            |             |         |
| MAP (mmHg)                         | 90±11.5         | 88.7±14.9   | 0.117   | 82.8±15.0  | 90.7±14.4   | <0.001  |
| Heart rate (bpm)                   | 82.6±14         | 87.2±14.9   | <0.001  | 91.2±18    | 85.8±13.5   | 0.010   |
| WBC (×10^9/L)                      | 7.0±4.4         | 9.8±6.5     | <0.001  | 12.2±7.2   | 9.0±6.1     | <0.001  |
| PLT (×10^9/L)                      | 99.3±62.3       | 104.3±69.6  | 0.186   | 111.4±77.5 | 101.9±66.7  | 0.190   |

*Estimated by MDRD. ALB: albumin; BUN, blood urea nitrogen; CTP, child-turcotte-pugh; eGFR, estimated glomerular filtration rate; HE, hepatic encephalopathy; INR: international normalized ratio; MAP, mean arterial pressure; MELD: model for end-stage liver disease; PLT: platelet; sCr: serum creatinine; TBIL: total bilirubin; WBC, white blood cells;
| Variables                  | Non-AKI N=357 | AKI N=217 | \( P \)-value | AKI CA-AKI N=56 | AKI HA-AKI N=161 | \( P \)-value |
|---------------------------|---------------|-----------|---------------|----------------|-----------------|--------------|
| ALB (g/L)                 | 29.4±5.1      | 27.3±5.1  | <0.001        | 26.6±4.5       | 27.5±5.3        | 0.140        |
| TBIL (µmol/L)             | 233.1±129.3   | 263.1±156.7| 0.009         | 261.3±154.4    | 263.7±157.9     | 0.462        |
| INR                       | 2.3±0.9       | 2.4±1.1   | 0.034         | 2.6±1.4        | 2.4±1.0         | 0.077        |
| PT (s)                    | 33.8±10.9     | 35.7±13.3 | 0.033         | 36.1±13.2      | 35.5±13.3       | 0.391        |
| BUN (mmol/L)              | 5.3±3.1       | 10.4±7.3  | <0.001        | 17.7±7.9       | 7.9±5.1         | <0.001       |
| sCr (µmol/L)              | 60.6±18.4     | 110.8±80.7| <0.001        | 213.1±91.7     | 75.2±31.1       | <0.001       |
| Serum Na⁺ (mmol/L)        | 134.3±5.8     | 132.3±6.1 | <0.001        | 130.9±7.2      | 132.8±5.6       | 0.021        |
| Serum K⁺ (mmol/L)         | 3.8±0.6       | 4.0±0.7   | 0.004         | 4.1±0.9        | 3.9±0.6         | 0.029        |
| eGFR (ml/min/1.73m²)*     | 134.6±43.1    | 105.2±62.9| <0.001        | 62.2±45.7      | 120.2±61.2      | <0.001       |
| CTP                       | 11.1±1.7      | 11.5±1.8  | 0.006         | 11.8±1.7       | 11.4±1.8        | 0.118        |
| MELD                      | 18.2±5.7      | 22.6±8.5  | <0.001        | 30.4±7.1       | 20.0±7.2        | <0.001       |
| MELD-Na                   | 22.5±8.5      | 29.3±10.9 | <0.001        | 38.9±9.8       | 26.0±9.2        | <0.001       |

**Initial ICA-AKI stage-n**
Stage 1/2/3: 132/58/27 vs. 30/14/12, \( P = 0.060 \)

**Peak ICA-AKI stage-n**
Stage 1/2/3: 84/60/73 vs. 25/9/22, \( P = 0.080 \)

*Estimated by MDRD. ALB: albumin; BUN, blood urea nitrogen; CTP, child-turcotte-pugh; eGFR, estimated glomerular filtration rate; HE, hepatic encephalopathy; INR: international normalized ratio; MAP, mean arterial pressure; MELD: model for end-stage liver disease; PLT: platelet; sCr: serum creatinine; TBIL: total bilirubin; WBC, white blood cells;*

Among 217 patients with AKI, 56 (25.8%) were community-acquired and 161 (74.2%) were hospital-acquired. There were no significant differences in the etiology of chronic liver disease, diabetes, hypertension, cirrhosis-related complications, or the initial and peak ICA-AKI stages between the two groups \( (P > 0.05) \). Patients with CA-AKI had a higher heart rate, baseline sCr, peak sCr, admission sCr, WBC counts, BUN, and serum potassium values, and lower MAP, serum sodium, and baseline eGFR values than those in the HA-AKI group \( (P < 0.05) \). Liver function severity scores, such as MELD and MELD-Na scores, were also higher in the CA-AKI group than those in the HA-AKI group \( (P < 0.05) \). However, there were no differences between the two groups in terms of CTP scores \( (P = 0.118) \) (Table 1).

**Risk Factors And Nomogram For Aki In Aclf**

Among the 574 patients with ACLF, 56 patients had community-acquired AKI on admission, and these were excluded. Next, the remaining 518 patients were used as the training cohort to identify the risk factors for
predicting the development of AKI and to establish a nomogram. A total of 174 patients with ACLF who were admitted to the Fifth Medical Center of PLA General Hospital (n = 82) and Beijing You’an Hospital (n = 92) were included as the validation cohort. Internal and external validations were performed based on the training and validation groups, respectively (Fig. 1).

Risk factors for predicting the development of AKI from multivariate binary logistic regression analysis included: age (P, OR, 95%CI) (0.009, 1.023, 1.006-1.041), GI bleeding (0.015, 1.892, 1.131-3.166), bacterial infection (<0.001, 2.967, 1.751-5.027), ALB (0.010, 0.942, 0.901-0.986), TBIL (0.001, 1.003, 1.001-1.004), BUN (<0.001, 1.128, 1.067-1.193), and PTs (0.015, 1.022, 1.004-1.041) (Table 2). The ability of KP-AKI model for predicting the occurrence of AKI constructed by multivariate binary logistic regression was: 0.023 · Age + 0.638 · GI bleeding (1 if GI bleeding, 0 otherwise) + 1.087 · bacterial infection (1 if bacterial infection, 0 otherwise) – 0.060 · ALB (g/L) + 0.003 · TBIL (µmol/L) + 0.121 · BUN (mmol/L) + 0.022 · PT(s)-2.828. The KP-AKI model showed goodness of fit, as demonstrated by the Hosmer-Lemeshow test (χ² = 11.042, P = 0.199) and Omnibus test (χ² = 89.203, P <0.001).

| Variables           | Estimate | OR (95%CI)            | Standard error | Wald X² | P-value |
|---------------------|----------|-----------------------|----------------|---------|---------|
| Age (years)         | 0.023    | 1.023(1.006-1.041)    | 0.009          | 6.746   | 0.009   |
| GI bleeding         | 0.638    | 1.892(1.131-3.166)    | 0.263          | 5.901   | 0.015   |
| Bacterial infection | 1.087    | 2.967(1.751-5.027)    | 0.269          | 16.333  | <0.001  |
| TBIL (µmol/L)       | 0.003    | 1.003(1.001-1.004)    | 0.001          | 11.591  | 0.001   |
| BUN (mmol/L)        | 0.121    | 1.128(1.067-1.193)    | 0.028          | 18.080  | <0.001  |
| ALB (g/L)           | -0.060   | 0.942(0.901-0.986)    | 0.023          | 6.716   | 0.010   |
| PT(s)               | 0.022    | 1.022(1.004-1.041)    | 0.009          | 5.956   | 0.015   |

Table 2
Risk factors for development into AKI in ACLF patients

The KP-AKI model from the training cohorts was visualized using a nomogram (Fig. 2A), which is presented online at https://tyhyue12.shinyapps.io/APP-Nomapp/. Users are required to input seven answers to predict the probability of AKI occurrence in ACLF patients. No answers will be stored. As shown in the nomogram, patients with a higher age, TBIL, BUN, and PT levels, GI bleeding, bacterial infection, and a lower ALB value were more likely to develop AKI. The C-index was 0.747 in the training cohort and 0.759 in the validation cohort (Table 1, Supplementary Digital Content 1). The trends of the calibration curves of the internal training cohort (mean absolute error = 0.019) and external validation cohort (mean absolute error = 0.029) were similar (Fig. 2B, Fig. 2C).

To compare the predictive performance of the KP-AKI model and the traditional scoring system in the occurrence of AKI in ACLF patients, the area under the receiver operating characteristics (AUROC) method was used. The AUROC of the KP-AKI model (AUC, 95% CI, P) (0.747, 0.702-0.792, <0.001) was the highest, followed by MELD-Na
Comparison among patients with AKI stage progression, regression and fluctuated in-situ

Among the 217 AKI patients, 81 (37.3%) progressed to a higher AKI stage, 96 (44.2%) regressed to a lower AKI stage, and 40 (18.4%) patients fluctuated in situ. At discharge from the hospital, 84 (38.7%), 60 (27.6%), and 73 (33.6%) patients had reached peak stage 1, 2, and 3 ICA-AKI, respectively. Patients with progression of AKI tended to have an older age, higher mortality, more presence HBV infection, encephalopathy, hepatorenal syndrome (HRS) and acute tubular necrosis (ATN), higher baseline and peak sCr values, higher value of TBIL, INR and BUN. higher CTP, MELD and MELD-Na scores at the time for diagnosis of AKI than patients without progression of AKI ($P < 0.05$). However, the initial ICA-AKI stage, ALB, WBC and PLT were not significantly different among the three groups ($P > 0.05$) (Table 3).
Table 3
Comparisons among patients with AKI progression, regression and fluctuated in-situ

| Variables                       | Fluctuated in-situ | Regression | Progression | P-value |
|---------------------------------|--------------------|------------|-------------|---------|
|                                 | N=40               | N=96       | N=81        |         |
| Age (years)                     | 55.5±9.1           | 50.6±12.1  | 56.4±12.7   | 0.003   |
| Male-%                         | 28(70.0)           | 81(84.4)   | 60(74.1)    | 0.107   |
| Death-%                        | 16(40.0)           | 32(33.3)   | 72(88.9)    | <0.001  |
| MAP (mmHg)                     | 90.6±11.9          | 86.1±17.3  | 90.8±12.7   | 0.074   |
| Heart rate (bpm)               | 88.4±15.9          | 89.0±16.1  | 84.5±12.6   | 0.115   |
| Baseline Cr(µmol/L)            | 78.7±39.3          | 78.4±33.0  | 95.8±65.4   | 0.041   |
| Baseline eGFR(ml/min/1.73m²)   | 110.3±53.5         | 111.2±47.6 | 107.1±77.3  | 0.903   |
| Peak Cr(µmol/L)                | 147.5±82.1         | 173.6±112.1| 295.3±154.1| <0.001  |
| CA-AKI/ HA-AKI- n              | 11/29              | 28/68      | 17/64       | 0.447   |
| Initial ICA-AKI stage-n        |                    |            |             |         |
| Stage 1/2/3                    | 28/10/2            | 58/23/15   | 46/25/10    | 0.383   |
| Peak ICA-AKI stage-n           |                    |            |             |         |
| Stage 1/2/3                    | 26/12/2            | 49/29/18   | 9/19/53     | <0.001  |
| Type of AKI-%                  |                    |            |             | <0.001  |
| ATN                            | 2(5.0)             | 15(15.6)   | 56(32.1)    |         |
| PRA                            | 22(55.0)           | 77(80.2)   | 8(9.9)      |         |
| HRS                            | 16(40.0)           | 15(15.6)   | 47(58.0)    |         |
| Etiology of liver disease- n   |                    |            |             | <0.001  |
| Hepatitis B                    | 19(47.5)           | 35(36.5)   | 48(59.3)    |         |
| Alcohol                        | 10(25.0)           | 50(52.1)   | 51(25.9)    |         |
| Other causes                   | 11(27.5)           | 11(11.5)   | 12(14.8)    |         |
| Complications during hospitalization- n (%) |                  |            |             |         |
| Ascites                        | 26(65.0)           | 70(72.9)   | 58(71.6)    | 0.643   |
| HE                             | 15(35.0)           | 19(19.8)   | 33(40.7)    | 0.008   |
| GI bleeding                    | 9(22.5)            | 22(22.9)   | 19(23.5)    | 0.992   |
| Bacterial infection            | 30(75.0)           | 74(77.1)   | 70(86.4)    | 0.198   |
| Shock                          | 2(5.0)             | 10(10.4)   | 13(18.0)    | 0.182   |
Multivariate logistic regression analysis was used to evaluate the independent factors associated with AKI progression. Based on the univariate analysis of parameters presented in Table 3, the independent factors associated with the progression of AKI were found to be HA-AKI, alcohol liver disease, BUN, INR, baseline eGFR, presence of PRA and ATN (Table 4).

### Table 4
Predictors for progression of AKI

| Variables        | estimate | OR (95% CI)  | Standard error | Wald X2 | P-value |
|------------------|----------|--------------|----------------|---------|---------|
| HA-AKI           | 1.459    | 4.301(1.599-11.57) | 0.505          | 8.350   | 0.004   |
| Alcohol liver disease | -1.246  | 0.288(0.116-0.716)  | 0.465          | 7.182   | 0.007   |
| BUN              | 0.057    | 1.058(1.012-1.107) | 0.023          | 6.259   | 0.012   |
| INR              | 0.381    | 1.463(1.092-1.96)  | 0.149          | 6.519   | 0.011   |
| PRA              | -3.666   | 0.026(0.009-0.077)  | 0.560          | 42.848  | <0.001  |
| ATN              | 1.751    | 5.763(1.724-19.263) | 0.616          | 8.093   | 0.004   |
| Baseline eGFR    | 0.011    | 1.011(1.003-1.019)  | 0.004          | 6.869   | 0.009   |
Impact Of Aki On 90-day Survival InACLEF Patients

The incidence of 90-day mortality in patients with AKI was 54.8% (CA-AKI, 58.9%; HA-AKI, 54.0%), which was higher than that in patients without AKI (21.6%) (Fig. 3A). The 90-day mortality rates of the patients with peak ICA-AKI stages 1, 2, and 3 were 40.4%, 46.6%, and 79.5%, respectively. Mortality increased in a stage-dependent manner with AKI severity (Fig. 3B). The 90-day mortality of AKI patients with a peak sCr ≥ 133 µmol/L (65.5%) was significantly higher than that of patients with a peak sCr < 133 µmol/L (33.3%) (Fig. 3C). Furthermore, we noted a strong relationship between AKI type and mortality. Patients with acute tubular necrosis had the worst prognosis, followed by those with HRS and pre-renal azotemia (PRA) (Fig. 3D). The 90-day mortality of patients with progression of AKI was 88.9%, followed by patients with fluctuation in situ (40%) and regression (33.3%) (Fig. 3E). Even in patients with regression of AKI (33.3%), the 90-day mortality rate was still much higher than that in patients without AKI (21.6%) (Fig. 3E). We also investigated the relationship between the KP-AKI model and 90-day mortality in ACLF patients. These patients were further classified into two groups using the cut-off value of the KP-AKI model score: a high group (KP-AKI score ≥ 0.28) and a low group (KP-AKI score < 0.28). The 90-day mortality rate in the high KP-AKI group was higher (46.0%) than that in the low KP-AKI group (19.4%) (P < 0.001) (Fig. 3F).

The results of the multivariate logistic regression analysis showed that the independent factors associated with an increased risk of mortality at 90-days were TBIL, INR, GI bleeding, hepatic encephalopathy and progression of AKI (Table 5).

| Variables      | Estimate | OR (95%CI)     | Standard error | Wald X² | P-value |
|----------------|----------|----------------|----------------|---------|---------|
| GI bleeding    | 1.131    | 3.099(1.376-6.977) | 0.414          | 7.460   | 0.006   |
| HE             | 0.933    | 2.543(1.088-5.944) | 0.433          | 4.639   | 0.031   |
| TBIL           | 0.003    | 1.003(1.001-1.005) | 0.001          | 6.158   | 0.013   |
| INR            | 0.628    | 1.874(1.168-3.005) | 0.241          | 6.790   | 0.009   |
| Progression of AKI | 2.965    | 19.404(8.18-46.027) | 0.441          | 45.280  | <0.001  |

Discussion

AKI is a common and rapidly progressive in patients with ACLF and is associated with significantly worse outcome. Although that approximately 2/3 of AKI episodes in patients with cirrhosis were functional or volume responsive and reversible [8]. The 30-day mortality of ACLF patients with AKI remains very high (about 50%) [15]. Because of the ominous prognosis and potential reversibility of AKI in ACLF patients, identifying the characteristics of AKI and its impact on outcome is essential for management of these patients.

In our study, 217 (37.8%) patients had AKI; of these, 56 (25.8%) had CA-AKI, and 161 (74.2%) had HA-AKI. This finding is consistent with those of previous studies. Xin et al [5]. reported that the prevalence of AKI was 42.6% in patients with ACLF with underlying cirrhosis (CA-AKI and HA-AKI accounted for 27.5% and 72.5%, respectively). However, they do not further evaluate the demographic and clinical characteristics, risk factors,
and clinical outcomes of HA-AKI and CA-AKI. A prospective study showed that the overall prevalence of AKI is 35% in patients with cirrhosis (CA-AKI and HA-AKI accounted for 25% and 10%, respectively) [14]. Compared with HA-AKI, CA-AKI had a significantly higher AKI stage both at AKI diagnosis and at peak, and is associated with increased mortality, de novo chronic kidney disease (CKD), and CKD progression. However, the initial and peak ICA-AKI stages and 90-day mortality rates were not significantly different between the two groups in our study. This difference is likely related to the differences in the patient population. Our patients were ACLF patients who met the APAPL criteria, which includes patients with an acute deterioration of liver function within a short-term period under acute precipitating insult, excluding patients with previous decompensated liver cirrhosis [11]. Moreover, serum sodium, bilirubin, and INR were all similar between the groups. The differences in the admission MELD and MELD-Na scores may simply be a function of the higher admission creatinine levels in CA-AKI. Nevertheless, our findings suggest that prompt identification and treatment of AKI affects outcomes, and patients with CA-AKI should be monitored closely after discharge to avoid poor outcomes.

In this study, almost 40% of the patients had AKI, which could be avoided by eliminating its risk factors. GI bleeding, bacterial infection, age, ALB, TBIL, BUN, PTs were the independent risk factors for AKI in ACLF patients. The predictive model of KP-AKI encompasses the above seven factors, which are more precise in predicting the incidence of AKI than the conventional scoring systems (CTP, MELD, and MELD-Na scores). None of these scores were developed for the prediction of AKI in patients with ACLF; therefore, it is not surprising that the KP-AKI score was superior to these scores for the prediction of AKI. Recently, a PRIO model was developed to predict AKI in ACLF patients [15]. This model was found to be superior to the MELD, MELD-Na, CTP, CLIF-SOFA, and CLIF-C ACLF scores for predicting the development of AKI and mortality in ACLF patients. However, the primary etiology of chronic liver disease is alcoholic liver disease (ALD). Moreover, the PRIO model does not distinguish between HA-AKI and CA-AKI [15]. Our study focused on the prediction of the occurrence of HA-AKI, which accounts for the majority of AKI cases; on the other hand, the predominant etiology of chronic liver disease is HBV infection.

Circulatory dysfunction and systemic inflammation are the primary pathogeneses of AKI [16]. Patients with liver cirrhosis frequently use diuretics, large-volume paracentesis, and liver-injury drugs; as such, these patients are particularly susceptible to intravascular volume depletion. Moreover, due to the hyperdynamic circulatory state of patients with cirrhosis, which results in low arterial blood volume, these patients are at an increased risk of adverse events associated with further decreases in effective arterial blood volume [4]. Presence of GI bleeding, or even hypovolemic shock, aggravates the shortage of effective arterial blood volume, further activating the sympathetic nervous system, renin-angiotensin-aldosterone system, and non-osmotic release of antidiuretic hormone [17]. As the disease progresses, splanchnic and systemic vasodilatations worsen and activate vasoconstrictive systems, leading to renal vasoconstriction. Additionally, insufficient cardiac output further contributes to the diminution of kidney perfusion and progression of kidney injury [17, 18].

Bacterial infection has multiple causes, including as altered gut microflora, loss of intestinal integrity, translocation of bacteria, immune dysfunction and portal systemic shunting on ACLF patients [19]; it is a common and fatal complication in patients with ACLF, and can also act as a trigger for AKI and ACLF development and progression [20]. Bacterial infection triggers inflammation through pathogen-associated molecular patterns, resulting in the release of inflammatory mediators that cause tissue damage, which in turn leads to the release of damage-associated molecular patterns, which further drives the inflammatory process. Indeed, serum levels of the pro-inflammatory cytokine interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-
reactive protein, and lipopolysaccharide are elevated in patients with cirrhosis in parallel with the severity of disease, and are associated with poor outcomes [21, 22]. An excessive inflammatory response can induce apoptosis/necrosis of renal parenchyma and interstitial cells through various inflammatory pathways, eventually causing kidney dysfunction [16].

Serum bilirubin, albumin, and coagulopathy were the primary parameters that were found to indicate the severity of liver dysfunction. ALB and bilirubin mirrored liver synthesis and hepatocellular injury. Hypoproteinemia and bilirubin levels were related to a high incidence of AKI. High bilirubin can lead to an underestimation of sCr, which can obscure renal insufficiency in clinical situations [23]. Accumulated unbound bilirubin inhibits oxidative phosphorylation, which leads to changes in renal tubular cell permeability and damage renal function [24,25]. Coagulation function is complicated in ACLF, which is characterized by a precarious balance between bleeding and thrombosis due to repeated hemostasis, organ failure, sepsis, and anticoagulant use in ACLF patients. Studies have shown that hypocoagulable and hypofibrinolytic states were correlated with systemic inflammation, and could contribute to organ failure and higher short-term mortality of ACLF patients [26, 27]. The abnormal coagulation regulating pathway in inflammation can damage renal function through immunothrombosis of the kidney, or coagulation-induced production of mitogenic factors (IL-6, IL-17, IL-22, and miRNAs), which can trigger epithelial cell proliferation [28]. In our study, ACLF patients with abnormal coagulation function were more likely to develop AKI.

Serum bilirubin, ALB, and coagulopathy were the primary variables of the CTP score, which indicates the severity of liver dysfunction and predicts the prognosis of patients with cirrhosis. Furthermore, both variceal bleeding and bacterial infection are frequent triggers of ACLF and AKI, and failure to control these factors contributes to high mortality. Therefore, by including the above factors in the KP-AKI model, which coincide with the pathophysiology and predictors of AKI in ACLF patients, it is possible to identify and stratify ACLF patients at risk of AKI and mortality.

In addition, among 217 AKI patients, 81 (37.3%), 96 (44.2%), and 40 (18.4%) patients had ICA-AKI stage progression, regression, and fluctuation in situ, respectively. This rate of progression is much higher than that reported by Fagundes et al [10] in a series of hospitalized patients with cirrhosis, which was only 22%. The discrepancy may be due to differences in the severity of disease among the patient populations, or the methods used for the prevention or treatment of AKI. A recent study showed that AKI in ACLF patients is more likely to be associated with structural kidney injury and is more progressive, showing a poorer response to terlipressin treatment and a worse prognosis than that of DC patients [29]. Independent factors associated with progression of AKI were HA-AKI (OR = 4.301), alcohol liver disease (OR = 0.288), BUN (OR = 1.058), INR (OR = 1.463), baseline eGFR (OR = 1.011), presence of PRA (OR = 0.026) and ATN (OR = 5.763). This means that patients with alcohol liver disease may have a better prognosis of AKI than those with other types of chronic liver disease. A recent study showed that the factors associated with the progression of AKI were hepatic encephalopathy, chronic kidney impairment, severe liver and circulatory failure, low serum sodium concentration, and high leukocyte count [10]. Surprisingly, progression of AKI was not related to serum creatinine concentration at the time of diagnosis. The 90-day mortality of patients with both ICA-AKI stage 3 and progression of AKI was the highest. Therefore, close monitoring outside the hospital for early identification, and timely treatment to prevent the progression of AKI is necessary to improve poor prognosis.
In summary, almost 40% of patients with ACLF develop AKI. Among these, 25% had CA-AKI, which may benefit from frequent monitoring after discharge to improve outcomes. On the other hand, HA-AKI accounts for approximately 75% of AKI cases and can be avoided by eliminating its risk factors. Furthermore, this study developed a KP-AKI model for predicting AKI occurrence in ACLF patients and constructed an online calculator that is more convenient and accurate than the traditional scoring systems (CTP, MELD, and MELD-Na scores). The progression of AKI is common in patients with ACLF, and patients with a greater AKI and ICA-AKI stage progression were associated with worse prognoses among ACLF patients. Further studies are needed to validate our findings and to establish more effective prevention and treatment strategies to improve poor outcomes.

**Abbreviations**

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; AUROC, receiver operator characteristic curve; albumin, ALB; c-index, concordance index; blood urea nitrogen (BUN); CLD, chronic liver disease; community-acquired AKI, CA-AKI; eGFR, estimated glomerular filtration rate; HA-AKI, hospital-acquired acute kidney injury; HE, hepatic encephalopathy; INR, international normalized ratio; MAP, mean arterial pressure; prothrombin time (PTs); sCr, serum creatinine; TBIL, total bilirubin;

**Declarations**

**Ethics approval and consent to participate**

This retrospective study was approved by the Ethics Committee of Tianjin Third Central Hospital, Beijing You’an Hospital Affiliated to Capital Medical University and the Fifth Medical Center of PLA General Hospital and conducted according to the principles of the Declaration of Helsinki (approved No. of ethic committee: SZX-IRB-SOP-016(F)-002-01). This trial was registered in the Chinese clinical trials registry: ChiCTR1900021539. We obtained written informed consent from all patients or their legal guardian.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declared no conflict of interests.

**Availability of data and materials**

The clinical data in the study will not be shared publicly due to participants were informed at the time of providing consent that only researchers involved in the project would have access to the information they provided. But are available from the corresponding author on reasonable request.

**Authors' contributions**

Study concept and design, acquisition of data, analysis and interpretation of data and drafting of the manuscript (YH, JJC), critical revision of the manuscript for important intellectual content (TH, JJC, YH, FSH,
BCG), administrative, technical, or material support (SJX, ZPD), study supervision (TH). All authors read and approved the final version of the manuscript.

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**Figures**

**Figure 1**

A flow chart explaining the patient’s selection process
Figure 2

A. The nomogram constructed by KP-AKI model in training cohort. As shown in the Fig 2A, a 59-year-old patient upon admission with a bacterial infection and gastrointestinal bleeding, the BUN was 7.39 mmol/L and TBIL was 193.1 $\mu$mol/L, PT was 47 second and ALB was 25.8 g/L, the total point added up to 224, which represents the occurrence of HA-AKI was 76.2%; B. Calibration curves in the internal training cohort. C. Calibration curves in the external validation cohort. D. ROC curves for several scoring systems in identified for the development of AKI.
Figure 3

Kaplan-Meier survival analyses of the 90-day mortality in ACLF patients. A. Patients without AKI, with CA-AKI and HA-AKI; B. Patients without AKI and with ICA-AKI stage 1, 2 and 3; C. Patient without AKI, with peak sCr \(\geq 133\) μmol/L and with peak sCr \(\geq 133\) μmol/L; D. Patient with ATN, HRS and PRA, respectively; E. Patient with progression of AKI, regression of AKI and fluctuated in-situ; F. Patients divided by cut-off value of KP-AKI: High group (KP-AKI score \(\geq 0.28\)) and Low group (KP-AKI score < 0.28).

Supplementary Files

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