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ORIGINAL ARTICLE

Acute kidney injury in hospitalized cirrhotic patients: Risk factors, type of kidney injury, and survival

Chitta Ranjan Khatua, Saroj Kanta Sahu, Dinesh Meher, Gautam Nath and Shivaram Prasad Singh

Department of Gastroenterology, Sriram Chandra Bhanja Medical College and Hospital, Cuttack, India

Key words
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Correspondence
Shivaram Prasad Singh, Department of Gastroenterology, Sriram Chandra Bhanja Medical College and Hospital, Cuttack 753007, Odisha, India.
Email: scb_gastro_dept@hotmail.com

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Abstract

Background and Aim: Acute kidney injury (AKI) is a common complication of chronic liver disease (CLD). We performed a prospective study to evaluate the risk factors and spectrum of AKI among decompensated cirrhosis (DC) patients and the impact of AKI on survival.

Methods: This study was conducted in consecutive DC patients hospitalized in SCB Medical College between December 2016 and October 2018. AKI was defined as per ICA criteria. Demographic, clinical, and laboratory parameters and outcomes were compared between patients with and without AKI.

Results: A total of 576 DC subjects were enrolled, 315 (54.69%) of whom had AKI; 34% (n = 106) had stage 1A, 28% (n = 90) stage 1B, 21% (n = 65) stage 2, and 17% (n = 54) stage 3 AKI. Alcohol was the predominant cause of CLD (66.7%). In 207 (65.7%) patients, diuretic/lactulose/nonsteroidal anti-inflammatory drugs use was noted, and infection was present in 190 (60.3%) patients. Compared to those without AKI, patients with AKI had higher leucocyte count, higher serum urea and creatinine, higher Child-Turcotte-Pugh, higher Model of End-Stage Liver Disease (MELD) scores ($P < 0.001$), longer hospital stay, and lower survival at 28 days and 90 days ($P < 0.001$). Besides, in patients with stages 1A to 3 AKI, there were differences in overall survival at 28 days ($P < 0.001$) and 90 days ($P < 0.001$).

Conclusions: Over half of DC patients had AKI, and alcohol was the most common cause of cirrhosis in them. Use of AKI-precipitating medications was the most common cause of AKI, followed by bacterial infection. AKI patients had increased prevalence of acute-on-chronic liver failure and had prolonged hospitalization and lower survival both at 28 days and 90 days.

Introduction

In cirrhosis of the liver, portal hypertension leads to severe arterial vasodilation as a result of the release of vasodilators in the splanchnic circulation.[1] This causes a reduction in circulating volume and a compensatory activation of endogenous vasoconstrictor systems (sympathetic nervous system, renin angiotensin aldosterone system, and nonosmotic release of vasopressin), resulting in hyperdynamic circulation and sodium and water retention and in ascites and/or dilutional hyponatremia. In the advanced stages, the maximal activation of vasoconstrictor systems may cause severe renal vasoconstriction, leading to hepatorenal syndrome (HRS), a functional renal failure associated with poor survival.[2,3] Along with portal hypertension, two other factors, namely, reduction in cardiac output and systemic inflammation, are responsible for the hemodynamic alterations and renal hypoperfusion.[4] Furthermore, systemic inflammation may also cause damage to organs other than the kidney, such as the brain, the heart, the lungs, or the liver itself, causing a multiorgan failure syndrome, which is encountered in acute-on-chronic liver failure (ACLF).[5]

As a result of multifactorial insults, patients with cirrhosis have a high prevalence of acute kidney injury (AKI), varying between 14 and 50% in patients of CLD, and this prevalence is around 20% in compensated cirrhosis and 50% in cirrhosis and ascites.[6,7] Furthermore, about 50% of acute decompensated cirrhosis (DC) patients have been observed to have AKI during hospitalization, a third of which develops during the course of treatment.[8-11] Even stable outpatients frequently develop AKI during follow-up.[12]

AKI is characterized by an acute significant reduction in glomerular filtration rate (GFR), decrease in urine output, and rise in serum creatinine (Scr). It has been observed that a meager increase of 0.3 mg/dL in serum creatinine is crucial and can impact survival.[13-15] As per International Club of Ascites criteria (ICA), AKI is defined as (i) an increase of SCr by 0.3 mg/dL (26.5 μmol/L) within 48 h or (ii) a percentage increase of SCr by 50% from baseline, known or presumed to have occurred within

the prior 7 days.[16] Furthermore, AKI has been classified by the ICA-AKI criteria into three stages (1–3) depending on the intensity of rise in SCr, and this staging classification correlates well with prognosis in patients with cirrhosis,[17,18] with stages 2 and 3 having worse prognosis compared with stage 1.[4,8,9,10,17,19] Recently, stage 1 has been further subdivided into two subgroups on the basis of serum levels of creatinine (SCr): stage 1A (SCr < 1.5 mg/dL) and stage 1B (SCr ≥ 1.5 mg/dL), and this subclassification is justified by the differential outcomes.[11,20]

The most common precipitants of AKI are prerenal injury (70%) and intrinsic renal causes (30%), followed by postrenal factors (<1%).[10,21] It has been reported that the presence of AKI in DC or ACLF patients adversely affects survival; hence, early recognition of AKI causes and its treatment is crucial for improving outcome.[22-25] For this, a thorough history and careful physical examination are crucial to evaluate causes for AKI, such as ongoing gastrointestinal losses (diarrhea/vomiting) leading to hypovolemia and hypotension, use of medications (i.e. diuretics, nonsteroidal anti-inflammatory drugs [NSAIDS], angiotensin-converting enzyme inhibiters, angiotensin II receptor blockers, vasodilators, and aminoglycoside antibiotics), and presence of cellulitis or other infections. An appropriate workup, such as obtaining pan cultures and chest radiography, urinalysis and urine microscopy, and urine biomarkers estimation, should be performed to detect infection and intrarenal injury.[16,21,26] Renal ultrasound is necessary to rule out postrenal injury.

The present study was conducted to evaluate the risk factors and spectrum of AKI among DC patients and the impact of AKI on the survival of these patients.

Methods

Study design. A prospective study was carried out in consecutive DC patients hospitalized in the Gastroenterology Department, SCB Medical College between December 2016 and October 2018; they were screened for AKI as per ICA-AKI criteria.[16]

Demographic, clinical, and laboratory parameters and type of kidney injury were recorded on admission; the risk factors for AKI were evaluated, and survival was compared between patients with and without AKI and also among different stages of AKI. Survival was compared during hospitalization and also at 28 and 90 days.

Patients were meticulously assessed for known risk factors causing AKI and were managed according to the standard of care. All drugs precipitating AKI were stopped; intravascular hypovolemic condition was corrected with intravenous saline; and variceal bleeding was treated with blood transfusions and intravenous terlipressin, followed by endotherapy. Intravenous albumin was used for initial volume expansion for 48 h, and patients with volume-nonresponsive AKI fulfilling the criteria for HRS were treated with intravenous albumin and terlipressin or noradrenaline; hemodialysis was planned when required. Patients with bacterial infection received empirical intravenous antibiotics and albumin; the antibiotics were later changed according to culture and sensitivity result. In the presence of septic shock, noradrenaline infusion was used.[16,27,28]

Furthermore, all cirrhotic patients were screened for the presence of ACLF as per the criteria of APASL, EASL-CLIF Consortium, or both. ACLF has been defined differently by various learned hepatology societies. As per the APASL consensus, "ACLF is an acute hepatic insult manifesting as jaundice (serum bilirubin ≥5 mg/dL (85 μmol/L) and coagulopathy (INR ≥1.5 or prothrombin activity <40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease or cirrhosis", and is associated with a high 28-day mortality.[29] However, the AASLD and EASL working group defines ACLF as "Acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multi-system organ failure".[30]

Inclusion criteria. All DC patients, diagnosed on the basis of clinical findings, laboratory test results, endoscopy, and radiologic imaging, with a SCr report within the previous 7 days were included in the study.

Exclusion criteria. Patients with chronic kidney disease, structural kidney disease, hepatocellular carcinoma, other malignancies, and cardiopulmonary diseases were excluded from the study.

The study was thoroughly explained to patients satisfying the inclusion criteria, and these patients were included if they agreed and signed an informed consent form and were followed up for 90 days.

Primary and secondary outcomes. Survival at 28 days was defined as the primary end-point, while that at 90 days served as the secondary end-point for our survival analysis. Duration of hospital stay was the other secondary end-point for comparing DC patients with and without AKI at admission.

Statistical methods. Demographic, clinical, and laboratory parameters and outcomes were compared between patients with and without AKI. Normally distributed continuous variables were reported as mean and standard deviation and compared using Student t test. Nonnormally distributed continuous variables were reported as median and interquartile range and compared using the Mann–Whitney *U* test. Categorical variables were reported as proportions and compared using the chi-square test or Fisher exact test, as appropriate. The 28-day and 90-day survival was estimated by the Kaplan–Meier method and compared by means of the log-rank test. Receiver operating characteristic curve (AUROC) analysis for prognostic parameters like admission serum urea, serum creatinine, presence of infection, variceal bleeding, gastrointestinal losses, and reversal of creatinine was carried out to evaluate the impact on survival both at 28 days and 90 days. All tests were two-tailed, and P values <0.05 were considered significant. A statistical analysis was performed using SPSS statistical package, version 20.0 (IBM Corp, Armonk, NY, USA).

Ethical clearance has been obtained from the Institutional Ethics Committee, SCB Medical College, Cuttack 753007, Odisha, Regd. No.ECR/84/Inst/OR/2013.

Results

A total of 613 DC patients were admitted; 37 patients were subsequently excluded because they either did not meet the inclusion criteria or were lost to follow-up. Of the remaining 576 patients, 315 (54.69%) had AKI and were enrolled in the study. Alcohol was not only the most common cause of underlying cirrhosis (58.7%) overall but was the most common cause of cirrhosis in patients with AKI (66.7%) (Table 1). In patients with AKI, other less common causes of cirrhosis were hepatitis B (HBV) or hepatitis C virus (HCV) infection (18.41%), NASH-related cirrhosis (5.08%), and other miscellaneous causes (9.84%) (Fig. 1a). AKI patients had used AKI-precipitating drugs (such as diuretic/lactulose/NSAIDS) more frequently (65.7% *vs* 31.4%; $P < 0.001$) and were more often admitted with associated bacterial infections (60.3% *vs* 32.2%; $P < 0.001$). However, the prevalence of variceal bleeding, diarrhea, and/or vomiting was comparable between patients with and without AKI. AKI patients were more often males (59%) and older (49.76 ± 11.87 *vs* 47.66 ± 12.69; $P = 0.043$). Furthermore, patients with AKI had a higher total leucocyte count (8600 *vs* 7200; $P < 0.001$), total bilirubin (3.80 *vs* 2.30; $P < 0.001$), serum creatinine (1.70 *vs* 0.90; $P < 0.001$), serum urea (49 *vs* 22; $P < 0.001$), INR (1.79 *vs* 1.55; $P < 0.001$), serum potassium (4.20 *vs* 4.00; $P = 0.018$), Model of End-Stage Liver Disease (MELD) (UNOS) (24.70 ± 9.03 *vs* 15.47 ± 7.70; $P < 0.001$), MELD (Na+) (26.69 ± 8.59 *vs* 18.02 ± 6.12; $P < 0.001$), and Child-Turcotte-Pugh score (11.42 ± 2.42 *vs* 10.08 ± 2.30; $P < 0.001$). They also had a higher proportion of Child C cirrhosis (78.73 *vs* 57.47%; $P < 0.001$) and ACLF as per APASL (34.9 *vs* 16.9%;

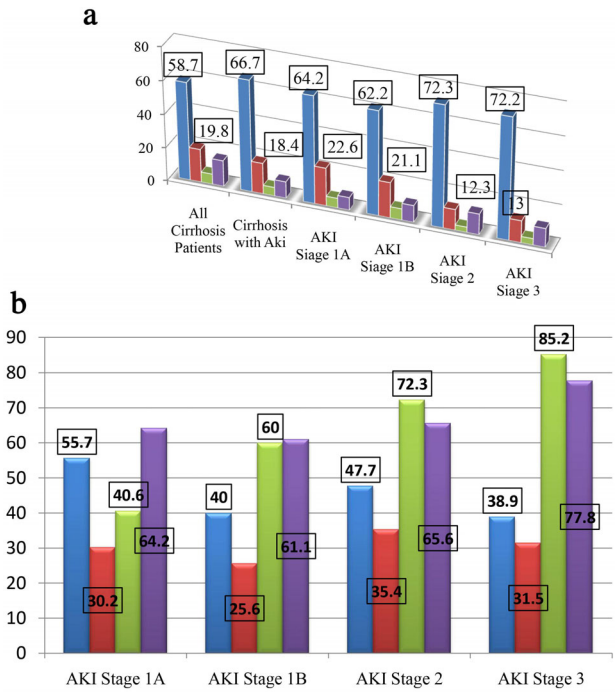

Figure 1 (a) Etiology of cirrhosis with and without acute kidney injury. (■), Alcohol; (■), HBV/HCV infection; (■), NASH/NAFLD; (■), others. (b) Precipitants of acute kidney injury (AKI) for stages AKI 1A, 1B, 2, and 3. (■), Variceal bleeding; (■), diarrhoea and/or vomitting; (■), infection; (■), drug precipitant.

Table 1 Comparison of baseline characteristics and acute kidney injury (AKI) precipitants at admission between patients with and without AKI

Sl. no	Parameters	Patients without AKI (n = 261)	Patients with AKI (n = 315)	P value
1	Age (mean ± SD)	47.66 ± 12.69	49.76 ± 11.87	0.043
2	Gender: Male (%)	198 (41%)	285 (59%)	<0.001
3	BMI (kg/m^2) (mean ± SD)	21.23 ± 3.70	21.82 ± 4.0	0.069
4	MAP (mmHg) (mean ± SD)	85.32 ± 8.42	83.62 ± 11.23	0.039
5	Etiology of cirrhosis (Alcohol [%])	128 (49.1%)	210 (66.7%)	<0.001
6	Serum creatinine (mg/dL) (Median [IQR])	0.90 (0.80–1.0)	1.70 (1.30–2.40)	<0.001
7	Urea (mg/dL) (Median [IQR])	22 (18–28)	49 (35–79)	<0.001
8	Serum bilirubin (total in mg/dL) (Median [IQR])	2.30 (1.10–4.40)	3.80 (1.50–7.60)	<0.001
9	INR (Median [IQR])	1.55 (1.31–1.84)	1.79 (1.46–2.36)	<0.001
10	Serum protein (g/dL) (Mean ± SD)	6.50 ± 0.90	6.48 ± 2.02	0.878
11	Serum albumin (g/dL) (Mean ± SD)	2.72 ± 0.49	2.64 ± 0.49	0.041
12	Serum sodium (mEq/L) (Mean ± SD)	134.65 ± 13.06	132.58 ± 10.99	0.043
13	Serum potassium (mEq/L) (Median [IQR])	4.00 (3.50–4.30)	4.20 (3.70–4.90)	0.018
14	SAAG (Mean ± SD)	2.28 ± 0.52	2.19 ± 0.53	0.041
15	Total leucocyte count (10^3 cells/dL) (Median [IQR])	7200 (6200–9200)	8600 (6800–12 000)	<0.001
16	Urine Sodium (mEq/L) (Median [IQR])	40.20 (22.00–76.93)	35.20 (20.00–65.00)	0.479
17	Variceal bleeding (%)	140 (53.6%)	147 (46.7%)	0.096
18	Diarrhea and/or vomiting (%)	93 (35.6%)	95 (30.2%)	0.163
19	Infection (%)	84 (32.2%)	190 (60.3%)	<0.001
20	Drugs precipitating AKI (%)	81 (31.1%)	207 (65.7%)	<0.001

BMI, body mass index; CTP, Child-Turcotte-Pugh; INR, International Normalized Ratio; IQR, interquartile range; MAP, mean arterial pressure; MELD, model for end-stage liver disease; SAAG, serum-ascites albumin gradient; SD, standard deviation; UNOS, The United Network for Organ Sharing.

Table 2 Comparison of indices of severity of liver disease and outcomes at admission between patients with and without acute kidney injury (AKI)

Sl. no	Parameters		Patients without AKI (n = 261)	Patients with AKI (n = 315)	P value
1	MELD (UNOS) (Mean ± SD)		15.47 ± 7.70	24.70 ± 9.03	<0.001
2	MELD (Na^+) (Mean ± SD)		18.02 ± 6.12	26.69 ± 8.59	<0.001
3	CTP score (Mean ± SD)		10.08 ± 2.30	11.42 ± 2.42	<0.001
4	Child class (%)	A	9 (3.45%)	4 (1.27%)	<0.001
		B	102 (39.1%)	63 (20%)	
		C	150 (57.5%)	248 (78.7%)	
5	ACLF (APASL) (n = 154)		44 (28.6%)	110 (71.4%)	<0.001
6	ACLF (EASL-CLIF Consortium) (n = 232)		44 (19%)	188 (81%)	<0.001
7	ACLF (APASL and EASL-CLIF Consortium) (n = 110)		20 (18.2%)	90 (81.8%)	<0.001
8	Duration of hospital stay (Median [IQR])		4 (3–5)	6 (4–8)	<0.001
9	Death during hospitalization		7 (2.7%)	56 (17.8%)	<0.001
10	28-day survival (%)		232 (88.9%)	210 (66.7%)	<0.001
11	90-day survival (%)		197 (75.5%)	140 (44.4%)	<0.001
12	HR of mortality during hospitalization		HR, 1.506; 95% CI, 1.362–1.666	<0.001	
13	HR of mortality at 28 days		HR, 1.430; 95% CI, 1.320–1.549	<0.001	
14	HR of mortality at 90 days		HR, 1.384; 95% CI, 1.290–1.484	<0.001	

ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF Consortium, European Association for the Study of the Liver Chronic Liver Failure Consortium; HRS, hepatorenal syndrome; IQR, interquartile range; HR, hazard ratios.

$P < 0.001$) and EASL-CLIF Consortium criteria (59.7 *vs* 16.9%; $P < 0.001$) individually and also as per both criteria combined (81.8 *vs* 18.2%; $P < 0.001$). Patients with AKI also had a longer hospital stay (6 days *vs* 4 days; $P < 0.001$) (Tables 1 and 2), increased death during hospitalization (17.8 *vs* 2.7%; $P < 0.001$), and decreased survival both at 28 days (66.7 *vs* 88.9%;

Table 3 Comparison of baseline characteristics and acute kidney injury (AKI) precipitants between patients with AKI stages 1A, 1B, 2, and 3, staged according to level of serum creatinine at admission

Sl. no	Parameters	Patients with AKI stage 1A (n = 106)	Patients with AKI stage 1B (n = 90)	Patients with AKI stage 2 (n = 65)	Patients with AKI stage 3 (n = 54)	P value
1	Age (Mean ± SD)	49.73 ± 11.75	50.88 ± 12.90	48.33 ± 12.63	49.66 ± 9.19	0.628
2	Gender: Male (%)	98 (34.4%)	81 (28.4%)	58 (20.4%)	48 (16.8%)	0.854
3	BMI (kg/m^2) (Mean ± SD)	22.00 ± 3.73	22.24 ± 4.11	21.10 ± 4.90	21.62 ± 2.96	0.331
4	MAP (mmHg) (Mean ± SD)	85.99 ± 9.61	83.88 ± 11.33	82.88 ± 9.75	79.44 ± 14.28	0.005
5	Etiology of cirrhosis (Alcohol [%])	68 (64.2%)	56 (62.2%)	47 (72.3%)	39 (72.2%)	0.659
6	Serum creatinine (mg/dL) (Mean ± SD)	1.26 ± 0.09	1.69 ± 0.15	2.39 ± 0.33	4.38 ± 1.61	<0.001
7	Urea (mg/dL) (Median [IQR])	33 (25–43)	46.5 (37–65)	65 (51–94)	109 (85–133)	<0.001
8	Serum bilirubin (total mg/dL) (Median [IQR])	2.7 (1.2–5.5)	3.9 (1.5–9.5)	5.5 (1.45–11.65)	4.65 (1.59–9.50)	<0.001
9	INR (Median [IQR])[II,III,V]	1.72 (1.47–2.13)	1.74 (1.39–2.37)	1.89 (1.47–2.36)	2.17 (1.57–3.16)	<0.001
10	Serum protein (g/dL) (Mean ± SD)	6.42 ± 0.86	6.84 ± 3.39	6.24 ± 0.98	6.32 ± 0.87	0.244
11	Serum albumin (g/dL) (Mean ± SD)	2.75 ± 0.51	2.62 ± 0.53	2.60 ± 0.43	2.47 ± 0.43	0.006
12	Serum sodium (mEq/L) (Mean ± SD)	135.36 ± 7.78	132.07 ± 15.54	132.43 ± 8.66	128.19 ± 7.95	0.001
13	Serum potassium (mEq/L) (Median [IQR])	4.20 (3.88–4.70)	4.20 (3.50–4.92)	4.10 (3.60–4.80)	4.65 (3.78–5.33)	0.429
14	SAAG (Mean ± SD)[III]	2.30 ± 0.55	2.21 ± 0.58	2.13 ± 0.46	2.03 ± 0.44	0.014
15	Total leucocyte count (10^3 cells/dL) (Median [IQR])	8400 (6400–10 250)	8650 (7150–12 350)	9600 (7200–12 700)	9800 (7800–12 650)	0.020
16	Urine sodium (mEq/L) (Median [IQR])	34 (19.25–64.83)	42 (22–74.25)	30.50 (15.30–62.55)	41.95 (19.65–72.48)	0.217
17	Variceal bleeding (%)	59 (55.7%)	36 (40%)	31 (47.7%)	21 (38.9%)	0.094
18	Diarrhea and/or vomiting (%)	32 (30.2%)	23 (25.6%)	23 (35.4%)	17 (31.5%)	0.616
19	Infection (%)	43 (40.6%)	54 (60%)	47 (72.3%)	46 (85.2%)	<0.001
20	Drugs precipitating AKI (%)	68 (64.2%)	55 (61.1%)	42 (65.6%)	42 (77.8%)	0.214

BMI, body mass index; CTP, Child-Turcotte-Pugh; INR, International Normalized Ratio; IQR, interquartile range; MAP, mean arterial pressure; MELD, model for end-stage liver disease; SAAG, serum-ascites albumin gradient; SD, standard deviation; UNOS, The United Network for Organ Sharing.

$P < 0.001$) and 90 days (44.4 *vs* 75.5%; $P < 0.001$). Of AKI patients, 62% ($n = 196$) had stage 1, 21% ($n = 65$) stage 2, and 17% ($n = 54$) had stage 3 AKI, and of the stage 1 AKI patients, 54.08% ($n = 106$) had stage 1A, and 45.92% ($n = 90$) had stage 1B AKI. On comparison of AKI precipitants, only infection was more commonly associated with higher grades of AKI (40.6% in stage 1A, 60% stage 1B, 72.3% stage 2, and 85.2% stage 3; $P < 0.001$) (Fig. 1b); all other known precipitants were comparable. Besides, it was also observed that there was increased prevalence of HRS in patients with higher grades of AKI ($P < 0.001$) (Table 3). AKI patients also had higher prevalence of ACLF as per the EASL-CLIF Consortium criteria ($P < 0.001$) and combined criteria ($P < 0.001$) but not as per APASL criteria (Tables 3 and 4). It was further observed that higher-grade AKI patients had decreased reversal of AKI, increased median duration of hospital stay ($P < 0.001$), and increased hospital mortality ($P < 0.001$) (Table 4), and the hazard ratios for mortality were significant in patients with AKI during hospitalization (hazard ratio [HR], 1.506; 95% confidence interval [CI], 1.362–1.666; $P < 0.001$) and also at 28 days (HR, 1.430; 95% CI, 1.320–1.549; $P < 0.001$) and 90 days (HR, 1.384; 95% CI, 1.290–1.484; $P < 0.001$). Furthermore, they had stage-wise decreased survival both at 28 days ($P < 0.001$) and 90 days ($P < 0.001$) from stage 1A to stage 3 AKI (Table 4). Kaplan–Meier survival analysis showed significant differences in survival between AKI stages 1A, 1B, 2, 3 and without AKI, both at 28 days (log-rank P value <0.001) and 90 days (log-rank P value <0.001) (Fig. 2a,b). ROC curve analysis showed admission serum creatinine (AUC 28 days; 0.69, AUC 90 days; 0.66, 95% CI), serum urea (AUC 28 days; 0.65, AUC 90 days; 0.62, 95% CI), and presence of infection (AUC 28 days; 0.56, AUC 90 days; 0.57, 95% CI), were able to predict death both at 28 days and 90 days (Fig. 2c,d), while reversal of AKI was a predictor of increased survival both at 28 days (AUC of 0.26, 95% CI, and 0.19–0.31) and 90 days (AUC of 0.33, 95% CI, and 0.27–0.39) (Table 4).

Discussion

In our study, the prevalence of AKI in DC patients was 54.69%, and alcohol was the most common underlying etiology of cirrhosis irrespective of AKI (Table 1). Use of AKI-precipitating medications was commonly seen, followed by presence of bacterial infection. In the present study, a greater proportion of patients was admitted with early stage 1 AKI (AKI 1A) (Table 4). However, increased prevalence of ACLF (as per EASL-CLIF Consortium and combined criteria) was seen in patients with higher grades of AKI from stage 1A to stage 3 ($P < 0.001$), but not as per APASL criteria ($P = 0.110$) (Table 4). The difference in ACLF prevalence as per different criteria was possibly because of the difference in defining criteria, with only the AASLD-EASL working group including serum creatinine level as ACLF-defining criteria.[29,30]

A comparison of the AKI prevalence and profile of our patients with other studies showed significant differences, which are demonstrated in Table 5. The prevalence of AKI in other studies varies between 46 and 67%, akin to our study (54.69%) (Table 5).[7,10,11,17,18,31,32] In our patients, alcohol was the most common underlying etiology of cirrhosis. In contrast, de Carvalho *et al.* (53.9%) and Montoliu *et al.* (51.7%) have reported

Table 4 Comparison of indices of severity of liver disease and outcomes between patients with acute kidney injury (AKI) stages 1A, 1B, 2, and 3, staged according to level of serum creatinine at admission

Sl. no	Parameters		Patients with AKI stage 1A ($n = 106$)	Patients with AKI stage 1B ($n = 90$)	Patients with AKI stage 2 ($n = 65$)	Patients with AKI stage 3 ($n = 54$)	P value
1	MELD (UNOS) (Mean ± SD)†,‡,§,¶,††,‡‡		18.79 ± 5.46	23.46 ± 7.12	28.21 ± 8.41	34.11 ± 8.73	<0.001
2	MELD (Na^+) (Mean ± SD)†,‡,§,¶,††,‡‡		21.26 ± 5.96	25.98 ± 7.21	29.84 ± 7.82	34.74 ± 8.25	<0.001
3	CTP score (Mean ± SD)‡,§,¶,††		10.63 ± 2.36	11.34 ± 2.29	11.89 ± 2.38	12.55 ± 2.26	<0.001
4	Child class (%)	A	1 (0.9%)	3 (3.3%)	0 (0%)	0 (0%)	0.143
		B	27 (25.5%)	18 (20%)	12 (18.5%)	6 (11.1%)	
		C	78 (73.6%)	69 (76.7%)	53 (81.5%)	48 (88.9%)	
5	HRS (%)		6 (5.7%)	24 (26.7%)	36 (55.4%)	38 (70.4%)	<0.001
6	ACLF (APASL) ($n = 110$)		28 (25.4%)	32 (29.1%)	27 (24.6%)	23 (20.9%)	0.110
7	ACLF (EASL-CLIF Consortium) ($n = 188$)		28 (14.9%)	49 (26.1%)	61 (32.4%)	50 (26.6%)	<0.001
8	ACLF (APASL and EASL-CLIF Consortium) ($n = 90$)		14 (15.6%)	26 (28.9%)	27 (30%)	23 (25.6%)	<0.001
9	Reversal of AKI (%)		90 (84.9%)	57 (63.3%)	28 (43.1%)	12 (22.2%)	<0.001
10	Duration of hospital stay (Median [IQR])‡,§,¶,††		4 (3–5)	5 (4–7)	7 (5.5–11)	8 (5–11)	<0.001
11	Death during hospitalization		2 (1.9%)	15 (16.7%)	17 (26.2%)	22 (40.7%)	<0.001
12	28-day survival (%)		88 (83%)	63 (70%)	38 (58.5%)	21 (38.9%)	<0.001
13	90-day survival (%)		65 (61.3%)	40 (44.4%)	20 (30.8%)	15 (27.8%)	<0.001

†Significant when compared between AKI stages 1A and 1B.
‡Significant when compared between AKI stages 1A and 2.
§Significant when compared between AKI stages 1A and 3.
¶Significant when compared between AKI stages 1B and 2.
††Significant when compared between AKI stages 1B and 3.
‡‡Significant when compared between AKI stages 2 and 3.
ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for the Study of the Liver; EASL-CLIF Consortium, European Association for the Study of the Liver Chronic Liver Failure Consortium; HRS, hepatorenal syndrome; IQR, interquartile range.

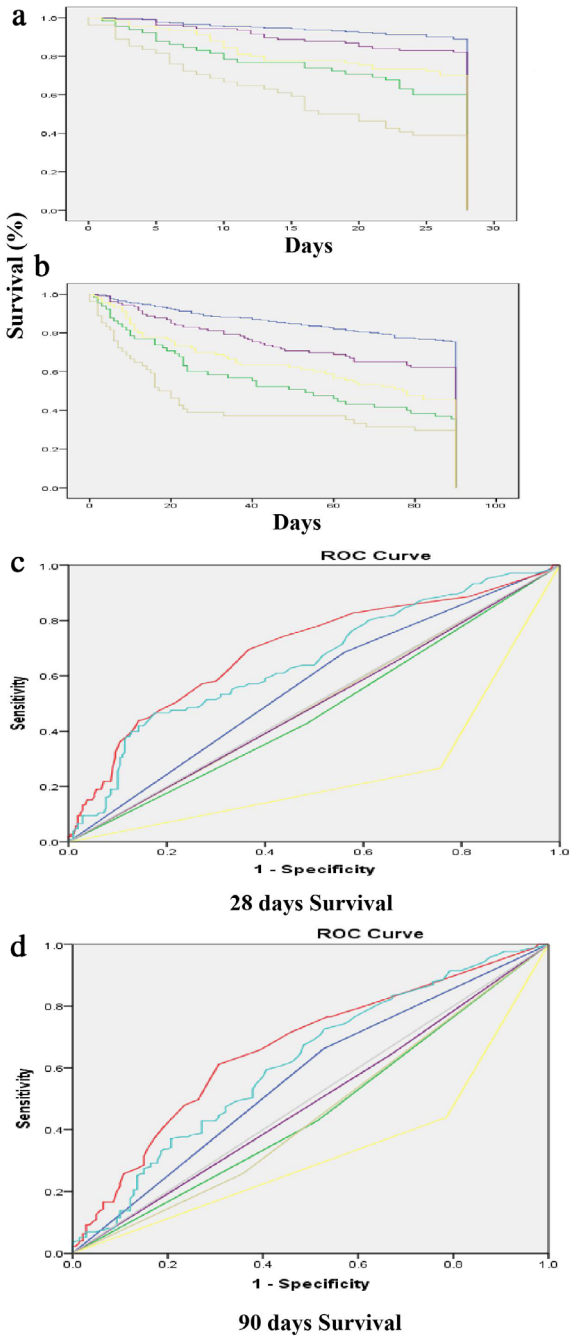

Figure 2 (a) Kaplan–Meier survival curves showed significant differences in survival between patients with acute kidney injury (AKI) 1A, AKI 1B, AKI 2, and AKI 3 and those without acute kidney injury at 28 days (log-rank *P* value <0.001). (——) without AKI; (——) AKI 1A; (——) AKI 1B; (——) AKI 2; (——) AKI 3. (b) Kaplan–Meier survival curves showed significant differences in survival between patients with acute kidney injury (AKI) 1A, AKI 1B, AKI 2, and AKI 3 and those without acute kidney injury at 90 days (log-rank *P* value <0.001). (——) without AKI; (——) AKI 1A; (——) AKI 1B; (——) AKI 2; (——), AKI 3. (c) Receiver operating characteristic curves (AUROC) for prognostic parameters for 28-day survival in patients with AKI. (——), Admission serum urea; (——), admission serum creatinine; (——), infection; (——), variceal bleeding; (——), diarrhoea/vomiting; (——), normal creatinine/reversal of AKI; (——), reference line. (d) Receiver operating characteristic curves (AUROC) for prognostic parameters for 90-day survival in patients with AKI.

chronic viral hepatitis as the most common etiology.[7,18] The prevalence of different stages of AKI in our study is not different from the reported prevalence by Belcher *et al*., Huelin *et al*., and de Carvalho *et al*. (stage 1 AKI [41.9–68%], stage 2 AKI [2.5–29%], stage 3 AKI [1.5–23%]).[10,11,18] However, AKI 1A (106, 54%) and AKI 1B (90, 46%) patients were equally

Table 5 Comparison of acute kidney injury (AKI) prevalence and profile of our patients along with etiology and precipitating factor and comorbidity

Author	Wong *et al.*[32]	Belcher *et al.*[10]	Huelin *et al.*[11]	Fede *et al.*[17]	de Carvalho *et al.*[18]	Montoliu *et al.*[7]	Shetty *et al.*[31]	Present study
Period of study	2010–2012	2012 (29 months)	2011–2015	1977–2010	2003–2007	1998–2002	2016 (January–December)	2016–2018
Total patients	337	†	547	8088	198	263	351	576
Prevalence of AKI	166 (49.3%)	192	290 (53%)	3946 (67%)	91 (46%)	129 (49%)	123 (35%)	315 (54.9%)
AKI stage 1	†	91 (48%)	197 (68%)	†	83 (41.9%)	†	19 (15.4%)	196 (62.2%)
AKI stage 2	†	56 (29%)	55 (19%)	†	5 (2.5%)	†	33 (26.8%)	65 (20.6%)
AKI stage 3	†	43 (23%)	38 (13%)	†	3 (1.5%)	†	71 (57.7%)	54 (17.1%)
Etiology of CLD Alcohol	75 (45%)	106 (56%)	152 (52%)	39%	19 (20.9%)	127 (48.3%)	92 (74.8%)	210 (66.7%)
HBV/HCV infection	42 (25%)	33 (17%)	75 (26%)	29%	49 (53.9%)	136 (51.7%)	7 (5.7%)	58 (18.4%)
Variceal bleeding	†	15 (8%)	14 (5%)	†	31 (34.1%)	†	48 (39%)	147 (46.7%)
AKI-precipitating drugs used	†	†	†	†	73 (81.1%)	†	80 (65%)	207 (65.7%)
Prevalence of bacterial infection	166 (49.3%)	12 (6%)	204 (71%)	†	66 (72.9%)	†	79 (64%)	190 (60.3%)
Hospital mortality	†	†	†	†	48 (52.7%)	†	55 (44.7%)	56 (17.8%)
Mortality at 1 month	34%	†	†	67%	†	†	†	105 (33.3%)
Mortality at 3 months	†	†	†	†	†	†	†	175 (55.6%)

†No data available.

CLD, chronic liver diseasel; HBV, hepatitis B virus; HCV, hepatitis C virus.

distributed in our cohort, in contrast to the study by Huelin *et al.* (AKI 1A [58, 29.4%] and AKI 1B [139, 70.6%]), in which over two-thirds had AKI stage 1B.[11] Variceal bleeding was much more common in our patients (46.7%) in comparison to other studies (5–34.1%).[10,11,21] Furthermore, de Carvalho *et al.* observed the use of AKI-precipitating medications in 81.1% of cases in contrast to 65.7% of cases in our study.[18] In our study, the prevalence of infection was 60.3%, whereas the reported prevalence was 6% by Belcher *et al.*, 71% by Huelin *et al.*, and 72.9% by de Carvalho *et al.*[10,11,18] (Table 5). Surprisingly, the hospital mortality rate in our study was much lower—only 17.8%—in contrast to 52.7% reported by de Carvalho *et al.* and 44.7% by Shetty *et al.*[18,31] In addition, the 28-day mortality rate in our AKI patients was 33.3%, which is similar to Wong *et al.* (34%) but much lower than the mortality rate reported by de Carvalho *et al.* (67%).[18,32]

Our study clearly demonstrated that the reversal of AKI was negatively associated with mortality (Fig. 2c,d), which implies that patients should be aggressively treated till reversal of renal failure, and if necessary, early renal replacement therapy with hemodialysis should be arranged for a better outcome. This is especially crucial in the light of the earlier observation that the pretransplant serum creatinine level affects postliver transplantation survival.[33]

During the selection of patients, we excluded patients with preexisting chronic kidney disease and structural kidney disease. On the subject of different forms of AKI, we ruled out acute tubular necrosis (ATN) and postrenal AKI on the basis of urinary examination and ultrasonography. However, identifying and excluding patients with intrinsic renal disease in this fashion, due to a lack of facilities for kidney biopsy and estimation of urine biomarkers at our center, was a distinct limitation of the study.

In the present study, over half of the DC patients had AKI, and in two-thirds of them, alcohol was the underlying etiology of cirrhosis. Furthermore, about two-thirds were admitted with stage 1 AKI, and more than half of them had early stage 1 AKI. There was stage-wise prolonged hospitalization and decreased survival of patients both at 28 days and 90 days, indicating the need for early detection and timely aggressive intervention for better survival of cirrhotic patients.

Besides, reversal of AKI resulted in increased survival both at 28 days and 90 days. Thus, in DC patients, AKI should be treated aggressively at the earliest till its reversal. An interesting observation in our study was the association of AKI with ACLF diagnosed on the basis of EASL-CLIF Consortium criteria but not on the basis of APASL criteria. This is because of the mechanistic etiological association between the two groups. Presence of AKI could well be deemed a surrogate marker of ACLF diagnosed by the EASL-CLIF Consortium criteria.

Regarding precipitants, use of medications was the most common AKI precipitant in our study, but bacterial infections were also significantly associated with higher grades of AKI. Besides, multiple precipitants of AKI were commonly seen in our study.

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