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Original Article

Determinants of Short-term Mortality in Liver Cirrhosis with Acute Kidney Injury: A Prospective Observational Study

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Abstract

Background: Acute kidney injury (AKI) occurs in 20-50% of patients with cirrhosis and is associated with a poor prognosis. The aim of the study is to identify the baseline factors affecting mortality in these patients at 30 and 90 days.

Methods: We enrolled 117 patients with cirrhosis and AKI and followed them up prospectively.

Results: Distribution of International club of ascites AKI stages was: 26 (22.03%) stage 1, 59 (50%) stage 2, and 33 (28%) stage 3. Mortalities at 30 and 90 days were 27 (22.8%) and 33 (27.9%) respectively. On multivariate analysis, variables affecting mortality at 30 days were serum creatinine level >2 mg% at 48 hours after AKI development (adjusted OR 7.93, $P=0.02$) and leukocytosis (total leucocyte count >11 000/mm^3) at admission (adjusted OR 6.54, $P=0.002$). Only leukocytosis at admission was a predictor of 90 days mortality (adjusted OR 4.76, $P=0.01$). Though not statistically significant, patients not responding to standard medical treatment had 3 times higher mortality at 30 days, while the maximum AKI stages (2 and 3) had eight times higher mortality at 90 days.

Conclusion: In cirrhosis, AKI increases short-term mortality. High serum creatinine at 48 hours affects mortality at 30 days, while leukocytosis at baseline predicts mortality at 30 and 90 days. Progression to a higher AKI stage impacts prognosis.

Keywords: Acute kidney injury, Chronic liver disease, Hepatorenal syndrome

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Introduction

Acute kidney injury (AKI) is a frequently occurring complication in patients with liver cirrhosis,[1] with a prevalence of approximately 20% and 50% in compensated and decompensated cirrhosis respectively.[2] AKI in liver cirrhosis has a high mortality rate of 50% and 65% in a month and a year respectively.[3] Progression of AKI has been associated with increased mortality as well as reduced survival even following liver transplants.[4] Associated complications like infections, gastrointestinal (GI) bleeding, and alcoholic hepatitis also worsen the prognosis.[5,6] This study aimed at the estimation of mortality rate with objectives of identifying baseline factors affecting mortality in patients with cirrhosis and AKI, at 30 and 90 days.

Materials and Methods

In a prospective observational study, enrolled cases were followed up until 3 months or death, whichever was earlier. The study was conducted over 2 years from January 2017 to January 2019 after getting approval from the Institutional Ethics Committee. This study was conducted using principles of the Declaration of Helsinki (revised in 2000).

Inclusion Criteria

Patients > 18 years of age admitted to a tertiary care center, who had liver cirrhosis with AKI on admission or at any time during their hospital stay, were included.

Exclusion Criteria

Patients already diagnosed with chronic kidney disease, malignancy, obstructive uropathy, cardiopulmonary disease, immunocompromised patients, and those with pregnancy were excluded.

Primary Outcome

Death at 30 and 90 days and baseline factors predicting mortality.

Method

A combination of clinical, laboratory, endoscopy, histology, and imaging findings were used for the diagnosis of liver cirrhosis. Laboratory investigations

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like complete blood count, renal function tests, liver function tests, international normalized ratio (INR), ascitic fluid analysis, urine sodium, and urinary neutrophil gelatinase-associated lipocalin (uNGAL) were performed at the time of diagnosis of AKI. Serum creatinine was done at the time of enrollment, at 48 hours, and the maximum value achieved was recorded. Radiological investigations as and when clinically indicated were done. Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score, MELD sodium (MELD-Na) score, the International Club of Ascites (ICA) AKI stage, and response to treatment were documented. All patients with cirrhosis were assessed for acute on chronic liver failure (ACLF) as per the criteria of the Asia-Pacific Association for the Study of the Liver (APASL).[5]

The etiology of AKI was categorized under the following major categories:

1) Infection
2) Hypovolemia related AKI
3) Parenchymal nephropathy- Urine protein > 500 mg/dL, abnormal sediment, urine RBCs > 50/HPF
4) Abnormal ultrasound of the abdomen in the absence of other causes of renal failure
5) Hepatorenal syndrome (HRS) as per ICA AKI diagnostic criteria.

A combination of the above-mentioned causes or other miscellaneous causes was included in this study.

The patients were managed according to the institutional standard care for cirrhosis and associated complications. To avoid superimposed drug-induced nephropathy, nephrotoxic drugs were stopped or replaced.[6,7]

Definitions

"Normal kidney function - serum creatinine (sCr) < 1.5 mg/dL and < 0.3 mg/dL above baseline."

"AKI - Increase in sCr ≥ 0.3 mg/dL (≥ 26.5 mmol/L) from baseline within 48 hours or increase up to ≥ 50% from the baseline, in last 7 days."

"Prerenal azotemia - Transient increase in sCr to > 1.5 mg/dL and 0.3 mg/dL above baseline, with a subsequent decrease in sCr to < 1.5 mg/dL or to mean baseline creatinine within 48 hours of treatment with diuretic withdrawal and intravenous albumin."

"Hepatorenal syndrome - according to the ICA-AKI guidelines. AKI (as defined above) with cirrhosis and ascites that failed to improve after 48 hours of diuretic withdrawal and volume expansion with albumin in the absence of shock, parenchymal kidney disease (as suggested by proteinuria > 500 mg/day, microhematuria > 50 RBCs/HPF and/or abnormal kidney imaging) or nephrotoxic medications."[8]

"Acute tubular necrosis (ATN)/intrinsic AKI (iAKI) - Presence of tubular epithelial cells on urinalysis with urine sodium > 10 mEq/L, and those who did not meet the ICA-HRS criteria."

To exclude postrenal causes of renal dysfunction, an ultrasound abdomen was performed.

ICA 2015

"Baseline serum creatinine (sCr) was defined as the value of sCr measured in the previous 3 months. When more than one value was present, the one closest to the admission was used. In case patients did not have previous sCr value, admission value was used as baseline sCr".

Staging of AKI

- "Stage 1: increase in sCr ≥ 0.3 mg/dL or an increase in sCr ≥ 1.5- to 2-fold from baseline"
- "Stage 2: increase in sCr ≥ 2-fold to 3-fold from baseline"
- "Stage 3: increase of sCr > 3-fold from baseline or serum creatinine ≥ 4 mg/dL with an acute increase of ≥ 0.3 mg/dL or requirement of renal replacement therapy (RRT)"
- Progression of AKI: Progressed to a higher stage and/or needed RRT.
- Regression of AKI: Regression of AKI to a lower stage.
- Response to treatment:
- "Full response: The return of sCr to a value within 0.3 mg/dL (26.5 mmol/L) of the baseline value."
- "Partial response was defined as regression of AKI stage with a reduction of sCr to ≥ 0.3 mg/dL (26.5 mmol/L) below the baseline value."
- "No response: was defined as no regression of AKI."

Statistical Methods

We used descriptive and inferential statistical analysis. Normally distributed continuous variables documented as mean and standard deviation, compared using paired student's t-test. The categorical variables were represented as proportions and compared by the chi-square test or Fisher's exact test. All tests were two-tailed, and *P* values < 0.05 were considered significant. Logistic regression analysis was used for the correlation of positivity with clinical variables. Receiver operating characteristics curve (ROC) curve analysis was performed for the predictability of study variables for predicting the outcome. SPSS software version 22.0 was used for the analysis.

Results

Clinical and Laboratory Parameters

Table 1 represents clinical and laboratory parameters of patients with cirrhosis and AKI.

In our study, we found that the most common cause of cirrhosis was alcohol-related chronic liver disease seen in 42.7% of cases with the commonest clinical presentation being ascites in 112 (95.7%).

Out of 117 enrolled patients, 100 (85.5%) had AKI at the time of admission. Out of the remaining 17 (14.5%) patients, 10 (8.5%) developed AKI within 48 hours, and 7 (5.9%) developed it after 48 hours of hospitalization.

Table 1. Clinical and laboratory parameters of 117 patients with cirrhosis and AKI

Variables	Total number of patients (N=117)
Male: Female	86:31 (2.7:1)
Age in years	47.71±12.32
Clinical features	
Abdominal distension (ascites)	112 (95.7%)
Decreased urine output	79 (67.5%)
Jaundice	79 (67.5%)
Abdominal pain	21 (17.9%)
Hepatic encephalopathy	32 (27.3%)
Fever	41 (35.1%)
Gastrointestinal bleed	28 (23.9%)
Hypotension	34 (29.1%)
Causes of AKI	
HRS	39 (33.3%)
Hypovolemia	34 (29.1%)
Infection	22 (18.8%)
Multiple	18 (15.4%)
Miscellaneous	4 (3.4%)
AKI present at admission	100 (85.5%)
AKI developed during the hospital stay	17 (14.5%)
Type of AKI	
Prerenal	56 (47.8%)
HRS	48 (41.02%)
Intrinsic renal	13 (11.1%)
CLD Etiology	
Alcohol-related	50 (42.7%)
Hepatitis B related	25 (21.4%)
Hepatitis C related	25 (21.4%)
Autoimmune hepatitis	13 (11.1%)
NAFLD related	4 (3.4%)
Clinical presentation	
ACLF	18 (15.4%)
Compensated cirrhosis	7 (5.9%)
Decompensated cirrhosis	92 (78.6%)
Response to treatment	
Complete	67 (57.3%)
No response	36 (30.7%)
Partial response	14 (11.9%)
CTP (overall score)	9.11±1.25
A	0 (0%)
B	69 (59%)
C	48 (41%)
MELD	18.51±6.78
MELD sodium	21.76±6.87
AKI stage	
Admission (0/1/2/3)	17 (14.5%)/ 45 (38.5%)/ 45 (38.5%)/ 10 (8.5%)
48 h (0/1/2/3)	7(6%)/ 31 (26.5%)/ 50 (42.7%)/ 29 (24.8%)
Maximum stage (1/2/3)	25 (21.3%)/ 59 (50.4%)/ 33 (28.3%)
Laboratory parameters	
Hemoglobin (g/dL)	8.30±1.79
Total leucocyte count / mL^3	9132.20±5860.92
Platelet count/ µL	140315.25±224769.61
SGOT (U/L)	103.82±90.18
SGPT (U/L)	60.97±43.21
Total protein (g/dL)	5.72±0.71
Serum albumin (g/dL)	2.61±0.50
INR	1.34±0.41
Total bilirubin (mg/dL)	5.93±6.46
Serum sodium (mmol/L)	131.93±8.09
MELD	18.52±6.78
MELD sodium	21.76±6.88
Serum creatinine (mg/dL)	
Baseline	1.23±0.76
Admission	1.92±0.97
At 48 hours	2.20±1.29
Maximum	2.62±1.25
Urine Sodium (mEq/L)	57.54±25.83
Urine NGAL (ng/mL)	392.16±398.99

SD, standard deviation; AKI, acute kidney injury; CLD, chronic liver disease; NAFLD, non-alcoholic fatty liver disease; ACLF, acute on chronic liver failure; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; INR, international normalized ratio; NGAL, neutrophil gelatinase-associated lipocalin; HRS, Hepatorenal syndrome.

Most of the patients had ICA AKI stage 2 (50.4%), followed by stage 3 (28.3%) and stage 1 (21.3%).

In our study, we found frequent etiologies of AKI were HRS in 33.3%, hypovolemic AKI in 29.1%, and infections in 18.8%. The most common infection in these patients was spontaneous bacterial peritonitis in 16 (72.7 %) followed by urinary tract infection and cellulitis seen in three patients (13.6%) each. Hypovolemia was secondary to diuretics observed in 15 (44.41%), gastrointestinal bleeding in 13 (38.23%), and lactulose-induced diarrhea in 6 (17.64%). Two patients had acute pancreatitis and two had alcoholic hepatitis.

Mean creatinine observed at baseline, on admission, and at 48 hours were 1.23±0.76, 1.92±0.97, and 2.20±1.29 mg% respectively. The average MELD and CTP scores were 18.51 (±6.78), and 9.11 (±1.25) respectively.

Overall 67 (57.3%) patients had a complete response to standard treatment, 36 (30.7%) had no response, 14 (11.9%) had a partial response; 15 (12.7%) underwent hemodialysis.

In this study mortality rates at 30 and 90 days were 27 (23%) and 33 (28%) respectively. There was no statistically significant effect of etiology of cirrhosis, the timing of onset of AKI (on admission, before or after 48 hours of

hospital stay), cause of AKI, admission serum creatinine, and MELD-Na on mortality either at 30 or 90 days.

Factors Affecting Mortality at 30 Days

These are shown in Tables 2 and 3. Non-survivors had a significant number of patients with fever, oliguria, hypotension, hepatic encephalopathy, and gastrointestinal bleeding at presentation than the survivors. Also, they had significantly raised total leukocyte counts (TLC) of 11 000 (40.7% vs 15.4%) ($P=0.018$).

Non-survivors also had significantly higher levels of INR, 48-hour serum creatinine level, maximum creatinine value, urine Na, urinary NGAL, CTP class, and MELD scores as compared to survivors (Table 2). Clinical presentation with ACLF was significantly more common in non-survivors (33.3% vs 10%) ($P=0.02$).

There was no AKI reversal among non-survivors (100% vs 81.1 %) ($P=0.012$). Most of them presented with iAKI, (29.6% vs 6.7%) ($P\leq0.001$). Majority of the survivors presented with prerenal AKI (55.5% vs 18.5%) ($P=0.001$). Although HRS was more common in non-survivors (51.9% vs 37.8%), it was not statistically significant ($P=0.178$).

We did not find a statistically significant effect of admission ICA-AKI stage on 30 days mortality. The 48-hour ICA-AKI stage was significantly higher in the non-survivor group: stage 2 AKI (51.8% vs 37.8%), stage 3 AKI (48.2% vs 16.6%) ($P<0.001$). Mortality rate increases with higher AKI stages (stage 3- 51.9% vs 21.1%) ($P\leq0.001$). The non-survivor group had either no response to treatment (51.9% vs 24.5%) or only partial response to treatment (22.2% vs 8.9%) ($P=0.001$).

Factors Affecting Mortality at 90 Days

These are shown in Tables 2 and 3. In the non-survivor group, 48 hours ICA AKI stage was seen significantly high: stage 2 (54.5% vs 39.3%), stage 3 (39.4% vs 19.1%) ($P<0.001$). The higher the AKI stage reached higher the mortality (stage 3- 42.5% vs 22.6%) ($P=0.003$)). The non-survivor group had no response to treatment (42.4% vs 26.2%) ($P=0.001$), or partial response (21.2% vs 8.3%) ($P=0.001$). Out of 33 patients who died by day 90, 26 had leukocytosis at baseline. 13/26 (50%) patients had infection associated with leukocytosis, among them at day 30, 7/13 (53.8%) died while 5/13 (38.4%) died in the group with leukocytosis without infection ($P=0.69$). In the following up six patients who survived at day 30 among the group with leukocytosis with infection until 90 days only 1/6 (16.6%) died, while in the leukocytosis without infection group none died ($P=0.42$).

On multivariate analysis (shown in Table 4), statistically significant variables associated with mortality at 30 days were serum creatinine at 48 hours and TLC > 11 000/mm^3, whereas mortality at 90 days was associated with only TLC > 11 000/mm^3. We found a serum creatinine cut-off value of 2 mg/dL at 48 hours for predicting mortality at 30 days with sensitivity and specificity of 81.48% and 62.64% respectively; ROC of the same is shown in Figure 1. The area under the curve (AUC) was 0.757. Though not statistically significant, patients not responding to standard medical treatment had 3 times higher mortality at 30 days (adjusted OR: 1.75), while maximum AKI stage (2 & 3) had 8 times higher mortality at 90 days (adjusted OR: 8.37).

Discussion

There are several parameters that affect mortality in patients with cirrhosis and AKI. These could be the symptoms of presentation, type of presentation like ACLF or acute decompensation, presence of other complications of portal hypertension, AKI stage, cause of AKI, AKI stage progression, baseline CTP grade and MELD score, variable symptoms, and biochemical parameters, and response to standard medical treatment. We have assessed all these parameters so as to enable us to act wisely to prevent mortality among these patients.

Previous literature has reported total bilirubin, prothrombin time, sodium (serum and urine), CTP score, and response to terlipressin as variables affecting prognosis among patients with cirrhosis and AKI on univariate analysis.[3] In our study fever, oliguria, hypotension, hepatic encephalopathy, gastrointestinal bleeding at presentation, leukocytosis (TLC > 11 000/mm^3), higher levels of INR, urinary NGAL, 48-hour serum creatinine, and highest AKI stage was associated with mortality. Serum bilirubin was found to affect mortality at 90 days but not at 30 days. Other parameters like the history of AKI, causes of AKI, etiology of cirrhosis, co-morbidities, and serum creatinine at admission did not differ significantly among survivors and non-survivors.[9,10]

A prospective observational study by Kumar and colleagues showed variables like serum glutamic oxaloacetic transaminase, serum bilirubin, INR, serum

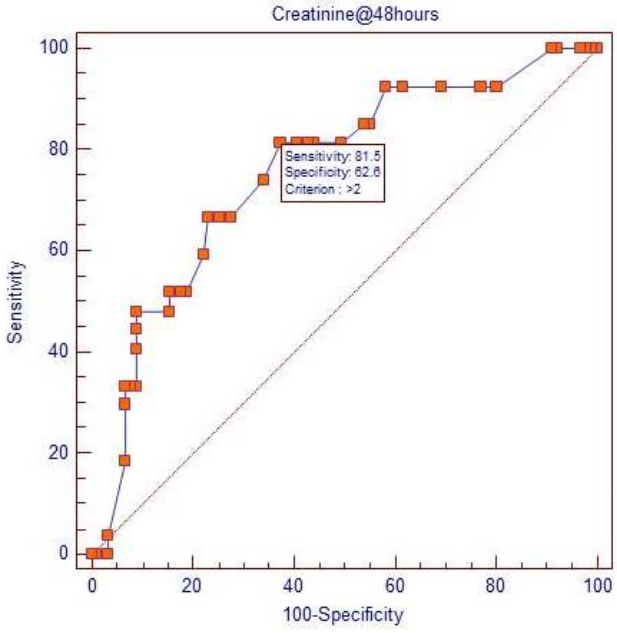

Figure 1. Receiver operating characteristics curve of creatinine at 48 hours.

Table 2. Comparison of baseline clinical parameters among survivors and non-survivors at 30 and 90 days

Variables	Outcome on day 30		*P* value	Outcome on day 90		*P* value
	Survivor (n = 90)	Non-survivor (n = 27)		Survivor (n = 84)	Non-survivor (n = 33)	
Clinical features						
Decreased urine output	56 (62.2%)	23 (85.2%)	0.022*	52 (61.9%)	27 (81.8%)	0.070+
Abdominal pain	11 (12.2%)	10 (37%)	0.003**	9 (10.7%)	12 (36.4%)	0.001**
Hepatic encephalopathy	15 (16.6%)	17 (63%)	<0.001**	13 (15.5%)	19 (57.6%)	<0.001**
Fever	26 (28.8%)	15 (55.6%)	0.010**	23 (27.4%)	18 (54.5%)	0.005**
Gastrointestinal bleeding	17 (18.8%)	11 (40.7%)	0.018*	13 (15.5%)	15 (45.5%)	0.001**
Hypotension	7 (7.7%)	9 (33.3%)	0.001**	4 (4.7%)	12 (36.4%)	<0.001**
History of AKI	16 (17.7%)	9 (33.3%)	0.079+,	16 (19.1%)	9 (27.3%)	0.313
AKI reversal						
No	73 (81.1%)	27 (100%)	0.012*	70 (83.3%)	33 (100%)	0.011*
Yes	17 (18.9%)	0 (0%)		14 (16.7%)	0 (0%)	
Response to treatment						
Complete	60 (66.6%)	7 (25.9%)		55 (65.5%)	12 (36.4%)	
No response	22 (24.5%)	14 (51.9%)	0.001**	22 (26.2%)	14 (42.4%)	0.011*
Partial response	8 (8.9%)	6 (22.2%)		7 (8.3%)	7 (21.2%)	
Causes of AKI						
HRS	30 (33.3%)	9 (44.4%)		28 (33.3%)	10 (30.3%)	
Hypovolemia	27 (0.3%)	7 (25.9%)		25 (29.7%)	8 (24.2%)	
Infection	16 (17.7%)	6 (22.2%)	0.121	14 (16.6%)	4 (12.1%)	0.671
Multiple	14 (15.5%)	4 (14.8%)		14 (16.6%)	4 (12.1%)	
Miscellaneous	3 (3.3%)	0 (0%)		3 (4.7%)	1 (3%)	
Type of AKI						
Prerenal	50 (55.5%)	5 (18.5%)	0.001**	48 (57.2%)	7 (21.2%)	<0.001**
HRS	34 (37.8%)	14 (51.9%)	0.178	31 (36.9%)	17 (51.5%)	0.135
Intrinsic renal	6 (6.7%)	8 (29.6%)	<0.001**	5 (5.9%)	9 (27.3%)	<0.001**
Clinical presentation						
ACLF	9 (10%)	9 (33.3%)		7 (8.3%)	11 (33.3%)	
Compensated cirrhosis	5 (5.5%)	1 (3.7%)	0.020*	5 (5.9%)	1 (3%)	0.003**
Decompensated cirrhosis	76 (84.5%)	17 (63%)		72 (84.8%)	21 (63.7%)	
AKI stage						
At admission						
0	12 (13.3%)	5 (18.5%)		12 (14.2%)	5 (15.1%)	
1	39 (43.3%)	6 (22.2%)	0.263	36 (42.8%)	9 (27.2%)	0.088+
2	32 (35.5%)	13 (48.1%)		30 (35.7%)	15 (45.4%)	
3	7 (7.7%)	3 (9.1%)		6 (7.1%)	4 (12.1%)	
At 48 hours						
0	7 (7.7%)	0 (0%)		7 (8.3%)	0 (0%)	
1	31 (34.5%)	0 (0%)	<0.001**	28 (33.3%)	3 (9.1%)	0.001**
2	34 (37.8%)	14 (51.8%)		33 (39.3%)	17 (51.5%)	
3	15 (16.6%)	13 (48.2%)		16 (19.1%)	13 (39.4%)	
Maximum stage						
1	25 (27.7%)	0 (0%)		24 (28.6%)	1 (3%)	
2	46 (51.2%)	13 (48.1%)	<0.001**	41 (48.8%)	18 (54.5%)	0.003**
3	19 (21.1%)	14 (51.9%)		19 (22.6%)	14 (42.5%)	

SD, standard deviation; AKI, acute kidney injury; NAFLD, non-alcoholic fatty liver disease; ACLF, acute on chronic liver failure; HRS, Hepatorenal syndrome.
** *P* value < 0.05 – statistically significant.

Table 3. Comparison of baseline laboratory parameters among survivors and non-survivors at 30 and 90 days

Variables	Outcome on day 30		*P* value	Outcome on day 90		*P* value
	Survivor (n=90)	Non-survivor (n=27)		Survivor (n=84)	Non-survivor (n=33)	
Total leucocyte count (cells/mm^3)						
Overall	8173.63±4882.39	12362.96±7616.18	0.001	8208.24±4855.10	11512.12±7457.12	0.005**
<4000	9 (9.9%)	2 (7.4%)		9 (10.6%)	2 (6.1%)	
4000-11000	68 (74.7%)	14 (51.9%)	0.018*	63 (74.1%)	19 (57.6%)	0.040**
>11000	14 (15.4%)	11 (40.7%)		13 (15.3%)	12 (36.4%)	
INR	1.24±0.26	1.67±0.61	<0.001**	1.23±0.26	1.62±0.57	<0.001**
Total bilirubin(mg/dL)	5.55±5.81	7.20±8.31	0.245	5.12±5.47	8.03±8.23	0.027*
SGOT (U/L)	100.56±97.45	114.81±59.66	0.473	99.55±100.31	114.82±56.12	0.412
SGPT (U/L)	57.57±39.24	72.44±53.79	0.117	56.67±40.46	72.06±48.51	0.082+
Serum creatinine						
Baseline	1.21±0.8	1.26±0.59	0.770	1.18±0.64	1.34±1.00	0.323
Admission	1.91±0.97	1.98±0.98	0.725	1.75±0.96	1.81±1.26	0.757
At 48 hours	1.97±1.23	2.98±1.20	<0.001**	1.95±1.23	2.85±1.23	0.001**
Maximum level	2.45±1.25	3.17±1.10	0.008**	2.42±1.23	3.14±1.19	0.005**
Urine sodium (mEq/L)	52.24±22.71	75.41±28.06	<0.001**	51.27±22.75	73.70±26.59	<0.001**
Urine NGAL (ng/mL)	293.51±299.12	718.47±508.32	<0.001**	275.29±268	697.53±514.04	<0.001**
CTP class						
A	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
B	56 (62.3%)	13 (48.1%)	0.035**,	53 (63.1%)	16 (48.5%)	0.062
C	34 (37.7%)	14 (51.9%)		31 (36.9%)	17 (51.5%)	
MELD (over all)	17.69±6.61	21.29±6.71	0.018**	17.49±6.16	21.15±7.66	0.008**
<9	8 (8.8%)	3 (11.1%)		7 (8.2%)	4 (12.1%)	
10-19	51 (56%)	4 (14.8%)	<0.001**	49 (57.6%)	6 (18.2%)	<0.001**
20-29	27 (29.7%)	18 (66.7%)		26 (30.6%)	19 (57.6%)	
30-39	5 (5.5%)	2 (7.4%)		3 (3.5%)	4 (12.1%)	

SD, standard deviation; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; INR, international normalized ratio; NGAL, neutrophil gelatinase-associated lipocalin; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.
** *P* value<0.05 - statistically significant
Data are expressed as mean±SD or No. (%).

creatinine at the time of enrollment, sCr value, MELD score, and CTP score between survived and non-survived groups were statistically significant.[9] Our study found an additional variable, serum creatinine at 48 hours, affecting mortality at 30 days.

AKI prevalence in our study was almost similar to the reported prevalence by various previous studies.[11-13]

In liver cirrhosis, AKI is potentially reversible when there is a transient elevation in serum creatinine like in hypovolemia secondary to laxatives-induced diarrhea, vomiting, diuretics, or upper GI bleeding. However, the persistent or progressive elevation of serum creatinine or partial recovery was significantly associated with an increase in 30-day mortality. Gessolo Lins et al showed that AKI progression and peak creatinine in the first 7 days of admission, were significant mortality predictors.[14] In our study, the ICA AKI stage at admission did not have any significant effect on mortality at 30 and 90 days, but the 48-hour ICA AKI stage on multivariate analysis had an impact on the 30-day mortality. Admission AKI had been shown a better mortality predictor in ACLF patients than persistent AKI at 48 hours in a prospective study by Khatua and colleagues.[15] These different findings could be because of the low rate of advanced AKI stage 3 (8.5 %) in our population at admission, suggesting AKI stage progression during the hospital stay is a factor independently associated with mortality.[2] This finding has prognostic implications.

Among various etiologies of AKI, the most frequent cause was HRS in 39 patients (33.1%), followed by hypovolemic AKI in 34 patients (28.8%), and infections in 22 (18.6%). The cause of AKI has been reported to be a useful tool for the assessment of prognosis. In this study, the 3-month probability of mortality was 85% for HRS, 69% for renal failure associated with infections, 54% for hypovolemia associated with renal failure, and 27% for parenchymal nephropathy ($P<0.0005$).[10] However, in our study, these etiologies were statistically insignificant predictors of mortality.

The mortality rate at 30 and 90 days were 27 (22.8%) and 33 (28%) respectively in our study population. This mortality rate is lower in contrast to a similar prospective

Table 4. Logistic regression analysis to predict mortality at 30 and 90 days

Variables	Logistic regression results to predict mortality at 30 days				95% CI	
	Logit co-efficient	SE	*P* value	Adjusted OR	Lower	Upper
CTP>10	0.08	0.58	0.895	1.08	0.35	3.33
No response to treatment	1.07	0.63	0.089	2.93	0.85	10.10
Baseline creatinine	-0.03	0.66	0.959	0.97	0.26	3.54
Creatinine at 48 hours	2.07	0.89	0.020*	7.93	1.38	15.69
MELD>10	-0.79	0.92	0.391	0.45	0.07	2.77
SGOT>40	0.72	1.01	0.474	2.06	0.28	15.04
SGPT>40	0.45	0.62	0.475	1.56	0.46	5.32
TLC>11000	1.88	0.62	0.002**	6.54	1.95	21.91
Variables	**Logistic regression results to predict mortality at 90 days**				**95% CI**	
	Logit co-efficient	**SE**	***P* value**	**Adjusted OR**	**Lower**	**Upper**
CTP>10	0.39	0.56	0.487	1.47	0.49	4.38
No response to treatment	0.56	0.61	0.359	1.75	0.53	5.81
Maximum AKI stage (2 & 3)	2.13	1.12	0.058	8.37	0.93	16.29
Baseline creatinine	0.33	0.68	0.624	1.40	0.37	5.29
Creatinine at 48 hours	1.10	0.74	0.137	3.02	0.70	12.96
MELD>10	-1.36	0.93	0.141	0.26	0.04	1.57
SGOT>40	1.07	1.07	0.315	2.92	0.36	23.71
SGPT>40	0.95	0.64	0.136	2.60	0.74	9.11
TLC>11000	1.56	0.61	0.010*	4.76	1.44	15.71

CI, confidence interval; OR, odds ratio; SE, standard of error; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; TLC, total leucocyte count; AKI, acute kidney injury.
** *P* value<0.05 - statistically significant.

study done by Wong et al, who found a 30-day mortality rate among 166 patients with cirrhosis and AKI was 34%.[16] Similarly, De Oliveira Gomes and colleagues had reported a mortality of 33% and 45% at 30 and 90 days, respectively.[17] A systematic review, including 74 studies conducted between 1977 and 2010,[3] reporting on more than 8000 patients with cirrhosis and renal dysfunction, depicted mortality rate at 30 and 90 days as 58% and 71% respectively. An improvement in short-term prognosis has been observed recently, although the mortality of patients with cirrhosis and AKI previously documented was high.[12,16,18] In our study mortality rate at 90 days was less as compared with the above studies. This can be explained by firstly, less proportion of patients at admission with ICA AKI stage 3; previous studies have shown that the mortality rate increases with the advanced stage of AKI.[12] Secondly, Allegretti and colleagues had shown a correlation between 90 days mortality rate with the type of AKI. Prerenal azotemia, HRS, and acute tubular necrosis showed 90 days mortality rates of 35%, 57%, and 58% respectively, suggesting prerenal AKI has lower mortality. This explains the lower mortality in our study as we had more patients with prerenal AKI (47.5%).[18] Lastly, our study had a lower percentage of patients with ACLF (15.7%) as compared with other studies in which a larger number had ACLF (25.7%) leading to higher mortality.[15]

In the literature on multivariate analysis following variables affecting mortality - MELD score, CTP score, and its components and age.[3,19] In our study creatinine at 48 hours (adjusted OR 7.93), TLC>11 000 (adjusted OR: 6.54) affected 30-day mortality, while only TLC>11 000/mm^3 (adjusted OR: 4.76) was significantly affecting mortality at 90 days. What is different from previous studies is that it is not CTP and MELD score that predict mortality on multivariate analysis which might be because not all parameters of CTP and MELD rise in all patients with CLD and AKI. Thus raised creatinine and counts needs to be given more weightage as per our findings. It does not matter whether these raised counts suggest sepsis or systemic inflammation as both are associated with a poor prognosis in cirrhosis patients with AKI. A recent study showed that patients with cirrhosis and AKI and infection had a greater rise in their serum creatinine.[20] Similar to our study, Khatua et al had shown that among various AKI precipitants, patients with infection had higher grades of AKI (85.2% stage 3, 72.3% stage 2, 60% stage 1B, and 40.6% in stage 1A; $P<0.001$) and thus affecting mortality.[2] Kumar and colleagues had shown bacterial infection as the most common precipitant for kidney injury among patients with cirrhosis, and the probability of survival was significantly reduced to 31% at 3 months once renal failure develops in infected patients.[9] Wong and others showed that 29.7% patients with cirrhosis and AKI had a bacterial infection that had significantly higher TLC and worse liver dysfunction.[16] Overall a recent systemic review and meta-analysis showed that the presence of sepsis was associated with statistically significant risk factors for AKI, thus increasing mortality.[21] Recently, PREDICT

study has shown that markers of systemic inflammation like TLC and serum C-reactive protein (CRP) were significantly higher in patients with pre-ACLF compared with patients with stable and unstable decompensated cirrhosis.[22] Moreover, patients in the pre-ACLF group with higher TLC count and CRP, who developed ACLF, had a higher 3-month and 1-year mortality rates compared with the other two groups. Thus, our study also supports the newly proposed systemic inflammation hypothesis by the CANONIC and PREDICT studies.[23] Of late, many studies have shown markers of systemic inflammation to increase across stages of advanced chronic liver disease, which correlates with decompensation and mortality.[24,25] Similar to our finding of serum creatinine at 48 hours affecting mortality, Maiwall and colleagues have shown that AKI persistence at 48 hours predicts mortality (73% had AKI at 48 hours vs 49% had no AKI at 48 hours, $P<0.001$) and found that presence of systemic inflammatory response syndrome is not only a predictor of AKI persistence but also an independent predictor of mortality in patients with ACLF. They have found a serum creatinine cut-off value of 1.14 mg/dL at 48 hours for predicting mortality at 30 days, while in our study it was 2 mg/dL.[26] This highlights the importance of dynamic changes in serum creatinine.

Our patients who did not respond to standard medical treatment had almost 3 times higher mortality at 30 days (adjusted OR: 2.93), while AKI stage (2 & 3) had almost 8 times higher mortality at 90 days (adjusted OR: 8.37), though it was not statistically significant (table 4). Wong and others found that 30-day mortality was highest among non-recovered patients (80%) compared with partially recovered patients (40%) ($P<0.0001$).[16] Thus, incomplete recovery is associated with higher mortality irrespective of the degree of AKI. In our study, none of the non-survivors had a reversal of AKI at 48 hours. Previous studies have demonstrated that the reversal of AKI was negatively associated with mortality, implying that patients should be aggressively treated until the reversal of renal failure for better outcomes.[2]

Limitations

It is a single-center study with a small sample size. A kidney biopsy was not performed for diagnosing intrinsic renal disease. Sepsis markers were not studied in detail to differentiate raised counts cause.

Conclusion

The occurrence of AKI in cirrhosis is associated with high mortality. Serum creatinine level at 48 hours is a predictor of mortality at 30 days, while leukocytosis at admission is a predictor of mortality at 30 and 90 days. Our study suggests that AKI stage progression at 48 hours is a predictor of mortality. Therefore, every effort should be made to improve and reverse any episode of AKI.

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Competing Interests

The authors declare no conflict of interest related to this work.

Ethical Approval

None.

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