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Research Article

Acute Kidney Injury Among Hospitalised Patients with Cirrhosis – Burden and Risk Factors

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Abstract

Background and Objectives: Acute Kidney Injury (AKI) in cirrhosis is a major determinant of morbidity and mortality. This study aims to assess the proportion, common predisposing factors and the mortality rate of hospitalised patients with AKI and cirrhosis. Methods: A single-center, longitudinal study was done in our setting including 186 patients with cirrhosis hospitalized to ward or ICU. AKI was diagnosed and staged as per ICA-AKI criteria. The proportion of AKI was calculated in percentage. Risk factors for AKI were recorded and their association was tested by chi-square test. Patient outcome (in terms of survived or deceased) was recorded and mortality rate was calculated in terms of percentage. Results: Proportion of AKI in hospitalized patients with cirrhosis was 39.7% (74/186). Alcoholic liver disease, NAFLD & hepatitis-B related cirrhosis comprised more than 90% of cirrhosis. Most patients with AKI had advanced stages of cirrhosis (CTP-A: 8, CTP-B: 18, CTP-C: 48). The common predisposing factors for AKI in cirrhotic patients were variceal bleeding (44.6%) and SBP (29.7%), while less common risk factors were infections like UTI (7%), LRTI (4%) and cellulitis (1.4%), along with large volume paracentesis (9.5%), recent over diuresis (8%), nephrotoxic drug intake (2.7%) and dehydration (1.4%). Most of the patients with cirrhosis who developed AKI had early stages of AKI. The mortality rate among hospitalized patients with cirrhosis and AKI was 32.4%. AKI was found to have a significant association with patient's survival in cirrhosis. Conclusion: Burden of AKI, in terms of prevalence, morbidity as well as mortality among hospitalized patients with cirrhosis is significantly high in our region. Patients with definite predisposing factors require close monitoring for early detection of renal impairment.

Keywords

Acute Kidney Injury, Cirrhosis, Proportion, Risk Factors, Mortality

1. Background

Cirrhosis is a complex disease process that leads to substantial volume shifts and increased vasodilation resulting in significant morbidity and mortality. Renal dysfunction adds to further complexity in cirrhosis contributing to worsened prognosis [1]. Pre-renal acute kidney injury (AKI) is the commonest cause of AKI in cirrhosis and majority of them

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are responsive to volume challenge. Hepato-renal syndrome (HRS) is the severe and volume unresponsive form of pre-renal AKI [2]. Model of End-stage Liver Disease (MELD) score is a strong predictor of 3-month mortality in patients with cirrhosis and it is also used to prioritize cirrhotic patients for orthotopic liver transplantation [3]. As cirrhosis advances, underlying portal hypertension causes profound hemodynamic derangement, which in turn leads to marked splanchnic vasodilation. As a result, both renin-angiotensin-aldosterone system and the sympathetic nervous system gets activated, leading to intense renal vasoconstriction, which then plays a major role in the pathogenesis of ascites, hepato-renal syndrome and hyponatremia [4].

Table 1. *Staging of AKI according to International Club of Ascites criteria [5].*

Stage 1	Increase in serum creatinine ≥0.3 mg/dl or ≥1.5-fold to 2-fold from baseline
Stage 2	Increase in serum creatinine > 2-fold to 3-fold from baseline
Stage 3	Increase of serum creatinine >3-fold from baseline or Increase in serum creatinine to ≥ 4 mg/dl with an acute increase by ≥0.3 mg/dl (or) Need for renal replacement therapy (RRT)

As per the revised definition of AKI by International Club of Ascites (ICA) in 2015, increase in serum creatinine ≥ 0.3 mg/dl within 48 hours or a percentage increase of serum creatinine ≥ 50% from baseline which is known, or presumed, to have occurred within the prior 7 days defines AKI in cirrhosis. ICA has also revised the staging (Table 1) and treatment response (Table 2) of AKI in cirrhosis [5]. In a cirrhotic patient with renal impairment, the crucial task is to identify the antecedent event that precipitated the renal failure. After ruling out the possibility of intrinsic renal disease, albumin infusion should be initiated which can improve the effective arterial blood volume, along with its antioxidant as well as anti-inflammatory properties [6, 7]. Inadequate response to albumin infusion after 48 hours of infusion or advanced stages of AKI recommends vasoconstrictors like Terlipressin, Norepinephrine or combination of Octreotide and Midodrine [8].

Table 2. *Treatment response to AKI - International Club of Ascites criteria (2015) [5].*

No Response	No regression of AKI
Partial Response	Regression of AKI stage with reduction of serum creatinine ≥ 0.3 mg/dl above baseline
No Response	No regression of AKI
Complete Response	Regression of AKI stage with reduction of serum creatinine to a value within 0.3 mg/dl of baseline

In the Indian context, various retrospective studies have been conducted in the past, but prospective studies, especially based on ICA-AKI criteria (2015), on AKI in cirrhosis are limited. Early identification of predisposing factors for AKI and immediate treatment at the onset is essential for a better prognosis in patients with cirrhosis.

2. Aim

(1) To study the proportion of AKI among hospitalized patients with Cirrhosis.
(2) To study the predisposing factors for AKI in cirrhosis.
(3) To study the mortality rate in cirrhotic patients with AKI during hospital stay.

3. Methodology

3.1. Design and Patients

This is an observational, prospective, longitudinal study where 186 patients admitted to IP department (ward and ICU) of the Department of Gastroenterology, Government Medical College, Kozhikode with a diagnosis of chronic liver disease over the period of one year (September 2020 - August 2021) were randomly selected and studied. Eligible patients were hospitalized patients aged ≥18 years with a known diagnosis of cirrhosis. Exclusion criteria included patients with prior kidney or liver transplant, patients with known underlying chronic kidney disease, patients with obstructive uropathy and pregnant females.

3.2. Methods

Hospitalized patients with cirrhosis were randomly selected. Detailed clinical history along with clinical examination were done at the time of admission. Major clinical events, including decompensation, were carefully evaluated and appropriate investigations were performed. Cirrhosis was staged based on Child-Turcotte-Pugh (CTP) classification and MELD scoring was also done. Etiology of cirrhosis was also determined based on history, biochemical and serological investigations along with liver biopsy (if needed). AKI in cirrhosis was defined based on revised ICA-AKI criteria (2015). The proportion of AKI in hospitalized cirrhotic patients was calculated. Predisposing factors for AKI in cirrhosis were analyzed based on clinical and laboratory evaluation and association in patients with and without AKI were stud-

ied. Baseline creatinine in the prior 3 months was collected. Serum Creatinine was measured at admission & subsequently monitored, until the discharge or death of patient. During hospitalization, peak serum creatinine value was noted and staging of AKI was done as per ICA-AKI criteria. All hospitalized patients with cirrhosis and AKI were managed as per the standard treatment guidelines, including the tackling of predisposing factors. Mortality rates in cirrhotic patients with and without AKI during hospital stay were measured as secondary objective.

3.3. Statistical Analysis

Statistical Analysis was done using SPSS 16 software. Patient characteristics were described with absolute frequencies, percentages and medians. The proportion of AKI in cirrhosis was analyzed as percentages. The risk factors for development of AKI in cirrhosis were evaluated by univariate analysis using chi-square test for categorical variables and univariate logistic regression for continuous variables (like Age & MELD score). The risk factors which were found to be significant in univariate analysis were taken into multivariate analysis using multiple logistic regression. Receiver Operating Characteristic (ROC) curve was used to evaluate the diagnostic capability of MELD score on AKI in cirrhosis. Mortality rates in cirrhotic patients with AKI also was analyzed as percentages. Comparison of MELD score among treatment response groups was done using ANOVA and post-hoc dunnet t-test.

4. Results

A total of 186 hospitalized patients with cirrhosis were enrolled in the study over a period of 1 year. 74 out of 186 patients with cirrhosis developed AKI, either at admission or during hospital stay. The proportion of AKI in hospitalized patients with cirrhosis is 39.7%. The demographic and clinical characteristics of cirrhotic patients with and without AKI are summarized in Table 3. The mean age of patients with cirrhosis who developed AKI (57.9 ±12.95 years) was higher than those without AKI (50.65 ± 13.04 years). Our study population showed male predominance (61.3%) and among patients who developed AKI (n=74), 45 (60.8%) were males and 29 (39.2%) were females. Most patients who developed AKI had advanced underlying cirrhosis, of which 48 patients had CTP-C and 18 patients had CTP-B stages out of 74 patients. Among patients without AKI, CTP-A and CTP-B (102 out of 112 patients) stages of underlying cirrhosis predominated. The mean MELD score of cirrhotic patients was higher among patients with AKI (26.97 ± 6.93) than those without AKI (15.44 ± 6). The utility of MELD score as a diagnostic marker for AKI in cirrhosis was evaluated using a receiver operating characteristic curve (ROC). The area under the curve was 0.888, indicating it is a fairly good marker bordering on excellent. Most common etiologies of cirrhosis in our study population were alcoholic liver disease (77 of 186 patients; 43.2%) followed by Non-Alcoholic Fatty Liver Disease (NAFLD) (51 of 186 patients; 37.8%), while HBV infection (11.3%), HCV infection (4.8%), autoimmune hepatitis (3.7%), Budd Chiari syndrome (3.2%) andWilson's disease (1.6%) constitutes minor population. 6.4% of patients were cryptogenic. In patients with NAFLD related cirrhosis, more than 50% (28 of 51 patients) developed AKI, while none of the patients with budd chiari syndrome and autoimmune hepatitis developed AKI in our study.

Table 3. *Demographic and clinical characteristics of the participants in the study.*

Characteristics (N=186)	Cirrhosis with AKI (N=74)	Cirrhosis without AKI (N=112)
Age*	57.9 (12.95)	50.65 (13.04)
Male	45	69
Female	29	43
Child-Turcotte-Pugh (CTP) score		
CTP - A	8	57
CTP – B	18	45
CTP - C	48	10
Model for end stage liver disease (MELD)*	26.97 (6.93)	15.44 (6)
Previous decompensation	62	49
Etiology of CLD		
Alcoholic liver disease	32	45
NAFLD	28	23
HBV	10	11
HCV	1	8
Wilson's disease	0	3
Autoimmune Hepatitis	0	7
Budd chiari syndrome	1	5
Cryptogenic	2	10

*All continuous variables are expressed as mean (Standard deviation)

4.1. Analysis of Risk Factors Associated with AKI in Cirrhotic Patients (Table 4)

Table 4. Univariate analysis of risk factors for AKI in cirrhosis.

Risk factors	Odds ratio	95% Confidence Interval	p value
Variceal bleeding	2.801	1.479 – 5.305	0.002
SBP	2.962	1.399 – 6.268	0.005
Recent LVP	5.746	1.160 – 28.477	0.031
Hyponatremia	15.117	7.318 – 31.227	< 0.001
Hepatic encephalopathy	13.256	6.279 – 27.985	< 0.001

As evaluated using univariate logistic regression, age (Odds Ratio [OR]-1.04; 95% Confidence Interval [CI]: 1.02-1.07) and MELD score (OR: 1.26; 95% CI: 1.18-1.34) were found to be significant risk factors for AKI in cirrhosis, while gender distribution had no significant association (OR: 1.03; 95% CI: 0.57 – 1.89). CTP score of underlying cirrhosis also had significant association with AKI ($\chi^2 = 68.50$, $p < 0.001$), as 82.8% of advanced CTP stage-C cirrhosis developed AKI in our study.

Common predisposing factors for AKI in cirrhosis seen in our study were variceal bleeding (44.6%), Spontaneous Bacterial Peritonitis (SBP) (29.7%), recent large volume paracentesis (LVP) (9.4%), recent history of over-diuresis (8%) and Urinary Tract Infection (UTI) (6.7%), while Non-Steroid Anti-Inflammatory Drugs (NSAID) use (2.7%), diarrhea (1.3%) and other infections like lower respiratory tract infection (LRTI), cellulitis and cholecystitis comprised only minority (< 5%). AKI was found to be associated with 56.9% of patients with variceal bleeding, 61.1% of patients with SBP, 77.8% of recent LVP, 100% of recent over diuresis. Hence, onset of AKI in cirrhosis was found to have significant statistical correlation with variceal bleeding ($\chi^2 = 10.30$, p=0.002), SBP ($\chi^2 = 8.47$, p=0.005), recent LVP ($\chi^2 = 5.70$, p=0.031) and recent history of over diuresis ($\chi^2 = 9.38$, p=0.003). Other infections like UTI, LRTI, cellulitis and cholecystitis were not found to have any statistical association with AKI in cirrhosis. Statistical significance was not tested with risk factors like diarrhea and recent intake of NSAID or any other nephrotoxic drug, as sufficient participants were not available for the analysis in our study, even though all 2 patients with NSAID intake and 1 out of 2 patients with diarrhea had associated AKI.

Among our cirrhotic patients, 75.3% of patients with hyponatremia and 78.3% of patients with hepatic encephalopathy had AKI. Significant statistical correlation was also established between AKI and hyponatremia ($\chi^2 = 63.42$, p< 0.001) as well as hepatic encephalopathy ($\chi^2 = 54.94$, p< 0.001).

After univariate analysis, the above-mentioned risk factors were taken into multivariate analysis using multiple logistic regression which has a very good predictive capability (Cox & Snell R-square – 0.434). In the multivariate analysis, MELD score (OR: 1.17; 95% CI:1.07 – 1.28) and variceal bleeding (OR: 4.16; 95% CI:1.49 – 11.63) were found to be significant risk factors for AKI when adjusted for other confounding factors (Table 5).

Table 5. Multivariate analysis of risk factors for AKI in cirrhosis.

Risk factors	Odds ratio	95% Confidence Interval	p value
Age	1.001	0.966 – 1.036	0.965
MELD score	1.172	1.072 – 1.282	< 0.001
Variceal bleed	4.165	1.491 – 11.635	0.006
SBP	2.383	0.80 – 7.098	0.119
Recent LVP	3.636	0.504 – 26.214	0.20
Hepatic Encephalopathy	1.891	0.605 – 5.907	0.273
Hyponatremia	1.754	0.499 – 6.171	0.381

The factors identified as significant in univariate analysis were entered into a multivariate logistic regression model as predictors of acute kidney injury.

MELD score was evaluated as diagnostic marker of AKI using receiver operating characteristic curve (ROC). MELD score of 20 offered approximately 80% sensitivity and specificity. AUROC of 0.888 indicated a fairly good marker bordering on excellent (Figure 2).

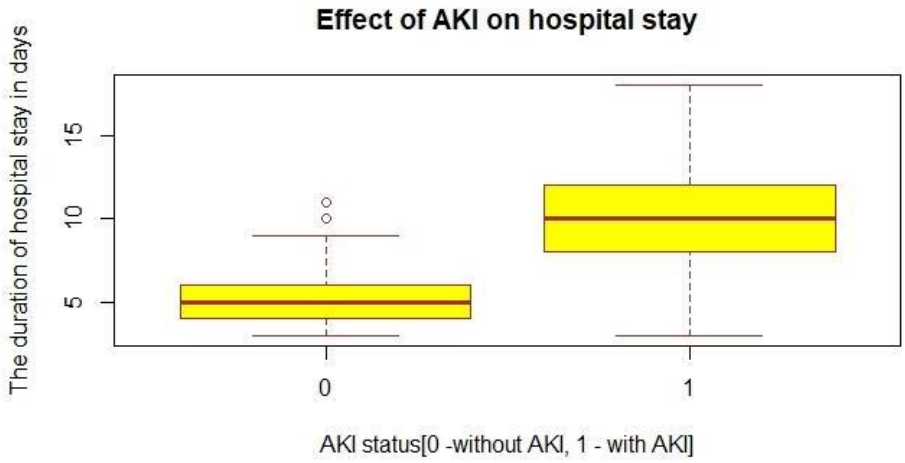

Figure 1. *Boxplot comparing duration of hospital stay in patients with and without AKI.*

(0 = Patients without AKI, 1 = Patients with AKI)
*The outliers in group 0 is shown with the serial number of data points

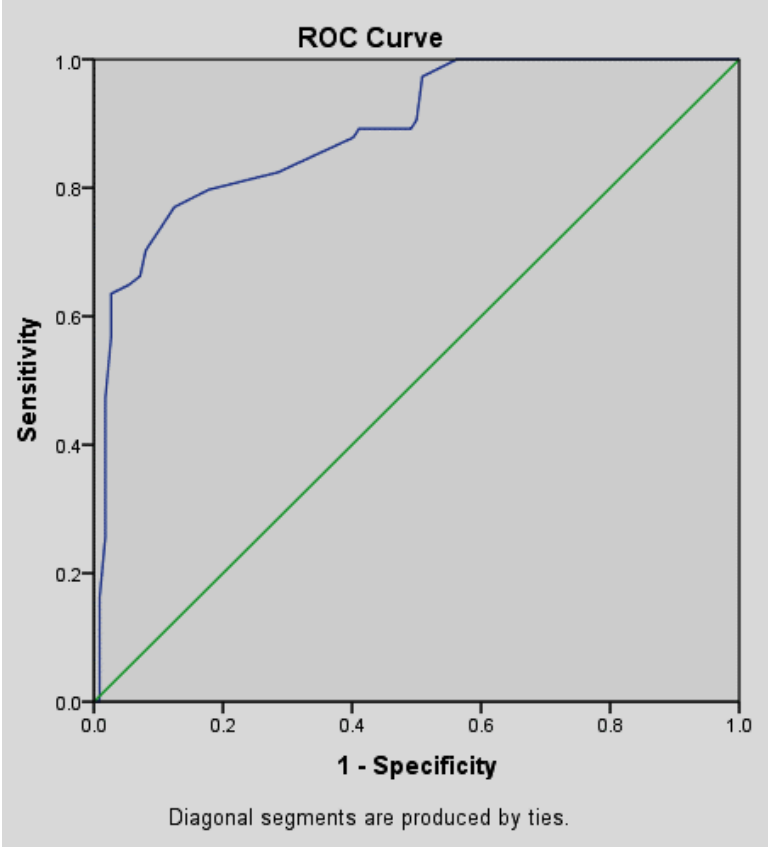

Figure 2. *The Receiver Operating Characteristic (ROC) curve showing the predictive capability of Model for end stage liver disease (MELD) score as a diagnostic tool for acute kidney injury in liver cirrhosis.*

4.2. Influence of AKI on Morbidity and Mortality of Patients with Cirrhosis

34 patients (18.3%) succumbed to their ailment, among which 24 had concurrent AKI and 10 patients had no associated AKI. Among patients with cirrhosis and AKI, 32.4% of patients succumbed to their illness. Therefore, AKI was found to be significantly associated with patient mortality in our study (OR – 4.89, 95% CI: 2.17-11.02).

Out of 59 patients (31.7%) who required ICU care during hospitalization, 83% (n=49) had AKI. 66.2% of patients with

cirrhosis and AKI required ICU monitoring and a significant statistical association was also seen between AKI and ICU requirement (OR – 19.99, 95% CI: 8.91 - 44.88). The mean duration of hospitalization in patients with cirrhosis who developed AKI (9.92 ± 3.157 days) was found to be higher than those without AKI (5.07 ± 1.587 days) (Figure 1).

Association between number of hospital days and MELD score was evaluated using simple linear regression and it was found that MELD score was a significant predictor for duration of hospital stay in our study population (R squared = 0.492).

4.3. Distribution & Influence of Peak Stages of AKI in Patients with Cirrhosis

Out of 74 patients with AKI in cirrhosis, stage-1 AKI (43.2% [n=32]) predominated, followed by stage-2 AKI (32.4% [n=24]) and stage-3 AKI (24.3% [n=18]).

Among the deceased patients with AKI and cirrhosis, the majority belonged to peak stage-3 AKI (66.7%) followed by stage-2 AKI (29.2%). Hence, the peak AKI stage has significant association with mortality in patients with cirrhosis and AKI ($\chi^2 = 38.84$, df = 2, $p < 0.001$). Advanced stages of AKI (stages 2 & 3) also had major ICU requirement (85%) and hence, found to have significant statistical correlation ($\chi^2 = 49.55$, $p < 0.001$).

4.4. Time of Onset of AKI in Patients with Cirrhosis

Among patients with cirrhosis, 66.2% (n=49) had AKI at admission or within 24 hours of admission, while 33.8% (n=25) developed AKI later (after 24 hours of admission).

In our study, mortality in cirrhotic patients with early onset AKI (46.9% [n=23]) was higher when compared to patients with delayed onset AKI (4% [n=1]), which was found to be statistically significant (OR: 0.047; 95% CI: 0.006-0.376).

4.5. Treatment Response in Patients with Cirrhosis

In our study, among patients with cirrhosis and AKI, 59.4% (n=44) had complete response, 23% (n=17) had partial response and 17.6% (n=13) had no response.

All patients with cirrhosis and AKI with no response to treatment had 100% mortality and survival was abysmal in partial responders also (10 of 17 patients; 58.8% mortality). Only 1 patient (2.3%) among complete responders didn't survive. Treatment response in AKI had significant statistical association with mortality of cirrhotic patients ($\chi^2 = 50.75$, $p < 0.001$).

The mean duration of hospital stay among complete responders was 8.9 days (SD-2.5) and in partial responders was 10.1 days (SD-3.4), while non-responders had relatively higher duration of hospital stay of 12.8 days (SD-3.2). Duration of hospital stay was found to significantly differ according to responder status of patients (F=9.304; p<0.001). Post-hoc comparison using dunnett t-test showed that duration of hospital stay was found to significantly differ between non-responder and complete responders (p<0.001).

4.6. Renal Replacement Therapy (RRT)

13.5% (n=10) of patients with AKI and cirrhosis, who had stage-3 AKI, received RRT in our study and none of them survived.

5. Discussion

A longitudinal study was conducted on randomly selected 186 hospitalized patients with cirrhosis. 74 out of 186 patients developed AKI and the proportion of AKI in hospitalized patients with cirrhosis in our study is 39.78%. Western data had pointed out a significant burden of AKI in cirrhotic patients. Earlier in 2001, retrospective study by *Hampel H et al* showed that 24.7% patients developed AKI within 15 days of hospitalization [9]. Later in 2013, a prospective study by *Fagundes C et al* showed a very high proportion of 47% developing AKI (as per AKIN criteria) in hospitalized patients with cirrhosis [10]. According to the Indian data, a retrospective study by *Shetty S et al* in 2018 showed that prevalence of AKI in hospitalized patients with cirrhosis was 35% [11]. In 2020, an observational study from North India by *Arora MS et al* showed 40.6% patients with AKI in patients with decompensated cirrhosis [12]. Another prospective observational study by *Kumar U et al* in 2020 showed that 28.4% patients with cirrhosis developed AKI [13].

In our study, the mean age of patients with cirrhosis who developed AKI (57.9 ±12.95 years) was higher than those without AKI (50.65 ± 13.04 years) and age had significant association with AKI in cirrhosis. In 2018, study by *Shetty S et al* showed mean age of 51.7 years for patients with cirrhosis and AKI [11], while mean age was 48 years as per study by *Kumar U et al* [13]. In another study by Arora MS et al in 2020, mean age of patients with cirrhosis with AKI (48.9 ±10.11 years) was lower than those without AKI (51.72 ± 12.01 years) and age had no association with development of AKI in cirrhosis [12].

Male population was higher in our study and predominated in both the groups of cirrhotic patients with and without AKI. However, sex distribution had no significant association with AKI in cirrhosis. Studies by *Shetty S et al* [11] and *Kumar U et al* [13] also showed predominantly males with AKI in cirrhosis.

In our study, large majority (> 80%) of patients with advanced cirrhosis (especially CTP - C) developed AKI. Hence, the risk of AKI is proportional with severity of the underlying cirrhosis. *Arora MS et al* also showed that CTP score was significantly higher in patients with AKI, implying that se-

verity of cirrhosis may contribute to development of AKI ($p < 0.05$) [12]. However, *Tsien C D et al* showed no significant difference in the CTP score between patients with AKI and without AKI [14].

In our study, the mean MELD score among patients with cirrhosis and AKI (26.97 ± 6.93) was higher than those without AKI (15.44 ± 6), which agrees with the study by *Arora MS et al* which also showed higher mean MELD score in patients with cirrhosis and AKI (27.9 ± 8.5) than in those without AKI (15 ± 6.3) [12]. MELD score (OR: 1.258; 95% CI:1.182-1.339) was found to be a significant risk factor for AKI in cirrhosis and a score of 20 or more was shown to have 80% sensitivity and specificity as a diagnostic tool for AKI in cirrhosis (AUROC - 0.88).

Majority (> 90%) of patients in our study had alcoholic liver disease, NAFLD or Hepatitis-B related cirrhosis and thus, AKI predominated in these 3 etiological groups of cirrhosis. Unlike other etiologies, more than half the population of NALFD developed AKI in our study. Alcoholic liver disease predominated in other studies by *Shetty S et al* [11], *Arora M S et al* [12] and *Kumar U et al* [13].

5.1. Predisposing Factors for AKI in Cirrhosis

In our study, variceal bleeding (44.6%) and SBP (29.7%) were the most common predisposing factors for AKI in cirrhosis, followed by large volume paracentesis (9.4%), recent over diuresis (8%), UTI (6.7%), while other infections, NSAID or nephrotoxic drug intake (2.7%) and diarrhea (1.3%) comprised only minority. Among these risk factors, variceal bleed, SBP, recent over diuresis and recent LVP were found to have significant association with the onset of AKI in cirrhosis. However, when these risk factors were subjected to multivariate analysis using multiple logistic regression, after adjusting for confounding factors, only variceal bleeding was found to be a significant risk factor for the development of AKI in cirrhosis. Since sufficient participants were not available for the analysis of risk factors like dehydration and recent NSAID use, its association with AKI could not be analysed, even though all patients with recent NSAID use had developed AKI. Other predisposing factors like UTI, LRTI, cellulitis and cholecystitis in cirrhosis were not found to have any significant association with AKI in our study.

In a study by *de Carvalho G C et al* in 2012, bacterial infections and hypovolemia accounted for more than 70% of cases of renal failure in patients with decompensated end stage liver disease [15]. In another study by *Tsien C D et al*, the most common precipitants for AKI were bacterial infections (including SBP), followed by large volume paracentesis and increase in diuretic doses [14]. As per Indian data, *Kumar U et al* showed that infections and hypovolemia were the most common causes of AKI in cirrhosis [13], while *Arora M S et al* showed SBP, sepsis and shock as common risk factors for AKI [12]. In concordance with above studies, variceal bleed, SBP were risk factors having significant association with AKI in our study. However, on the contrary, other bacterial infections (except SBP) were not found to have any significant association with AKI in cirrhosis.

In our study, hyponatremia and hepatic encephalopathy were found to have significant association with AKI in cirrhosis. *Shetty S et al* showed that a large proportion (85%) of patients with cirrhosis and AKI had hepatic encephalopathy [11]. *Kumar U et al* also showed similar association between AKI and hepatic encephalopathy in 21% of patients with decompensated cirrhosis, which had significant association with patient mortality [13].

5.2. Influence of AKI on Mortality and Morbidity Indices of Cirrhosis

In our study, 32.4% (n=24) of patients with cirrhosis and AKI succumbed to their illness and AKI was found to have significant impact on patient's survival. 66.2% of patients with cirrhosis and AKI required ICU monitoring indicating higher morbidity than those without AKI. *Scott R A et al* showed that cirrhotic patients with AKI had higher mortality rate than those without AKI (31.8% vs 3.8%, p<0.001) [16]. Indian data also agrees with relatively higher mortality rate among cirrhotic patients with AKI as per studies by *Shetty S et al* (44.7%) [11], *Arora MS et al* (33.8%) [12] and *Kumar U et al* (26.68%) [13].

Our study also showed relatively longer mean duration of hospital stay in cirrhotic patients with AKI (9.92 ± 3.157 days) than those without AKI (5.07 ± 1.587 days), which complies with the data by *Shetty S et al* (mean duration: 11 days) [11] and *Scott R A et al* (16 days vs 6 days, $p < 0.01$) [16].

5.3. Stages of AKI and Its Impact on Patients with Cirrhosis

Early stages of AKI predominated our study, with peak AKI stage 1 (43.2%) being more common followed by stage 2 AKI (32.4%) & stage 3 AKI (24.3%). *Arora MS et al* also showed similarly higher proportion of early stages of AKI in cirrhosis that majority (stage 1: 77.4%, stage 2: 19.7%, stage 3: 2.8%) [12]. On the contrary, relatively higher proportion of advanced stages of AKI was depicted in studies by *Shetty S et al* (stage 1: 15.4%%, stage 2: 26.8%%, stage 3: 57.7%%) [11] and *Belcher J M et al* (stage 1: 26%, stage 2: 24%, stage 3: 49%) [17].

Among patients with cirrhosis and AKI, most of the deceased patients belonged to stage 3 (66.7%) and stage 2 (29.2%) AKI, while only 1 patient (4.2%) had stage 1 AKI. Peak stage of AKI in cirrhosis was found to have significant association with mortality. 85% of patients with stage 2 and 3 AKI required ICU monitoring, depicting worse morbidity among advanced stages of AKI in cirrhosis. This data complies with studies by *Shetty S et al* (stage 1: 15.8% vs stage 2:

27.3% vs stage 3: 60.6%) [11], *Kumar U et al* (stage 2: 45.8% vs stage 3: 62.8%) [13] and *Scott R A et al* (stage 1: 13.5% vs stage 2: 37.8% vs stage 3: 43.2%) [16].

5.4. Time of Onset of AKI in Patients with Cirrhosis

In our study population with cirrhosis, the majority had early onset AKI (at or within 24 hours of admission) rather than a delayed onset of AKI (onset after 24 hours of admission) (66.2% vs 33.8%). A relatively higher mortality rate was seen in cirrhotic patients with early onset AKI when compared to late onset AKI (46.9% vs 4%). *Kumar U et al* also showed relatively higher proportion of cirrhotic patients with AKI at the time of admission than those with AKI during hospital course (67.2% vs 32.8%) [13].

Hemodialysis: In our study, 13.5% of patients with cirrhosis and AKI, who all belonged to stage 3 AKI, underwent RRT and none of them survived. *Shetty S et al* showed 17% patients with cirrhosis and AKI required hemodialysis [11], while in the study by *Arora MS et al*, 21.1% of cirrhotic patients with AKI underwent RRT [12].

5.5. Treatment Response in Patients with Cirrhosis and AKI

Among patients with cirrhosis and AKI, more than half made complete response (59.4%) when compared to partial responders (23%) and non-responders (17.6%). Mortality rate was significantly higher among non-responders (100%) and partial responders (58.8%) when compared to those who had complete response to treatment (2.3%). *Wong F et al* also showed higher mortality rate among cirrhotic patients without renal recovery (80%) when compared to partial (40%) or complete recovery (15%) or patients without AKI (7%) ($p < 0.001$) [18].

Treatment response significantly influenced the duration of hospital stay in patients with cirrhosis and AKI, as mean duration was higher in non-responder (12.8 ± 3.2 days), when compared to partial responders (10.1 ± 3.4 days) and complete responders (8.9 ± 2.5 days) to treatment. Mean duration of hospitalization significantly differed between non-responders and complete responders and thus, treatment response had significant impact on morbidity rate.

Our study is not without limitations. Firstly, the data provided in our study was based only on hospitalized patients with cirrhosis and hence, generalizing the data to the community may not be feasible. Secondly, renal biopsy to establish the definite cause of AKI could not be done due to inherent risk of bleeding in our cirrhotic patients. Thirdly, long term follow-up was not done in our study to assess long-term mortality rate and requirement for simultaneous liver-kidney transplantation. Finally, even though the need for liver transplantation (for patients fitting the criteria) was counselled to both patient and relatives, none of them could be taken up for transplantation primarily due to financial constraints.

6. Conclusion

The proportion of AKI in hospitalized patients with cirrhosis is significantly high (39.78%) in Northern Kerala. Patients with advanced cirrhosis, indicated by high CTP score, have a higher risk for AKI during hospitalization. Alcoholic liver disease, NAFLD and Hepatitis-B related cirrhosis comprised the majority of cirrhosis. Variceal bleeding and SBP are the most common risk factors for AKI in cirrhosis. Onset of AKI has a significant impact on the mortality and morbidity indices of patients with cirrhosis. Early stages of AKI are predominant among cirrhotic patients and mortality risk proportionately increases as the stage of AKI advances. Among the hospitalized cirrhotic patients with definite risk factors for AKI, close monitoring for early detection of the onset of AKI is essential for rapid institution of treatment.

Abbreviations

AKI	Acute Kidney Injury
AKIN	Acute Kidney Injury Network
ANOVA	Analysis of Variance
AUROC	Area Under the Receiver Operating Characteristics
CI	Confidence Interval
CTP	Child-Turcotte-Pugh
df	Degrees of Freedom
HRS	Hepato-renal Syndrome
ICA	International Club of Ascites
ICU	Intensive Care Unit
LRTI	Lower Respiratory Tract Infection
LVP	Large Volume Paracentesis
MELD	Model for End-stage Liver disease
NAFLD	Non-alcoholic Fatty Liver Disease
NSAID	Non-Steroidal Anti-inflammatory Drugs
OR	Odds Ratio
RRT	Renal Replacement Therapy
SBP	Spontaneous Bacterial Peritonitis
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
UTI	Urinary Tract Infection
UGI	Upper Gastrointestinal

Ethical Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

Availability of Data and Material

The datasets used and analysed during the current study are available from corresponding author on reasonable request.

Author Contributions

Sandeep Menon: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing

Sunil Kumar Kandiyil: Investigation, Supervision, Validation

Sithara Balagopal: Supervision

Kadavanoor Srijith: Supervision

Sandesh Kolassery: Supervision

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Conflicts of Interest

The authors declare no conflicts of interest.

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