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ORIGINAL ARTICLE

Acute Kidney Injury in Cirrhosis of Liver: it's Clinical Spectrum and Association of Various Clinical Outcomes with Advancing Cirrhosis of the Liver

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ABSTRACT

Background & Objectives: Pakistan in tandem marks mortality of advance cirrhosis due to complications like hepatic encephalopathy, upper gastrointestinal bleeding and Acute kidney injury (AKI) contributing further morbidity and mortality. The study aimed to determine frequency, types and severity of AKI among cirrhotics and find association between AKI with various clinical outcomes among advance cirrhotics.

Methods: All cirrhotics (both genders), age > 18 years of various aetiologies with confirmed AKI were included and analysed retrospectively. Clinical, antiviral treatment and biochemical predictors of mortality in AKI were analysed by univariate regression however independent risk factors were analysed by multi regression (significant P values < 0.05).

Results: Out of 271 cirrhotics, 188 (69.37%) had AKI. Commonest to least common AKI pattern was pre-renal (59.5%), intrinsic (37.7%) post-renal (2.1%). Majority (45.2%) had international club of ascites (ICA-AKI) stage 3, (33.5%) ICA-AKI stage 2 and (21.3%) ICA-AKI stage 1. The overall mortality with AKI at 1,6 and 12 months were 12.8%, 39.1% and 54.3% respectively (significant p 0.001). Increased creatinine, international normalized ratio (INR), bilirubin, albumin, Child Turcotte Pugh (CTP) and Model of end stage liver disease (MELD) were in-hospital predictors of mortality where INR and albumin proved significant.

Conclusion: AKI being frequent challenge among cirrhotics has commonest pattern as pre-renal with majority having severe AKI, ICA-Stage 3. Patients with AKI had higher mortality versus non-AKI. Rising creatinine, serum bilirubin, severity of cirrhosis (CTP and MELD score) were the significant predictors of in-hospital mortality where INR and albumin were most significant.

Keywords: Acute kidney injury, international club of ascites, cirrhosis of liver, child Turcotte Pugh, International normalized ratio

INTRODUCTION

The manifestation of acute kidney injury (AKI) in patients with advance cirrhosis of liver institutes a grimly encountered clinical situation. Compromised kidney function in advanced cirrhosis is due to AKI, either with or without underlying chronic kidney disease (CKD). An overall reported prevalence of AKI is 14 to 40% among hospitalized patients whereas it reaches up to 50% among patients having ascites.[1,2]AKI is pertinently caused by pre-renal,renal or post-renal factors. The traditional theme of prerenal impairment eventually leading to intrinsic renal failure or acute tubular necrosis is akin to cirrhotic patients.More than 80% cases of AKI in cirrhosis have pre-renal and intrinsic renal origin (49% prerenal and 35% ATN). There are quite many precipitating events for AKI among cirrhotic such as gastrointestinal bleeding, diuretics overdosage, repeated paracentesis without cover of albumin replacement and superimposed bacterial infections.[2] The reported frequency of post-renal injury is about 0.2%.[3]A prospective cirrhotic cohort of patients waiting for liver transplantation had shown 76% (pre-renal injury) followed by intrinsic renal (33%) as a cause of underlying AKI, none so from post-renal cause.[4]

AKI definition has been recently revised and put as a proposal by the International Club of Ascites (ICA) which removed previous criterion of serum creatinine > 2.5 mg/dL along with the 2-week extent threshold for Hepatorenal syndrome (HRS) diagnosis and define AKI"whereas within 2 days (48 hours) of hospital admission increase in serum creatinine ≥26.5 mol/L (≥0.3 mg/dl); or, ≥50% upsurge of serum creatinine in the time off shock, without current use of nephrotoxic substances or pre-existing structural renal disease.[5]With the new ICA classification, HRS is now labelled as one of the forms of AKI and known as HRS-AKI.

For assessment of better prognosis AKI classified into 3 stages on the bases of increasing severity. A recent study has shown more survival probability 0f three months (84%) in AKI stage 1 versus 34 % with AKI stage 3 among patients with cirrhosis of liver.[6,7,] Early detection of stages of AKI among patients of advance cirrhosis is of paramount importance to reduce mortality.

Chronic kidney disease (CKD) with a prevalence of 8% to 16% in general population is also a comorbidity among patients with cirrhosis where superimposed AKI is particularly very harmful and lead to poor outcome.[7]Six time increase hospital mortality has been reported in patients of cirrhosis with AKI[8]which even remained high till 1 year follow-up. Cirrhosis related health indices of Pakistan lodges a massive burden of advanced cirrhosis, where over three decades (1980 to 2010) the mortality has increased from 10,324 (6,129–16,651) to 31,373 (16,325–61,028).[9] Cirrhosis related age-standardized mortality rate (per 100,000) is reported between 21.7% to 27.5% in Pakistan.[9]Pakistan with already high burden of mortality of advance cirrhosis due to its well-known complications like hepatic encephalopathy, upper gastrointestinal bleeding, AKI with or without underlying CKD causes further contribution to its morbidity and mortality.Thus, this study designed toassess the frequency, types, severity as well as aetiologies of AKI among patients with cirrhosis of liver. This study further intended to determinean association between AKI with various clinical outcomes among patients with advance cirrhosis.

MATERIALS AND METHODS

Study Protocol: All patients (both genders), age > 18 years having cirrhosis of liver with various aetiologies and confirmed AKI admitted in XXXfrom 1st August 2020 to July 2021 were included and analysed retrospectively. As this study is a retrospective analysis of data informed consent of patientswere not required, however ethical exemption was sought from institutional review board. All demographic, clinical, and biochemical details were retrieved. Patients with age <18 or >85 years, not having previous baseline serum creatinine value before admission, hepatocellular carcinoma, HIV infection, malignancies and having incomplete record were excluded. Clinical data were included like record of direct antiviral treatment in case of HCV and nucleoside/tide treatment in HBV, prior renal disease, medical comorbidities, complications related to cirrhosis like ascites, hepatic encephalopathy, gastrointestinal bleeding, and bacteraemia (defined by a positive blood culture upon hospital admission).

Cirrhosis of liver: Cirrhosis was confirmed on clinical, biochemical, sonological basis and with liver biopsy wherever required.

Acute kidney injury (AKI): AKI confirmed in accordance to International Club of Ascites (ICA) criteria recently endorsed and included in the EASL guidelines, was where within 2 days (48 hours) of hospital admission increase in serum creatinine ≥26.5 mol/L (≥0.3 mg/dl); or, ≥50% upsurge of serum creatinine,considered to have elevated within the past 07 days.[10,11]
Stages of AKI/Severity of AKI: AKI was classified into 3 stages in accordance with the modified ICA criteria.[10]
ICA-AKI Stage 1: It was defined as(Serum creatinine ≥0.3 mg/dl or ≥26.5 mol/L) or an increase (≥1.5-fold to 2-fold) from baseline
ICA-AKI Stage 2: Rise of (>2-fold to 3-fold) from baseline in serum creatinine
ICA-AKI Stage 3: Rise of (>3-fold from baseline) or serum creatine ≥4.0 mg/dl (353.6 mol/L) with a sudden rise of ≥0.3 mg/dl (≥26.5 mol/L) or start of dialysis.
Patterns of AKI: Patients with AKI were classified into following patterns
Prerenal AKI: Volume responsive AKI: Pre-renal azotemia was defined on clinical (oliguria, hypotension, orthostatic hemodynamic changes and tachycardia) and laboratory parameters (raised serum creatinine, increase urinary specific gravity >1.02. It was included for both volume responsive and unresponsive AKI.[12]
Volume non - responsive AKI-HRS: AKI-HRS (previously called HRS type 1) with an alteration of total serum creatinine from ≥ 0.3 mg/dL or within last 2 days (48 hours) rise in serum creatinine ≥ 50% from baseline with a failure in volume restoration in the absence of shock, without new use of nephrotoxic substances or pre-existing architectural renal disease.[10]

Non-AKI-HRS(NAKI) previously called Type 2 HRS was outlined according to the ICA criteria where diagnostic criteria were fulfilling HRS criteria but not the AKI.[10]
Intrinsic AKI: Acute tubular necrosis: Intrinsic AKI will be diagnosed with a prior history of renal parenchymal injury or increase in serum creatinine which fails to improve even after an effective volume resuscitation along with exclusion of other causes of renal injury. ATN was diagnosed with prolonged hypotension, tachycardia along with the presence of granular casts (epithelial cell casts) on urinalysis, > 2%, or a urinary Na concentration > 40 mmol/L.[12]
Post renal AKI: Post-renal AKI was confirmed in the setting of oliguria or anuria with the evidence of hydronephrosis on imaging.
Biochemical parameters: Along with baseline investigations (CBC, urine analysis and UCE), all laboratory parameters related to cirrhosis like liver chemistries such as bilirubin, albumin, transaminases Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and prothrombin time (PT) were also retrieved. Outcomes were reported through the course of index hospitalization.
Statistical analysis: Data was analysed through SPSS Version 23 (Chicago, IL). Descriptive statistics were applied for demographic, clinical and laboratory parameters. All-cause mortality was the primary outcome measure in this study. Mortality rate of AKI was compared among various causes and patterns through exact X^2 test for proportions difference; 95% confidence interval (CI) was computed by an exact binomial distribution. Clinical and biochemical predictors of mortality in AKI were assessed by univariate regression analysis however independent risk factors were determined by using multi regression analysis. P values of < 0.05 were kept statistically substantial.

RESULTS

A total of 281 patients having cirrhosis got admitted to the hospital from 2020 to 2021. 10 patients (3.66%) were excluded due to incomplete clinical and biochemical data, setting out a cohort of 271 patients for study enrolment and analysis. Out of 271 patients of cirrhosis, 188 (69.37%) had AKI whereas 83 (30.62%) did not have AKI and were labelled as non-AKI. The demographic profile of both groups of cirrhosis, with and without AKI has shown in Table 1.Most of the patients among both groups were males. Mean age of patients with cirrhosis having AKI and non-AKI were 64.78 and 57.79 years respectively. Upon comparison of groups, the age was statistically significant (p <0.001) for patients having AKI. Among the aetiologies of cirrhosis in patients having AKI, HCV infection (52.7%) was the most common followed by HBV infection (36.2%), AIH (6.4%), Wilson's disease (2.1%), alcohol (1.6%) and cryptogenic (1.1%) Table 1, whereas non-AKI patients had HCV infection (55.4%) as the commonest followed by HBV infection (31.3%), AIH (8.4%), Wilson's disease (2.4%) and alcohol (2.4%).

Table 1: Characterstics of the Study Cohort (n=271)

Variables	Cirrhosis with AKI (n-188)	Cirrhosis without AKI (n-83)	Total	T-test / Chi square test	Variables	Cirrhosis with AKI (n-188)	Cirrhosis without AKI (n-83)	Total	T-test / Chi square test
	n	%/±SD	n	%/±SD	n	%	Statistics	df	P-Value
Demographic Profile:									
Age	64.78	±9.655	57.79	8.699	62.64	9.898	-5.666	269	<0.001
Gender:							0.021	1	0.885
Male	73	38.8	33	39.8	106	39.1			
Female	115	61.2	50	60.2	165	60.9			
Aetiology:							1.928	5	0.859
AIH	12	6.4 1.6	7 2	8.4 2.4	19	7 1.8			
Alcohol	3	36.2 52.7	26 46 2	31.3 55.4	5	34.7 53.5			
HBV	68	2.1 1.1	0	2.4 0.0	94	2.2 0.7			
HCV	99				145				
Wilson	4				6				
Cryptogenic	2				2				
CTP Stages							0.663	2	0.718
CTP- A	9	4.8 42.6	6 34	7.2 41.0	15	5.5 42.1			
CTP- B	80 99	52.7	43	51.8	114 142	52.4			
CTP- C									
*Scores									
CTP Score	9.94	±2.36 ±3.51	8.60 19.42	±1.57 ±3.20			-4.725	269	<0.001
MELD Score	22.59						-7.029	269	<0.001
Complications		45.5	25	30					0.02
UGIB	85	58	45	55	110	40.5			0.512 0.534
HE	110	24	17	21	155	57.2	-0.66	1	
Bacteremia	45				62	22.9	-0.62	1	
*Biochemical Parameters	Value	SD	Value	SD			Statistics	df	P value
Hb	11.1	±2.5	11.5	±2.1			1.18	1	0.238
Leucocytes, 1000/uL	10.3	(8-12.5)	9.1	(7.3-11.9)			-2.125	1	0.034
(median,IQR)		(87.2-132.8)		(110-152.4)					
Platelets, 1000/uL	110.6		130.7				-4.4	1	<0.001
(median,IQR)				±2.0					
Serum Na		±1.7		±10					

ALT	135	±18	137	±10			-6.22	1	<0.001
AST	136	±14	133				0.321	1	0.747
	126		123				1.912	1	0.057
Bilirubin(mg/dL)	2.61	±0.62	1.29	±0.19			-18.855	269	<0.001
Albumin (g/dl)									
INR	2.68 1.68	±0.47 ±0.39	2.85 1.39	±0.65			2.372 -5.481 -	269	0.018
Baseline	1.61	±0.31	1.24	±0.43 ±0.28			9.355	269	<0.001
Creatinine								269	<0.001
(mg/dL)									
Rise in Creatinine	4.57	±1.57	1.29	±0.19			18.5		
(mg/dL)								1	<0.0001
APACHE II									
	22.45	±5.3	14.4	±2.1			13.4		
								1	<0.0001

*Data is shown in Mean with standard deviation

AIH ; autoimmune hepatitis, HBV ; hepatitis B virus, HCV; hepatitis C virus, CTP; Child turcotte pugh, MELD; model of end stage liver disease, ALT; Alanine amino transfrase, AST; Aspartate transaminase, INR; International normalized ratio

Table 2: Pattrens, severity and mortality in patients having AKI

Severity and causes of AKI	Cirrhosis with AKI (n=188)		Mortality (n=102)	
	N	%	n	%
Stages of AKI				
ICA-AKI Stage 1	40 63	21.3 33.5	0 24	0 38.1 91.8
ICA-AKI Stage 2	85	45.2	78	
ICA-AKI Stage 3				
Patterns of AKI				
Pre-Renal AKI	112	59.5	47	41.9
1. Volume Responsive	78	70.0	24	30
2. Volume Non-Responsive	34	30.0	23	67.44
• AKI-HRS (Type-1)				
• HRS-Type 2	24	70.6	20	83.33
	10	29.4	04	40
Intrinsic-Renal AKI				
Post-Renal AKI	71	37.7 2.1	54	76.1
	4		0	0

AKI; acute kidney injury, ICA-AKI; international club of ascites- acute kidney injury, AKI-HRS; acute kidney injury-hepatorenal syndrome

Table 3: Impact of treatment of HVB and HCV related cirrhosis on AKI related mortality

	Cirrhosis with AKI (n=188)		Cirrhosis without AKI (n=83)		P-Value
	n	%	n	%	
HCV related cirrhosis	99	52.7	46	54	0.98
Patients who have been taking DAA	28	28.2	13	28	
Patients who have not been taking DAA	71	70.8	33	71.3	
Mortality in HCV related cirrhosis	53	53.5	17	62.9	0.84
Patients who have been taking DAA	17	32.1	5	29.4	
Patients who have not been taking DAA	36	67.9	12	70.6	
HBV related cirrhosis					
Patients on nucleoside/nucleotide analogues	68	36.1	26	25.4	0.20
Patients who have not taken nucleoside/nucleotide analogues	22	32.2	12	46.1	
Mortality in HBV related cirrhosis					
Patients on nucleoside/nucleotide analogues	46	67.6	14	53.7	
Patients who have not taken nucleoside/nucleotide analogues	36	36.5	10	37.1	0.57
	11	30.5	4	40.0	
	25	69.5	6	60.0	

HCV: hepatitis C virus; DAA: direct antiviral agents; HBV: Hepatitis B virus;

Table 4: Predictors of in-hospital mortality in cirrhotic patients having AKI and Non-AKI

Variables	Parameter Estimate	SE	OR	95 % C.I Lower Upper		P
Univariate Analysis						
Group Age Male						
CTP MELD	0.688 -0.014	0.270 0.013	1.989 0.986	1.172 0.960	3.378 1.012 1.646	0.011 0.275
Bilirubin AlbuminINR	0.004 0.504	0.252 0.072	1.004 4.523	0.613 0.564	36.29	0.986 <0.001 <0.001
Rise in Creatinine	1.004 3.801	0.124 0.509	2.729 44.759	2.141 16.51	3.479 121.3	<0.001 <0.001 <0.001
Serum Na+	-2.458 3.157	0.343 0.446	0.086 23.505	0.044 9.798	0.168 56.39	<0.001
UGIB	1.552	0.203	4.719	3.169	7.027	
Bacteremia						0.214
HE	0.079	0.064	1.083	0.877	2.300	0.153
APACHE II	0.351	0.246	1.421	0.848	0.957	0.210
HBV patients	-0.365	0.291	0.694	0.392	0.229	1.787
On	0.099	0.246	1.104	0.687	0.682	0.036
nucleoside/tide	-0.044	0.021	0.957	0.918	0.997	0.529
HCV patients on DAA	-0.112	0.177	-0.636	-0.472	0.247	
Multivariate analysis						0.176
	-0.215	0.156	-1.377	-0.532	0.101	
Group Age Male	0.012 -0.007	0.361 0.016	1.012 0.993	0.498 0.962	2.055 1.026	0.974 0.684 0.539
CPT Albumin INR	-0.189 0.220	0.308 0.088	0.828 1.246	0.453 1.049	1.513 1.479 0.554	0.012 <0.001
Serum Na+	-1.334 1.545	0.379 0.531	0.263 4.687	0.125 1.657	13.258	0.004
UGIB	0.061	0.066	1.063	0.934	1.210	0.354
Bacteremia	0.301	0.251	1.351	0.826	2.210	0.231
HE	-0.422	0.298	0.665	0.366	1.175	0.656
APACHE II	0.164	0.250	1.178	0.720	1.927	0.515
	-0.041	0.022	0.960	0.920	1.001	0.049

CTP; Child turcotte pugh, MELD; Model for end stage liver disease, INR; International normalized ratio, DDA; Direct antiviral agents

Among complications of cirrhosis upper gastrointestinal bleed (UGIB), hepatic encephalopathy (HE) and bacteraemia were present in both groups of cirrhosis with and without AKI Table 1. UGIB was found statistically significant (p 0.02) in cirrhotic patients with AKI when compared to non-AKI group Table 1.This cohort had considerable evidence of liver dysfunction as shown by the severity scores of Child-Turcotte-Pugh (CTP) and MELD, which were (8.60±1.56, 19.42±3.20) in non-AKI and (9.94±2.36 ± 22.59±3.51) in AKI groups respectively Table 1. Severity of cirrhosis assessed by CTP and MELD score was significant when compared for AKI with non-AKI group (p <0.001, p <0.001) respectively.Haemoglobin, Platelets and leucocytes were[11.1±2.5g/dL,10.3(8-12.5)/1000µL,110.6(87.2-132.8)/1000µL]and[11.5±2.1g/dL,9.1(7.3-11.9)/1000µL,130.7(110-152.4)/1000µL)in both groups of cirrhosis with and without AKI respectively Table 1.Leucocytes and platelets were significant (p 0.034 and <0.001) when comparedTable 1.Serum sodium was 135 mmol/L±1.7 and 137±2.0 in both groups of cirrhosis with and without AKI respectively Table 1.

Patients of cirrhosis with AKI had liver chemistries as of ALT (136±18 IU/ml), AST (126±14 IU/ml), serum bilirubin (2.61±0.62), albumin (2.68±0.47 g/dL) and INR (1.68±0.39) Table 1. Liver chemistry of cirrhotic non-AKI patients have shown ALT (133±10 IU/ml), AST (123±10 IU/ml), serum bilirubin (1.29±0.19 mg/ dL), albumin (2.85±0.65 g/dL) and INR (1.39±0.43) Table 1. Liver chemistry on comparison among the groups (AKI and non-AKI) have shown statistical significance for bilirubin and INR (p <0.001, p <0.001) Table1. This cohort of cirrhosis in AKI and non-AKI had a baseline creatinine of 1.61±0.31 and 1.24±0.28 mg/ dL respectively. Baseline serum creatinine when compared among groups were significant for AKI (p <0.001) Table 1. APACHE II score was 22.45±5.3 and 14.4±2.1 respectively and found to significant when compared in both groups of cirrhosis with and without AKI respectively Table 1.

The most common pattern of renal injury among the patients having cirrhosis with AKI was pre-renal (59.5%) tracked by intrinsic (37.7%) and post-renal (2.1%) Table 2. Considering severity stages of AKI among the patients, majority (45.2%) had ICA-AKI stage 3 followed by ICA-AKI stage 2 (33.5%) and (21.3%) accounted for ICA-AKI stage 1 Table 2. 112 patients (59.5%) were admitted with pre-renal azotemia where 78 (70%) patients had volume responsive and 34 (30%) had volume unresponsive pre-renal azotemia (table 2). Among patients having volume non-responsive AKI, 24 (70.6%) were AKI-HRS (Hepatorenal syndrometype 1) whereas 10(29.4%) were non-AKI HRS (Hepatorenal syndrome type 2) Table 2. The pre-renal azotemia was mainly because of gastrointestinal haemorrhage however intrinsic renal AKI was mainly because of acute tubular necrosis. Out of 99 patients of HCV in AKI group only 22 (28.28%) have taken DAA whereas out of 46 patients of HCV in non-AKI group only 13(28%) have taken DAA, which remains statistically insignificant (p 0.98) on comparisonTable 3. Out of 68 patients of HBV in AKI group only 22 (32.2%) have taken nucleoside/nucleotide analogue, whereas out of 26 patients of HBV in non-AKI group only 12(46.1%) have taken nucleoside/nucleotide analogue, which remains statistically insignificant (p 0.20) on comparisonTable 3.

Mortality Analysis: The overall mortality among patients with AKI at 1,6 and 12 months were 12.8%, 31.9 % and 54.3% whereas in non-AKI were 8.4 %, 21.7% and 37.3% respectivelyFigure1. When comparisons were made among AKI and non-AKI patients with cirrhosis mortality was only statistically significant (p 0.01) at 12 monthsFigure 1. Among patients of cirrhosis having AKI, severity wise, ICA-AKI stage 3 had highest mortality (91.8%) followed by 38.1% in ICA-AKI stage 2 Figure2.The survival probability of patients with cirrhosis having AKI, non-AKI and their comparison have been shown Figure 3A, 3B, 3C. Mortality of patients having AKI in accordance to the pattern of renal injury has been shown in Table 2. The overall mortality was 41.9%, 76.1% and 0% in pre-renal, intrinsic renal and post-renal AKI respectively (table 2). Amongst patients with pre-renal AKI having volume responsive group had 30% mortality, whereas the mortality was around 67.44% in the volume non responsive group (AKI-HRS (HRS Type 1 and NON-AKI HRS (HRS Type 2), werequite high (83.33%, 40%) Table 2. The impact of DAA in HCV patients on mortality related to AKI when compared among groups was found statistically insignificant (p 0.84) Table 3. The impact of nucleoside/nucleotide in HBV patients on mortality related to AKI when compared among groups was found statistically insignificant (p 0.57)Table 3.

Mortality Predictors: Various linical and laboratory factors like age, gender, CTP, MELD, bilirubin, albumin, INR, platelets, serum sodium, APACHE II score and rise in creatinine from basal value along with impact of DAA and nucleoside/nucleotide treatment in HCV and HBV on mortality related to AKI were assessed as in hospital mortality predictors on univariate analysis Table 4. Rise in creatinine (OR, 4.719, 95% CI, 3.169-7.027, p<0.001), INR (OR, 23.505, 95% CI, 9.798-56.39, p<0.001), bilirubin (OR, 44.759, 95% CI, 16.51-121.3, p<0.001), albumin (OR, 0.086, 95% CI, 0.044-0.168, P <0.001), CTP (OR, 4.523, 95% CI, 0.564-36.29, p<0.001), MELD (OR, 2.729, 95% CI, 2.141-3.479, p<0.001)and APCHE II(OR, 0.957, 95% CI, 0.918-0.997, p0.036) were the significant predictors of in-hospital mortality. On multivariate analysis only INR

(OR, 4.687, 95% CI, 1.657-13.258, p<0.004), albumin (OR, 0.263, 95%CI, 0.125-0.554, P<0.001) and APACHE II (OR, 0.960, 95% CI, 0.920-1.001, p<0.049) were significant predictors of mortality Table 4.

DISCUSSION

This study has shown 69.3% overall incidence of AKI in patients with liver cirrhosis. Gessolo Lins et al [13] have also shown 53.9% incidence of AKI among cirrhotic patients. However, the cirrhotic patients have shown variable incidence of AKI from 20 to 40% in earlier studies.[14,15] Mean age of patients with cirrhosis having AKI and non-AKI were 62.64 and 57.79± years, respectively. When compared among groups in this study, advanced age was statistically significant (p <0.001) for patients having AKI with cirrhosis. R Karogozain et al[16] have also shown advanced age to be statistically significant for patients having AKI with cirrhosis.

Viral related aetiology with chronic HCV and HBV are the dominant aetiology of cirrhosis among both groups with and without AKI in this cohort. Gessolo Lins et al[13] and Bassegoda O et al [17] have shown alcohol as main aetiology of cirrhosis followed by hepatitis C among patients of cirrhosis with AKI and non-AKI.However, de Carvalho et aland Montoliu et al have also shown viral related chronic hepatitis as the commonest aetiology of 53.9% and 51.7% respectively, similar to this study.[18,1] Among complications of cirrhosis like upper gastrointestinal bleed (UGIB), hepatic encephalopathy (HE) and bacteraemia in this study only UGIB was found statistically significant in cirrhotic patients with AKI when compared to non-AKI group. Kim, J.H. et al [19] andDuah A et al[20] have also shown significant association of UGIB with AKIamong patients with cirrhosis.However,Xiong J et al[21]have contrasted to this study where only bacteraemia or sepsis was significant among cirrhotic patients with AKI when compared to non-AKI whereas UGIB and HE were not significant.

Leucocytes and plateletswere significant in AKI group when compared to non-AKI among cirrhotic patients in this study,howeverthey remained statistically insignificant on univariate and multi variate analysis.Gessolo Lins PR et al[13]have shown similar results in their study.The serum sodium in this study was statistically significant when compared in AKI versus non-AKI patients with cirrhosis of liver. however, it remained statistically insignificant on univariate and multi variate analysis.Khatu CR et al[22] have also shown sodium as significant when compared among AKI and non-AKI patients.This cohort had considerable evidence of liver dysfunction as shown by the severity scores of Child-Turcotte-Pugh (CTP) and MELD, which were 8.60±1.56 and 19.42±3.20 respectively showing statistical significance when compared between patients having AKI or non-AKI. Khatua CR et al[22] have also observed more severe liver disease (MELD24.70 ± 9.03 & CTP 11.42 ± 2.42 score) with AKI as compared to non-AKI (MELD 15.47 ± 7.70 and CTP 10.08 ± 2.30) inferring statistically significant as in this study.

Earlier study[17] have also shown statistically significant severity of cirrhosis (MELD score) among patients having AKI when compared with non-AKI patients. Liver chemistries like ALT, AST, serum bilirubin, albumin and INR were more raised in patients having AKI set against non-AKI. However, only serum bilirubin and INR were found to be significant via statistics in patients of AKI group when compared with patients having non-AKI. An earlier study[13] have only shown INR to be significant via statistics in AKI group when compared to non-AKI. Bassegoda O et al[17] have also shown similar results to this study where serum bilirubin and INR were statistically significant in AKI group when compared to non-AKI patients. The most common pattern of AKI among the patients' having cirrhosis was pre-renal (59.5%) followed by intrinsic (37.7%) and post-renal (2.1%) in this study whereas Warner NS et al[12]have shown intrinsic renal pattern of AKI to be the most common followed by pre-renal and post-renal. Earlier data [23] is observed to show 45 % pre-renal, 35% intrinsic renal (acute tubular necrosis) and (0.2%) post-renal causes among the aetiologies of AKI in cirrhosis. Russ KB et al[4] in their prospective research on cirrhotic patients waiting for liver transplantation, observed the commonest AKI pattern that of pre-renal injury (76%) followed by intrarenal cause (33%) and none with post-renal aetiology. Majority of cirrhotic patients with AKI in this study had severity of stage 3 trailed by stage 2 and 1. Khatua CR et al[22] have contrasted to this study where most of the AKI patients had stage 1 severity followed by stage 2 and 3. Gessolo Lins PR et al[13]have shown similar trend of severity of AKI among cirrhotic to this study, where stage 3 was the most common pattern followed by stage 2, and 1. However Gessolo Lins PR et al[13] have used KIDGO criteria to classify AKI in contrast to ICA criteria used in this study. Warner et al[12]have also shown similar pattern of severity of AKI in their study.

Most of the patients having pre-renal azotemia in this study had volume responsive type (70%) followed by non-volume responsive (30%) AKI. Earlier studies[3,24-26] have also shown 66% of volume responsive AKI among patients of cirrhosis which is in agreement to this study. Majority of patients (70.6%) among non-volume responsive AKI in this study had AKI-HRS (HRS Type 1) trailed by (29.4%) had NON-AKI HRS (HRS Type 2) which is also well consistent to earlier studies. [3,2,26,27]This study has shown intrinsic renal AKI (37.7%) which is similar to earlier studies where reported frequency was 32.3%. [3,23-27] Post-renal AKI in this study was also similar to earlier reported study.[3]

The overall mortality among patients with AKI in this study had a rising trend at 1,6 and 12 months were 12.8%, 39.1% and 54.3% respectively. However, overall mortality in patients of cirrhosis without AKI at 1,6 and 12 months were 8.4%, 21.7% and 37.3% respectively. Mortality only at 12 months were found significant when compared in cirrhotics with and without AKI in the current study. Earlier study[22] has shown [33.3%, 55.6%] and [11.1%, 24.5 %] mortality with and without AKI in patients having cirrhosis of liver at 28 and 90 days and found statistically significant<0.001 when compared. A large cohort of 32,285 cirrhotics from USA[16]have shown higher crude in-hospital mortality among patients with AKI (15% versus 1.8%, < 0.001) compared to non-AKI patients which is similar to this study. This study has shown highest mortality in ICA-AKI stage 3 (98.1%) followed by 38.1% in ICA-AKI stage 2 which is similar to earlier study.[22] Shetty et al[28] have shown an overall in-hospital mortality 44.7% in cirrhotics with AKI to be highest in AKI stage 3 (p = 0.001).

A meta-analysis (eight studies)[11, 27, 29-34] has shown 3 times higher 30 days mortality in patients with AKI (422/995 (42.4%) versus patients without AKI 841/3973 (21.1%), OR [95% CI]: 3.37 [2.35-4.84], p>0.0001) like this study. Likewise, similar analysis also showed higher mortality at 90 days and at 1-year follow-up among patients AKI (68.3% vs. 45.1%, OR [95% CI]: 5.37 [2.45-11.79], p>0.00001) versus without AKI (47.1% vs. 16.4%, OR [95% CI]: 4.43 [2.93-6.70], p>0.00001).[35]

Rise in creatinine from baseline (OR, 4.719, 95%CI, 3.169-7.027), INR (OR, 23.5, 95%CI, 9.798-56.390), bilirubin (OR, 44.75, 95%CI, 16.514 -121.309, p<0.001), albumin (OR, 0.086,95% CI, 0.044-0.168, P <0.001), CTP (OR, 4.523, 95% CI, 0.564 -36.290, P<0.001) and MELD (OR, 2.729,95%CI,2.141-3.479, P<0.001) were found the predictors of in hospital mortality on univariate.An earlier study [35] have shown similar results to this study where the clinical (hepatic encephalopathy, stages of AKI and type of AKI) and biochemical (bilirubin, serum glutamic oxaloacetic transaminase (SGOT), Child-Turcotte-Pugh (CTP), INR and model for end-stage liver disease (MELD) scores) parameters were found as predictors of mortality (p < 0.05) on bivariate regression analysis. Altamirano J et al[36] have shown serum bilirubin (P .01), systemic inflammatory response syndrome (P < .0001) and INR at admission (P .03) as independent predictors of mortality in alcoholic hepatitis patients.

This study has shown INR and albumin as significant predictors of mortality on multi variate analysis. Gessolo Lins PR et al[13] in their study have shown cancer, AKI and progression of AKI as independent predictors of hospital mortality. In resemblance to present study, Duah A et al[20] have recently shown INR, severity of

cirrhosis (MELDNa) and BUN as independent factors predicting in-hospital mortality among patients of cirrhosis having AKI. APACHE II score was significant predictor for mortality in this study which is similar to earlier study by Xiong J et al.[21]

As the most common cause of cirrhosis in this study was HCV and HBV related, the impact of treatment like DAA and nucleoside / nucleotides were assessed on AKI related mortality.A large retrospective cohort [37] has recently shown that AKI is frequently reportedamong chronic HCV patients with an independent predictor of mortality having substantial overall mortality. This study did not show any difference in mortality related to AKI between DAA treated and non-treated patients (p 0.84) in HCV patients which is in contrast to earlier study [38,] where anti-viral treatment among HCV patient has shown independent predictor of mortality. This study has not shown any difference in mortality among patients of HBV between nucleoside/nucleotide treated and non-treated groups hence not as a predictor of AKI related mortality. Earlier studies [39,40] have shown compromised renal functions (decrease in GFR) in patients of HBV but more of related to drug related.

The retrospective design of this particular study entails its limitation which could be changed, had it been prospective research.

CONCLUSION

AKI is a frequently reported challenge among patients having cirrhosis of liver with various aetiologies in this study. The most common pattern of renal injury amongst AKI was pre-renal followed by intrinsic and post-renal. Majority of patients had severe AKI evidenced by ICA-Stage 3 disease tracked by ICA-AKI stage 2 and ICA-AKI stage. In-hospital mortality at 1, 6 and 12 months was higher in patients of cirrhosis having AKI versus Non-AKI. Rise in creatinine from base line, serum bilirubin, severity of cirrhosis (CTP and MELD score) were the significant predictors of in-hospital mortality on univariate analysis. The INR,albumin and APAHCE II score were significant predictors of mortalityon multivariate analysis. Furthermore, DAA and nucleoside/nucleotide analogues treatment in HCV and HBV patients were not found risk factors of AKI related mortality.

Conflict of interest: All authors declare that they have no conflicts of interest.

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