ACUTE KIDNEY INJURY IN PATIENTS WITH CIRRHOSIS- CAUSES AND OUTCOME

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ABSTRACT

BACKGROUND

Acute Kidney Injury (AKI) is a common complication in patients with cirrhosis leading to high mortality. Creatinine-based criteria for defining AKI are validated in general hospitalised patients, but their application to cirrhotic patients is less certain. This study was undertaken to evaluate current definition of AKI by International Club of Ascites (ICA) and assess clinical course of hospitalised cirrhosis patients with AKI and to study the impact of AKI on mortality.

MATERIALS AND METHODS

We prospectively studied patients with AKI and cirrhosis for a period of 1 year and assessed the association between AKI severity and progression with complications, including death.

RESULTS

48 cirrhotic patients with AKI were enrolled in the study period. Mean age of patients was 56.81 ± 9.78 years. The aetiology of cirrhosis included alcohol (52.1%), HBV (2.2%), HCV (4.2%), NASH (27.1%) and cryptogenic (14.6%). 13 patients (27.1%) had mortality while 35 patients (72.9%) survived. 39 patients (81.25%) had AKI at admission while 9 patients (18.75%) developed later after admission. Patients achieved a peak severity of AKI stage 1, 10.41%; stage 2, 60.41%; and stage 3, 37.5%. The incidence of mortality, increased with severity of AKI in stepwise manner with peak AKI stage 1 has no mortality; stage 2 has 4 (30.76%); stage 3, 9 (69.23%). SIRS was present in 17 patients (35.4%) and was significantly associated with mortality.

CONCLUSION

AKI, as defined by new ICA criteria, in patients with cirrhosis is associated with mortality in a stage-dependent fashion. Early intervention and preventing progression by timely and specific treatment may improve outcomes.

KEYWORDS

Cirrhosis, Acute Kidney Injury, Creatinine.

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BACKGROUND

Acute Kidney Injury (AKI) is a common and devastating complication in patients with cirrhosis. The development of AKI is often associated with the presence of other complications such as variceal bleeding and Spontaneous Bacterial Peritonitis (SBP) and occurs in up to 19% of hospitalised patients with cirrhosis.[1,2] The most common causes of AKI in cirrhosis are Prerenal Azotaemia (PRA), Acute Tubular Necrosis (ATN) and Hepatorenal Syndrome (HRS). The presence of renal dysfunction is an important predictor of outcome including death in these patients and has been used in Model for End-Stage Liver Disease (MELD), which is worldwide accepted scoring for determining prognosis and to allocate patients for liver transplantation.[2]

Renal impairment in cirrhosis has been identified using serum creatinine as an indicator of renal function. However, serum creatinine is a poor marker of Glomerular Filtration Rate (GFR) patients with decompensated cirrhosis and ascites.[3] Also, creatinine is insensitive to a decline in Glomerular Filtration Rate (GFR) in the setting of cirrhosis. The reliance on elevated creatinine values leads to an over selection of the most cases limiting the ability to evaluate factors associated with disease progression and the bearing of AKI severity on outcomes.

The Kidney Disease- Improving Global Outcomes (KDIGO) diagnostic criteria is the most recent, which combines both Acute Kidney Injury Network (AKIN)[4] and Risk of renal dysfunction; Injury to the kidney; Failure of kidney function; Loss of kidney function; and End-stage kidney disease (RIFLE) classifications.[5,6] The use of these criteria has been validated in a variety of settings including the critically ill and general-hospitalised patients.[7]

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International Club of Ascites (ICA) proposed a new criteria for the diagnosis of AKI[8] where urine output has been deducted from scoring system since with cirrhosis patients' maybe oliguric with normal creatinine. Further, two other changes to the KDIGO criteria were adopted, namely- (1) A sCr within the last 3 months before admission is considered a baseline value for the diagnosis of AKI when a value within the previous 7 days is not available; and (2) The calculation of the baseline sCr by the reverse application of the Modification of Diet in Renal Disease (MDRD) formula using an arbitrarily defined normal value of GFR of 75 mL/min./1.73 m2 was not included.

Due to various classification systems, enrollment criteria of patients in previous studies have varied significantly. Also, the newer classification proposed by ICA appears to be more physiological classification of AKI in this setting. This study was undertaken to determine causes of AKI in patients with cirrhosis and to prospectively assess the clinical course and complications of these patients.

MATERIALS AND METHODS

This was a prospective observational study conducted in Department of Gastroenterology in a tertiary care center in north Kerala over a period of 1 year from January 2016 to December 2016. Adult patients of age >18 years with cirrhosis (diagnosed based on clinical, sonological, haematological and endoscopic evidence) admitted with AKI (as per new International Club of Ascites (ICA) definition) or who developed AKI during the course of hospitalisation were recruited in the study. Patients with prior kidney or liver transplant, evidence of chronic kidney disease (based on urine albumin/protein-creatinine ratio or sonological evidence), patients undergoing renal replacement therapy at the time of enrollment, pregnancy, obstructive uropathy, malignancy, other causes of renal insufficiency such as glomerulonephritis or hydronephrosis were excluded from the study. ICA definition for diagnosis of AKI in patients with cirrhosis are shown in table 1. Patients were evaluated for cause of AKI like prerenal AKI secondary to diuretics, infections (Spontaneous Bacterial Peritonitis (SBP), Urinary Tract Infection (UTI), Lower Respiratory Tract Infection (LRTI), cellulitis, etc.), development of other complications like hypotension, sepsis, variceal bleed, hepatic encephalopathy and were followed up till recovery/mortality. Informed consent was taken from patient/relatives and the Institutional Ethics and Research Committee Clearance was obtained before starting the study.

Statistical Analysis

Statistical analysis was carried out using SPSS software package for Windows version 18. Categorical variables were expressed as proportions and compared using the Chi-square and Fisher's exact test as appropriate. Near-normally distributed variables were reported as means with Standard Deviations (SDs) and compared by Student's t-test. Non-normally distributed continuous variables were reported as medians with Interquartile Ranges (IQR) and compared by the Kruskal-Wallis test.

RESULTS

A total of 48 patients with cirrhosis and AKI were enrolled into the study in this period. Baseline demographic, clinical and laboratory data of the 48 patients are shown in Table 2. The mean age of patients was 56.81 ± 9.78 years and were predominantly male 45 (93.81%). The aetiology of cirrhosis included alcohol (52.1%), hepatitis B related (2.2%), hepatitis C related (4.2%), nonalcoholic fatty liver disease (27.1%) and cryptogenic (14.6%). There was no difference in aetiologies between patients who survived and in patients with mortality. Majority of patients had suffered from complications of cirrhosis like ascites (n=85.4%), SBP (n=25%), Hepatic Encephalopathy (HE) (n=25%) and variceal bleed (n=29.2%) prior to admission as shown in table 2. Reasons for admission were similar in between the two groups and include worsening ascites (31.3%), hepatic encephalopathy (16.7%), variceal bleed (9.2%), jaundice (6.3%), AKI (4.2%), SBP (10.4%) and other infections like cellulitis included 10.4%. Majority of patients were belonging to CTP class C status (89.6%) and mean MELD Na score was 30.81 ± 6.56. Mean bilirubin value was 6.24 ± 5.9 in the study group and it was slightly higher in patients who died during the study. Mean INR and sodium were 2.31 ± 0.87 and 125.8 ± 8.3, respectively. It was observed that patients who had SIRS at enrollment had significantly higher mortality.

Kidney Variables and Association of Mortality

Association of kidney variables and mortality are shown in Table 3. A total of 30 patients (62.5%) had baseline GFR <90 mL/min./m^2, out of which 21 (43.75%) patients had GFR between 60-89, 8 (16.6%) patients had GFR between 30-59 and 1 (2.08%) patient had GFR below 30 mL/min./m^2. AKI at admission was present in 39 patients (81.25%), while it developed later in 9 patients (18.75%). Mortality was significantly more when AKI developed after admission than those presented with AKI at admission. Mean creatinine at admission was 2.1 ± 1.07 and at enrollment 2.4 ± 0.77, which was not statistically significant between survivors and non-survivors. Peak creatinine as expected was significantly higher in non-survivors. Patients whose creatinine decreased within first 48 hours (n=27 (56.25%)) were more likely to have survived as compared to those patients whose creatinine did not improve (n=21 (43.75%)) (P value <0.001). With progressive increase in renal dysfunction as identified with increase in grade of AKI, mortality also increased substantially as shown in Table 3.

Medical and Hepatic Complications

The various associated medical complication like UTI, sepsis, shock, LRTI, cellulitis and hepatic complications like ascites, SBP, HE, variceal bleed are listed in table 4. It was observed that presence of sepsis and HE was significantly more in non-survivors.

Subject	Definition		
Baseline sCr	A value of sCr obtained in the previous 3 months when available can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used in patients without a previous sCr value, the sCr on admission should be used as baseline.		
Definition of AKI	Increase in sCr ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hrs.; or a percentage increase sCr ≥50% from baseline, which is known or presumed to have occurred within the prior 7 days.		
Staging of AKI	Stage 1- Increase in sCr ≥0.3 mg/dL (26.5 µmol/L) or an increase in sCr ≥1.5 fold to 2 fold from baseline; Stage 2- Increase in sCr >2 to 3 fold from baseline; Stage 3- Increase of sCr >3 fold from baseline or sCr ≥4.0 mg/dL (353.6 µmol/L) with an acute increase ≥0.3 mg/dL (26.5 µmol/L) or initiation of renal replacement therapy.		
Progression of AKI	Progression		Regression
	Progression of AKI to a higher stage and/or need for RRT		Regression of AKI to a lower stage
Response to treatment	No response	Partial response	Full response
	No regression of AKI	Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dL (26.5 µmol/L) above the baseline value	Return of sCr to a value within 0.3 mg/dL (26.5 µmol/L) of the baseline value

Table 1. International Club of Ascites (ICA-AKI)- New Definitions for the Diagnosis and Management of AKI in Patients with Cirrhosis

	Total (n=48)	Survived (n=35)	Mortality (n=13)	P value
Age in years mean ± SD	56.81 ± 9.78	56.37 ± 23.3	58 ± 9.67	0.61
Male sex (%)	45 (93.81%)	32 (71.1%)	13 (28.8%)	NA
Cirrhosis Aetiology (n%)				
Alcohol	25 (52.1)	20 (57.14)	5 (38.46)	0.25
HBV	1 (2.22)	1 (2.85)	0	0.5
HCV	2 (4.2)	2 (5.71)	0	0.37
NASH	13 (27.1)	8 (22.85)	5 (38.46)	0.2
Autoimmune	0	0	0	
Cryptogenic	7 (14.6)	4 (11.43)	3 (23.07)	0.31
Previous Complication of Cirrhosis- n (%)				
Ascites	41 (85.4)	29 (82.85)	12 (92.30)	0.41
SBP	12 (25)	8 (22.85)	4 (30.77)	0.57
Hepatic encephalopathy	12 (25)	6 (17.14)	6 (46.15)	0.03
Variceal bleed	14 (29.2)	10 (28.57)	4 (30.77)	0.88
Reason for Admission				
Ascites	15 (31.3)	12 (34.28)	3 (23.07)	0.45
Hepatic encephalopathy	8 (16.7)	5 (14.29)	3 (23.07)	0.46
Variceal bleed	11 (22.9)	8 (22.86)	3 (23.07)	0.98
Jaundice	3 (6.3)	2 (5.71)	1 (7.69)	0.81
AKI	2 (4.2)	1 (2.85)	2 (15.38)	0.46
SBP	5 (10.40	3 (8.57)	2 (15.38)	0.49
Infection other than SBP	5 (10.4)	4 (11.43)	1 (7.69)	0.76
SIRS	17 (35.4)	8 (28)	9 (69.23)	<0.05
Child-Pugh Class- n (%)				
A	0	0	0	
B	5 (10.4)	5 (14.29)	0	
C	43 (89.6)	30 (85.71)	13 (100)	0.15
Child-Pugh score- median (SD)	10.75 (± 1.26)	10.51 ± 1.29	11.38 ± 0.87	0.03
MELD Na score-mean ± SD	30.81 (± 6.56)	30.40 (± 6.7)	31.92 (± 6.3)	0.48
Bilirubin mean ± SD	6.24 (± 5.9)	5.48 (± 5.25)	8.26 (7.5)	0.15
INR-mean ± SD	2.31 (± 0.87)	2.25 (± 0.95)	2.48 (± 0.61)	0.41
Sodium mean ± SD	125.8 (± 8.3)	126.7 (± 7.4)	122.4 (0.61)	0.48

Table 2. Baseline and Clinical Characteristic of all Patients and Comparison of Data Among Patients With and Without Mortality

	Total (n=48)	Survivors (n=35)	Non-Survivors (n=13)	P value
GFR 60-89 mL/min./m^2	21 (43.75)	16 (45.7)	5 (38.46)	0.65
GFR 30-59 mL/min./m^2	8 (16.66)	4 (11.42)	4 (30.76)	0.11
GFR 29-15 mL/min./m^2	1 (2.08)	1 (2.85)	0	0.53
Creatinine on admission median (IQR)	2.1 (1.6-2.67)	2.27 (± 0.85)	2.09 (± 1.26)	0.59
Creatinine at enrollment median (IQR)	2.4 (2-2.77)	2.56 (± 0.85)	2.6 (± 1.02)	0.85
Peak creatinine	2.97 (± 1.05)	2.72 (± 0.86)	3.6 (± 1.2)	<0.05

Decrease Creatinine Within First 48 Hours				
Yes	27 (56.25)	26 (79.28)	1 (7.69)	<0.001
No	21 (43.75)	9 (25.71)	12 (92.30)	
Proteinuria	4 (8.33)	4 (11.42)	0	0.2
Timing of AKI				
At admission	39 (81.25)	32 (91.42)	9 (53.84)	<0.05
Developed later	9 (18.75)	3 (8.57)	4 (46.15)	
Stage of AKI at Enrollment				
Stage 1	10 (20.83)	6 (17.14)	4 (30.77)	0.30
Stage 2	29 (60.41)	23 (65.71)	6 (46.15)	0.21
Stage 3	9 (18.75)	6 (17.14)	3 (23.08)	0.64
Peak AKI stage				
Stage 1	5 (10.41)	5 (14.28)	0	0.15
Stage 2	25 (52.08)	21 (60)	4 (30.76)	<0.05
Stage 3	18 (37.5)	9 (25.71)	9 (69.23)	<0.05
Stage Progressed				
Yes	14 (29.16)	4 (11.42)	10 (76.92)	<0.001
No	34 (70.83)	31 (88.57)	3 (23.8)	

Table 3. Comparison of Renal Variables in Patients With and Without Mortality

	Total (48)	**Survivors (35)**	**Non-Survivors (13)**	**P value**
Medical Complications				
UTI	16 (33.33)	12 (34.28)	4 (30.76)	0.81
Sepsis	10 (20.8)	4 (11.42)	6 (46.15)	<0.05
Shock	4 (8.33)	2 (5.71)	2 (15.38)	0.28
LRTI	1 (2.08)	1 (2.85)	0	0.53
Cellulitis	9 (18.75)	7 (20)	2 (15.38)	0.72
Other	3 (6.25)	2 (5.71)	1 (7.64)	0.34
Hepatic Complications				
Hepatic encephalopathy	34 (70.83)	21 (60)	13 (100)	<0.05
SBP	15 (31.25)	9 (25.71)	6 (46.15)	0.18
Ascites	43 (89.58)	30 (85.71)	13 (100)	0.15
Variceal bleed	16 (33.33)	9 (25.71)	7 (53.85)	0.06

Table 4. Medical and Hepatic Complications During Hospital Stay

DISCUSSION

The development of AKI in the setting of cirrhosis has long been considered to cause grave prognosis and is independently associated with mortality in patients with SBP.[9] Cirrhosis is a state of constant diminished renal blood flow, and frequent volume shifts accompanying due to diuretics or complications like GI bleed, precipitate numerous episodes of AKI in these patients. Unfortunately, estimates of the incidence of AKI in cirrhosis have suffered from a lack of standardisation in the definition of AKI. Serum creatinine being an insensitive marker of AKI in cirrhotics, leads to masking of many cases of renal dysfunction. Recently the definition of AKI in cirrhotics were modified and it has been followed in the present article. Although, AKI has high mortality, it is no longer an irreversible condition. The present change in classification mainly aimed in identifying AKI at the earliest and to treat as early as possible.

In this study, a total of 48 patients were admitted with AKI, among which 13 patients had mortality. Among this, 52%, 37.5% and 10.4% patients were categorised to stage II, III and I AKI as per ICA criteria. Patients with higher AKI grade had a greater mortality rate. 18.7% patients developed AKI after admission and they had a higher risk of mortality (46.1%) due to multiple complications in hospitalised patients compared to primary AKI cases. Carvalho et al retrospectively studied 91 patients with cirrhosis and AKI at the time of hospital admission.[10] The majority of patients had mild renal dysfunction (91% had stage 1 AKI) and patients with AKI had a hospital mortality rate of 52.7%. Presence of AKI conferred an Odds Ratio (OR) of 2.6 for hospital mortality, but quantifying the risk by stage was limited by the small numbers of patients with more severe AKI. Belcher et al prospectively studied 192 hospitalised cirrhotic patients with AKI. AKIN criteria were used to identify AKI, with 50 (26%) patients with AKI stage 1, 47 (24%) in stage 2 and 95 (49%) in stage 3. Overall, mortality was 26% and severity of AKI was independently associated with mortality.[11]

The overall mortality in our study was 27%, which is comparable to Belcher et al study (26%). We observed that higher AKI stage increases mortality, AKI stage 3 having mortality of 69.2% compared to stage 2 (30.7%). The mortality rate is lower when compared to previous studies.[12,13]

This may be due to inclusion of patients with less severe AKI as per ICA criteria, where mortality gradually increases with stage of AKI. This is important to identify less severe grades of AKI at the earliest and treating it successfully. With AKI, patients are more prone for other complications like HE, hypotension, sepsis and ultimately death. Also, presence of Systemic Inflammatory Response Syndrome (SIRS) at enrollment was significantly associated with mortality in the

study, which can be used as predictor of mortality in AKI patients.

Major limitation of the study was that it was an observational study and progress/recovery of AKI with volume expansion or other treatment were not studied.

In conclusion, the results of the current study confirm that AKI as defined by International Club of Ascites Criteria is associated with in-hospital mortality in the setting of cirrhosis in a stage-dependent manner. Although, those patients who exhibit early recovery from AKI do well, worsening of AKI is associated with mortality. Also, presence of SIRS is significantly associated with mortality.

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