A Clinical Study on Acute Kidney Injury in Cirrhotic Patients

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ABSTRACT

BACKGROUND

The increased propensity for acute kidney injury (AKI) in patients with cirrhosis stems from haemodynamic abnormalities typical for patients with cirrhosis and ascites.[15] which is due to development of portal hypertension and portosystemic collaterals with splanchnic and systemic vasodilatation, resulting in decrease in effective arterial blood volume with increase in renin angiotensin-aldosterone system (RAAS), sympathetic nervous system and non-osmotic release of antidiuretic hormone causing sodium retention, increased intravascular volume, and a hyperdynamic circulatory state,[16] complemented with increased production of nitric oxide which is considered the main cause of vasodilatation in cirrhosis. Mechanism of renal dysfunction in cirrhosis includes portal hypertension & its accompanying haemodynamic abnormalities[15] leading to increased synthesis of endogenous vasodilatory compounds such as nitric oxide leading to vasodilatation in splanchnic & systemic arterial systems ultimately leading to activation of renin-angiotensinogen–aldosterone system causing compensatory renal vasoconstriction & hypo-perfusion resulting into renal failure. We wanted to study the clinical profile of patients with AKI who presented to a tertiary care hospital in Bangalore.

METHODS

Ninety-four patients of either gender admitted in the department of gastroenterology at a tertiary care hospital with age > 18 years with either diagnosed or newly diagnosed case of cirrhosis of liver (including both compensated & decompensated cases) admitted with acute kidney injury diagnosed according to International Club of Ascites Classification were enrolled in this study. The sample size was based on number of eligible patients admitted to tertiary care hospital during the study period. Details of the study were explained to them and consent was taken either from the patient or their attender.

RESULTS

Most patients were in the age group > 60 yrs. with 32 male patients (45.07 %) in the age group of 40 - 60 years & 13 female patients (56.52 %) in the age group of > 60 yrs. 78.7 % of patients developed AKI before hospital admission i.e., at community level; whereas 21.3 % of patients developed AKI after hospital admission i.e., they had normal creatinine level on admission.

CONCLUSIONS

Pre renal AKI was the most common cause of AKI followed by hepatorenal syndrome & acute tubular necrosis (ATN) comprising 52.1 %, 28.7 % & 19.1 % respectively.

KEYWORDS

AKI, Cirrhosis, ATN

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BACKGROUND

Cirrhosis is the final stage of chronic liver disease & is detected in 4.5 to 9.5 % of all necropsies. In 2001, it was the fourteenth most frequent cause of death worldwide & is expected to reach to twelfth position by 2020. Most of the deaths were related to decompensation & complications of cirrhosis used to describe its natural history in four stages.[2] & more recently as five or six stages, the last of which includes sepsis & / or renal failure.[3,4] & renal failure has a poor prognosis in cirrhotic patients.[4] Acute kidney injury (AKI) is a common and devastating complication in patients with cirrhosis, occurring in an estimated 19 % of hospitalisations.[5-11] and is associated with significant mortality of 55 - 91 %.[1]

Acute kidney injury is defined as acute significant reduction in glomerular filtration rate according to International Club of Ascites criteria for acute kidney injury defined as increase in serum creatinine greater than 0.3 mg / dl within 48 hour or percentage increase of serum creatinine of greater than or equal to 50 % from baseline which is known or presumed to have occurred within the prior 7 days, where baseline is the creatinine level in previous 3 months or creatinine level closest to admission (in case multiple creatinine level reports in previous 3 months) or creatinine level at the time of investigation if no previous creatinine levels were available for previous 3 months.[2]

Mechanism of renal dysfunction in cirrhosis includes portal hypertension & its accompanying haemodynamic abnormalities.[15] leading to increased synthesis of endogenous vasodilatory compounds such as nitric oxide leading to vasodilatation in splanchnic & systemic arterial systems ultimately leading to activation of renin-angiotensinogen–aldosterone system causing compensatory renal vasoconstriction & hypo-perfusion resulting into renal failure.[3]

Patients with cirrhosis who are already inclined to renal dysfunction.[15] due to vasoconstriction & if they are exposed to precipitants that can lead to more haemodynamic abnormalities, it can cause frank filtration failure and AKI which can be seen both in outpatients and inpatients. Among hospitalised patients, bacterial infections most commonly spontaneous bacterial peritonitis due to endotoxemia & accelerated vasodilatation can lead to frank AKI. Similar to infections, gastrointestinal haemorrhage or large volume paracentesis can also be a contributory factor. Although hospitalised patients develop renal failure but same can also occur in outpatient individuals as a result of frequent fluctuations in intravascular volume owing to use of diuretics and lactulose-associated diarrhea.[4]

Despite advances in our understanding about the pathophysiology of AKI in cirrhosis, it was still difficult to distinguish between different causes of AKI as in our diagnostic criteria there was more emphasis on use of creatinine, which is marker of filtration & not injury and it doesn't provide any information about the area of renal injury, henceforth hindering determination of which patients are at the highest risk of adverse outcomes therefore delaying treatments. To overcome this, the emerging concept of urinary biomarkers which are specific proteins released & specific for different renal structures, aiding in correct diagnosis & treatment are used. Most promising of these biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1). While NGAL has been studied for early detection of AKI following liver transplant, cardiac surgery & ICU settings and for differential diagnosis of AKI in cirrhosis, this urinary biomarkers can help to distinguish structural from functional causes of AKI, noteworthy mostly for hepatosis renal syndrome vs. ATN & may serve to identify patients at highest risk for the worst outcomes, who may derive maximal benefit from early and aggressive interventions & also provide vital information about prognosis which can be determined by serial biomarkers measurements.[5,6]

We wanted to study the clinical profile of patients with AKI who presented to a tertiary care hospital in Bangalore.

METHODS

This is a descriptive cross-sectional study which was conducted at gastroenterology department, attached to Medical College for a period of one and half year from July 2017 to Dec 2018.

Sample Size

Total 94 patients were enrolled during this period. The sample size was based on number of eligible patients admitted to tertiary care hospital during the study period. Detail of study was explained to them and consent was taken either from patient or their attender.

Inclusion Criteria

All participating patients of either gender admitted to Department of Gastroenterology at a tertiary care hospital with age > 18 years with either diagnosed or newly diagnosed case of cirrhosis of liver (including both compensated & decompensated cases) admitted with acute kidney injury diagnosed according to International Club of Ascites Classification were enrolled in this study.

Exclusion Criteria

- Parenchymal kidney disease.
- Receiving renal replacement therapy / renal or liver transplant pregnant or nursing patient.
- Patient's refusal to participate in study.

Statistical Analysis

The data was analysed using proportion, mean definition of variables:

- Cirrhosis: Diagnosis of cirrhosis was made based on past history of cirrhosis or on clinical evaluation using laboratory values, liver imaging ultrasound sonography (USG or fibroscan), endoscopy & liver biopsy (when

available) & both compensated & decompensated cirrhosis were included in the study.

- Acute kidney injury: Defined according to International Club of Ascites–Acute Kidney Injury (ICA-AKI.[12]) criteria.
- Prognosis prediction: Defined according to acute kidney injury – chronic liver failure – sequential organ failure assessment index (AKI CLIF SOFA) which was used to predict outcome of patient including need for renal replacement therapy & mortality. Prognosis has also been predicted using urinary NGAL measurement.
- Severity of disease is determined by using Model for End-Stage Liver Disease (MELD) score, Child Turcotte Pugh score (CTP), Child score.

Outcome: Defined by either hospital survival or death which include death due to renal, liver or cardio-respiratory conditions.

RESULTS

Age	Male	Percent	Female	Percent	Total	Percent
< 40 yrs.	9	12.6 %	1	4.34 %	10	10.63 %
40 – 60 yrs.	32	45.07 %	9	39.13 %	41	43.61 %
> 60 yrs.	30	42.25 %	13	56.52 %	43	45.74 %
Total	**71**	**100 %**	**23**	**100 %**	**94**	**100 %**

Table 1. Age Wise Distribution

Most patients were the in age group > 60 years with 32 male patients (45.07 %) in age of 40 - 60 yrs. & 13 females (56.52 %) in age > 60 years

Type of AKI	Frequency	Percent
Prerenal	49	52.1
Hepatorenal syndrome	27	28.7
Acute tubular necrosis	18	19.1
Total	**94**	**100.0**

Table 2. Types of AKI

Pre renal was the most common cause of AKI followed by hepatorenal syndrome & ATN comprising 52.1 %, 28.7 % & 19.1 % respectively

Cause of Pre Renal AKI	Frequency	Percent
Blood stream infection	19	20.2
Cellulitis	3	3.2
Drugs	2	2.1
Drugs (Diuretics)	11	11.7
Drugs (NSAID)	1	1.1
GI bleed	13	13.8
HAV	1	1.1
Intra-abdominal abscess	1	1.1
Pneumonia	9	9.6
Ruptured umbilical hernia	5	5.3
Spontaneous bacterial peritonitis	9	9.6
Scrub typhus	1	1.1
Urosepsis	18	19.1
Urosepsis + SBP	1	1.1
Total	**49**	**100.0**

Table 3. Causes of Pre Renal AKI

Blood stream infection & urosepsis is the most common cause of pre renal AKI comprising 20.2 % & 19.1 % of patients respectively.

Time of AKI	Frequency	Percent
Community	74	78.7
After hospital admission	20	21.3
Total	**94**	**100.0**

Table 4. Time of AKI

78.7 % of patients developed AKI before hospital admission i.e. at community level whereas 21.3 % of patients developed AKI after hospital admission i.e. they had normal creatinine level at the time of admission.

DISCUSSION

Acute kidney injury is one of the most common cause of mortality in patients with liver cirrhosis and is seen in 20 % of hospitalised cirrhotic patients. It can be a part of natural history of cirrhosis due to progressive increase in splanchnic vasodilatation causing progressive renal vasoconstriction resulting into development of hepatorenal syndrome (HRS) or it can be part of acute event like bleeding, hypovolaemia, drugs causing pre renal AKI or due to injury to the renal tubules mostly secondary to hypoxic injury resulting into acute tubular necrosis (ATN). Despite the overall poor outcomes, there is likelihood that specific treatments are available which have been shown to improve renal function and improve mortality.

In addition to mortality & morbidity associated with AKI, there has been absence of standardised definitions resulting into low sensitivity, specificity causing inability to predict prognosis. There had been consistent transition over the last several years about consensus guidelines for AKI like Injury, Failure, Loss of kidney function and End-stage renal failure (RIFLE), Acute Kidney Injury Network (AKIN), Kidney Disease Improving Global Outcomes (KDIGO) to recently ICA-AKI (International Club of Ascites Classification of AKI) criteria in 2015. ICA – AKI is more appropriate than earlier consensus as it does not use urine output and creatinine estimation is more dynamic in nature than earlier consensus which uses static creatinine level.

Despite improved understanding of precipitants and physiology of underlying AKI in cirrhosis, considerable confusion still continues to surround its diagnosis due to arbitrary use of creatinine which is effected by several factors like diet, volume status, protein intake, muscle mass, interference with assays of creatinine by elevated bilirubin level 26 making traditional criteria of AKI with serum creatinine greater than 1.5 gm / dl not suitable as diagnostic criteria as it can delay the detection of AKI, further delaying treatment & prognosis. Henceforth ICA AKI criteria is being validated & accepted for definition of AKI. The benefits of adopting the new, more sensitive definition are two-fold. First, lowering the threshold for a diagnosis of AKI will increase sensitivity and the association between even mild acute increases in creatinine and adverse outcomes has been well established. Second, the lower threshold of AKIN will identify those more severe case of AKI significantly earlier, thus facilitating earlier interventions and potentially improving prognosis. In this study, out of 94 patients there were 23 female patients (24.5 %) & 71 male patients (75.5 %) & most patients were in age group > 60 yrs with 32 male patients (45.07 %) in age of 40 - 60 yrs. & 13 female patients (56.52 %) in age > 60 yrs with mean age in study was 56.79 + 11.74 yrs. This is comparable with following study of Scott et al.[7] where mean age of 56.8 ± 14 years & Chen et al.[8] where it was 58.99 + 12.2 years.

NASH is the most common cause of cirrhosis comprising of total 39 patients (41.5 %) followed by alcohol which was seen in 27 patients (28.7 %) with pre renal AKI the most common cause of AKI followed by hepatorenal syndrome & ATN seen in 52.1 %, 28.7 % & 19.1 % respectively. This result is similar to Allegretti et al.[9] & Garcia et al.[10] where Pre renal AKI was the most common cause of AKI. In this study, blood stream infection & urosepsis was the most common cause of Pre renal AKI seen in 20.2 % & 19.1 % of patients respectively. This is similar to study conducted by Wong et al.[11] where urosepsis was most common cause of infection which was seen in 27 % of patients. Similar results were shown in Peron et al.[12] & Fang et al.[13] where AKI in 51 % were precipitated by infection.

Allegretti et al. showed that in 120 participants with cirrhosis and acute kidney injury examined the ninety-day mortality was 14 / 40 (35 %) with prerenal azotaemia, 20 / 35 (57 %) with hepatorenal syndrome, 21 / 36 (58 %) with acute tubular necrosis, and 1 / 9 (11 %) with other causes. Overall mortality was lower in prerenal azotaemia as compared to hepatorenal syndrome and acute tubular necrosis.

Scott RA et al.[14] where 162 patients were studied with mean age of 56.8 + 14 years. They predominantly had male patients in 65.4 % with alcoholic liver disease in 78.4 %. 44, 32, 34 patients were enrolled in stage 1, 2, 3 respectively. AKI was associated with increased mortality (31.8 % vs 3.8 %). Mortality increased with each AKI stage; 3.8 % in cirrhotics without AKI, 13.5 % stage 1, 37.8 % stage 2 and 43.2 % stage 3. Worsening liver disease (Child–Pugh class) correlated with increased mortality: 3.1 % class A, 23.6 % class B and 32.8 % class C. AKI was associated with increased length of stay: median 6.0 days versus 16.0 days. Multivariate analysis identified AKI and Child–Pugh classes B and C as independent factors associated with mortality.

Belcher et al.[85] showed that out of 192 patients, 44 % progressed to higher stage with 26 % in stage 1, 24 % in stage 2, 49 % in stage 3. Progression was higher in nonsurvivors than survivors.

Treeprasertsuk et al.[15] showed that out of 137 cirrhotic hospitalised patients, 121 cirrhotic patients (88.3 %) with AKI-prone conditions were included with mean age of 57.3 ± 14.7 years with thirty-five patients (29 %) developed AKI within 72 hrs. of admission. Main causes of AKI were prerenal azotaemia (68.6 %), acute tubular necrosis (25.7 %), hepatorenal syndrome (5.7 %). The area under curve (AUC) of urinary neutrophil gelatinase-associated lipocalin (uNGAL) for diagnosing AKI was 0.83 with the optimal cut-off level of 56 ng / mL, providing 77.1 % sensitivity and 73.3 % specificity and mean uNGAL levels were significantly higher in the mortality group with AUC of uNGAL in predicting mortality was 0.75, with a best cut-off level of 72 ng / mL providing 70.6 % sensitivity and 69.2 % specificity.

Hamdy et al.[16] showed that the patients included in their study were 41 males and 29 females with mean age 54.27 ± 6.08 years. Hepatitis C virus (HCV) was the aetiology of cirrhosis in 69 cases while one had combined Hepatitis B virus (HBV) and HCV infection. More than 50 % of patients were classified as Child C. Causes of kidney injury were prerenal, hepatorenal syndrome (HRS) and intrinsic tubular injury (iAKI) in 39 patients (55.7 %), 17 patients (24.3 %) and 14 patients (20 %) respectively. mean value of uNGAL in prerenal, HRS and iAKI was 21.70 ± 7.31, 115.53 ± 68.19 and 240.83 ± 116.94 ng / mg creatinine respectively. MELD above 20 and uNGAL above 32 were predictors of mortality.

CONCLUSIONS

Acute kidney injury is still a major cause of mortality in the natural history of cirrhosis of liver. Advanced disease with pre renal AKI is still a major cause but with ATN having maximum mortality.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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