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EVALUATION OF ACUTE KIDNEY INJURY (AKI) IN CASES OF CHRONIC LIVER DISEASE (CLD) IN A TERTIARY CARE HOSPITAL IN NORTH EASTERN INDIA

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ABSTRACT

Background: Clinicians adopt the published KDIGO definition of AKI as one of the following: • An increase in serum creatinine by ≥0.3 mg/dl within 48 hrs. • An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days • Urine volume ≤0.5 ml/kg/h for consecutive 6 hrs. Whereas Chronic liver disease in clinical context is the disease process of liver involving progressive destruction and regeneration of hepatocytes causing fibrosis and thereby resulting in cirrhosis or it may include any disease of the liver lasting over six months including chronic hepatitis or malignancy. **Aims and objectives:** The present study was undertaken to evaluate the incidence of AKI in patients with CLD. **Materials and methods:** The study included 100 patients of CLD admitted in a tertiary care hospital in north eastern India over a period of 18 months. Patients were subjected to thorough history taking, examination, necessary investigations and were analyzed using simple statistical methods. **Results and observations:** AKI was found in 40% of the cirrhotic patients of whom 90% were ICU admitted patients. The most predominant type was the prerenal AKI. Sepsis and GI bleeding were major cause in this study. We found that hemoglobin and serum albumin were lower in patients with AKI compared with those without AKI. **Conclusion:** The incidence of AKI is common in patients of CLD. A thorough evaluation and detailed clinico-biochemical monitoring of the patients is necessary as it has etiological variations thereby influencing the final outcome.

KEYWORDS: AKI, hemoglobin, serum albumin, sepsis, cirrhotic.

INTRODUCTION

Acute kidney injury (AKI) is a common and life-threatening problem for patients with cirrhosis.[1,4] The differential diagnosis of AKI in this population is large. It occurs in 15% to 20% of hospitalized patients with cirrhosis. The most common etiologies are prerenal azotemia, acute tubular necrosis, hepatorenal syndrome but other causes such as glomerulonephritis, medication toxicity and abdominal compartment syndrome from tense ascites occur as well. Patients with cirrhosis caused by Wilson's disease and primary biliary cirrhosis predominantly have interstitial renal disease.[2,3]

The spectrum of causes for AKI in cirrhosis includes.[1]

- Prerenal AKI (i.e. hypovolemia due to gastrointestinal bleeding, aggressive diuretic treatment, lactulose-induced diarrhea or infections).
- The hepatorenal syndrome-type AKI (HRS-AKI), which is defined as a potentially reversible deterioration of renal function unresponsive to volume resuscitation, caused by renal vasoconstriction in the absence of alternative identifiable cause.
- Intrinsic causes such as acute tubular necrosis.
- Postrenal causes rarely.
- The most important differential diagnosis of renal failure in cirrhosis is between type 1 HRS and "true" AKI with tubular damage.
- Prerenal AKI must be excluded by withdrawal of diuretics and fluid challenge either with 1.5 liters of normal saline or preferably with albumin, 1 g/kg body weight per day up to the maximum of 100 g/day for 2 days.
- Absence of microhematuria and proteinuria of less than 500 mg/day help exclude significant coexisting glomerular or tubulointerstitial disease leading to renal failure and support the diagnosis of HRS.[1]
- The parameters traditionally used to differentiate AKI with tubular damage from functional renal failure (urinary sodium excretion and urinary-plasma osmolality ratio) are of no value in patients with cirrhosis and ascites.
- The determination of the neutrophil gelatinase–associated lipocalin (NGAL) level, a urinary biomarker of tubular damage, could be of help to differentiate these two entities.
- Several biomarkers are there to detect acute kidney injury like.[5]
    1. Serum creatinine.
    2. Serum Urea.
    3. Cystatin C.

4. β2-Microglobulin (β2M).
5. β-trace protein (βTP).
6. Serum neutrophil gelatinase lipocalin (sNGAL).
7. Urine neutrophil gelatinase lipocalin (uNGAL).

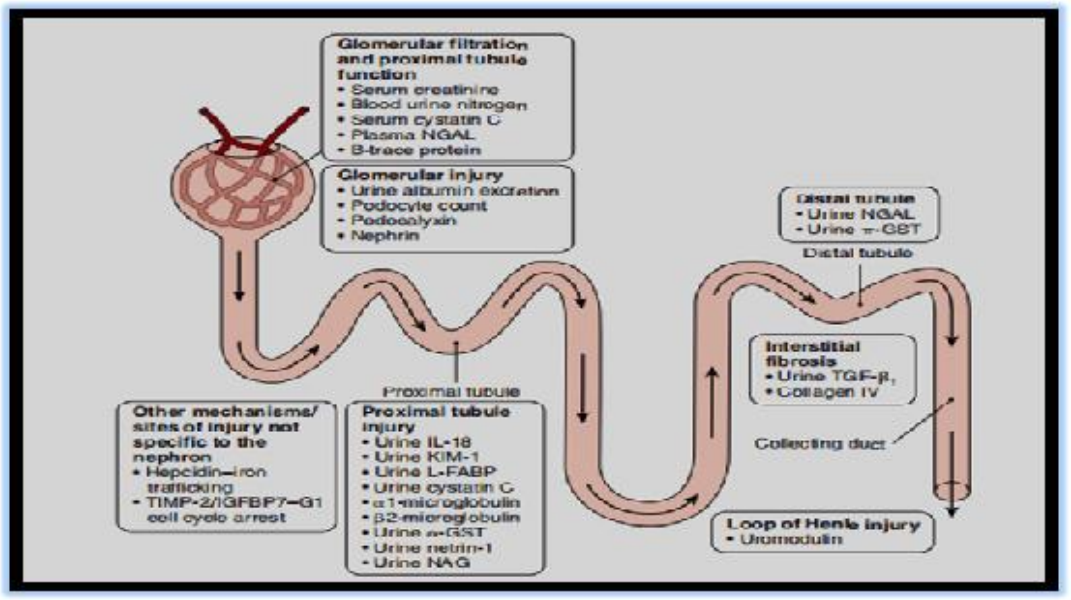


Figure 1: Biomarkers in relation to their site of injury in the nephron.[5]

- The AKIN criteria were used to diagnose AKI, which required an absolute increase in serum creatinine of 0.3mg/dL (26.4 μmol/L) above baseline or an increase of serum creatinine to 150% of baseline within 48 hours .In our study we used KDIGO, the most accepted criteria for defining AKI.[6,7]
- An increase in serum creatinine by ≥0.3 mg/dl (≥26.5 µmol/l) within 48 hrs.
- An increase in serum creatinine to ≥1.5 times baseline within the previous 7 days.
- Urine volume ≤0.5 ml/kg/h for 6 hrs.
- The AKIN criterion for decline in urine output was not used in the initial diagnosis of AKI as it was felt to be unreliable in patients with ascites and without a bladder catheter.
- "Chronic liver disease" refers to disease of the liver which lasts over a period of six months. It consists of a wide range of liver pathologies which include inflammation (chronic hepatitis), liver cirrhosis, and hepatocellular carcinoma.[8]
- Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage. The usual precipitants are infections,

gastrointestinal bleeding, alcohol-related hepatitis or drug-induced liver injury although no specific cause is found in approximately 50% of cases.[16]

- Renal dysfunction is a common complication of liver cirrhosis and of utmost clinical and prognostic relevance. Patients with cirrhosis are more prone to developing acute kidney injury (AKI) than the non-cirrhotic population. Pre-renal AKI, the hepatorenal syndrome type of AKI (HRS-AKI, formerly known as 'type 1') and acute tubular necrosis represent the most common causes of AKI in cirrhosis.

Aim: The present study was undertaken to evaluate the incidence of acute kidney injury in patients with chronic liver disease and also study the different etiologies of acute kidney injury in Barak Valley.

METHODS

- We prospectively identified hospitalized patients with AKI having clinical, radiological or histological evidence of cirrhosis and assessed the association between AKI severity and progression with in-hospital mortality.
- All consecutive patients who presented at Silchar Medical College, Silchar, Assam from 1st April 2018 to 30th September 2019 with diagnosis of CLD formed the study group.
- All patients were evaluated for presence of AKI. Etiological work up was done in all patients for CLD. Similarly work up was done to find out etiologies of AKI among patients who had it. Treatment outcome was also measured among AKI patients.

Inclusion Criteria

- Inpatient.
- Age> 18 yrs.
- All chronic liver disease patients.
- Patients giving written and informed consent.

Exclusion Criteria

- Malignancy and Malnourished patients.
- Patients who didn't give written and informed consent.
- Known case of chronic kidney disease or preexisting and previous history of kidney disease.
- History of usage of known nephrotoxic drugs or NSAIDS in recent past.

- Autoimmune and metabolic causes of chronic liver disease.
- Heart failure patients (to avoid cardiorenal syndrome).
- History of congenital disease of kidney or liver.
- Total bilirubin more than 10 mg/dl.
- Absence of microhematuria, proteinuria <500mg/day and abnormal USG findings of kidney.

All patients had a detailed clinical history and examination, a standard set of investigations including complete blood counts, liver function tests, serum creatinine, serum urea, electrolytes, random blood sugar, chest radiograph, ultrasonagram whole abdomen, ascitic fluid study, prothrombin time and INR. All patients were monitored till the end of their hospital stay. Serum creatinine was measured using the modified Jaffe's kinetic alkaline picrate method (colorimetry) without deproteinization using an automated chemistry analyzer Olympus AU 2700.

RESULT AND OBSERVATIONS

Our study was conducted on 100 cirrhotic patients 62(62%) men and 38 (38%) women, AKI was found in 40% of patients. 64% of them were men and 36% were women. The mean age of the patients who developed AKI was 62.87±5.42 years with a significant increase in the age of AKI patients compared with non AKI patients. Out of 100 chronic liver disease patients 80 patients had ascites and 20 patients had no ascites. Out of these, 80 patients with frank ascites 45% of them had deranged kidney function test.

Presenting Complaint	With ascites = 80 Patients	Without ascites = 20	Acute kidney Injury
1. Pain abdomen	32(14)	0	14
2. Melena	10(4)	8(2)	6
3.Hematemesis	8(2)	2(2)	4
4.Reduced urine output	12(10)	0	10
5.Altered sensorium	6(1)	0	1
6. Hematochezia	2	6	0
7.Jaundice	2	4	0
8.pain abd + ↓ urine output	8	0	5
TOTAL	80(36)	20(4)	40

In above table the patients are categorized with their main and major presenting complaint. Few patients had 2 or 3 presenting complaints too. Around 12.5% of patients who presented with pain abdomen (32 patients) developed AKI and were found to have spontaneous

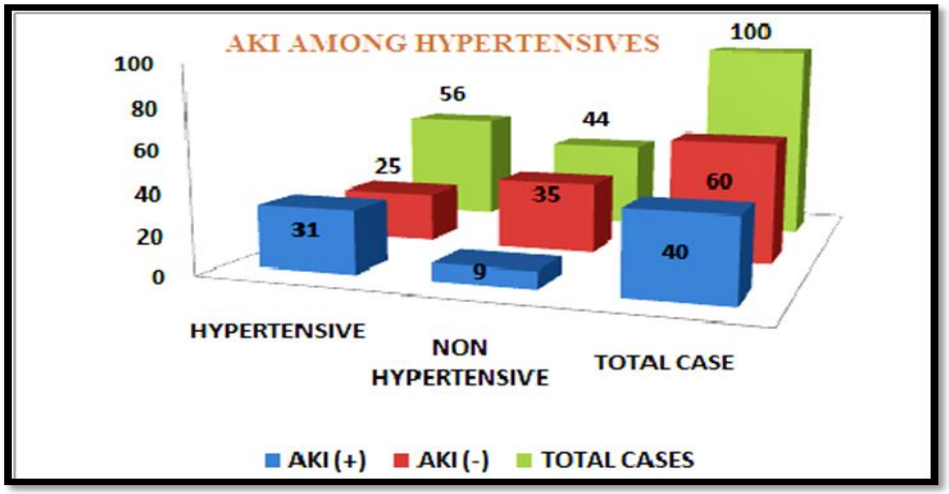
bacterial peritonitis. And patients who presented with reduced urine output 41.6% developed AKI. Patients with both pain abdomen and reduced urine output 75% developed AKI.

Distribution of Acute Kidney Injury Among Diabetics.

Diabetic patient	AKI(+)	AKI (-)	Total
yes	26	20	46
no	14	40	54

Out of 100 patients, 46 were diabetic, among them 56% developed AKI. And among non diabetics (54) 26% developed AKI.

Distribution of Acute Kidney Injury Among Hypertensives



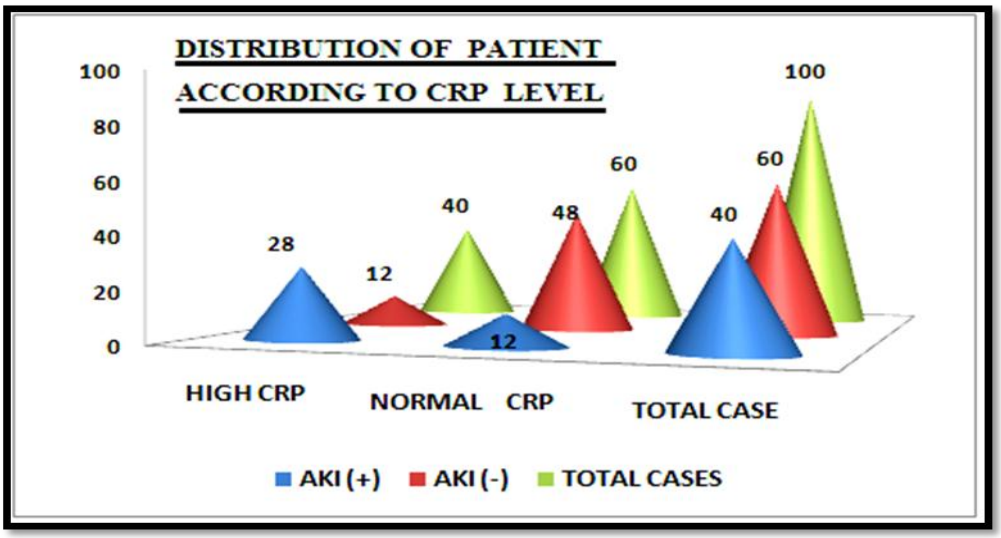
Out of 100 patients, 56% were hypertensive, among them 55.3% developed AKI. And among non hypertensive (44%) 20% developed AKI.

Distribution of AKI Patients According To Hemodialysis.

AKI	Done Hemodialysis	Not done Hemodialysis	Total
yes	28	12	40
no	0	60	60

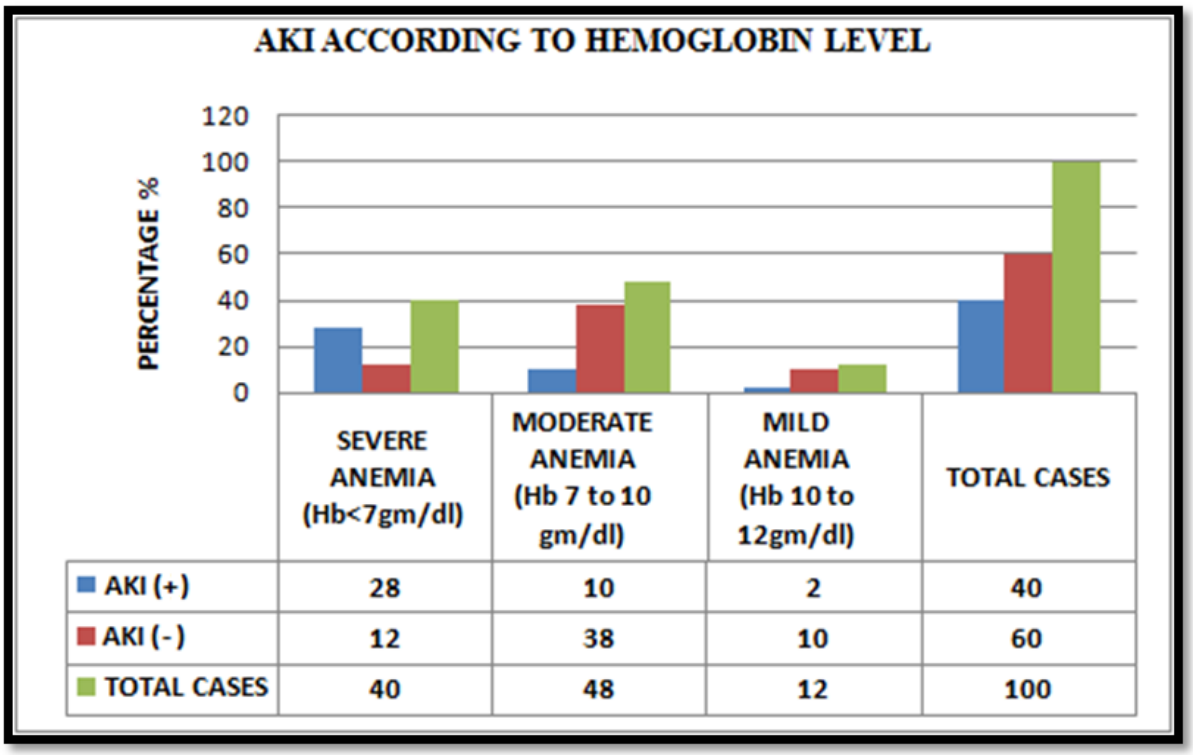
Out of 40 AKI patients, 70% underwent hemodialysis.

Distribution of AKI patients according to c-reactive protein (crp) level



There was a significant positive correlation between AKI and CRP level with a p value <0.05.

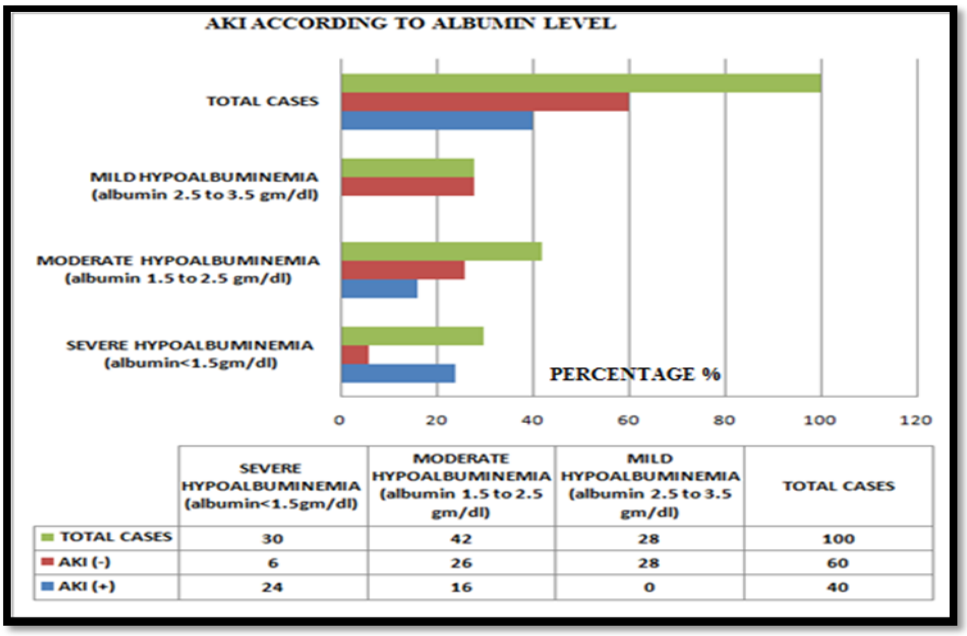
Distribution of AKI Patient According To Hemoglobin Level



	SEVERE ANEMIA (Hb<7gm/dl)	MODERATE ANEMIA (Hb 7 to 10 gm/dl)	MILD ANEMIA (Hb 10 to 12gm/dl)	TOTAL CASES
AKI (+)	28	10	2	40
AKI (-)	12	38	10	60
TOTAL CASES	40	48	12	100

The mean hemoglobin level among patients with AKI was 6.8 $\pm$ 1.6 gm/dl. There was a significant association between AKI and anemia with a p value <0.05.

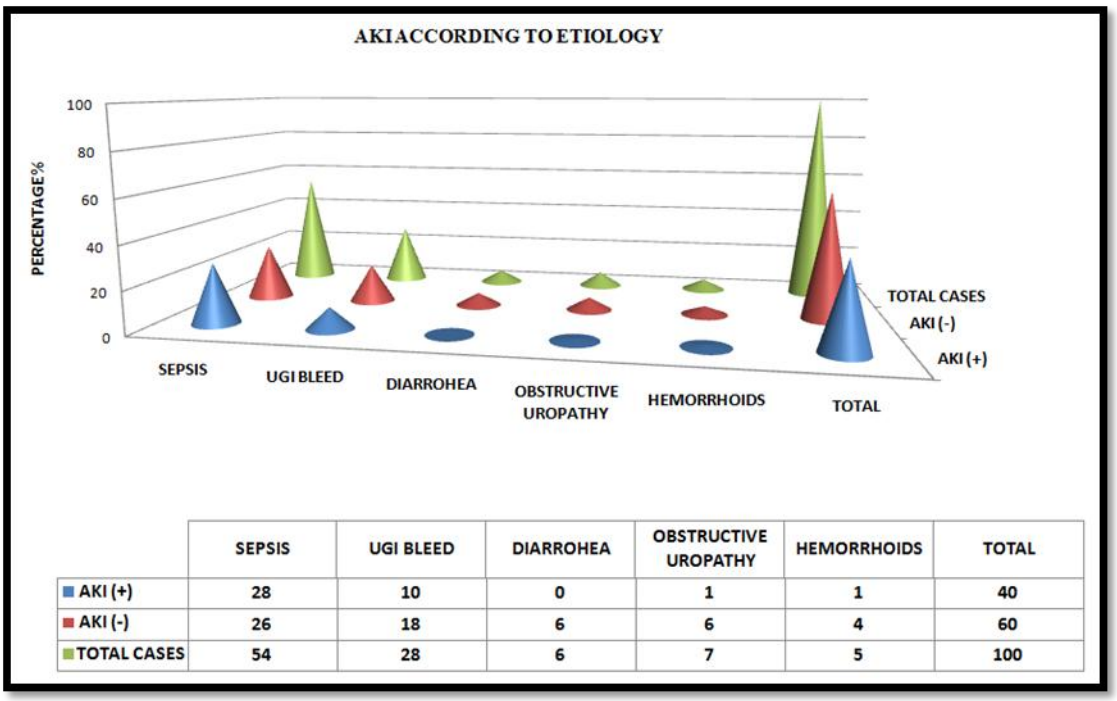
Distribution of AKI Patient According To Albumin Level



	SEVERE HYPOALBUMINEMIA (albumin<1.5gm/dl)	MODERATE HYPOALBUMINEMIA (albumin 1.5 to 2.5 gm/dl)	MILD HYPOALBUMINEMIA (albumin 2.5 to 3.5 gm/dl)	TOTAL CASES
TOTAL CASES	30	42	28	100
AKI (-)	6	26	28	60
AKI (+)	24	16	0	40

The mean value of albumin level among AKI cases was 1.9 $\pm$ 0.4 gm/dl. There was a significant association between AKI cases and hypoalbuminemia with a p value <0.05.

Distribution of AKI Patient According To Etiological Factor



	SEPSIS	UGI BLEED	DIARROHEA	OBSTRUCTIVE UROPATHY	HEMORRHOIDS	TOTAL
AKI (+)	28	10	0	1	1	40
AKI (-)	26	18	6	6	4	60
TOTAL CASES	54	28	6	7	5	100

Sepsis (54%) which included LRTI, UTI and SBP, UGI bleed (28%), obstructive uropathy(7%), diarrhea (6%), hemorrhoidal bleed (5%) were the various major causes of AKI. Among various causes, AKI was mainly seen in patients who developed sepsis.

DISCUSSION

Among our 100 cirrhotic patients, AKI was found in 40%.The mean age of patients who developed AKI was 62.87±5.42 years. 64% of them were men and 36% were women. According to our data, the prerenal causes of AKI were the most predominant. Prerenal causes included Sepsis and UGIB.

In our study, septic causes of AKI were significant. We found that SBP was the cause of AKI in 27% of cirrhotic patients, chest infections were found in 23% and urinary tract infection were reported in 15% of AKI patients and some of the cases had mixed infection.

Similar to our study, Thabut et al.[18] and Martín et al.[20] found that the most frequent cause of renal failure among cirrhosis patient was sepsis and hypovolemia was one of the most important causes of AKI among our cirrhotic patients which was mainly due to UGIB. Infections like spontaneous bacterial peritonitis, urinary tract infection due to catheterization for urine output monitoring, lower respiratory tract infection etc are common among cirrohosis patients because of portosystemic shunting of blood and dysregulated immune system.

Similar to our study, Levey et al.[19] and Michael et al. found that the presence of anemia, hypoalbuminemia, increase the risk of AKI in cirrhotic patients. Hypoalbuminemia and anemia had a negative correlation with risk of developing AKI ($P < 0.05$). Hypoalbuminemia results in decreased oncotic pressure which leads to decrease in the intravascular volume, resulting in reduced glomerular perfusion and prenal AKI. Anemia in CLD patients are commonly due to result of GI bleed which results in AKI.

Similar to our study, Thabut et al. also found that CRP a marker of sepsis was significantly higher in cirrhotic patients who developed AKI ($P<0.05$).

Limitations

- Eventhough serum Creatinine is an easily measurable and widely available marker of excretory renal function, it has limitations in assessing glomerular filtration rate (GFR) in patients with cirrhosis.
- Creatinine is non enzymatically converted from creatinine, which is produced by the liver and stored in muscle cells, and eliminated via glomerular filtration.

- Due to impairment in liver function, muscle wasting, decreased creatinine synthesis and increased tubular secretion of creatinine at advanced stages of cirrhosis, baseline creatinine production is lower in patients with cirrhosis compared to the non-cirrhotic population, thus serum Creatinine-based equations (i.e. Modification of Diet in Renal Disease MDRD) tend to overestimate GFR in cirrhosis.
- Nonetheless, due to its wide applicability, the MDRD-6 formula has been recommended to estimate GFR in patients with cirrhosis until better alternatives become available in clinical routines.
- GFR estimates using CysC, a non-glycosylated low-molecular weight protein of the cystatin superfamiliy of cysteine protease inhibitors, have been proposed to be superior predictors of renal function than serum Creatinine-based equations.
- Unlike serum Creatinine, Cystatin C is not influenced by age, muscle mass, gender, race, the presence of high bilirubin (interferes with the Jaffe reaction for creatinine quantification and may cause falsely low results.) or malignancy. Measurement of CysC has, however, been reported to be influenced by factors such as low serum albumin levels, elevated white blood cell count and elevated C-reactive protein levels. These abnormalities are frequently present and are thus likely to impair the reliability of cystatin C based equations in cirrhosis.
- Several studies have shown that equations combining serum Creatinine and CysC predict glomerular filtration more accurately than those using serum Creatinine or CysC alone (i.e. the CKD-EPI equation combining serum Creatinine and CysC).

CONCLUSION

- The incidence of AKI in cirrhotic patients is significantly high. Predominant type was prerenal AKI. Anemia, hypoalbuminemia, diabetes, hypertension, gastrointestinal bleeding, and sepsis increase the risk of AKI among cirrhotic patients.

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