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A study of acute kidney injury in cirrhosis of liver

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Abstract

Background: The prevalence of renal dysfunction has been reported to vary from 14-50% in patients with cirrhosis. The prevalence is estimated to be approximately 50% among patients with cirrhosis and ascites and 20% of patients with advanced cirrhosis admitted to the hospital [3,4]. The wide range in prevalence is likely due to different study populations and varying definitions of renal dysfunction. Patients with HRS who fail to respond to medical therapy or those with severe renal failure of other etiology may require renal replacement therapy. Simultaneous liver kidney transplant (SLK) is needed in many of these patients to improve their post-transplant outcomes. However, the criteria to select patients who would benefit from SLK transplantation are based on consensus and lack strong evidence to support them. Heath care system has evolved over the last decade and newer drugs are available for the management of complication of cirrhosis. We attempt to study its impact on course and outcome of acute kidney injury. Also few of the patients could possibly be on the antiviral drugs for hepatitis B and hepatitis C. If these patients are admitted they will be included in study and we would study the effect of the effect of this drug on acute kidney injury and vice versa. Hence, the present study was conducted to study clinical profile of patients with acute kidney injury in liver cirrhosis.
Aims and Objectives: To study clinical profile, etiological factors, comparison of the course of acute kidney injury in cirrhosis with different etiologies and to study the association of acute kidney injury and liver cirrhosis with respect to hospital stay and mortality.
Materials and Methods: A total of 86 patients selected by simple random sampling with liver cirrhosis with AKI were included in the study.
Results: The difference observed between AKI due to PRA vs. HRS and PRA vs. ATN was statistically significant but the difference between HRS and ATN was not significant.
Conclusion: The occurrence of AKI in patients with liver cirrhosis is a common event associated with a worsening of the prognosis. This warrants special attention in the monitoring of the renal function in these patients.

Keywords: Acute, kidney, injury, cirrhosis, liver

Introduction

Acute Kidney Injury (AKI), earlier termed Acute Renal Failure, is a very common entity

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affecting patients suffering from a wide variety of illnesses. It refers to a clinical entity characterized by a rapid decrease in renal excretory function with increase in levels of urea and creatinine and decreased urine output. Other abnormalities include accumulation of metabolic acids, increased potassium and phosphate concentrations [1]. Acute kidney injury (AKI) occurs commonly in patients with advanced cirrhosis and negatively impacts pre-and post-liver transplant outcomes. Physiologic changes that occur in patients with decompensated liver cirrhosis with ascites, place these patients at high risk of AKI. The most common causes of AKI in cirrhosis include prerenal azotemia, acute tubular necrosis (ATN) and the hepatorenal syndrome (HRS), accounting for more than 80% of AKI in this population [2]. Distinguishing between these causes is particularly important for prognostication and treatment [1, 2]. The prevalence of renal dysfunction has been reported to vary from 14-50% in patients with cirrhosis. The prevalence is estimated to be approximately 50% among patients with cirrhosis and ascites and 20% of patients with advanced cirrhosis admitted to the hospital [3, 4]. The wide range in prevalence is likely due to different study populations and varying definitions of renal dysfunction. As AKI significantly impacts the outcome of patients with cirrhosis, it is important to prevent the development of AKI if possible and to identify the cause early enough so that appropriate treatment measures can be instituted [5, 6]. A thorough history and careful physical examination are important to evaluate for potentially reversible and/or treatable causes for AKI, such as hypovolemia; hypotension; medications such as diuretics, NSAIDS; skin findings of cellulitis; and ongoing GI losses, such as nausea, vomiting or diarrhea. The threshold should be low for underlying infection as a cause of AKI, particularly SBP. Appropriate work up for infections should be performed by obtaining ascitic fluid culture, blood culture and chest radiography. Urinalysis and urine microscopy should be obtained to examine for urine sediment and detect findings suggestive of intrarenal injury such as tubular casts of ATN, microscopic hematuria and RBC casts in glomerulonephritis or proteinuria [5-7]. Treatment of HRS with vasoconstrictors and albumin improves short term survival and renal function in some patients while awaiting liver transplantation. Patients with HRS who fail to respond to medical therapy or those with severe renal failure of other etiology may require renal replacement therapy. Simultaneous liver kidney transplant (SLK) is needed in many of these patients to improve their post-transplant outcomes. However, the criteria to select patients who would benefit from SLK transplantation are based on consensus and lack strong evidence to support them. In this regard, novel serum and/or urinary biomarkers such as neutrophil gelatinase-associated lipocalin, interleukins-6 and 18, kidney injury molecule-1, fatty acid binding protein and endothelin-1 are emerging with a potential for accurately differentiating common causes of AKI [7, 8, 9]. Heathcare system has evolved over the last decade and newer drugs are available for the management of complication of cirrhosis. We attempt to study its impact on course and outcome of acute kidney injury. Also few of the patients could possibly be on the antiviral drugs for hepatitis B and hepatitis C. If these patients are admitted they will be included in study and we would study the effect of the effect of this drug on acute kidney injury and vice versa. Hence, the present study was conducted to study clinical profile of patients with acute kidney injury in liver cirrhosis.

Aims and Objectives

1) To study clinical profile of patients with acute kidney injury in liver cirrhosis.
2) To study the etiological factors of acute kidney injury in cirrhosis of liver.
3) To study and compare the course of acute kidney injury in cirrhosis with different etiologies of acute kidney injury.
4) To study association of acute kidney injury and liver cirrhosis with respect to hospital stay and mortality.

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Materials and Methods

Study design

The present study was an observational prospective study carried out at Tertiary Institute to study acute kidney injury in cirrhosis of liver.

Duration of study

This study was conducted over a period of one and half years.

Study setting

The study was conducted in the Department of Medicine of Medical College and Hospital.

Study population

Patients with liver cirrhosis with acute kidney injury admitted to department of Medicine of Hospital during the study period were included in the study.

Sample size

A total of 86 patients selected by simple random sampling with liver cirrhosis with AKI were included in the study.

Ethical approval

The study was conducted after obtaining clearance from the institutional ethics committee and permission from the appropriate authority.

Inclusion criteria

1) Patients admitted in wards of tertiary care hospital and diagnosed as liver cirrhosis who presented with AKI or developed AKI during hospital stay.
2) Age > 12 years.
3) Patient and/or relative willing to give consent.

Exclusion criteria

1) Patient with liver cirrhosis without AKI.
2) Patients with end stage renal disease.
3) Patient not willing to give consent.

Definitions

- **Cirrhosis of liver:** cirrhosis of liver is defined as a diffuse process with fibrosis and nodule formation. It is the end result of the fibrogenesis that occurs with chronic liver injury.

Classification/Staging system for acute kidney injury according to akin: 10

Stage	Sr. creatinine criteria	Urine output criteria
Stage 1	Increase in sr. creatinine >0.3 mg/dl or increase in >150-200% from baseline	Urine output < 0.5 ml/kg/hr for > 6 hrs

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Stage 2	Increase in sr. creatinine increase in > 200-300% from baseline	Urine output < 0.5 ml/kg/hr for > 12 hrs
Stage 3	Increase in sr. creatinine >300% from baseline	Urine output < 0.3 ml/kg/hr for > 24 hrs

Causes of AKI

1) **Hepatorenal syndrome:** Hepatorenal syndrome is diagnosed on the basis of serum creatinine concentration of more than 1.5 mg/dl which is not reduced to <1.5 mg/dl with the administration of albumin (1 gm/kg of body weight) and after minimum of 2 days of diurectics along with absence of current or recent treatment with potential nephrotoxic drug, the absence of shock and the absence of finding suggestive of parenchymal renal disease (urinary excretion = 500 mg of protein/day, >50 RBCs/HPF or abnormal kidneys on ultrasonography.
2) **Prerenal azotemia:** Participants were classified as having PRA if they presented with AKI, clinical history consistent with pre renal state (such as bleeding or GI fluid losses) and their serum creatinine improved following the administration of volume or withdrawal of diuretics.
3) **Acute tubular necrosis:** Participants were classified as ATN if they had proteinuria (>500 mg/day) or haematuria (>50 RBCs/ HPF) or presence of granular cast.

Data collection

- All Patients admitted in tertiary care hospital and diagnosed with liver cirrhosis with acute kidney injury were included.
- Detailed history and examination was carried out.
- Routine hematological and biochemical investigations asked by the treating physician were noted.
- Other specific investigation asked by the treating physician were noted.
- No investigation solely for the purpose of study were asked for.
- The course in ward of the patient was noted.
- Patient were included in the study till the creatinine reached normal range or was expected to reach the normal range and hence deemed fit for discharge by treating physician or till death.

Outcomes measured

Prognosis of AKI in patients which liver cirrhosis with different etiologies of AKI measured as:

- Discharge.
- Death.

Statistical analysis

The statistical analyses performed using the Statistical Package for Social Science (SPSS) version 21 for Windows. Data were expressed as mean values ± standard deviations (SD) for continuous variables. Frequency and proportions were reported for categorical variables. The p-value of < 0.05 was considered statistically significant.

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Results

Table 1: Age-wise distribution of patients (n=86)

Age	No. of Patients (n=86)	Percentage
12-20	0	0.00
21-30	3	3.49
31-40	32	37.21
41-50	38	44.19
51-60	9	10.47
>60	4	4.65
Total	86	100

Table 2: Gender wise distribution of patients (n=86)

Sex	No. of patients (n=86)	Percentage
Male	72	83.72
Female	14	16.28

Table 3: Age and gender wise distribution of patients (n=86)

Age group	Male		Female	
	No. of patients (n=72)	%	No. of patients (n=14)	%
12-20	0	0.00	0	0.00
21-30	3	4.17	0	0.00
31-40	27	37.50	5	35.71
41-50	32	44.44	6	42.86
51-60	7	9.72	2	14.29
>60	3	4.17	1	7.14
Total	72	100.00	14	100.00

Table 4: Distribution according to etiology of AKI (n=86)

Etiology of ARF	No. of patients	Percentage
PRA	33	38.37
HRS	25	29.07
ATN	28	32.56

Table 5: Gender-wise Distribution according to etiology of AKI

Type of ARF	PRA (n=33)	HRS (n=25)	ATN (n=28)
Male	26 (78.79%)	22 (88%)	24 (85.71%)
Female	7 (21.21%)	3 (22%)	4 (14.29%)
Total	33 (100%)	25 (100%)	28 (100%)

X2= 1.007, df=2, p=0.6.44 (not significant)

Table 6: Distribution according to etiology of liver cirrhosis (n=86)

Etiology	No. of patients	Percentage
Alcohol	64	74.42
Hepatitis B	11	12.79
NASH	5	5.81
Hepatitis B+ alcohol	4	4.65
Undiagnosed	2	2.33
Total	86	100.00

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Table 7: Distribution of AKI according to etiology of liver cirrhosis

Etiology	PRA (n=33)		HRS (n=25)		ATN (n=28)	
	No. of patients	%	No. of patients	%	No. of patients	%
Alcohol	24	72.73	20	80.00	20	71.43
Hepatitis B	3	9.09	3	12.00	5	17.86
NASH	2	6.06	1	4.00	2	7.14
Hepatitis B + alcohol	2	6.06	1	4.00	1	3.57
Undiagnosed	2	6.06	0	0.00	0	0.00
Total	33	100.00	25	100.00	28	100.00

Yates' X2= 1.413, df=8, p= 0.994 (not significant)

Table 8: Distribution according to clinical presentation

Clinical symptoms	PRA		HRS		ATN		Total	
	No. of patient	%	No. of patient s	%	No. of patient s	%	No. of patient s	%
Fever	18	54.55	5	20.00	15	53.57	38	44.19
Hypotension	20	60.61	2	8.00	12	42.86	34	39.53
Encephalopathy	11	33.33	14	56.00	8	28.57	33	38.37
Tense ascites	12	36.36	20	80.00	9	32.14	41	47.67
GI Bleed	6	18.18	5	20.00	6	21.43	17	19.77
SBP	5	15.15	5	20.00	4	14.29	14	16.28

Yates' X2= 20.708, df=10, p= 0.023 (significant)

Table 9: Distribution according to stage of AKI (AKIN classification)

Stage of AKI	PRA (n=33)		HRS (n=25)		ATN (n=28)		Total (n=86)	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Stage 1	4	12.12	2	8.00	3	10.71	9	10.47
Stage 2	7	21.21	5	20.00	5	17.86	17	19.77
Stage 3	22	66.67	18	72.00	20	71.43	60	69.77

Yates' X2= 0.982, df=4, p= 0.998 (not significant)

Table 10: Clinical findings and lab findings

Parameters	PRA (n=33)	HRS (n=25)	ATN (n=28)	P value
Temperature (F)	99.75 ±1.45	98.62 ±1.12	99.87 ±1.18	0.23
Pulse (/min)	95.78±13.17	94.19 ±13.10	95.35±13.26	0.45
SBP (mm of Hg)	129.25±15.74	132.11±16.13	128.12±15.19	0.32
DBP (mm of Hg)	84.15±8.53	84.03 ±8.11	85.12±8.88	0.71
RR (/min)	18.69±3.29	18.11±3.03	18.78 ±3.12	0.56
Hb (g %)	10.12±3.16	10.98 ±3.96	10.72±3.22	0.23
TC(x103/cumm)	20.19±8.94	20.11 ±8.11	20.76±8.19	0.11
Urea (mg/dl)	132.63±67.12	130.19±65.21	132.78±67.23	0.13
Creatinine (mg/dl)	3.83 ±2.4	3.12 ±2.1	3.08 ±2.3	0.23

Table 11: MELD Score

	Mean	SD
MLED Score	19.6	6.1
Child Pugh Score	10.5	2.2

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Table 12: Distribution of mean MELD score among AKI according to etiology of liver cirrhosis

Etiology	PRA	HRS	ATN	P value
Alcohol	18.4±4.4	21.9±4.8	22.3±9.1	0.29
Hepatitis B	15.5±6.3	16.2±7.1	16.4±7.3	0.43
NASH	14.7±7.2	20.5±5.3	21.3±8.3	0.07
Hepatitis B+ alcohol	21.7±5.4	21.6±6.4	22.7±5.5	0.61
Undiagnosed	18.8±3.5	19.3±8.2	20.9±6.7	0.34
Total	17.82±5.36	19.9±6.36	20.72±7.38	0.21

Table 13: Distribution according to cause of PRA: (n=33)

Etiology	No. of patients	Percentage
Diarrhoea	12	36.36
GI bleed	8	24.24
Sepsis	11	33.33
Excessive diuretics	02	06.06
Total	33	100

Table 14: Distribution according to improvement of PRA: (n=33)

Characteristics	No. of patients	Percentage
PRA improved with fluids	19	57.58
PRA improved after stopping diuretics	02	06.06
Did not improve	12	33.36

Stage	PRA (n= 23)	HRS (n=24)	ATN (n=23))	Total (n=70)
Albumin	3	2	2	7 (8.13%)
Albumin + Terlipressin	9	9	11	29 (33.72%)
Albumin + nor adrenaline	11	13	10	34 (36.04%)

Table 19: Distribution according outcome and treatment received (n=70)

Stage	Death	Survived
Albumin	2	5
Albumin+ Terlipressin	13	16
Albumin+ nor adrenaline	16	18

Yates' X2= 0.946, df=2, p= 0.623 (not significant)

Table 20: Outcome with respect to dialysis

Dialysis	PRA (n=33)		HRS (n=25)		ATN (n=28)		Total (n=86)	
	Survive d	Death	Survived	Death	Survived	Death	Survived	Death
Don't received	20	11	11	13	12	13	43	37
Received	1	1	0	1	1	2	2	4

Table 21: Hospital stay according to stage of AKI

Stage of AKI	Mean Duration of stay
Stage 1	5.2±3.1
Stage 2	8.7±2.7
Stage 3	15.3±3.3

Stage 1 Vs Stage 2: p=0.008 (Significant) Stage 1 Vs Stage 3: p=0.000 (Significant)
Stage 2 Vs Stage 3: p=0.000 (Significant).

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Table 22: Hospital stay according to etiology of AKI

Etiology of AKI	Mean Duration of stay
PRA	7.5±2.5
HRS	15.2±3.2
ATN	14.8±3.9

PRA Vs HRS: p=0.000 (Significant) PRA Vs ATN: p=0.000 (Significant) HRS Vs ATN: p=0.863 (Not Significant).

Discussion

It was observed that majority of the patients were in the age group of 41-50 years (44.19%) of age followed by 31-40 years (37.21%) and 51-60 years(10.47%). It was observed that majority of the patients in the study were male (83.72%). It was observed that majority of the male and female patients were in the age group of 41-50 years of age. The most common etiology of acute kidney injury was observed to be prerenal azotemia (38.37%) followed by acute tubular necrosis (32.56%) and hepatorenal syndrome (29.07%). It was seen that among PRA, HRS and ATN 78.79%, 88% and 85.71% were male respectively. The gender wise distribution according to etiology of AKI was not statistically significant. It was seen that alcohol was the most common etiology for cirrhosis followed by hepatitis B. Both Hepatitis B and alcohol was seen in 4.65%. Nonalcoholic steatohepatitis was seen in 5.81%. The patients with NASH were already biopsy proven. Alcohol was the most common cause of liver cirrhosis in all the three subgroups: prerenal azotemia, hepatorenal syndrome and acute tubular necrosis. The distribution of AKI according to etiology of liver cirrhosis was not statistically significant. The most common presenting symptom in patients of liver cirrhosis with AKI was tense ascites (47.67%) followed by fever (44.19%), hypotension (39.53%) and encephalopathy (38.37%). Among the PRA cases hypotension (60.61%) was the most common presenting feature followed by was fever (54.55%). Among the HRS cases tense ascites (80%) was the most common presenting symptom while among the ATN cases fever (53.57%) was most common presenting symptom. The difference observed in clinical presentation and etiology of AKI was statistically significant. Taking AKIN classification into account, the majority of cases of liver cirrhosis with AKI presented with Stage 3 AKI. The clinical parameter such as Temperature (F), Pulse(/min), SBP(mm of Hg), DBP(mm of Hg) and RR(/min) were compared among PRA, HRS and ATN patients was compared and it was seen that the difference observed was not statistically significant. Similarly the difference in Hb (g%), TC(x103/cumm), Urea(mg/dl) and Creatinine(mg/dl) was also not significant. Maximum MELD score was seen among the ATN patients due to Hepatitis B with alcohol (22.7±5.5) followed by alcohol (22.3±9.1). The lowest MELD score was seen among the PRA due to NASH patients (14.7±7.2). The MELD score was 19.6±6.1 while mean Child Pugh Score was 10.5±2.2. The most common cause of PRA was Diarrhoea (36.36%) followed by sepsis (33.33%) and GI bleed (24.24%). Out of total 21 patients showing improvement; 19(57.58%) improved with fluids while 2(6.06%) improved after stopping diuretics. It was observed that out of total 86 cases of AKI with cirrhosis 45 (52.33%) cases survived. The survival rate was maximum among PRA cases as compared to HRS and ATN cases (44% and 46.43% respectively) but the difference observed was not statistically significant. It was seen that encephalopathy was the most common clinical presentation among patients in whom mortality was seen followed by hypotension and tense ascites were observed (39.02% each). The difference observed in the distribution of clinical feature among the survived and death cases was statistically significant. It was observed that majority of the cases in whom mortality was seen were belonging to stage 3 of AKI. The distribution of expired cases according to stages of AKI and etiology of AKI was not statistically significant. Out of total 86 cases 70 received either albumin alone or albumin in combination either terlipressin or nor adrenaline. It was seen that majority of the patients received Albumin and nor adrenaline (36.04%) while Albumin and Terlipressin was received

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by 33.72% and only albumin was given to 8.13% patients. It was seen that 18 patients out of 45 who survived had received Albumin and nor adrenaline during treatment. It was seen that 16 patients out of 45 who survived had received Albumin and Terlipressin during treatment. The outcome and treatment received was not statistically significantly associated. It was seen that total 6 patients received dialysis and out of them 4 patients died and 2 survived. The mean duration of hospital stay of stage 3 AKI patients was 15 days whereas that of stage 2 patients was 8 days and of stage 1 was 5 days. Thus the stage 3 patients required more duration of hospital as compared to stage 2 and stage 1 and the difference observed was statistically significant. The mean duration of hospital stay of AKI patients due to PRA was 7 days where as that of HRS and ATN was 15 days and 14 days respectively. The difference observed between AKI due to PRA Vs HRS and PRA Vs ATN was statistically significant but the difference between HRS and ATN was not significant.

Conclusion

The occurrence of AKI in patients with liver cirrhosis is a common event associated with a worsening of the prognosis. This warrants special attention in the monitoring of the renal function in these patients. Using RIFLE/AKIN classification to detect AKI and determine its severity could allow earlier diagnosis of AKI and adaptation of its treatment according to the level of severity. Recognizing the common causes of AKI in cirrhosis along with early diagnosis and treatment is imperative for improving outcomes.

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