

## Original Research Article

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# Study of hepato-renal syndrome in patients of cirrhotic ascites in an academic hospital

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## ABSTRACT

**Background:** Acute renal impairment is common in patients with chronic liver disease, occurring in approximately one fifth of hospitalized patients with cirrhosis. Considering limited evidence of epidemiological information of this topic, the study was designed to identify the number of patients suffering from hepatorenal syndrome (HRS) among patients of cirrhotic ascites admitted in an academic hospital.

**Methods:** This hospital based cross-sectional type observational study was conducted at the department of medicine and gastroenterology. Total 100 subjects were interviewed. Data were collected by researcher with a structured questionnaire. After the interview the investigator recorded the collected information and later on transcribed into statistical software. Finally, data were analyzed by the SPSS 21.

**Results:** Total 100 subjects were studied and mean age was  $46.31 \pm 10.75$  years, ranging from 22 to 65 years. Majority of the participants were male (69%). The most common cause of cirrhosis of liver was chronic hepatitis B infection (45%), followed in second and third by NAFLD (25%) and chronic hepatitis C (18%). In according to the Child-Turcotte-Pugh class, about 51% were in CP class A, 36% were in class B and remaining 13% were in class C. Overall frequency of HRS was 17% and type 2 was predominant (7%-type 1 HRS vs 10%-type 2 HRS).

**Conclusions:** Less than one fifth of the patients developed HRS and it is associated with higher Child-Pugh class. However, further studies are needed to establish and use the findings.

**Keywords:** Hepatorenal syndrome, Cirrhosis of liver, Ascites, Renal dysfunction, Serum creatinine, eGFR

## INTRODUCTION

Cirrhosis is a result of advanced liver disease and is characterized by fibrosis of liver tissue and conversion of normal architecture into regenerative nodules, leading to a loss of liver function.<sup>1</sup> According to the center for disease control, cirrhotic liver disease is responsible for 15,000 deaths per year. It causes significant morbidity and mortality, mainly due to its complications. Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal

hypertension, variceal bleeding and HRS.<sup>2</sup> Acute renal impairment is common in patients with cirrhosis of liver occurring in approximately 19% of hospitalized patients with cirrhosis. A variety of types of renal impairment are recognized.<sup>3</sup> The most important of these is the HRS, which is characterized by development of renal failure in patients with advanced liver cirrhosis, who have portal hypertension and ascites, in the absence of kidney disease.<sup>4</sup> During the 19th century, Frerichs and Flint first reported an association between advanced liver disease and a type of renal impairment.<sup>5</sup> HRS is the most frequently fatal

complication of cirrhosis, because nearly half of patients die within 2 weeks of this diagnosis. The annual incidence of HRS is estimated at 8% to 40% in cirrhosis.<sup>6</sup> The model for end stage liver disease (MELD) score in patients with cirrhosis and ascites parallels the risk of developing HRS. Onset of ascites in patients with MELD scores of about 10 is associated with an 8% and 11% risk of HRS at 1 and 5 years, respectively. If the MELD score approaches 18, nearly 40% of patients develop HRS within 1 year.<sup>7</sup> The frequency of HRS in severe acute alcoholic hepatitis and in fulminant liver failure is about 30% and 55%, respectively.<sup>8</sup> Although the pathogenesis is not fully understood. Multiple mechanisms are probably involved. The distinctive hallmark feature of HRS is the intense renal vasoconstriction caused by interactions between systemic and portal hemodynamics. This results in activation of vasoconstrictors and suppression of vasodilators in the renal circulation.<sup>9</sup> Two subtypes of HRS have been identified: Type 1 HRS is a rapidly progressive renal failure that is defined by doubling of initial serum creatinine to a level  $>2.5$  mg/dl or by 50% reduction in creatinine clearance to a level  $<20$  ml/min in  $<2$  weeks. Type 2 HRS is a moderate, steady renal failure with a serum creatinine of  $>1.5$  mg/dl. In type 1 HRS, a precipitating factor frequently is identified, whereas type 2 HRS arises spontaneously and is the main underlying mechanism of refractory ascites.<sup>10</sup>

Due to the lack of specific biochemical or radiologic markers, the diagnosis of HRS is based on criteria for excluding other causes of renal impairment. But there are some risk factors which are easily recognized are low mean arterial blood pressure ( $<80$  mmHg), dilutional hyponatremia, and severe urinary sodium retention (urine sodium  $<5$  mEq/L). Others precipitating factors are sepsis, variceal hemorrhage, shock, severe acute alcoholic hepatitis, or use of nephrotoxic drugs.<sup>11</sup> Although, HRS is common complication in patients with cirrhosis and ascites, but the fewer studies are noticed regarding this topic.

For that reason, the study was planned to assess the prevalence of HRS in patients of cirrhotic ascites admitted in an academic hospital.

## METHODS

Cross sectional type observational study department of medicine and department of gastroenterology in an academic hospital six months. Due to time and resource constraints 100 subjects were included in the study. Cirrhosis patients with ascites who were admitted in an academic hospital in medicine and gastroenterology department.

### Inclusion criteria

Patients with age: $>18$  years, sex: both sex, patient of cirrhosis and clinically or sonographically evident ascites and willing to participate were included in the study.

### Exclusion criteria

Patients with history of GI bleeding in last 1 month, presence of hepatic encephalopathy, Patients with SBP, Patient with low SAAG ascites, cirrhosis with mixed ascites (High SAAG with lymphocytic ascites), Severely ill and pre-existing renal disease or renal impairment were excluded.

### Study procedure

Before commencement of the study, ethical permission was sought from ERC of DMC. After admission of a patient in the hospital ward, the case was seen by the indoor medical officer and study physician was informed. The study physician will immediately see the patient and examine thoroughly. All other measurements included in this study were done as follows: Firstly, S. creatinine; then withdrawal of diuretic for 2 days and again do a S. creatinine; then expansion of volume with albumin (1 g/kg of body weight/day upto 100 g/day) and again do a S. creatinine. Pulse, arterial pressure (three measurements at 10-minute intervals), postural drop was determined in all cases; exclusion of any nephrotoxic drugs to aid in diagnosis, after that, determination of 24-hour UTP, Creatinine clearance rate, microalbuminuria, urine R/E were done; USG of HBS, pancreas and KUB to exclude renal parenchymal disease and obstructive uropathy. Finally, when all data collection was complete, all were checked and verified and total 100 data were summarized using spread sheet of statistical software. After completion of the collection, data will be analyzed by SPSS.

### Ethical issues

The protocol was submitted to the ethical review committee and research review committee of DMCH. Then after getting clearance, it was submitted to BCPS. After admission into the hospital, patients meeting the inclusion criteria were thoroughly evaluated by the researcher. Details of the study and related information were read out and explained in local language from a printed handout.

After giving all the information, signed written informed consent was obtained. It was made clear to the patient that his/her confidentiality will be maintained, that there is no monetary benefit of the patient in this study, he/she can refuse to participate in the study at any time and it will in no way hamper his/her treatment. It was made clear to the patient that there is no invasive procedure in this study.

### Data processing and analysis

Data were statistically analyzed using SPSS (statistical package for social science) program version 21 for windows. Before starting the analysis, the normality test was performed to check whether the data are distributed normally or not. Student t-test were done for normally distributed quantitative variables to measure mean and

standard deviation. Besides this, Mann-Whitney U test will be done for quantitative variables which are not normally distributed. Chi square test will be done for qualitative variable analysis. For all the analysis a  $p<0.05$  will be considered statistically significant. Data will be shown as mean, range or value and 95% confidence interval (95% CI) and frequency and percent.

## RESULTS

Total 100 patients of cirrhosis with ascites were included in this study. Mean age was  $46.31 \pm 10.75$  years, ranging from 22 to 65 years.

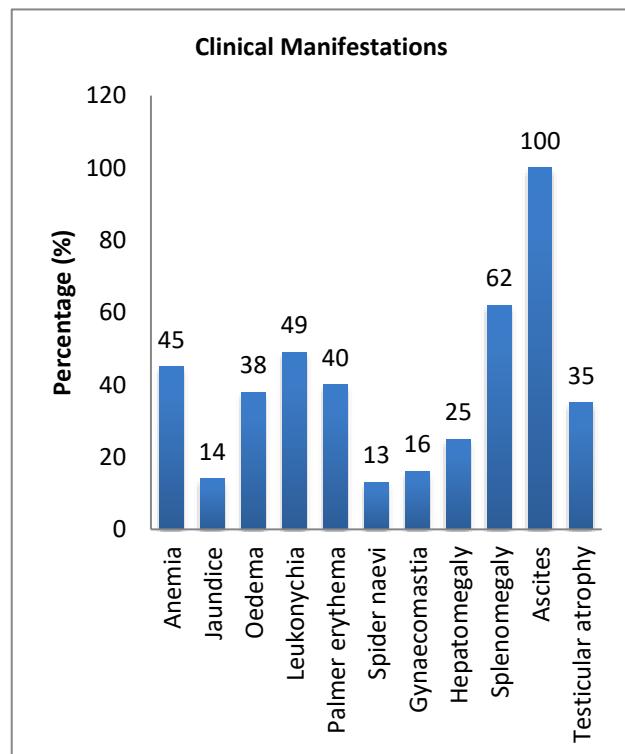
**Table 1: Demographic characteristics of the study subject, (n=100).**

Variables	N	Percentage (%)
<b>Age (in years)</b>		
21-30	7	7
31-40	25	25
41-50	30	30
51-60	33	33
61-70	5	5
<b>Sex</b>		
Male	69	69
Female	31	31
<b>Residence</b>		
Urban	43	43
Rural	57	57
<b>Education</b>		
Illiterate	28	28
Primary	25	25
SSC	21	21
HSC	11	11
Graduate	15	15
<b>Occupation</b>		
Govt. service	15	15
NGO service	10	10
Business	19	19
House wife	26	26
Farmer	17	17
Day laborer	2	2
Unemployed	11	11

Majority patients (33%) were aged 51-60 years. Among 100 patients 69% were male and 31% were female. Fifty seven percent patients came from rural area and 43% came from urban area. Most of the patients completed primary (25%), followed in decreasing order by SSC (21%), graduate (15%) and HSC (11%). Twenty eight percent patients were illiterate. Most of the patients were housewives (26%) followed in decreasing order by businessman (19%), farmers (17%), government service holder (15%), non-government service holder (10%) and day laborer (2%). Eleven percent patients unemployed.

This study included cirrhosis patients with ascites, therefore all patients had ascites. Next 2 common

presentations were splenomegaly (62%) and leukonychia (49%).



**Figure 1: Clinical manifestations of cirrhosis patients, (n=100).**

**Table 2: Causes of cirrhosis of liver, (n=100).**

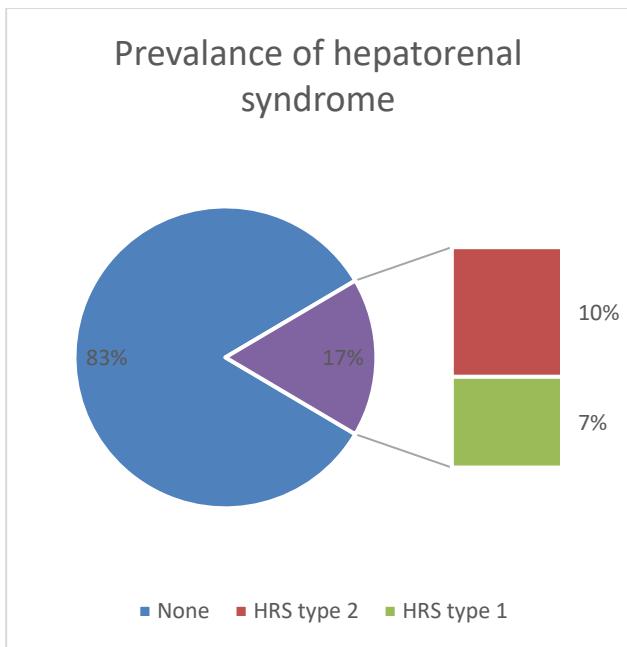
Causes of cirrhosis	N	Percentage (%)
Hepatitis B	45	45
Non-alcoholic fatty liver disease	25	25
Hepatitis C	18	18
Other	12	12

The most common cause of cirrhosis of liver was chronic hepatitis B infection (45%), followed in second and third by NAFLD (25%) and chronic hepatitis C (18%). Rest of the patients had other causes of cirrhosis including Wilson's disease, Haemochromatosis, Primary biliary cirrhosis, autoimmune hepatitis and cryptogenic cirrhosis.

**Table 3: Child-Turcotte-Pugh classification of cirrhosis patients, (n=100).**

Child-Turcotte-Pugh class	N	Percentage (%)
A	51	51
B	36	36
C	13	13

The most common Child-Turcotte-Pugh class was A (51%), followed by B (36%) and C (13%).



**Figure 2: Prevalence of HRS in patients, (n=100).**

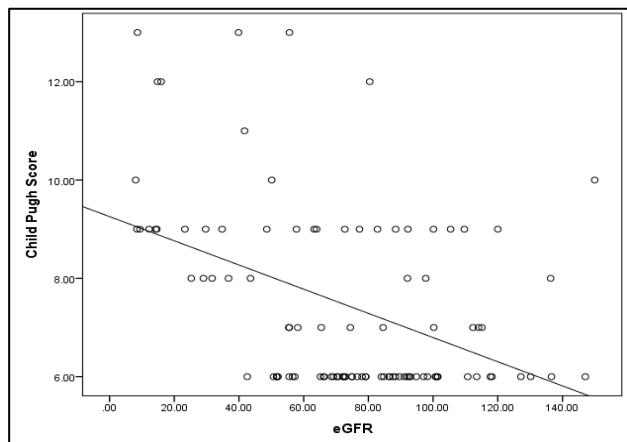
HRS was present in 17% patients. Among them 7% had type 1 HRS and 10% had type 2 HRS. HRS was absent in 83% patients.

**Table 4: Association of Child-Pugh class of cirrhosis with presence of hepatorenal syndrome, (n=100).**

Child-Pugh class	HRS present, (n=17)	HRS absent, (n=83)	P value*
Child-Pugh A	0	51 (100)	
Child-Pugh B	12 (33.3)	24 (66.7)	<0.001
Child-Pugh C	5 (38.5)	8 (61.5)	

\*The difference was statistically significant (p<0.001).

Proportion of HRS was higher in cirrhosis patients with higher Child-Pugh class. Among Child-Pugh C patients 38.5% had HRS and among Child-Pugh B patients 33.3% had HRS. None of the Child-Pugh A patients had HRS.



**Figure 3: Correlation of eGFR with Child-Pugh score.**

Child-Pugh score showed a significantly negative linear correlation with eGFR (Pearson's  $r=-0.436$ ,  $p<0.001$ ).

**Table 5: Comparison of laboratory parameters between patients with and without HRS, (n=100).**

Variables	HRS present, (n=17)	HRS absent, (n=83)	P value
Serum bilirubin (mg/dl)	1.87±1.04	1.44±0.93	0.09*
Serum ALT (U/L)	35 (14-90)	55 (11-250)	0.002**
Serum AST (U/L)	47 (26-101)	68 (19-261)	0.004**
Serum albumin (g/dl)	2.57±0.44	3.71±0.88	<0.001*
Prothrombin time (sec)	15.94±3.92	14.62±1.73	0.193*
Serum creatinine (mg/dl)	3.67±1.76	1.02±0.24	<0.001*
eGFR	21.20±11.35	84.08±25.15	<0.001*

\*Serum ALT, AST, albumin, and eGFR was significantly lower in patients with HRS than those without HRS ( $p<0.05$ ). \*\*Serum creatinine was significantly higher in patients with HRS ( $p<0.05$ ).

## DISCUSSION

HRS is a unique form of functional renal failure due to diminished renal blood flow, which occurs typically in histologically normal kidneys. It is a severe complication of advanced liver disease and characteristically affects patients with cirrhosis and ascites. Several treatment options exist for HRS, and early diagnosis and treatment provide the best hope of survival.<sup>3</sup> This study was done with an aim to find out the incidence of HRS among patients with cirrhosis and ascites admitted in a tertiary care hospital. Hundred patients of cirrhosis with mild to moderate ascites was included in this study. A mean age of  $46.31\pm10.75$  years was found which is lower than the findings of Khan et al (49.4 years) in Pakistan, and Qua and Goh (58.8 years) in Malaysia.<sup>12,13</sup> In the present study majority patients belonged to age group 51-60 years (33%). In the United States prevalence of cirrhosis was found to be highest among patients aged 45-54 years followed in second by patients aged 55-64 years.<sup>14</sup> The age at presentation of cirrhosis patients varies with underlying cause. Sajja et al studied more than two thousand cirrhotic patients to assess the relationship of age and ethnicity with cirrhosis. They found an average age of  $52\pm11$  years among their study population and noted that patients with cryptogenic/NAFLD/NASH cirrhosis were older (age 60) and those with autoimmune cirrhosis were younger (age 43). A male predominance constituting 69% patients in

this study was found. This result is similar to the findings of Das et al in BMU during 2014.<sup>15</sup> They found 68.18% male and 31.82% female among their study population. Khan et al found 59.1% male and 40.9% female in their study in Pakistan.<sup>12</sup> In this study 57% patients came from rural area and 43% came from urban area. Cirrhosis is an advanced chronic liver disease and therefore patients of cirrhosis are usually referred to tertiary care centers. As a result, the rural-urban distribution found in this study may represent regional distribution of population in the country.<sup>16</sup> According to a world bank estimate in 2017 approximately 64% people dwelled in rural area of Bangladesh.<sup>17</sup> This explains the higher proportion of rural residents in this study. Among all patients 72% were educated most of whom completed primary education (25%). Twenty eight percent patients were illiterate. Education level of cirrhosis of patients was higher than that found in Pakistan (41.7% having no education) by Khan and colleagues.<sup>12</sup> The most common cause of cirrhosis of liver was hepatitis B virus (45%) followed in second and third by NAFLD (25%) and hepatitis C virus (18%). Das et al observed that 49.22% of total cases presented with cirrhosis was due to hepatitis B virus.<sup>15</sup> Choon-Seng Qua and Khean-Lee Goh found that most of their patients in Malaysia with HBV infection (46.1%), presented with established cirrhosis.<sup>13</sup> NAFLD was found as a cause of cirrhosis in 21.4% cases in the study done.<sup>15</sup> In patients with NAFLD inflammation causes non-alcoholic steatohepatitis (NASH). Alam et al found that 42.4% patients of NAFLD develop NASH in Bangladesh.<sup>18</sup> Das et al also observed infection of HCV in 14.68% of cirrhotics, while Qua and Goh, has reported 18.5% due to infection with HCV and 12.6% due to alcohol.<sup>13,15</sup> In India hepatitis B, hepatitis C and NAFLD was found to be first, second and third cause of cirrhosis in a national wide study.<sup>16</sup> In this study the most common Child-Turcotte-Pugh class was A (51%), followed by B (36%) and C (13%). In comparison Hossain et al observed that 63% patient fell in Child Pugh class A group, 32% fell in Child Pugh class B and 5% fell in Child Pugh class C.<sup>19</sup> Another study by Khan and Iman found that 70.1% patient fall in child Pugh class A group, 24.9% patient fall in child Pugh class B group, 5.1% patient fall in child Pugh class C group.<sup>20</sup> HRS was found in 17% patients in this study. This is higher than that (15.09%) found by Seetlani et al and lower than that (29.1%) found by Siregar and Gurnig.<sup>21,22</sup> Russ, Stevens and Singal found that among cirrhotic patients' prevalence of renal dysfunction varies from 14 to 50%. The wide range in prevalence is likely due to different study populations and varying definitions of renal dysfunction. Among patients with HRS, majority had type II HRS (10%) and 7% had type I HRS in this study. Similarly, Licata et al found higher proportion of type-2 HRS (54.5%) than type-1 HRS (45.5%) in their study.<sup>23</sup> Child-Pugh class was found to be significantly associated with presence of HRS in this study ( $p<0.005$ ). A higher class was associated with higher incidence of HRS. In addition, a significant negative linear correlation between Child-Pugh score and eGFR was also found in this study. This finding recapitulates the findings of

Siregar and Gurnig.<sup>22</sup> On a similar note Qureshi et al found a significantly higher Child-Pugh score among patients with renal dysfunction.<sup>24</sup>

## CONCLUSION

In this study, conclusion it was observed that less than one fifth of the patients developed HRS. Among them type 2 HRS are more common. Furthermore, it was also seen that development of HRS was correlated with higher Child-Pugh class. However, further study with larger sample size is recommended to finalize the findings.

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