e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(2); 1396-1401

Original Research Article

Evaluation of Renal Dysfunction in Patients with Liver Disease to Identify Hepatorenal Syndrome

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Received: 25-11-2023 / Revised: 23-12-2023 / Accepted: 26-01-2024

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Conflict of interest: Nil

Abstract:

Background: Acute renal injury can be due to hepatorenal syndrome that can occur in people with acute or chronic liver illness. The objective of present study was to evaluate renal dysfunction in patients having liver disease to identify HRS.

Methods: This prospective observational study was conducted on patients of liver disease admitted in medicine ward and gastroenterology ward of tertiary care teaching hospital. Patients aged more than 18 years with clinical biochemical or ultrasonographic features of liver disease admitted to hospital were included. Central venous pressure and other investigations to exclude diseases causing liver and renal failure was performed on day of admission and patients were followed up every month till 6 months. Other relevant biochemical investigations were done to diagnose hepatorenal syndrome.

Results: Total seventy consecutive patients with liver disease were enrolled. Overall, hepatorenal syndrome was present in 27.14 percent of the patients. Among them, hepatorenal syndrome-1 and hepatorenal syndrome 2 was seen in 24.28 percent and 2.86 percent of the patients respectively. Among the 19 patients with hepatorenal syndrome, mortality was seen in 68.42 percent of the patients while among the remaining 51 patients without hepatorenal syndrome, mortality was seen in 15.68 percent of the patients. Significantly higher mortality rate was associated among patients with hepatorenal syndrome.

Conclusion: This study concluded that patients with liver disease who have HRS have a substantial mortality rate. Therefore, early diagnosis and treatment can lower the rate of HRS-related mortality in patients with hepatic disorders.

Keywords: Hepatorenal Syndrome, Liver Disease, Cirrhosis, Renal Dysfunction.

Introduction

Hepatic disorders like hepatitis B and hepatitis C, alcoholic liver disease as well as cirrhosis, hepatic insufficiency along with hepatocellular carcinoma are frequent etiologies of morbidity as well as mortality [1,2].

The pathogenesis of liver pathologies in children has undergone a paradigm shift similar to that in adults, having metabolic liver diseases, such as obesity-related liver disease, predominating and "Indian childhood cirrhosis" gradually vanishing. In contrast to most other nations, extrahepatic portal vein obstruction (EHPVO) is most frequent reason for paediatric portal hypertension in India. EHPVO is linked to portal cavernous cholangiopathy, a condition that is hardly ever documented outside of India [2]. A patient not having cirrhosis or any pre-existent liver disease experiences acute hepatic injury, hepatic encephalopathy, reduced synthetic function. While reports disagree on the time course which separates acute liver failure from chronic liver failure, standard cut-off is illness duration less than 26 weeks.

Acute insults such viruses, hepatotoxic medications (like acetoaminofen), or ischemia are to blame. Patients with vertically acquired hepatitis B virus, autoimmune hepatitis, or Wilson disease who had not previously received a diagnosis may also have it. Various cut off points and the length of the patient's illness can be used to subcategorize it.

Classification of acute liver failure is done as hyperacute (less than seven days), acute (seven to twenty one days), or subacute (more than twenty one days and < twenty six weeks). The associations reflect the underlying causes, which are true determinants of prognosis [3-6].

Acute-on-chronic liver failure (ACLF) is a term that has become more routinely accepted to explain acute decrease in hepatic function in cirrhosis patients. One of the main contributing factors is thought to be uncontrolled inflammation. Rapid development, the need for numerous organ supports and increase frequency of short-term mortality of fifty to ninety percent are all characteristics of ACLF [7].

Acute renal injury can be due to hepatorenal syndrome that can occur in people with acute or chronic liver illness. Hepatorenal syndrome affects about four percent patients with decompensated liver failure.

The majority of these individuals have portal hypertension brought on by metastatic malignancies, cirrhosis, or alcoholic hepatitis. In individuals with decompensated liver disease, cumulative likelihood of developing HRS at one year is eighteen percent, and at five years, it is thirty nine percent. Patients having hyponatremia and high plasma renin activity posed the greatest risk. A third of people who experience spontaneous bacterial peritonitis may later develop HRS [8].

Hepatorenal syndrome is characterized in patients with advanced liver disease by severe renal failure brought on by splanchnic vasodilatation, which reduces the effective circulation volume and causes renal vasoconstriction, which then reduces glomerular filtration.

There are two basic clinical varieties of HRS, designated as HRS types 1 and 2. The two variants have different clinical profiles, with HRS1 being more severe and advancing faster.

The most prevalent death outcome for cirrhotic patients is believed to be this syndrome. In individuals with HRS1, it has an eighty percent 2-week mortality rate and a 10% overall 3-month survival rate without treatment [9,10].

Numerous researches have been carried out to look into possible predictors of HRS. In a study involving 234 patients, 16 factors were shown to be potential univariate predictors of HRS.

On multivariate analysis, only three non- dependent variables, high plasma renin activity, and less serum sodium—were discovered as significant predictors of HRS [11]. So this study was taken up to evaluate renal dysfunction in patients having liver disease to identify HRS.

Material and Methods

This prospective observational study was conducted on patients of liver disease admitted in medicine ward and gastroenterology ward of tertiary care teaching hospital of Rajasthan. Patients aged more than 18 years with clinical biochemical or ultrasonographic features of liver disease admitted to hospital were included. Evidence of Pre-existing known renal disease and patients who didn't give consent for participation were excluded. Purposive consecutive sampling was done to enroll the patients. Ethical approval was obtained from institutional ethical committee. Written consent was obtained from all the patients after explaining in detail the entire research protocol.

Detailed history and clinical examination were done in all patients. Relevant blood investigation like Hemogram (Hb, TLC, platelet count), peripheral blood smear for band forms, Urine analysis under microscopy and routine, protein, Blood urea and serum creatinine at admission was done. Blood urea and serum creatinine if altered then monitor every day till discharge.

Serum electrolytes, Ultrasonography abdomen, ABG if required, Central venous pressure and other investigations to exclude diseases causing liver and renal failure was performed on day of admission and patient was follow up every month till 6 months.

Demographic characteristics, risk factors, family history, neurological examination, diagnostic data and treatment details were collected.

Sample Size:

It was calculated by using formula $\eta = [(Z\alpha)^2 P(1 - P)]/E^2$ where; η = Sample size, $Z\alpha$ = 1.96 at 95% confidence level, P= 16.8% (the prevalence of renal dysfunction in liver disease), E =10% (absolute error). Minimal sample size came out to be 54 patients.

Statistical analysis: Data was collected according to a predefined Performa. All the data were recorded in Microsoft excel and were analyzed by SPSS Software. For inferential analysis, Chi-square test and correlation was done in order to find association and relationship between the variables.

The diagrammatic presentation was performed by using bar diagram, or Pie chart as required. For descriptive analysis, mean standard deviation, ratio and proportion with percentages were utilized. P-value of less than 0.05 was taken as significant.

Results

Total seventy consecutive patients with Liver Disease were enrolled and analyzed in this study. 31.43 percent of the patients belonged to the age

group of 51 to 60 years. 20 percent of the patients belonged to the age group of 61 to 70 years. Mean age of the patients was 54.3±11.3 years. 82.86 percent were males while the remaining were females. Alcohol was the main etiologic factor found to be present in 74.29 percent of the patients while viral etiology of cirrhosis of liver was found to be present in 14.29 percent of the patients. Ascites was seen in 40 percent of the patients. 7.14 percent of the patients belonged to Child Pugh score A, while 50 percent of the patients and 42.86 percent of the patients belonged to Child Pugh score B and Child Pugh score C respectively. Overall, mortality was found to be present in 30 percent of the patients. (Table 1)

Table 1: Demographic and other characteristics details of the patients

	Number of patients	Percentage
Age group (years)		
Less than 40	9	12.86
40 to 50	17	24.29
51 to 60	22	31.43
61 to 70	14	20
More than 70	8	11.43
Gender		
Males	58	82.86
Females	12	17.14
Etiologic profile		
Alcohol	52	74.29
Viral	10	14.29
Autoimmune	03	4.28
Others	05	7.14
Ascites		
Present	28	40
Absent	42	60
Child Pugh score		
A	5	7.14
B	35	50
C	30	42.86
Outcome		
Mortality	21	30
Survived	49	70

Mean blood urea levels and serum creatinine levels were found to be 44.8mg/dL and 1.3 mg/dL respectively. Mean serum creatinine levels at Day 1 and Day 3 were 1.29 mg/dL and 1.51 mg/dL respectively. Mean urine output was 362.16 mL. Kidney size was enlarged in 2.86 percent of the patients. Abnormal renal profile was seen in 34.29 percent of the patients. Overall, hepatorenal syndrome was present in 27.14 percent of the patients. Among them, hepatorenal syndrome-1 and hepatorenal syndrome-2 was seen in 24.28 percent and 2.86 percent of the patients respectively. (Table 2)

Table 2: Renal dysfunction in liver patients

	Mean	SD
Renal profile		
Blood urea (mg/dL)	43.3	37.79
Serum creatinine (mg/dL)	1.26	0.46
Serum creatinine (mg/dL)		
Day1	1.29	0.48
Day3	1.51	0.91
Urine output (ml/day)	362.16	42.96
	Number	**percentage**
Kidney size on USG		
Normal	68	97.14
Enlarged	2	2.86
Renal profile		
Normal	46	65.71

Abnormal	24	34.29
Hepatorenal syndrome		
Hepatorenal syndrome-1	17	24.28
Hepatorenal syndrome-2	2	02.86

Among the 19 patients with hepatorenal syndrome, mortality was seen in 68.42 percent of the patients while among the remaining 51 patients without hepatorenal syndrome, mortality was seen in 15.68 percent of the patients. Significantly higher mortality rate was associated among patients with hepatorenal syndrome ($p<0.001$). (Table 3)

Table 3: Correlation of outcome with Hepatorenal syndrome

Hepatorenal syndrome	Mortality		Survived		Total		p-value
	Number	Percentage	Number	Percentage	Number	Percentage	
Present	13	68.42	6	31.58	19	27.14	0.001*
Absent	8	15.68	43	74.32	51	72.86	
Total	21	30	49	70	70	100	

*significant.

Mean blood urea levels among patients who survived and who died were 77.57mg/dl and 28.62 mg/dl respectively. Mean serum creatinine levels among patients who survived and who died were 1.58 mg/dl and 1.12 mg/dl respectively. While comparing the renal profile among mortality and survived patients, significant results were obtained. (Table 4)

Table 4: Comparison of renal profile among patients divided on the basis of outcome

Renal profile	Mortality		Survived		P value
	Mean	SD	Mean	SD	
Blood urea (mg/dL)	77.57	46.16	28.62	23.84	0.001*
Serum creatinine (mg/dL)	1.58	0.49	1.12	0.37	0.023*

*Significant

Discussion:

Hepatorenal syndrome (HRS), an uncommon illness, is mainly treated in settings with high levels of complexity. It is a secondary consequence of cirrhosis and severe liver failure. Patients with liver illness frequently develop renal impairment. In this population, renal failure may be acute or develop from underlying chronic kidney disease (CKD). It is linked to higher morbidity and death under any circumstance. Understanding the pathophysiology and natural history of renal failure in cirrhosis has advanced significantly in recent years [9,10].

In present study, 31.43 percent of the patients belonged to the age group of 51 to 60 years and mean age of the patients was 54.3±11.3 years. Our results were similar to results obtained by previous studies [12,13]. These finding suggests that increased incidence of liver disease with increase in age [14].

82.86 percent of the patients in the present study were males while the remaining were females. In a study conducted by Das et al, 72 percent of the patients were males [13]. Majority of patients in a study conducted by Fleming et al, were also males [14].

Alcohol was the main etiologic factor in 74.29 percent of the patients. Similar results have been reported in the past literature [13]. National and worldwide policy measures to reduce alcohol consumption have been prompted by known negative consequences of alcohol intake and its high relationship with death from liver cirrhosis. In order to hasten the implementation of a global strategy to lessen the negative consequences of rising alcohol consumption, WHO most recently organized a high-level meeting. Variations in alcohol intake, alcohol type and quality, iatrogenic viral hepatitis C infection, and viral hepatitis B infection were the main causes of death levels varying between regions and nations [14,15].

Mean blood urea levels and serum creatinine levels were found to be 43.3 mg/dL and 1.26 mg/dL respectively. In a study conducted by Fida et al, mean creatinine levels were 1.7 mg/dL [12]. Ascites was seen in 40 percent of the patients while it was absent in 60 percent of the patients. In a study conducted by Fasalato et al, authors observed ascites in 75.4% with liver diseases.

Renal accumulation of sodium and the splanchnic circulation's disruption of the Starling balance leads to the development of ascites. The sympathetic nervous system, the renin-angiotensin-aldosterone axis, and non-osmotic AVP secretion are all activated, which causes the kidney to retain sodium and water. Portal hypertension causes a rise in hydrostatic pressure and a decrease in oncotic

pressure in the intestinal capillary, which promotes hepatic lymph production [16].

7.14 percent of the patients belonged to Child Pugh score A, while 50 percent of the patients and 42.86 percent of the patients belonged to Child Pugh score B and Child Pugh score C respectively. In a study conducted by Papatheodoridis GV et al, similar classification of patients as per Child-Pugh score A, B and C [17].

In the present study, abnormal serum urea levels and serum creatinine levels were seen in 34.29 percent of the patients each. Similar results have been reported by Mohan et al, who observed that 22 percent of the patients with liver disease of their study had renal dysfunction [18]. Aggarwal et al reported the presence of renal dysfunction in 37 percent of patients with liver diseases [19]. Fida et al, in another study reported that 33.8 percent of the patients had renal dysfunction [12].

Mean serum creatinine levels increased from day 1 to day 3 in present study. Serum creatinine has also been recognized as an independent predictor of mortality in patients with decompensated cirrhosis. A variety of alterations take place in early cirrhosis when portal hypertension emerges, and these have previously been thoroughly documented. In short, alterations in peripheral and liver vascular biology lead to a number of modifications, such as arterial vasodilation in the splanchnic circulation, which results in peripheral systemic vascular vasoconstriction. In an effort to maintain arterial blood pressure, splanchnic vasodilation results in secondary peripheral vasoconstriction, activation of the renin- angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS), which increases vasopressin secretion. Additionally, increased hyper-dynamic circulation, which promotes cardiovascular dysfunction, is made worse by splanchnic vasodilation, which also causes a decrease in cardiac output and worsens peripheral vasoconstriction. This causes cirrhotic cardiomyopathy, which affects the heart [10]. Aldosterone and renin levels rise when the GFR falls, further destabilising the RAAS, which worsens ascites and fluid overload by causing sodium retention. Vasopressin is further activated locally and centrally, which results in a sequence of modifications that cause the nephron to retain water. Additionally, there may be an increase in renal vasoconstriction, a decrease in renal perfusion, and subsequentrenal ischemia. These events lead to decreased GFR, which increases the risk of developing HRS [10].

Overall, hepatorenal syndrome was present in 27.14 percent of the patients. Among them, hepatorenal syndrome-1and hepatorenal syndrome-2 was seen in 24.28 percent and 2.86 percent of the patients respectively. Our results were in concordance with the results obtained by previous authors who also reported similar findings. In a study conducted by Fida et al the prevalence of HRS observed was of 23.9%. They also reported significantly higher proportion of HRS type 1 (16.24 percent) in comparison to type 2 (7.69 percent). Several studies determine the prevalence of HRS, finding a significant variation depending on the HRS definition used and the inclusion and exclusion criteria considered [12]. Recently, in a study 15% patients with cirrhosis were diagnosed with HRS [20]. However, Salerno et al reported 45.8% had HRS (30% HRS-1 and 15.8% HRS-2) [21].

The most current report of evidence supporting this last concept of an approach to the diagnosis and treatment of this illness was published in 2015 by Angeli et al. A bacterial infection episode (spontaneous bacterial peritonitis is the most frequent), intravascular volume contraction owing to haemorrhage, excessive diuretic usage, large volume paracentesis, severe surgery, or acute liver failure are some of the medical literature's descriptions of HRS triggers. Rather than HRS type 2, these are more typically linked to the emergence of type 1 HRS [22,23].

In the present study, among the patients with hepatorenal syndrome, mortality was seen in 68.42 percent of the patients. While among patients without hepatorenal syndrome, mortality was seen in 15.68 percent of the patients. Significantly higher mortality rate was associated among patients with hepatorenal syndrome. In a study conducted by Fida et al, authors also observed significantly higher mortality rate among patients with HRS [12]. Also while comparing renal profile, blood urea and serum creatinine was statistically significant high in patients who died.

Aggarwal et al study found renal dysfunction in 37 percent of the patients among liver cirrhosis patients. Renal impairment in patients with advanced liver disease is not an uncommon phenomenon and is more commonly associated with a more advanced disease. Presence of portal hypertension and various signs of decompensation increase the chances of renal derangements in these patients. In view of rising incidence of CLD and higher survival, one should be vigilant for the renal derangements in these patients [19].

Conclusion:

This study concluded that patients with liver disease who have HRS have a substantial mortality rate. Since there are no established biomarkers for HRS, the diagnosis is based on a mix of clinical and laboratory standards. There are numerous treatment options, and the highest chance of survival comes from early diagnosis and treatment. Therefore, early diagnosis and treatment can lower

the rate of HRS-related mortality in patients with hepatic disorders.

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