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PREVALENCE OF HRS IN DECOMPENSATED CIRRHOSIS PATIENTS SUFFERING FROM SPONTANEOUS BACTERIAL PERITONITIS

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Abstract

Objective: *To observe the prevalence of HRS in decompensated cirrhosis patients suffering from spontaneous bacterial peritonitis.*

Study Design: *A Cross sectional observational study*

Study Duration: *06 months*

Study Place: *Tertiary Care Hospital, Lahore*

Methods: *A cross-sectional observational study was conducted over six months in the Gastroenterology Department of a tertiary care hospital in Lahore. Using ICA criteria, HRS prevalence was assessed in 150 SBP patients. Data were analyzed using SPSS 25, with significance set at $p<0.05$. Ethical approval was obtained beforehand.*

Results: *Out of 150 patients with SBP, 64 (42.7%) developed HRS–60.9% Type 1 and 39.1% Type 2. HRS patients had higher MELD scores (28.4 vs. 20.1), creatinine, bilirubin, and ALT levels. Median time to HRS onset was 4.2 days. Hospital mortality was significantly higher in HRS patients (53.1% vs. 18.2%; $p<0.001$). Hepatitis C was the leading cause of cirrhosis (51.5%).*

Conclusion: *HRS significantly worsens outcomes in SBP patients, marked by higher mortality and rapid renal and hepatic deterioration. Early intervention with vasoconstrictors and albumin may improve survival.*

INTRODUCTION

Hepato-renal Syndrome (HRS) is a serious complication of advanced liver disease, i.e., cirrhosis with ascites. It is characterized by renal functional failure without intrinsic kidney disease. It is the result of profound renal vasoconstriction secondary to circulatory failure. HRS is classified as: HRS-AKI (Acute Kidney Injury) – Acute presentation, formerly Type 1 and HRS-CKD (Chronic Kidney Disease) – Insidious development, formerly Type 2 [1, 2]. HRS results due to host of multifactorial circulatory and hormonal changes such as splanchnic Vasodilation, leading to an increased production of vasodilators (e.g., nitric oxide), and leading to peripheral arterial under filling. The second mechanism is associated with reduced Effective Circulating Volume leading to fluid retention, blood pressure falls and activating

RAAS (Renin-Angiotensin-Aldosterone System), SNS (Sympathetic Nervous System) and ADH (Antidiuretic Hormone). These compensatory mechanisms lead to renal vasoconstriction, resulting in a significant decrease of GFR (Glomerular Filtration Rate). Interestingly, the kidneys are structurally normal, which differentiates HRS from other forms of acute kidney injury (AKI) like acute tubular necrosis [2, 3].
HRS occurs in approximately 8–20% of patients with cirrhosis and ascites who are hospitalized [4]. It is most frequent in patients with SBP or sepsis. The prognosis of HRS-AKI is very bleak, with median survival <2 weeks without intervention [5]. Complications of HRS include acute kidney injury, hyponatermia, refractory ascites, infection risk, hepatic encephalopathy and death eventually. Cirrhosis is a terminal stage of progressive liver fibrosis with the replacement of normal liver parenchyma by scar tissue, leading to liver dysfunction.
It follows as a result of chronic liver damage, wherein repeated damage and inflammation lead to hepatocellular necrosis and regenerative nodules, eventually destroying the liver architecture. The causes of cirrhosis are diverse, with the top causes being infection with chronic hepatitis B and C, alcoholism over long periods, and non-alcoholic fatty liver disease (NAFLD). Autoimmune hepatitis, genetic disorders such as hemochromatosis and Wilson's disease, and chronic exposure to hepatotoxic drugs also cause cirrhosis. [6]
One of theworld's 20 most prevalent causes of death, the World Health Organization (WHO) states, and carries a significant burden particularly in low- and middle-income countries due to hepatitis infections and in high-income countries due to NAFLD and alcoholic liver disease. [7]
Decompensated cirrhosis is a more advanced phase where the liver is no longer able to carry out its usual tasks and decompensation occurs. Complications include ascites, hepatic encephalopathy, bleeding from varices, and jaundice. Decompensation greatly worsens the prognosis, and a one-year mortality rate of as much as 20% is seen. [8]
One of the severe complications of decompensated cirrhosis is hepatorenal syndrome (HRS), a form of functional renal dysfunction without structural kidney injury.
The pathophysiology between both conditionsis essentially determined by secondary hemodynamic alterations due to portal hypertension and systemic circulatory disturbance.
In decompensated cirrhosis, worsening liver function and portal hypertension lead to splanchnic vasodilation, which is mediated by increased nitric oxide and other vasodilators. Splanchnic vasodilation leads to reduced effective arterial blood volume and induces compensatory activation of the RAAS, sympathetic nervous system, and the release of antidiuretic hormone. [9] These neurohormonal activations lead to marked renal vasoconstriction and sodium retention, ultimately leading to renal perfusion and glomerular filtration compromise, which defines the pathophysiology of HRS.
Spontaneous Bacterial Peritonitis (SBP) is a severe and common complication of cirrhosis that is characterized as infection in ascitic fluid without an obvious intra-abdominal surgically correctable source.
It predominantly occurs among patients with end-stage liver disease and ascites. Escherichia coli, Klebsiella pneumoniae, and Streptococcus species are most frequently isolated in SBP. Diagnosis is usually made by paracentesis with ascitic fluid polymorphonuclear leukocyte (PMN) count ≥250 cells/mm³, with or without a positive bacterial culture. SBP is highly lethal if not treated promptly. Early detection, early management, and measures of prevention must then be undertaken to improve the outcome in cirrhotic patients with ascite. [10,11]The purpose of our study is to find prevalence of HRS in decompensated cirrhosis patients suffering from spontaneous bacterial peritonitis in our population sample size.

Methodology:

The sample size of 150 patients was determined by the use of the WHO sample size calculator, taking study confidence to be 85% and margin of error 5%. The study was carried out at the Territory care hospital Lahore from ____ to ____. The study was carried out after getting approval from the hospital ethical board. The study design employed was a cross sectional observational study and was undertaken for 06 months in the department of Gastroenterology. The

main aim was the prevalence of hepatorenal syndrome (HRS) in patients with decompensated liver cirrhosis who developed spontaneous bacterial peritonitis (SBP). The diagnosis of SBP was made based on ascitic fluid polymorphonuclear (PMN) leukocyte count of ≥ 250 cells/mm³ and/or positive ascitic fluid culture with no intra-abdominal source of infection. The diagnosis of HRS was made by the updated International Club of Ascites (ICA) criteria, which are an increase in serum creatinine of ≥0.3 mg/dL within 48 hours or an increase ≥50% from baseline and is not explained by other causes of acute kidney injury (AKI). The inclusion and exclusion criteria of the study are as follows:

Inclusion criteria:

- Patients of either gender
- Confirmed diagnosis of liver cirrhosis, either clinically or radiologically, and with SBP
- Age ≥ 18 years

Exclusion criteria:

- Pre-existing chronic kidney disease
- Secondary peritonitis
- Malignancy or malignant ascites
- Patients on nephrotoxic agents

Upon admission, a detailed clinical history and physical examination were conducted. Relevant laboratory investigations including complete blood count, liver function tests, renal function tests, serum electrolytes, and ascitic fluid analysis were performed. HRS was diagnosed according to the International Club of Ascites (ICA) criteria, focusing primarily on HRS-AKI (acute kidney injury variant). Criteria included a rise in serum creatinine ≥0.3 mg/dL within 48 hours or a ≥50% increase in serum creatinine from baseline, in the absence of shock, nephrotoxic drugs, or parenchymal kidney disease. The data were analyzed using SPSS version 25. Descriptive statistics were calculated for continuous and categorical variables. The prevalence of HRS among patients with SBP was calculated as a proportion, and subgroup analyses were conducted to evaluate associations with variables such as age, sex, and MELD score. A p-value <0.05 was considered statistically significant.

Results:

Out of the 150 patients studied, 89 were males and 61 were females. 64 (42.7%) patients developed HRS secondary to SBP. Among them, 39 patients (60.9%) developed Type 1 HRS while 25 patients (39.1%) developed Type 2 HRS. The mean age of patients who developed HRS was 56.3 ± 9.7 years, and 71.9% were male.

The most common etiology of cirrhosis in HRS patients was hepatitis C infection (51.5%), followed by non-alcoholic steatohepatitis (25%) and heptatoxic drugs (13%).

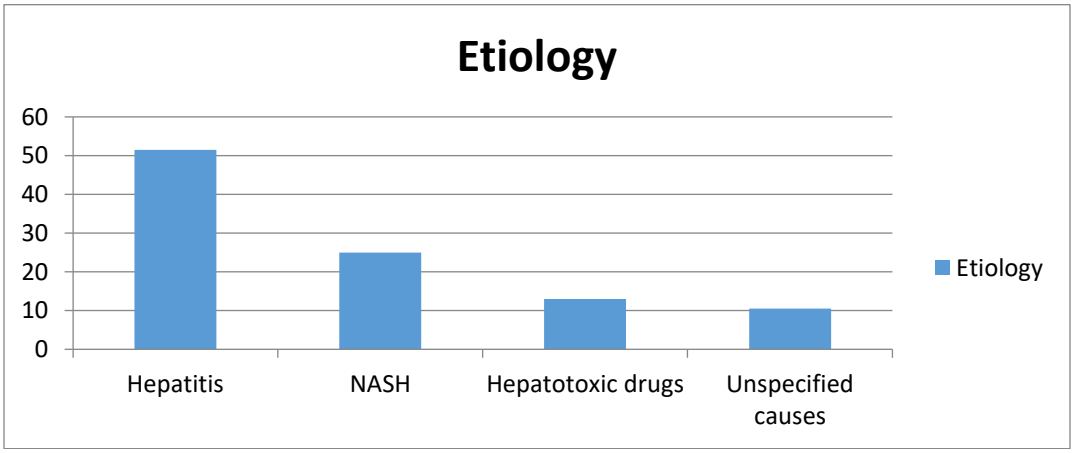
Patients who experienced HRS had a significantly higher baseline Model for End-Stage Liver Disease (MELD) score (mean 28.4 ± 4.6) than did those without HRS (mean 20.1 ± 3.9; p<0.001). Serum creatinine at the time of SBP diagnosis was higher in the HRS group (mean 1.6 ± 0.4 mg/dL) than in the non-HRS group (mean 1.1 ± 0.3 mg/dL; p<0.01). The HRS group also had a lower MAP. The mean serum creatinine in the HRS group was 1.61 ± 0.42 mg/dL, which increased over the first 5 days to a peak mean of 2.48 ± 0.56 mg/dL. Patients who did not develop HRS had a baseline mean serum creatinine of 1.12 ± 0.31 mg/dL, which only fluctuated minimally during hospitalization (p<0.001). A creatinine increase of ≥0.3 mg/dL within 48 hours was noted in 71.8% of HRS patients. This rapid increase in creatinine was a strong early indicator of renal dysfunction.

Patients with HRS also had statistically higher concentrations of total serum bilirubin. At initial diagnosis of SBP, the mean bilirubin level in the HRS group was 6.8 ± 2.1 mg/dL and increased to 9.5 ± 3.3 mg/dL during the course of the illness. Conversely, in non-HRS patients the mean bilirubin level was 4.1 ± 1.7 mg/dL, only slightly increasing during follow-up (p<0.001). In summary, hyperbilirubinemia was documented in the HRS patients who also demonstrated decremented liver function and associated poor outcome. The levels of ALT were also statistically significantly higher in the HRS group when compared to the non-HRS. The mean level of ALT at the initial diagnosis was 76 ± 21 U/L (compared to 54 ± 18 U/L in the non-HRS group; p<0.01). Hospital mortality was significantly higher for patients who developed HRS (53.1%) compared to patients who did not develop HRS (18.2%; p<0.001). The median number of days between initial diagnosis of SBP to development of HRS was 4.2 days. Surviving patients with HRS who received early administration of vasoconstrictors (terlipressin) and albumin, had a slightly higher survival (47.8%)

compared to patients without HRS specific treatment (31.6%).

Parmeters	HRS n=64	Non-HRS n=86	p-value
Male	71.9%	60.5%	.15
MELD Score	28.4 ± 4.6	20.1 ± 3.9	<0.001
Creatinine at SBP (mg/dl)	1.6 ± 0.4	1.1 ± 0.3	<0.001
Creatinine inc by 0.3mg/dl in 48 h	2.48 ± 0.56	9.3 %	<0.001
Bilurubin	71.8 %	4.1 ± 1.7	<0.001
ALT	6.8 ± 2.1	54 ± 18	<0.001
Hospital Mortality	76 ± 21	18.2 %	<0.001

Table 1.1- Parameters of the research



Discussion:

Hepatorenal syndrome (HRS) is a serious and sometimes fatal complication of end-stage liver disease in patients with decompensated cirrhosis. Among all the triggers of HRS, spontaneous bacterial peritonitis (SBP) is the most significant. The relationship between SBP and HRS is an important pathway in the and clinical monitoring of declining liver function and systemic hemodynamics in cirrhotic patients that require vigilant monitoring and aggressive management. Decompensated liver cirrhosis is characterized by the appearance of complications such as ascites, variceal hemorrhage, hepatic encephalopathy, and jaundice. SBP, an infection of the ascitic fluid without a source within the abdomen, occurs in 10-30% of hospitalized patients with cirrhosis and ascites.[12]

Multiple studies have demonstrated an association between SBP and the development of HRS. One study found that up to 30% of cirrhotic SBP patients eventually develop HRS if not treated early with effective antimicrobials. It is well established that cold intravenous antibiotics (rather than per os antibiotics) with third-generation cephalosporins significantly reduce morbidity in patients and risk of renal dysfunction. Nevertheless, even with these optimal conditions for using antibiotics, we still noted that many developed HRS. Considering this, it suggests that while infection control is critical, it may not be the sole factor in preventing renal failure [13,14].

In addition, the development of HRS as a complication of SBP has a poor prognosis. The median survival in untreated patients with HRS-AKI is about two weeks and also has a poor prognosis even with supportive care including vasoconstrictors, (e.g., terlipressin), and albumin without the patient receiving a liver transplant. Therefore, the management of decompensated cirrhosis includes the prevention of SBP, and the early recognition of HRS. [15]. A retrospective study from the US, by Sigal et al,

(2007) also found SBP and a serum creatinine >1.5 mg/dL at presentation were associated with significantly higher mortality, thereby supporting the belief that renal impairment at diagnosis of an infection is a very important prognostic marker. The corresponding Spanish study by Sort et al, (1999) is well known/studied throughout the world for establishing the connection between SBP and HRS and the benefit of albumin treatment. The intravenous albumin and cefotaxime reduced HRS (33% to 10%) and mortality (29% to 10%) significantly in this randomized clinical trial of 126 patients treated with antibiotics versus those receiving cefotaxime with intravenous albumin alone. [16,17]

In a subsequent study by Singh et al. (2013) that compared outcomes related to HRS due to SBP with albumin infusion and SBP with placebo, though confirming the efficacy of albumin, the paper noted the elevated baseline proportion of patients with multidrug-resistant organisms (MDRO), which contributed in part to the efficacy of antibiotics. [18]

In a South Korean study Kim et al. (2016), which included 142 patients with SBP, AKI occurred in 44% of cases and HRS occurred in an estimated 18% of cases. The authors identified early terlipressin and albumin therapy as crucial and proposed scoring models based on creatinine, bilirubin, and infection for their predictions. [19]

In a Chinese study Wang et al. (2020) found that 38% of SBP cases were caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria, with an associated increase in HRS and treatment failure rates noted. This study suggested carbapenem-based empiric therapy for at-risk patients. [20]

Limitations:

This study is single center study with small population size and short span of study, hence its results cannot be generalized into a whole population. To get more results, a multi-center study should be done, with large population size and more duration of study.

Conflict of study: NIL

Funding: NIL

Conclusion:

In conclusion, the relationship between SBP and HRS in patients with decompensated cirrhosis is a well-established and clinically significant phenomenon. SBP acts as a major precipitant of HRS by exacerbating circulatory dysfunction and triggering inflammatory cascades that culminate in renal vasoconstriction and failure. Early recognition, prompt antibiotic therapy, and albumin infusion are the cornerstone strategies to prevent HRS and improve outcomes.

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