Original Article

Frequency of Hepatorenal Syndrome in Cirrhotic Patients Presenting with Spontaneous Bacterial Peritonitis

Rania Hidayat, Ummarah Raiz, Raees Ahmad, Muhammad Rahim, Adil Naseer and Hafizullah Khan

ABSTRACT

Objective: To determine the prevalence of hepatorenal syndrome in people who had spontaneous bacterial peritonitis and to pinpoint the important clinical and biochemical factors that are related to this condition.
Study Design: A descriptive cross-sectional study
Place and Duration of Study: This study was conducted at the Gastroenterology Unit of Ayub Teaching Hospital from March 2018 to April 2019.
Methods: 113 patients with spontaneous bacterial peritonitis were examined after being admitted to the gastroenterology unit of the Ayub Teaching Hospital. The patients were managed per department protocols for liver cirrhosis (ascites) and spontaneous bacterial peritonitis.
Results: 31 individuals (27.40%) were diagnosed with hepatorenal syndrome (HRS). In comparison to individuals with SBP who did not have HRS, patients with hepatorenal syndrome had considerably lower levels of serum sodium, 24-hour urine sodium, diastolic blood pressure, and mean arterial blood pressure, as well as significantly higher levels of serum creatinine ($p = 0.00$). Age, sex, the lack of hepatomegaly, and variceal haemorrhage were not associated ($p > 0.05$).
Conclusion: Patients with SBP often have the deadly consequence of hepatorenal syndrome. Rapid detection and treatment might lower the condition's morbidity and fatality rates.
Key Words: End-stage liver disease, SBP (ascites), Liver Cirrhosis, Hepatorenal Syndrome, Liver transplantation.

Citation of article: Hidayat R, Raiz U, Ahmad R, Rahim M, Naseer A, Khan H. Frequency of Hepatorenal Syndrome in Cirrhotic Patients Presenting with Spontaneous Bacterial Peritonitis. Med Forum 2023;34(10):114-119. doi:10.60110/medforum.341025.

INTRODUCTION

Ascites is an abnormal peritoneal fluid buildup greater than 25 ml.[1] Cirrhosis, hepatocellular carcinoma, Budd-Chiari syndrome, veno-occlusive disease, and metastatic liver disease cause more than 90% of (ascites). In 60% of liver cirrhosis patients, (ascites) is the initial sign of liver disease and develops within a decade. (ascites) development affects prognosis 40% of (ascite) patients die in the first year, and the 5-year survival rate is less than 50%. In liver cirrhosis and portal hypertension patients, ascites have a 50% 3-year death risk[2,3]. Bacterial infections and sepsis are more prevalent in individuals with ascites and liver cirrhosis, with a four-fold greater mortality risk than the general population[4].

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Received: May, 2023
Accepted: July, 2023
Printed: October, 2023

One of the most prevalent life-threatening infections in liver cirrhosis patients is spontaneous bacterial peritonitis (SBP)[5]. It is an ascitic fluid bacterial infection without a known aetiology. Ascitic fluid polymorphonuclear (PMN) leucocyte > 250 cells/mm3 indicates SBP, related to 10%-50% in-hospital mortality in liver cirrhosis patients6. Bacterial overgrowth in the intestine due to decreased motility, structural and functional impairment of intestinal mucosa, bacterial translocation, and impaired local immune system response have been linked to SBP by promoting ascitic fluid contamination and bacteremia[6,7]. SBP worsens circulatory function in cirrhotic individuals and causes bacteremia and sepsis. Portal hypertension in decompensated cirrhosis produces CO and NO, which cause splanchnic vasodilation and activate the RAAS and adrenergic systems, causing vasoconstriction and vasopression[8]. The impact is increased cardiac output and salt and water retention, facilitating significant organ perfusion.[6] SBP upsets the delicate balance between vasoconstrictors and vasodilators in cirrhotics. Toll-like receptors (TLR) (TLR-4 & TLR-2) activate monocytes, releasing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α upon recognizing bacteria and their products. High IL-6 and TNF-α levels indicate acute renal damage in SBP patients[9].

Pro-inflammatory chemicals boost CO and NO production, maximizing splanchnic circulation vasodilation. The vasoconstrictor reaction is maximized to meet splanchnic circulation's vasodilation[10]. Hepatorenal syndrome (HRS) is characterized by significant renal vascular vasoconstriction, which lowers renal perfusion, and GFR TNF-α decreases cardiac output via promoting NO production and lowering contractility[11].

The ensuing decrease in mean arterial pressure and effective circulation volume is crucial to SBP. In SBP patients with HRS, cardiac out is much lower than in those without HRS, and is "a functional renal failure in patients with (ascites) and cirrhosis" with no known cause. HRS Type-1 (rapid progression) and Type-2 (gradual start and progression) exist. Different HRS types have different clinical presentations[12]. Type 1 HRS occurs when serum creatinine doubles 20, causing acute kidney injury, while type-2 HRS occurs when serum creatinine slowly rises to more than 1.5 g/dl and is refractory.[6] Besides SBP, large-volume paracentesis without albumin infusion, haemorrhage, and infections may cause HRS[13]. Absence of hepatomegaly, high serum renin, hyponatremia, and inadequate cardiac output are further HRS risk factors. SBP patients had a 20%-30% HRS rate. The final treatment for HRS is liver transplantation. However, volume expansion and vasoconstrictors are commonly used as a bridge. High death rates characterize both kinds of hepatorenal syndrome[14]. With a median lifespan of fewer than 14 days, type-1 HRS patients seldom survive more than ten weeks. Type 2 HRS patients can exhibit diuretic resistance and live 3-6 months[15].This descriptive cross-sectional study was designed to determine the incidence of hepatorenal syndrome in our setup and identify risk factors to enable early diagnosis, management, and intervention of SBP[16].

METHODS

Advanced liver disease Hepatorenal syndrome (HRS) causes unexplained renal failure. HRS was diagnosed by removing renal failure causes as there is no test. Ultrasound showed cirrhosis with coarse liver texture, portal vein dilation above 13 mm, spleen enlargement, prothrombin time over 16 sec, and serum albumin < 50 g/dl. Without intra-abdominal infection, absolute neutrophilic count > 250/mm3 suggested SBP. Culture positive neutrocytic (ascites) had >250/mm3 absolute neutrophilic count, whereas culture negative was culture negative. Cultures of bacteria have 250/mm3 neutrophils. Type-1 HRS was named hepato-renal syndrome if serum creatinine reached 2.5 mg/dl before 14 days.18 In type-2 HRS, renal function declines.

From March 2018 to April 2019, Abbottabad's Ayub Teaching Hospital's gastrointestinal department performed this descriptive cross-sectional research. SBP cirrhotics had 25% HRS incidence, 95% confidence, and 8% absolute accuracy in 113 individuals. The research used non-probability sequential sampling. Cirrhosis and SBP individuals aged 20–60, all genders, with normal renal function were studied. The research eliminated CKD patients, cirrhotics without SBP, and both for bias reduction.

The Ayub Teaching Hospital gastrointestinal unit assessed all spontaneous bacterial peritonitis and cirrhosis patients with ethics committee permission. Families or patients consented. SBP patients on nephrotoxic drugs were checked for shock and infection. HRS was separated from acute renal impairment by urinalysis, abdomen and pelvic ultrasonography, and albumin volume expansion

MAP = DBP + ([SBP DBP] / 3) was the study participants' mean arterial pressure. Treatment followed SBP and cirrhosis departmental protocols. The 24-hour urine salt content was measured. SPSS 20 analyzed data. The frequency and percentage define categories. The mean SD defines quantitative variables. Age, gender, hepatomegaly, variceal haemorrhage, mean arterial blood pressure, and urine salt stratified SBP HRS. 5% significance post-stratification Chi-square test. ANOVA compared age, serum creatinine, urine salt content, systolic, diastolic, and mean arterial blood pressure. An independent samples t-test verified group differences.

RESULTS

The mean±SD serum creatinine level was 1.85±0.59 mg/dl in the study population. Likewise, the mean±SD mean arterial blood pressure and 24-hour urine sodium concentration were 85.65±5.49 mmHg and 6.60±2.03 mEq/l, respectively. These and other numerical variables of the study population are given in Table 1.

Hepatorenal syndrome affected 31 (27.43%) people. Hepatomegaly occurred in 37 (32.74%). The research comprised 53 men (46.90%) and 60 women (53.10%). 77 (68.14%) had upper esophageal variceal bleeding. 40 people (35.40%) had hyponatremia. Stratifying the outcome variable by age, sex, mean arterial blood pressure, variceal haemorrhage, hepatomegaly, and 24-hour urine salt content was significant.

An association was found between mean arterial blood pressure and 24-hour urine sodium concentration and hepatorenal syndrome (p=0.00) (Table 2).

An Independent sample t-test was used to examine the significance of the difference in continuous variable means between SBP patients with HRS and those without HRS. A significant difference was seen in serum creatinine, serum sodium, diastolic blood pressure, mean arterial blood pressure, and 24-hour urine sodium concentration (p=0.00) (Table 3).

Table No.1: Numerical variables of the study population.

Variable	Mean	Standard Deviation	Minimum	Maximum
Age (yrs)	44.16	7.43	31.00	56.00
Serum Sodium (mEq/l)	132.17	3.14	126.00	139.00
Serum Creatinine (mg/dl)	1.85	0.59	1.00	3.30
Systolic Blood Pressure (mmHg)	109.77	5.63	100.00	120.00
Diastolic Blood Pressure (mmHg)	73.59	7.37	60.00	88.00
Mean Arterial BP (mmHg)	85.65	5.49	76.67	98.33
24-hr Urine Sodium (mEq/l)	6.60	2.03	3.00	10.00

Table No.2: Cross-tabulation of hepatorenal syndrome with different variables

Hepatorenal syndrome	Age (yrs)		Total	p-value
	upto 44	More than 44		
Present	13.00	18.00	31.00	0.85
Absent	36.00	46.00	82.00	
Total	49.00	64.00	113.00	
Hepatorenal syndrome	Sex		Total	p-value
	Male	Female		
Present	15.00	16.00	31.00	0.85
Absent	38.00	44.00	82.00	
Total	53.00	60.00	113.00	
Hepatorenal syndrome	Mean Arterial BP		Total	p-value
	≤ 80 mmHg	> 80 mmHg		
Present	16.00	15.00	31.00	0.00
Absent	6.00	76.00	82.00	
Total	22.00	91.00	113.00	
Hepatorenal syndrome	24-hr urine sodium (mEq/l)		Total	p-value
	≤ 5	> 5		
Present	28.00	3.00	31.00	0.00
Absent	16.00	66.00	82.00	
Total	44.00	69.00	113.00	
Hepatorenal syndrome	Variceal Bleeding		Total	p-value
	Present	Absent		
Present	17.00	14.00	31.00	0.062
Absent	60.00	22.00	82.00	
Total	77.00	36.00	113.00	
Hepatorenal syndrome	Hepatomegaly		Total	p-value
	Present	Absent		
Present	10.00	21.00	31.00	0.95
Absent	27.00	55.00	82.00	
Total	37.00	76.00	113.00	

Table No.3: Independent sample t-test results

	Levene's Test for Equality of Variances			t-test for Equality of Means						
				95% Confidence Interval of the Difference						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Age (yrs)	Equal variances assumed	.00	.947	.06	111.00	.954	.09	1.57	-3.03	3.21
	Equal variances are not assumed.			.06	53.23	.954	.09	1.59	-3.09	3.27
Serum	Equal variances	.09	.770	-5.44	111.00	.000	-3.21	.59	-4.38	-2.04

Sodium (mEq/l)	assumed									
	Equal variances are not assumed.			-5.94	65.37	.000	-3.21	.54	-4.29	-2.13
Serum Creatinine (mg/dl)	Equal variances assumed	6.75	.011	29.12	111.00	.000	1.25	.04	1.16	1.33
	Equal variances are not assumed.			25.63	43.43	.000	1.25	.05	1.15	1.35
Systolic Blood Pressure (mmHg)	Equal variances assumed	16.37	.000	-.82	111.00	.415	-.97	1.19	-3.33	1.38
	Equal variances are not assumed.			-1.00	85.56	.321	-.97	.97	-2.91	.96
Diastolic Blood Pressure (mmHg)	Equal variances assumed	23.37	.000	-7.71	111.00	.000	-9.71	1.26	-12.20	-7.21
	Equal variances are not assumed.			-10.73	109.88	.000	-9.71	.90	-11.50	-7.92
Mean Arterial BP (mmHg)	Equal variances assumed	28.61	.000	-7.02	111.00	.000	-6.80	.97	-8.72	-4.88
	Equal variances are not assumed.			-9.72	109.35	.000	-6.80	.70	-8.18	-5.41
24-hr Urine Sodium (mEq/l)	Equal variances assumed	31.25	.000	-9.12	111.00	.000	-2.96	.32	-3.61	-2.32
	Equal variances are not assumed.			-12.52	108.39	.000	-2.96	.24	-3.43	-2.49

DISCUSSION

Subacute bacterial peritonitis may cause hepatorenal syndrome. Ascites and liver cirrhosis frequently produce spontaneous bacterial peritonitis, which kills over 60% of patients within a year.[7] Although the literature suggests 54% acute renal impairment, this group has variable rates[17].

HRS frequency was 27.44%, demonstrating a link to SBP. Our study found lower HRS prevalence than prior renal failure and bacterial infection investigations, including SBP. Population demographics, study technique, and sample size may explain this difference. In SBP patients, HRS is independently associated with blood bilirubin and creatinine. HRS and SBP patients showed greater blood creatinine ($p=0.00$)[17]. No serum biliruin testing.

A Karachi research identified 15% HRS in cirrhosis patients (ascites). However, 36 (47.4%) of 76 renal dysfunction patients had HRS. Despite not including SBP patients in their research, they mentioned SBP as a cause of renal impairment following HRS[18]. An Islamabad study identified HRS in 10% and renal impairment in 41% of end-stage liver disease patients. Although hepatorenal syndrome was not the study's major focus, the results advise monitoring this preventable cause of mortality in this patient population[19]. Another Karachi study reported HRS in 15% of cirrhosis patients. The study population comprised liver cirrhosis patients, not SBP patients. Men comprise about 70% of HRS patients, although our study identified no gender-specific link ($p > 0.05$)[20]. Our results match earlier studies. While HRS is common among seniors, HRS was not significantly associated with patient age. Similar discoveries in literature. Serum creatinine, diastolic blood pressure, arterial blood pressure, serum sodium concentration, and urine sodium concentration differed significantly between HRS with SBP and SBP alone. Cirrhosis often causes hyponatremia, but HRS patients had more[21]. Hyponatremia was seen at 35.40% serum sodium below 130 mEq/l42. It may reach 28% for cirrhosis and new-onset hyponatremia. This original HRS frequency study included just SBP patients. Most of our investigations assessed HRS frequency in cirrhosis patients alone or with both (ascites). We discovered no local HRS frequency study for SBP patients[22]. As a single-centre, small study with a limited sample size, these results should be interpreted carefully. Liver cirrhosis produces acute or acute-on-chronic damage more commonly than usual, including hepatorenal syndrome. Many variables, not all included in this study, cause renal failure in this

population. Future studies should incorporate as many risk factors as possible to determine hepatorenal syndrome frequency[23].

CONCLUSION

Hepatorenal syndrome is a functional renal dysfunction leading to renal failure in patients with liver cirrhosis. It is usually the result of numerous pathophysiologic processes in play in patients with cirrhosis liver that usually end in reduced renal perfusion. Therefore, it is necessary to diagnose this condition as soon as possible to allow for prompt patient population management to reduce the morbidity and, possibly, mortality associated with the disease.

Author's Contribution:

Concept & Design of Study:	Rania hidayat
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Conflict of Interest: The study has no conflict of interest to declare by any author.

Source of Funding: None

Ethical Approval: No. Nil, dated 12.02.2018

REFERENCES

1. Doğantekin A. Cirrhosis of the liver. Abdominopelvic Diseases and Emergencies 2023;2:47.
2. Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatol 2021; 74(2):1014-48.
3. Azoulay D, Ramos E, Casellas-Robert M, Salloum C, Lladó L, Nadler R, et al. Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension. JHEP Reports 2021;3(1):100190.
4. Wong F, Piano S, Singh V, Bartoletti M, Maiwall R, Alessandria C, et al. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. J Hepatol 2021;74(2):330-9.
5. Elsaid A, Mokhtar AR, Seif S, Ahmed N, El-Mashad N, Anwar R. Mini-dose albumin can reduce renal impairment in cirrhotic patients with spontaneous bacterial peritonitis. Med J Viral Hepatitis 2020;5(1):13-8.
6. Mwinyi SA, Sindato E. Diagnostic efficacy of leukocyte esterase dipstick in diagnosing spontaneous bacterial peritonitis among cirrhotic patients in tertiary hospitals, Dodoma, Tanzania. medRxiv. 2023:2023-08.
7. Di Vincenzo F, Nicoletti A, Negri M, Vitale F, Zileri Dal Verme L, Gasbarrini A, et al. Gut Microbiota and Antibiotic Treatments for the Main Non-Oncologic Hepato-Biliary-Pancreatic Disorders. Antibiotics 2023;12(6):1068.
8. Biggins SW, Angeli P, Garcia-Tsao G, Ginès P, Ling SC, Nadim MK, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatol 2021; 74(2):1014-48.
9. Chromium T. Causes of Kidney Disease in Patients with Liver Disease. National Kidney Foundation Primer on Kidney Diseases, E-Book 2022;6:295.
10. Aly RH, Ahmed AE, Hozayen WG, Rabea AM, Ali TM, El Askary A, et al. Patterns of toll-like receptor expressions and inflammatory cytokine levels and their implications in the progress of insulin resistance and diabetic nephropathy in type 2 diabetic patients. Frontiers Physiol 2020; 11:609223.
11. Jung CY, Chang JW. Hepatorenal Syndrome: Current Concepts and Future Perspectives. Clinical Molecular Hepatol 2023;4.
12. Ginès P, Solà E, Angeli P, Wong F, Nadim MK, Kamath PS. Hepatorenal Syndrome. Nat Rev Dis Primers 2018;4:23.
13. Flamm SL, Brown K, Wadei HM, Brown Jr RS, Kugelmas M, Samaniego-Picota M, et al. The current management of hepatorenal syndrome–acute kidney injury in the United States and the potential of terlipressin. Liver Transplantation 2021;27(8):1191-202.
14. Xu XY, Ding HG, Li WG, Xu JH, Han Y, Jia JD, et al. Chinese guidelines on managing liver cirrhosis (abbreviated version). World J Gastroenterol 2020;26(45):7088.
15. Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. BMJ 2020;7;370.
16. Hayward KL, Weersink RA. Improving medication-related outcomes in chronic liver disease. Hepatol Communications 2020;4(11): 1562-77.
17. Marciano S, Diaz JM, Dirchwolf M, Gadano A. Spontaneous bacterial peritonitis in patients with cirrhosis: incidence, outcomes, and treatment strategies. Hepatic Med : Evidence Res 2019;1: 13-22.
18. Rey RM, Delgado AF, De Zubiria A, Pinto R, De la Hoz-Valle JA, et al. Prevalence and short-term

outcome of hepatorenal syndrome: A 9-year experience in a high-complexity hospital in Colombia. PLoS One 2020;15(10):e0239834.

19. Tinti F, Umbro I, D'Alessandro M, Lai S, Merli M, Noce A, et al. Cholemic nephropathy is the cause of acute and chronic kidney disease. Update on an under-diagnosed disease. Life 2021;11(11):1200.
20. Fida S, Khurshid SM, Mansoor H. Frequency of hepatorenal syndrome among patients with cirrhosis and outcome after treatment. Cureus 2020;12(8).
21. Di Iorio BR, Bellasi A, Raphael KL, Santoro D, Aucella F, Garofano L, et al. Treatment of metabolic acidosis with sodium bicarbonate delays progression of chronic kidney disease: the UBI Study. J Nephrol 2019;32:989-1001.
22. Qaiser MA, Baig MA, Syed IA, Shah SH, Butt N, Najmi F. Severity of hyponatremia and its influence on various complications of decompensated chronic liver disease. Pak J Med Health Sciences 2022;16(11):878.
23. Kulkarni AV, Ravikumar ST, Tevethia H, Premkumar M, Kumar K, Sharma M, et al. Safety and efficacy of terlipressin in acute-on-chronic liver failure with hepatorenal syndrome-acute kidney injury (HRS-AKI): a prospective cohort study. Scientific Reports 2022;12(1):5503.