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Comparison of Clinico-Epidemiological Profile in Hepatitis C Patients with and without Spontaneous Bacterial Peritonitis

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Abstract

Introduction: Chronic HCV infection is a serious public health concern worldwide. In Pakistan, its prevalence has been reported as 4.7%. An estimated 20%-25% cases of hepatitis C results into cirrhosis. The collection of free fluid in peritoneal cavity is known as ascites and an important complication of advanced cirrhosis that sometimes gets complicated by Spontaneous Bacterial Peritonitis (SBP). Present study was designed to compare the clinico-epidemiological profile in hepatitis C patients with and without SBP.

Methodology: A cross sectional comparative study was conducted in the Department of Gastroenterology, Pakistan Institute of Medical Sciences, Islamabad. Study duration was one year from January 2020 to December 2020. Adult patients 18 to 65 years of age and both genders with established diagnoses of liver cirrhosis secondary to hepatitis C and those having moderate to severe ascites were included. The study was approved by hospital ethics committee and written informed consent was taken. SPSS version 21.0 was utilized to enter and analyze data.

Results: Of total 73 cases, 38 (52.05%) were male with male/female ratio of 1.1:1. The mean age was 56.45 ± 9.71 years. There were 30 (41.1%) patients with positive for SBP. In SBP group major clinical presentations were jaundice 27 (90%), fever 24 (80.0%), abdominal pain and tenderness 22 (73.3%), tachycardia 13 (43.3%), hepatic encephalopathy 11 (36.7%) and HRS in 8 (26.7%). It was noted that in SBP group, fever, abdominal pain and tenderness were significantly greater than in the non-SBP group (P<0.05).

Conclusion: SBP was found in significant percentage of patients who had HCV related CLD. Fever, abdominal pain and tenderness were significantly higher in SBP group.

Keywords: Hepatitis C; Clinical features; CLD; Spontaneous bacterial peritonitis

Introduction

Acute/chronic hepatitis, liver cirrhosis and hepatocellular carcinoma can be caused by Hepatitis C Virus (HCV). Chronic HCV infection is becoming a serious public health concern worldwide and the risk of progressive CLD is expected to rise considerably in the coming decades. The prevalence of chronic HCV infection varies worldwide and figures between 0.1% to 12% have been reported [1].

In Pakistan, the Hepatitis C Virus (anti HCV) prevalence was reported 4.7% in a "National General Population Survey" by WHO conducted from 2007 to 2008. The sero-prevalence of hepatitis C ranges from 2.2% to 13.5% in various regions of Pakistan during the last 5 years. The highest prevalence of HCV reported from Lahore and Jamshoro/Mardan, 13% and 9% respectively [2]. An estimated 20%-25% cases of hepatitis C results into cirrhosis, which is characterized by diffuse destruction and regeneration of hepatic parenchymal cells with ultimate disorganization of lobular architecture. The collection of free fluid in peritoneal cavity is known as ascites and an important complication of advanced cirrhosis that sometimes gets complicated by Spontaneous Bacterial Peritonitis (SBP).

SBP, as an entity, was first documented by Conn in 1964. It is defined as an abrupt beginning of acute bacterial peritonitis irrespective of any 4 seemingly course of infection in the abdomen. High rates of mortality 20%-40% have been reported due to CLD with ascites complicated by SBP [3]. The exact etiology of SBP is not known, though bacterial translocation is considered as main cause. The reported prevalence of SBP's among cirrhotic hospitalized cases with ascites is about 10% to 30% [4]. The prognosis is considerably better if diagnosis is made

earlier and prompt treatment is initiated. The culture is positive and if ascitic fluid has PMN count about ≥ 250 cells/mm^3 and there is no secondary cause of infection, then a diagnosis of SBP is confirmed. Approximately 10%-60% of patients with clinical presentation of SBP have negative ascitic fluid cultures [5]. An empiric use of antibiotic therapy is usually recommended in such cases [6].

Ceftriaxone, a third-generation cephalosporin, has been reported as effective therapy against almost all organisms isolated from SBP patients except bacteriodes fragilis and enterococcus faecalis, which are rarely predisposing organisms [7]. Prophylactic antibiotics (Norfloxacin 400 mg BD) are recommended for patients who have high risk of developing SBP like patients with upper GIT bleed. Norfloxacin 400 mg OD is also being recommended in patients with prior history of SBP. The definite treatment of SBP is liver transplantation and antibiotics are given until the surgery. Long-term use of antibiotics is recommended for patients in whom transplantation is contraindicated [5].

Present study was designed to compare the clinic-epidemiological profile in hepatitis C patients with and without SBP. Limited data on this particular subject was available at both local and national level. It is expected that data collected will help the physicians in the better management of these patients that will eventually reduce the related morbidity and mortality.

Methodology

This cross sectional comparative study was conducted in the Department of Gastroenterology, Pakistan Institute of Medical Sciences, Islamabad. Study duration was one year from January 2020 to December 2020. Adult patients 18 to 65 years of age and both genders with established diagnoses of liver cirrhosis secondary to hepatitis C and those having moderate-severe ascites (diagnosed clinically and on ultrasonography) were included in the study. The patients with a history of antibiotics use in past 10 days, patients with history of hypersensitivity to penicillin or cephalosporins, pregnant women and those with other chronic medical conditions like diabetes mellitus, hypertension and ischemic heart disease were excluded from the study.

The study was approved by hospital ethics committee at Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Pakistan Institute of Medical Sciences (PIMS), Islamabad. Patients, who were admitted from the OPD and emergency department for various complications of portal hypertension and cirrhosis, were selected and enrolled who meet the study criteria.

The study information was gathered on a specifically designed structured proforma. History and clinical data regarding abdominal pain/tenderness, jaundice, hepatic encephalopathy, hematemesis, melena and fever were obtained. Venous blood samples were drawn for blood count, serum bilirubin, serum albumin, prothrombin time. Ascitic fluid was tapped and analyzed in the laboratory at PIMS hospital for cell count, polymorph nuclear cells and protein. The patients were classified as a positive case of SBP on the basis of these investigations. Child Pugh class of the patients was determined on the basis of ascitic fluid, hepatic encephalopathy, serum bilirubin, serum albumin and prothrombin time to evaluate the severity of chronic liver disease.

The sample size was calculated using a sample calculator using confidence level of 95%, anticipated population proportion with SBP of 37.1% and assumed precision of 12% [4]. The study sample size was 73 patients who were enrolled using non-probability based consecutive sampling technique. SPSS version 21.0 was utilized to enter and analyze the collected data. Quantitative variables of the study were age, ascitic fluid analysis, serum bilirubin, serum albumin, prothrombin time were presented as mean and standard deviation. The categorical variables of the study were gender, Child Pugh classification, SBP, abdominal pain/tenderness, jaundice, hepatic encephalopathy, hematemesis, melena, fever and study outcome were analyzed as frequency and percentages. The clinical manifestations like fever, jaundice, abdominal distension/ascites, hepatic encephalopathy, melena/hematemesis, hypotension, abdominal pain and nausea/vomiting, *etc*. and epidemiological profile like frequency of SBP were compared among hepatitis C patients with or without SBP using chi-square test for categorical and student t-test for quantitative variables. A p-value of <0.05 considered significant.

The study outcomes were judged in terms of clinical and epidemiological presentation of hepatitis C patients with or without SBP.

Results

Out of the total 73 study patients, 38 (52.05%) were male and 35 (47.95%) were females, the male/female ratio was 1.1:1 and the mean age was 56.45 ± 9.71 years with established diagnoses of liver cirrhosis secondary to hepatitis C. There were 30 (41.1%) patients having positive for SBP as per study operational definition. In the SBP group, 15 (50%) cases were in CTP class C, 13 (43.3%) in CTP class B and 2 (6.7%) in CTP class A **(Table 1)**.

Table 1: Demographic characteristics in the study (n=73).

	No of cases	**%Age**
Gender		
Male	38	52.0%
Female	35	48.0%

Age (years)		
Mean ± SD	56.45 ± 9.71	
Type of peritonitis		
SBP	30	41.1%
Non-SBP	43	58.8%

The biochemical parameters in both groups are tabulated in **Table 2**. All the SBP's cases had the mean MELD score of 20.8 ± 8.6 on admission. The mean ascitic TLC was 2310.5 ± 2766.7/ cm^3, the mean neutrophils counts was 1706.8 ± 2318.6/cm^3 the mean lymphocytes count was 710.4 ± 703.5/cm^3 and the mean LDH concentration was 257.4± 157.7 IU/dL which were considerably raised in SBP group (P<0.05). No other significant difference noted. The reason for higher ascitic total protein in Non SBP group then SBP group is the higher number of CTP class C cases (62.8% *vs.* 50.0%) respectively **(Table 2).**

Table 2: Baseline MELD score and biochemical parameters in both groups.

	SBP (n=30) (mean ± SD)	**Non-SBP(n=43)** (mean ± SD)	
Meld Score	20.8 ± 8.6	21.4 ± 7.6	0.736
Ascitic TLC (/uL)	2310.5 ± 2766.7	231.1 ± 267.5	<0.001
Lymphocytes (/uL)	710.4 ± 703.5	160.1 ± 214.7	<0.001
Ascitic neutrophils (/uL)	1706.8 ± 2318.6	69.6 ± 69.2	<0.001
Peripheral TLC (/uL)	10436.7 ± 7431.6	7731.4 ± 4228.1	0.052
Ascitic protein (g/dL)	1.4 ± 1.1	0.8 ± 0.5	0.004
Ascitic glucose (mg/dL)	109.1 ± 58.8	111.6 ± 56.1	0.565
Ascitic LDH (IU/dL)	257.4 ± 157.7	105.3 ± 65.6	<0.001

The study results showed that in SBP group major clinical presentations were jaundice 27 (90%), fever 24 (80.0%), abdominal pain and tenderness 22 (73.3%), tachycardia 13 (43.3%), hepatic encephalopathy 11 (36.7%) and HRS in 8 (26.7%). Comparatively, in non SBP group major clinical presentations were jaundice 35 (81.4%), hepatic encephalopathy 29(67.4%), abdominal pain and tenderness 23 (53.5%), fever 17(39.5%), tachycardia 18(43.3%) and HRS 10(23.3%). It was noted that in SBP group, fever, abdominal pain and tenderness were significantly greater than in the non-SBP group (P<0.05). No other significant difference was noted in clinical features of patients **(Table 3)**.

Table 3: Clinical presentation pattern in both groups.

	Groups		**p-value**
	SBP (n=30)	**Non-SBP (n=43)**	
Abdominal pain tenderness	22 (73.3%)	23 (53.5%)	0.086
Hematemesis melena	3 (10.0%)	8 (18.6%)	0.312
Abdominal distension ascities	30 (100.0%)	43 (100.0%)	
Jaundice	27 (90.0%)	35 (81.4%)	0.312
Hypotension	1 (3.3%)	0 (0.0%)	0.228
Hepatic encephalopathy	11 (36.7%)	29 (67.4%)	0.009
Fever	24 (80.0%)	17 (39.5%)	<0.001

Tachycardia	13 (43.3%)	18 (43.3%)	
HRS	8 (26.7%)	10 (23.3%)	0.592
Chills	1 (3.3%)	3 (6.9%)	0.501

Discussion

Spontaneous Bacterial Peritonitis (SBP) is considered as a frequent complication in cirrhotic and ascitic patients, it is a highly fatal complication. This study was planned to relate the clinic-epidemiological profile in hepatitis C patients with and without SBP, because limited data is available at local and national level regarding these patients.

In this study a total of 41.1% patients were positive for SBP while remaining were negative. Previous local data also revealed a similarly high incidence of SBP with variable reports. A study from KP witnessed 25.1% SBP patients [8]. Another study from Ghana witnessed 21.4% cases of SBP [9]. Similar, data has been witnessed in this region as well. A study from Bulgharia reported SBP in almost 14.9% of their patients [10]. Another study from Saudi Arabia reported 29.6% patients diagnosed with SBP [11]. Another study reported in-hospital SBP frequency of 8% to 27.0% [12]. Other reports from western world show a significantly lower frequency of SBP and most of the data ranges between 7% to 30% cases per annum [13]. Jarcuska, et al. assessed incidence of SBP, in 169 cirrhotic patients and witnessed 16.0% patients with SBP [14]. These variable report on SBP incidence show a growing trend in regions and countries where hepatitis is more common and resultantly chronic liver conditions are more frequent.

In this study, though no significant difference was witnessed regarding gender, Child Pugh classification and mean MELD score between SBP and non-SBP patients. But the frequency of SBP was high in the CTP class C in SBP group. The incidence rate of SBP is not equal in the CLD patients in different region of the world.

In the current study the frequency of fever, abdominal pain and tenderness and tachycardia were significantly higher in SBP group and the frequency of hepatic encephalopathy was substantially elevated in non-SBP group ($P<0.05$). The reason of high PSE in non-SBP group is the higher number of PSE's patients which were compared to the SBP Group. No other significant difference was noted ($P>0.05$).

Comparatively, different studies reported various frequencies of clinical features. A study from Peshawar reported abdominal pain, tenderness, fever, jaundice and hepatic encephalopathy as significant clinical manifestations of SBP [15]. In a study conducted in Abbottabad, abdominal tenderness was present in 80.7% and abdominal pain in 73.1% and splenomegaly in 76.9% of SBP patients [16]. These local studies have witnessed higher frequency of abdominal pain, tenderness, fever, jaundice and hepatic encephalopathy. The study from KP has documented tenderness, jaundice, abdominal pain, hepatic encephalopathy and fever in SBP patients [8]. Western studies have reported fever in 67.5% to 75% patients, abdominal pain in 51.5% and abdominal tenderness in 53% of SBP patients [17,18]. The classical features of patients with CLD and SBP are quite similar; however, their proportion may vary from region to region and community to community.

In the present study the investigational findings showed that mean ascitic TLC, lymphocytes, neutrophils and LDH was considerably higher in SBP group than those in non-SBP group ($P<0.05$). The study results are comparable with other studies conducted either locally or internationally [19]. In a case control study by Talaat, et al. conducted in 45 ascitic patients secondary to cirrhosis and SBP, had considerably high PMN neutrophil count and LDH level, whereas total proteins, glucose and albumin level markedly decreased in SBP group than non SBP group [20]. The corner stone for the SBP diagnosis was high ascitic fluid neutrophil count. On the other hand, the risk factors for SBP were low protein and albumin concentration in the ascitic fluid, while ascitic fluid glucose could be consumed by bacteria during uncontrolled infection. Another study by Danulescu, et al. reported that bilirubin and creatinine were considerably raised in SBP patients, and total protein, albumin and prothrombin time level decreased significantly in patients with SBP, hepatic impairment correlated with the degree of biochemical parameters and may be considered risk factors for SBP [21].

The study by Schwabl, et al. assessed and found independent risk factors of Child-Pugh stage C, ascitic fluid PMN count and decreased serum sodium for development of SBP [22]. It is well known that in patients with chronic liver disease and SBP the biochemical profile becomes very compromised and based on these results, the resultant mortality may be assumed. Evidence suggests that at least 50% of the patients with SBP do not survive and die eventually and recurrence of SBP is also very high and then resultant mortality is similar after a second episode of the condition [17,18].

Older studies have even witnessed 80% to 100% lethality associated with SBP, which was mainly due to poor treatment opportunities and dearth of efficacious antibiotics. However, the recent trials have reported quite better outcomes and witnessed 20%-40% mortality due to timely diagnosis and treatment [23]. The SBP is diagnosed on the basis of cell count of PMN's neutrophils in the ascitic fluid. Diagnostic paracentesis should also be conducted together with PMN's count in ascites among all cases when they admit in the hospital or when patients condition become worsen in advance cirrhosis or sudden increase in ascites. If the number and sum of PMN's in ascitic fluid are "≥ 250 cells/ml", a positive culture report has no significance, SBP is diagnosed and treatment should be initiated [24]. This suggests that the continuous monitoring of patients with chronic liver diseases, cirrhosis and ascites may prove as a

preventive measure due to timely diagnosis and management of severe cases such as SBP.

The current study has many advantages, firstly, this is one first of its type in the local settings. The frequency of hepatitis and chronic liver diseases is on the rise in the country and region, evidence regarding its repercussions in terms of ascites and SBP are an added advantage for the management and diagnosis of these patients and healthcare workers alike.

Conclusion

SBP was found in significant percentage of patients who had HCV related CLD in this study. Major clinical presentation was similar in SBP and non-SBP patients. However, fever, abdominal pain and tenderness were significantly higher in SBP group while hepatic encephalopathy was the major presentation in non-SBP group.

It is recommended that all cirrhotic patients with detectable ascites should undergo for routine ascitic examination to rule out SBP.

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