Impact of Spontaneous Bacterial Peritonitis and Cellulitis on Outcome of Cirrhosis and Effect of Early Intervention on The Prognosis- A Prospective Cross-Sectional Study.

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ABSTRACT

Background: Spontaneous bacterial peritonitis and cellulitis are the two major prevalent infections in cirrhotic patients and responsible for morbidity and mortality. The present study was aimed to evaluate the burden of these two infections in cirrhotic patients.

Materials and Methods: This prospective study was conducted in 120 cirrhotic patients at a tertiary hospital in Chennai. The patients were divided into three groups, SBP group including 57 patients, Cellulitis group including 58 patients and Common group including 5 patients with both infections.Time of hospitalisation and antibiotics therapy intiation, Site of cellulitis (upper limb, lower limb, scrotal), per abdomen examination for ascites and tenderness was noted. Laboratory investigations containing complete blood count (CBC), liver function test (LFT), international normalized ratio (INR), renal function test (RFT), Alpha feto protein, HBsAg, anti HCV, ultrasound

abdomen, upper gastrointestinal endoscopy, ascitic fluid analysis, polymorphonuclear neutrophil count, wound, blood and ascitic fluid cultures were analysed.Prognostic scores like CTP (Child Turcott Pugh) and MELD (Model for End stage Liver Disease) was calculated. Interventions done like debridement, albumin injection, terlipressin injection, need for hemodialysis etc. also were analysed. The obtained data was analysed using Student's T-test and Chi-square test.

Results:The study reports revealed comparable incidence and male preponderance. Out of 120 total patients, 22 died (18.33%) during the course of hospitalization. Mortality was 13 in the SBP group (22.8%), 6 in cellulitis group (10%) (p- 0.055)and 3 in combined infection group (60%).

Conclusion:In this study, spontaneous bacterial peritonitis has shown more mortality and,the prevalence of SBP and cellulits were comparable in cirrhotic patients.

Keywords: *Cirrhosis, Model for End stage Liver Disease, Child Turcott Pugh.*

INTRODUCTION

Cirrhotic patients are more prone to serious bacterial infections.[1] These infections precipitate decompensation of cirrhosis and thus lead to increased morbidity and mortality.[2] The increased incidence of infections in cirrhotic patients is due to the defect in immune system.[3- 6] Cellulitis and spontaneous bacterial peritonitis (SBP) are one of the major bacterial infections seen in cirrhosis. Others are urinary and respiratory tract infections. Once infection develops, the excessive response of pro-inflammatory cytokines on a preexisting hemodynamic derangement in cirrhosis further facilitate the development of severe complications such as septic shock, acute-on-chronic liver failure (ACLF), multiple organ failure, and death.[5]

The prevalence of cellulitis and SBP in cirrhosis is 10.5-12.5% and 10-30% respectively.[7,8] These infections account for around 9% of hospitalisations in patients with cirrhosis.[8] When in a cirrhotic patient, new decompensation occurs, infection should be suspected.[9] Factors which affect and drive outcome of infective episode are not modifiable. So, the only two factors which can be modified to improve the outcome are timely diagnosis, early and appropriate choice of first line antibiotic therapy.[10]The present study is intended to study the microbiological profile whenever feasible in these infections, impact of early *versus* late presentation to the hospital and early *versus* late antibiotic initiation on the outcome of hospitalized patients.The primary objective of the study is to quantify burden of spontaneous bacterial peritonitis and cellulitis in cirrhosis. The secondary objectives include clinical profiling of these infections and to assess likely outcome of early *versus* delayed intervention.

MATERIALS AND METHODS

This prospective cross sectional study was conducted in the Department of Medical Gastroenterology, Sri Ramachandra Institute of Higher Education and Research, Chennai. One hundred twenty patients admitted with cirrhosis during the study period (January 2018 – January 2020) in the department of medical gastroenterology who met inclusion and exclusion criteria were enrolled for the study. All the eligible subjects were recruited into the study consecutively until the sample size was reached. There was no invasive procedure or radiation exposure to the patients as a part of this study. All the investigations carried out was a part of the routine evaluation of cirrhotic patient. No extra or hidden cost was incurred on the patient as a part of the study. The institutional human ethics committee had approved the study.

All patients either new or diagnosed as cirrhotic and got admitted at SRIHER hospital during January 2018 to January 2020 were included in the study. The other inclusion criteria were; age >18 years, Patients with suspicion of cellulitis or spontaneous bacterial peritonitis on clinical grounds.Patients with other source of infection (e.g. lung, kidney etc.), Pregnancy, Hepatocellular carcinoma or other

malignancy, Patients on immunosuppressants or on chemotherapy, less than 1 year of life span due to various co morbidities were excluded from the study.

The diagnosis of cirrhosis of the liver was based on clinical presentation, imaging (heterogenous echotexture of the liver with an irregular outline or presence of portosystemic collaterals), laboratory (low serum albumin, aspartate aminotransferase/alanine aminotransferase ratio>1), endoscopic findings (> grade 2 oesophagal varices) and previous liver histology were evaluated.All cirrhotic patients either new or diagnosed cases admitted at SRIHER during January 2018 to January 2020 were enrolled. Detailed history of the patients was taken from the case sheets available at records room. History of present and past events of complications of cirrhosis like upper GI bleed, hepatic encephalopathy, ascites, kidney injury was documented. History of other co morbidities like diabetes, hypertension, HIV, hepatitis B, hepatitis C, chronic kidney disease, liver transplantation, kidney transplantation etc. was obtained. History of symptoms like abdominal pain, lower limb pain, swelling, redness, fever was recorded. Time of presentation to hospital from symptom onset (<7 days *versus*>7days) and when antibiotics were started (within 48 hours *versus* after 48 hours of hospitalization) and length of hospital stay were recorded. Detailed clinical examination as available from records pertaining to general examination, signs of liver cell failure, presence or absence of hepatic encephalopathy were noted. Site of cellulitis (upper limb, lower limb, scrotal), per abdomen examination for ascites and tenderness was noted.Laboratory investigations containing complete blood count (CBC), liver function test (LFT), international normalized ratio (INR), renal function test (RFT), Alpha feto protein, HBsAg, anti HCV, ultrasound abdomen, upper gastrointestinal endoscopy, ascitic fluid analysis, polymorphonuclear neutrophil count, wound, blood and ascitic fluid cultures were documented.

Prognostic scores like CTP (Child Turcott Pugh) and MELD (Model for End stage Liver Disease) was calculated from available blood parameters and culture reports (blood, urine, ascitic fluid) whenever available were documented. Interventions done like debridement, albumin injection, terlipressin injection, need for hemodialysis etc. also were documented.

The primary end point isto find prevalence of these infections in cirrhosis in our setup and to find predominant type of infection and causative organism. The secondary end points are impact of early *versus* late presentation to hospital on clinical outcome, impact of early *versus* late initiation of antibiotics on clinical outcomes, burden of individual and combined infection on the natural history of cirrhosis.

Statistical Methods

Descriptive analysis was carried out by the mean and standard deviation for quantitative variables, N and proportion for categorical variables.For normally distributed Quantitative parameters the mean values were compared between both groups using Independent sample t-test (2 groups). Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.)P value < 0.05 was considered statistically significant.MedCalc version 12.5.0 was used for statistical analysis.

RESULTS

A total of 554 patients were admitted with cirrhosis of liver during the study period, out of which 57 patients fulfilled the criteria as having SBP, 58 patients fulfilled the criteria for cellulitis and 5 patients had both infections. So, a total of 120 patients were taken for the analysis. The SBP group patients had a mean age of 50.43 ± 11.12 years and were predominantly male (91%). In the cellulitis group (n=58), patients had a mean age of 52.55 ± 10.94, were predominantly male (98%). In the combined infections group (n=5), patients had a mean age of 51.80 ± 7.94 years, were all male (100%), predominant etiology of chronic liver disease was alcohol (60%), 60% had single comorbidity, majority (60%) had presented

late (after 1 week) to the hospital after symptom onset, antibiotics were started early in 80% of patients and all (100%) had either single or multiple complications of cirrhosis (Figure 1).
The biochemical parameters in the SBP group showed mean total count of 12567 ± 8894/cu.mm, mean platelets were 0.96 ± 0.48/cu.mm, mean PT INR was 2.28 ± 0.56, mean serum bilirubin was 7.99 ± 8.22 mg/dl, mean serum albumin was 2.31 ± 0.44 g/dl and mean serum creatinine was 1.86 ± 1.80 mg/dl. In the cellulitis group, mean total count was 10150 ± 6960/cu.mm, mean platelets were 1.10 ± 0.65/cu.mm, mean PT INR was 1.71 ± 0.43, mean serum bilirubin was 5.44 ± 6.22 mg/dl, mean serum albumin was 2.25 ± 0.52 g/dl and mean serum creatinine was 1.58 ± 1.53 mg/dl. In the combined infections group, mean total count was 14400 ± 5170/cu.mm, mean platelets were 0.93 ± 0.40/cu.mm, mean PT INR was 2.10 ± 0.36, mean serum bilirubin was 9.53 ± 4.93 mg/dl, mean serum albumin was 2.34 ± 0.70 g/dl and mean serum creatinine was 1.52 ± 0.63 mg/dl (Table 1).
Majority of the patients in SBP group were in class C (70%), in cellulitis group they were in class B (53%) followed by class C (43%) and in Common infections group, all patients (100%) were in class C. Mean MELD score in SBP group was 26.8 ± 8.4, in cellulitis group was 23.2 ± 5.9 and in combined infections group was 30.8 ± 4.8. The patients in the SBP group had presented with predominant symptoms of abdominal distension followed by abdominal pain, pedal edema and fever. Whereas patients in the cellulitis group had presented predominantly with pedal edema followed by limb pain and fever. Common infection group had mixture of both the symptoms (Table 1).
In deceased patients, mean age of the deceased patients was 50.59 ± 13.74 years. In hospital mortality in SBP, cellulitis and combined infections group was 22%, 10% and 60% (p-0.055). Presence of other comorbidities did not have major impact on prognosis. 7 out of 73 patients (9.5%) died who presented early (within 1 week) to the hospital whereas 15 out of 47 patients (32%) died when they presented late to the hospital (p- 0.0045). 13 out of 103 patients (12%) died in the early antibiotic initiation group whereas 9 out of 17 patients (53%) died in delayed antibiotic initiation group (p- 0.0003). No mortality was seen in patients with no additional complications of cirrhosis whereas 2 out of 43 patients (4%) died who had single complication and 20 out of 39 patients (51%) died who had more than one complications of cirrhosis (p- <0.0001). Twenty patients out of 22 who died were in CTP class C (p- <0.0001). Mean MELD of deceased and recovered patients was 32.86 ± 7.95 and 23.49 ± 6.17 respectively (p- <0.0001). Other interventions in the form of either albumin alone or albumin with terlipressin, hemodialysis or debridement was done in total of 35 out of 120 patients (29%). 11 patients out of 22 received one or more form of interventions in the deceased group as compared to recovery group in which 24 patients received interventions (p- 0.78).

Table 1: Patient Characteristics and Study Parameters

Patient Characteristics		**SBP (n=57)**	**Cellulitis (n=58)**	**Common (n=5)**	**P value**
Age (years)		50.4 ± 11.1	52.55 ± 10.94	51.80 ± 7.94	0.01**
Gender	**Male**	52	57	5	0.9**
	Female	5	1	0	
Etiology	**Alcohol**	41	31	3	0.06**
	Hepatitis B	6	8	-	0.8**
	NASH	9	17	2	0.12**
	Autoimmune	1	1	-	0.9**
	Wilson's disease	-	1	-	0.3**
Comorbidities	**None**	33	20	2	0.02**
	Single	15	18	3	0.7**

	Multiple	9	20	0	0.04**
Presentation	**Within 1 wk**	34	38	2	0.01**
	After 1 wk	23	20	3	
Antibiotics started	**Within 48 hr**	48	52	4	0.03**
	After 48 hr	9	6	1	
Other complications of cirrhosis	**None**	14	29	0	0.008**
	Single	26	14	1	0.02**
	Multiple	17	15	4	0.8**
Total counts (cu.mm)		12567 ± 8894	10150 ± 6960	14400 ± 5170	0.35*
Platelets (cu.mm)		0.96 ± 0.48	1.10 ± 0.65	0.93 ± 0.40	0.2*
PT INR		2.28 ± 0.56	1.71 ± 0.43	2.10 ± 0.36	0.6*
S. Bilirubin (mg/dl)		7.99 ± 8.22	5.44 ± 6.22	9.53 ± 4.93	0.8*
Albumin (mg/dl)		2.31 ± 0.44	2.25 ± 0.52	2.34 ± 0.70	0.1*
Creatinine (mg/dl)		1.86 ± 1.80	1.58 ± 1.53	1.52 ± 0.63	0.01*
CTP	**A**	0	2	0	0.5**
	B	17	31	0	0.01**
	C	40	25	5	0.006**
MELD Na		26.8 ± 8.4	23.2 ± 5.9	30.8 ± 4.8	0.01*
Culture	**Blood**	7	9	2	0.8**
	Pus	0	21	3	0.0001**
	Ascitic fluid	7	0	1	0.01**
Symptoms	**Abdominal distension**	57	0	0	0.0001**
	Abdominal pain	27	0	0	0.0001**
	Fever	9	19	2	0.05**
	Limb pain	0	31	5	0.0001**
	Pedal edema	15	58	5	0.005**

Comparison was done between SBP group and cellulitis group. *, P value obtained with student's t-test.**, P value obtained with Chi-square test.

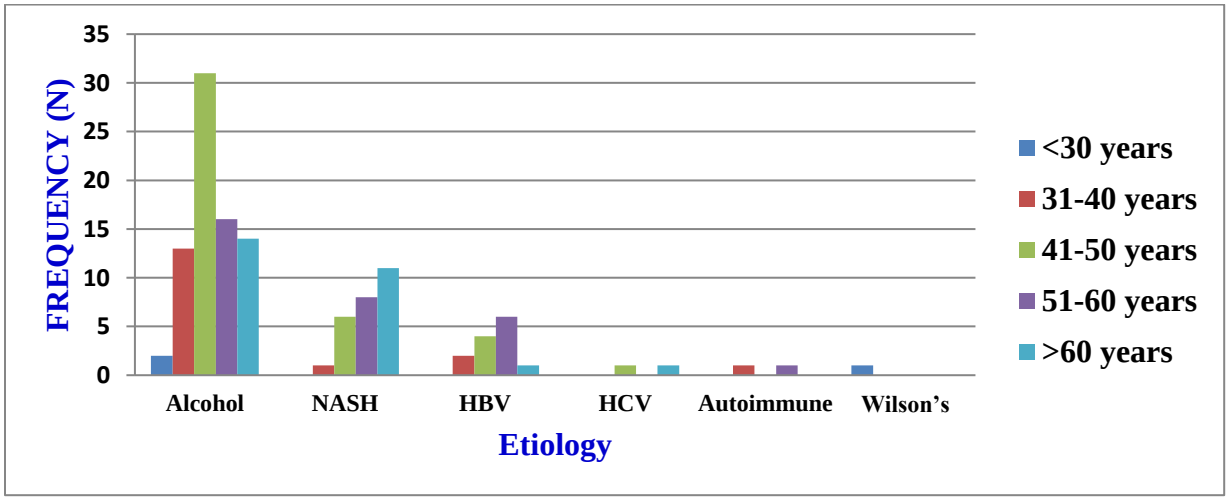

Figure 1: Etiology and age groups.

DISCUSSION

The prevalence of SBP in patients admitted with cirrhosis is found to be 10.24% in this study. It is similar to the previous studies done so far where prevalence is reported to be between 10-30%.[11-15] The prevalence of cellulitis in this study is found to be 10.46%. Studies from India and across the world have reported the prevalence to vary between 6.7 and 21%.[16-21]

Ascites was seen in all patients, abdominal pain in 47%, fever in 15.8% and pedal edema in 26%. Mihas *et al*,[22] reported fever in 54% and abdominal pain in 57%. In the study by Amarapurkar DN *et al*,[23]abdominal pain was the predominant symptom (16%) followed by fever (13%) and encephalopathy (6%). Cirrhosis being an immunocompromised state may have masking of some symptoms like fever, so patients do not always have the classical signs and symptoms of SBP. Asymptomatic SBP is been described in various clinical studies. Predominant presentation in cellulitis group was pedal edema, seen in all, limb pain in 53% and fever in 33% which is comparable to study done by Raff A. B. *et al*,[24] who reported fever in 22.5% to 77.3%. In a study by Rooby Erachamveettil Hamza *et al*,[21] pedal edema was commonest in 77% followed by leg pain and redness in 46% and fever in 26%.

Mean age of SBP patients in this study was 50.43 years with male predominance (91%) which is comparable with previous studies.[21, 22, 25]Predominant etiology of chronic liver disease in SBP group in the present study is alcohol (72%) followed by NASH (16%) and hepatits B (10%) and in cellulitis group it is alcohol (53%) followed by NASH (29%) and hepatitis B (14%). This was in concordance with other studies.[12, 16-18, 26-28]

In this study of 120 patients, amongst 57 SBP patients, 40 (70%) were in CTP class C and in 58 cellulitis patients, 25 (43.1%) were in CTP class C and in combined infection group 100% patients were in CTP class C which is consistent with other studies.[23, 29, 30] One important finding from this study was a statistically significant association of a higher MELD score with infections. The risk of bacterial infections increases in patients with moderate to high MELD scores. This may indicate that MELD score can be used as a tool in predicting the development of SBP and other infections and its association with mortality. This was also seen in other studies.[21,23, 31-35]

Cultures (blood and pus) was positive in 30 out of 58 cellulitis patients (52%). Predominant organism found in ascitic fluid in this study was *E.coli*(87%) followed by *K.pneumoniae*. In pus culture also predominant organisms isolated were E.coli (41%) followed by K.pneumoniae (29%) and coagulase negative staphylococcus (12.5%). In a study by Filik L &Unal S (2004),[25]ascitic fluid culture positivity was 25.4% with gram negative organism being most frequent isolate (76%). In a study by Jain *et al*,[17] predominant organism isolated in cellulitis patients was E.coli (46%) followed by K.pneumoniae (31%) which is comparable to findings of this study.

The characteristics of deceased group in this study were in line with other studies.[23, 25]In this study age >60 years, delayed presentation to the hospital, late initiation of antibiotics, serum creatinine >1.5 mg/dl and MELD Na >30 were associated with higher mortality. In a study by Nobre S R *et al*, mortality was higher with mean age of 66 years *versus* 59 years. In 22 deceased patients, 20 patients had etiology of alcohol with one death in NASH and hepatitis group each (4.5%). High mortality was found in alcohol related chronic liver disease patients having SBP.[26]In a study by Andreu M *et al*,[11] alcohol was most common etiology in SBP patients which is comparable to the present study. In a study by Mayank Jain *et al*,[17] predominant etiology of bacterial skin infections including cellulitis was alcohol and mean age of the deceased patients in this study was 50.1 year both of which are comparable to the present study. Similar results on etiology and mortality was found in study by Sood A *et al*,[18]In the present study, early presentation to the hospital (within 1 week) was associated with better in hospital outcome and mortality. Also, early initiation of broad- spectrum antibiotics within 48 hours of admission was associated with mortality benefit (p- 0.0003). In a review by Chalermrat Bunchorntavakul*et al*,[36] early presentation and

early initiation of antibiotics were better survival predictors in hospitalized cirrhotic patients. Song K H*et al*, also concluded in his study that early initiation of broad-spectrum antibiotics before culture and sensitivity report was associated with survival benefit.[37]Presence of other complications of cirrhosis like hepatic encephalopathy, UGI bleed, acute kidney injury, hepatorenal syndrome, septicemia etc. were associated with increased in- hospital mortality and strongest association was found for hepatic encephalopathy, septicaemia and kidney injury. Presence of more than one complication also increased the mortality (51%) in the present study.Total counts more than 14000, elevation of prothrombin time >10 seconds, serum creatinine >2mg/dl and serum albumin below 2.5 gm/dl were significant predictors of in-hospital mortality in the present study. In a study by Liu BM (28) serum creatinine > 1.5 mg/dl, serum albumin < 2.5 gm/dl and prothrombin time prolongation > 5 seconds were predictors of mortality. Jain M also concluded that mortality was more in infected cirrhotic patients with serum albumin of <= 2.2 g/dl as opposed to albumin > 2.4 g/dl.[17] Sood A*et al*, in his study noted that the mortality group had statistically significant high total counts, creatinine and PT INR which is consistent with the present study.[18]The reason for this finding is probably the advanced immunocompromised status in cirrhotic patients who have infections, poor hepatic reserve making them more prone for infections and thus in turn building poor immune response to the infections. Mohan P*et al*, also reported higher mortality when serum albumin was < 2.5 g/dl.[16]

Mortality was higher in Child's class C as compared to class B or A. The Mean MELD was significantly higher in deceased group. Child class C was single most predictor of mortality in the study done by Liu BM *et al*.[28] In study by Jain M *et al*,[17] mean MELD score was higher in expired patients as compared to recovered group. The Sood A*et al*,[18] also reported higher CTP score and MELD score amongst nonsurvivors *versus* survivors in cirrhotic patients having skin infections. These findings in all studies and also in the present study is due to the finding that patients with advanced liver disease have more bacterial translocation making them more prone for bacterial infections and mortality due to advanced nature of the disease and due to poor immune function.[1,3]Other interventions in the form of albumin, terlipressin, dialysis and debridement although reduced hospitalization, failed to yield statistically significant impact on mortality. In a study by Nobre *et al*,[26] lower risk of renal dysfunction and mortality was observed in SBP patients who received albumin at day 1 and day 3. The reason for this may be due to more baseline albumin (2.5g/dl) in the study subjects as compared to low albumin of 2.2 g/dl in study by Nobre *et al*,[26] resulting in better overall clinical picture and less severity. Also, patients in the present study received early interventions within mean of 2 days of hospitalization which may have resulted in better outcomes.

Majority of the deaths was in SBP group and due to predominant E.coli organism. This reflects that septicaemia in a cirrhotic patient is the single most important predictor of mortality. Mortality in patients with pus culture positivity and with ascitic fluid positivity of these patients had associated blood culture positivity too, emphasizing that septicaemia is the major driver of mortality in local infections also. In a study by Song K H*et al*,[37] infection with extended spectrum beta lactamase E.coli was associated with higher mortality at 7 and 30 days of hospitalization. In the same study, patients with bacteremia and septic shock were twice as likely to die as compared to those who didn't have septicaemia.

LIMITATION

One of the limitations of our study was a smaller sample size. This led to a small number of patients in certain subgroups like only 5 patients were in combined infection group. Observations were collected from inpatients of a tertiary care centre, the sample may not exactly represent the general population of cirrhotic patients. Even though the number is small, the statistical significance suggests that the association is relevant.

CONCLUSION

The prevalence of SBP and cellulitis was comparable between SBP group and cellulitis group, and less in common group having both infections. The mortality burden of spontaneous bacterial peritonitis was high in cirrhotic patients in comparison to cellulitis patients. The delayed hospitalization and intervention have shown high mortality.

CONFLICT OF INTEREST

None

FUNDING SOURCE (S)

Nil

ACKNOWLEDGEMENT

Nil

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