

Evidence to the Empirical: A Novel Clinical Score to Predict Spontaneous Bacterial Peritonitis (SBP) in Patients of Chronic Liver Disease Using Ascitic Fluid (AF) Appearance, Symptoms & Severity of Cirrhosis

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1. Abstract

1.1. Background and objectives: Ascitic fluid cell count is definitive to diagnose SBP. Timely availability of cell count is crucial, especially in peripheral setting. Study aims to identify reliable predicting factors and to arrive at a five point Novel Non- invasive clinical score for SBP in CLD which in turn provides evidence to justify empirical use of antibiotics in these high risk patients before availability of AF analysis reports.

1.2. Methodology: A prospective observational cohort study, enrolling 75 CLD patients with ascites was conducted. Baseline characteristics were noted; Logistic regression modeling was used to identify the best predictors for the presence of SBP. A combination of 5 predictive variables including the Opaque AF appearance, presence of tense ascites and pain abdomen, CTP grade C and MELDS scores ≥ 14 , was embraced to formulate a score for prediction of SBP in cirrhotics. ROC curve used to select cutoff points for MELDS and CHILD scores and to assess the performance of the score.

1.3. Result: Out of 75 patients, 37 patients had SBP. Above factors were found to have a significant relation with presence of SBP as Chi Square P value was < 0.05 . The score ranges from 0-5 points, with 0 showing least and 5 depicting the highest probability of an existing SBP in the cirrhotic patients. For confirmation AF cell counting was done.

1.4. Conclusion: A CLD patient with presenting with tense ascites, pain abdomen, and opaque AF with advanced cirrhosis can be started on broad spectrum antibiotics without waiting for AF analysis reports.

2. Keywords: Novel Non- invasive score; SBP (spontaneous bacterial peritonitis); ascitic fluid (AF); MELD score; Child status; chronic liver disease

3. Introduction

Development of ascites is an important part in the natural history of cirrhosis of liver. It in fact has prognostic significance. But development of SBP in this normally sterile ascetic fluid is something that raises our concerns, being a significant cause of morbidity and mortality. SBP is the most common life threatening complication in ascitic patients [1]. The incidence of SBP in patients with cirrhosis varies from 7 to 30% per year [2, 3]. Mortality rate even after a single episode 20- 40% [4, 5]. SBP by definition is a monomicrobial infection of ascitic fluid with an indeterminate source [6]. Bacterial overgrowths, deterioration of intestinal barriers and changes in local immunity are the suspected factors in pathogenesis of SBP. These factors combined together can help transfer the microorganisms into the mesenteric lymph nodes and further into the ascitic fluid leading to peritonitis [7, 8]. Our knowledge of ascitic fluid albumin levels and its co-relation with development of SBP is well proven [9].

Clinically SBP is characterized by development of fever with chills and pain abdomen. Presence of rebound tenderness over abdomen and absence of bowel sounds is a noticeable feature. Full blown

syndrome is often not present and sometimes presentation may be only as fever or hypothermia or may be encephalopathy or even unexplained deterioration without any other obvious symptom [10-12].

Ascites fluid analysis forms cornerstone of diagnostic work up. It includes gross examination, cell count, cell differentiation, protein, albumin analysis and finally the cultures. On gross inspection the ascitic fluid from a patient with SBP can be clear, milky, bloody or opaque in appearance [9, 13]. Milky also known as chylous ascites suggest presence of chylomicrons and can be due to trauma, malignancy, infection or cirrhosis. Cloudy or Opaque appearance of ascites known as pseudo-chylous ascites is indicative of peritonitis, pancreatitis or perforated bowel. Bloody ascites is generally seen in cases of malignancies or trauma [14-16].

Long-term prognosis of patients having SBP is poor although early diagnosis helps in adequate treatment of the current episode [17]. Timely initiation of therapy reduces the burden of disease to a great extent. Sincere efforts have been made in recent years to develop alternative tests to help identify the condition sooner rather than later. From presentation to having ascitic fluid analysis report in hand takes considerable time, especially in our part of the world. At this time the stage of cirrhosis being early or advanced, patient's clinical features and the appearance of ascitic fluid can help us to arrive at a definitive diagnosis at an early stage. And we can control the loss of precious time and can start antibiotics in an evidence based way.

Our study is one such attempt to correlate existing data and factors to aid the diagnosis and help starting treatment on the earliest possible hour, for the betterment of the patients.

4. Materials and Methods

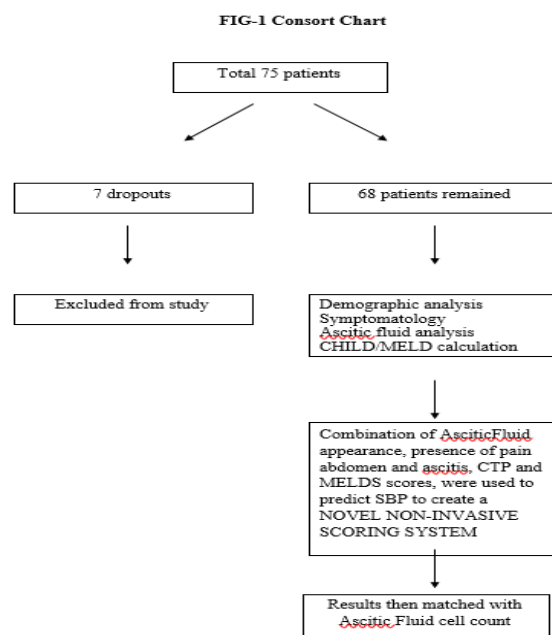
A prospective observational cohort study was conducted over a period of 8 months on patients of chronic liver disease with ascites. 75 patients were included in the study. Sample size was calculated as per the no. of eligible patients, admitted in the hospital between Nov 2018 and June 2019. Patients of any gender 18 to 75 years of age having a confirmed diagnosis of chronic liver disease with ascites were included in the study. Patients with ascites due to any other cause except chronic liver disease and patients already on prophylaxis for SBP were eliminated from the study. Patients of age less than 18 years and more than 75 years were also excluded. Written informed consent from the patients was taken before data collection was done and patient's details were recorded in a preformed Performa. Individual parameters including demographic details, history of presenting illness, symptoms and signs etc. were recorded. Baseline characteristics were noted, and ascitic fluid sampling was done for investigations including ascitic fluid cell count and differential, total protein, albumin and sugar. Assessment of severity of disease was done using Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores.

Within 2 hours of admission the ascitic fluid sample was withdrawn

and sent for analysis. Antibiotics were given only after obtaining the sample. Logistic regression modelling was used to identify the best predictors for the presence of SBP. The primary outcome i.e. SBP was considered a dependent variable and various potential predictive variables were selected from the known risk factors for development of SBP. For clinical plausibility and practical issues the predictive variables were converted to binary variables as follows: tense ascites (present or absent), pain abdomen (present or absent), AF appearance (opaque or otherwise), CHILD Grade (A/ B Or C) and MELD Score (<14 or ≥ 14). For selecting the Cutoff point as 14 and between A/B and C in MELD and CHILD scoring system respectively, Youden's Index was applied after plotting the ROC curve. The statistical analysis was conducted using Graph pad and Microsoft excel. Chi square test and unpaired t tests were used for analysis of the collected data. A P value <0.05 was considered significant in both the tests.

Finally a combination of 5 predictive variables was embraced to formulate a five point Novel Non- invasive score for prediction of SBP in cirrhotics including the Opaque AF appearance, presence of tense ascites and pain abdomen, CTP grade C and MELDS scores ≥ 14 , wherein presence of each predictive variable is allotted 1 point and absence as 0 point. The scale ranges from 0-5 points, with 0 showing least and 5 depicting the highest probability of an existing SBP in the cirrhotic patients. For confirmation of diagnosis, AF cell count was done with, more than 250 PMN or 500 WBC per cubic millimeter of ascitic fluid was considered as presence of SBP. The process has been summarized in Consort Chart (Figure 1).

ETHICAL CONSIDERATIONS: The study was conducted after obtaining ethical clearance from institutional ethical committee. Written informed consent from the patients was taken before data collection was done. Below shown is the CONSORT CHART.



5. Results

The study was started with 75 patients, showing amale predominance with 60 males and 15 females, shown in (Figure 2). Complete data for only 68 patients could be tracked, so the 7 drop outs were not included in the results. All patients were suffering from chronic liver disease with ascites due to various etiologies and the most common cause was identified as alcoholic liver disease, as shown in (Figure 3). Out of these, diagnosis of SBP was confirmed in 37 patients while 31 patients did not show any evidence of SBP. Commonly encountered symptoms included fever, pain abdomen, nausea, vomiting and altered sensorium. Detailed assessment of no of patients showing various symptoms is shown in (Table 1). On analyzing the presence of pain abdomen among the group of patients with SBP and those without SBP, 34 out of 37(92 %) patients with SBP had pain abdomen, while only 4 patients without SBP complained of pain abdomen. This was assessed significant on basis of CHI Square Test as the P value was less than 0.0001, making it statistically significant. It is shown in (Table 2). Another clinical factor we assessed was presence of fever, but no conclusive relationship could be established between SBP and fever, as shown in Table -2. Assessment of the presence or absence of ascites in patients with SBP also showed a positive correlation with P value being 0.0002 on basis of CHI Square Test, making it statistically significant, this is also shown in Table-2.

On assessment of the Co-relation of Ascitic fluid color with SBP among the group of patients with SBP and those without it, appearance of AF was opaque for 14 patients with SBP, while no patient without SBP reported to have opaque colored AF. This was again assessed using CHI Square Test and the P value observed was less than 0.0001, making it statistically significant. It is shown in Table-2.

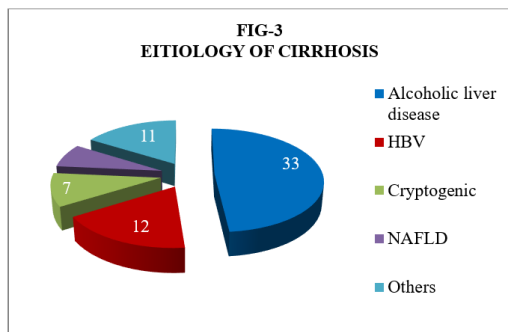
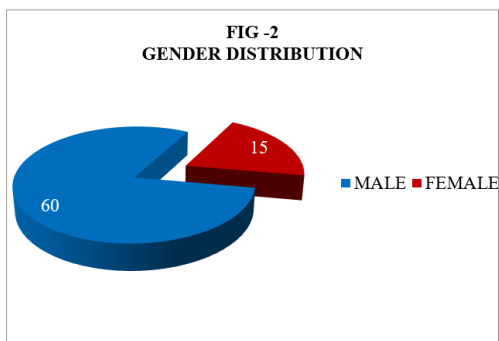


TABLE -1
Symptom analysis of patients

Symptom	Number of patients
Pain abdomen	38
Nausea	25
Vomiting	10
Fever	6
Altered sensorium	3
Others	12

Table -2
Co-relation of various Predictive variable with SBP

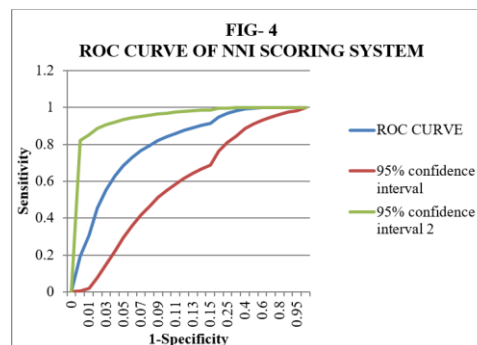
Predictive variable	No. of patients with SBP	No. of patients without SBP	Total	Test applied	
Fever	Present	4	2	6	CHI Square Test: P value equals 0.5279, not statistically significant.
	Absent	33	29	62	
Pain abdomen	Present	34	4	38	CHI Square Test: P value is less than 0.0001, statistically significant.
	Absent	3	27	30	
Ascitic fluid color	Opaque	14	0	14	CHI Square Test: P value is less than 0.0001, statistically significant.
	Straw /Clear/ Red	23	31	54	
Tense Ascitis	Present	34	16	50	CHI Square Test: P value is 0.0002, statistically significant.
	Absent	3	15	18	
MELD SCORE	≥14	36	20	56	CHI Square Test: P value is 0.0007, statistically significant.
	<14	1	11	12	
CTP SCORE	CTP A/ CTP B	9	24	33	CHI Square Test: P value is less than 0.0001, statistically significant.
	CTP C	28	7	35	

When assessment of the grade of liver cirrhosis in correlation with presence of SBP was done, it was observed that mean MELD score of patients with SBP was higher at 19.5676 +/- 4.4630 compared with patients without SBP having a lower MELD score of 14.3214 +/- 3.6823. This was assessed using unpaired t test and was found to be statistically significant, with P value being less than 0.0001. This is depicted in (Table 3). The analysis of CTP scores, also showed a positive correlation with the P value being less than 0.0001 on basis of CHI Square Test, making it statistically significant, this is also shown in Table -2. The ROC curve of the scoring system in determining the presence of SBP yielded an AUC of 0.9479 (Estimated std. error = 0.0275) (Figure 4). The performance of the NNI Scoring System is shown in Table 4.

Table -3
Co-relation of MELD score with SBP

	No. of patients	MELD SCORE (Mean +/- SD)	STATS
With SBP	37	19.5676 +/- 4.4630	Unpaired t test: p-Value =less than 0.0001.
Without SBP	28	14.3214 +/- 3.6823	

SD: Standard deviation



6. Discussion

SBP is a grave consequence in the natural history of liver cirrhosis. Keeping in mind the higher mortality and morbidity a high index of suspicion is essential to identify the cases early [18]. Prompt initiation of therapy improves patient outcome with less of *Acute Kidney Injury* (AKI), and other complications of SBP [19]. Our study had 75 participants in the beginning; including 60 males and 15 females. Complete data for only 68 patients could be tracked, so the 7 drop outs were not included in the analysis. Patients ranged from 18 to 75 years in age; with the mean age of the participant's being 45.656 ± 10.368 . All patients were suffering from chronic liver disease with ascites due to various etiologies. The most common cause was identified as alcoholic liver disease; this is also substantiated by another similar study done by Vemuganti S et al [1]. Spontaneous bacterial peritonitis an established life threatening complication of cirrhosis with ascites, has not only been reported with alcoholic cirrhosis, but also in other conditions such as post-necrotic cirrhosis, chronic active hepatitis, Nephrotic syndrome, Cardiac cirrhosis, malignant ascites and primary biliary cirrhosis [1]. Out of 75 patients included in our study, diagnosis of SBP was confirmed in 37 patients while 31 patients did not show any evidence of SBP.

Presenting symptoms included fever, pain abdomen, nausea, vomiting and altered sensorium. On assessment of the symptoms, presence of pain abdomen was noted in 92 % patients with SBP, this was assessed significant on basis of CHI Square Test represented in Table 2. A study of Spontaneous bacterial peritonitis by Vemuganti Sushanth et al showed that more than 50% of their patients of SBP complained of pain abdomen [1]. Supporting the findings that pain abdomen has a significant relationship with SBP. Another symptom assessed was fever, but no conclusive relationship could be established between SBP and fever, as only few patients with SBP complained of fever, it is represented in Table-2.

On assessment of the presence of tense ascites and theco-relation of Ascitic fluid colour with SBP, using CHI Square Test, a significant association could be seen with opaque coloured ascetic fluid, depicted in table-2. A study on diagnostic efficacy of ascites fluid gross appearance in detection of spontaneous bacterial peritonitis by Hamed Aminiahidashiti, shows clear coloured AF is less frequently observed with SBP, but AF alone has poor diagnostic value [8].

Through our study assessment of the grade of liver cirrhosis in correlation with presence of SBP was also done, it was observed that mean MELD score of patients with SBP was higher with mean being >18 and was assessed to be statistically significant using unpaired T test. This is depicted in table -3. A MELD score ≥ 14 and CTP grade C scores were also noted to have a significant correlation with occurrence of SBP on the basis of CHI Square Test, results depicted in table-2. Similar results were also observed in a study by Thiele GB et al [20], reporting MELD scores higher than 19 in patients with

SBP. Supporting our results is another study by Mounzer R et al. which also reported that patients of SBP had higher MELD and CTP scores [21].

On the basis of all these observations our study presents a five-point NOVEL NON INVASIVE SCORING SYSTEM combining 5 best predictive variables namely; opaque AF appearance, presence of tense ascites and pain abdomen, MELDS scores ≥ 14 and CTP grade C for prediction of SBP in cirrhotics. The ROC curve of the score is shown in Fig-3 and the performance of the score showing sensitivity and specificity pertaining to each score is depicted in (Table 4).

Score	No.of patients	Sensitivity	specificity
0	5	1	0
1	11	0.9998	0.16
2	11	0.9856	0.52
3	14	0.8398	0.81
4	15	0.509	0.93
5	12	0.131	1

Our study concludes that NNI scoring system can be an effective tool to decide whether a particular cirrhotic patient with ascites has SBP or not. Timely initiation of therapy has proven benefits for outcome of the patients. Ascitic fluid analysis is time consuming and complete battery of test availability is also an issue which needs to be addressed. This has more importance for the registered cirrhotic patients in a developing country like ours where Ascitic fluid analysis facility is not available especially in the peripheral regions and timely initiation of prophylaxis can be the only thread between life and death. Hence we are justified in starting empirical parenteral antibiotics in cirrhotic patients on the basis of the NNI score and general condition of the patient.

Nevertheless, the study still has several limitations. First and foremost, the sample size was relatively small as it was restricted by no. of patients first time presenting to the hospital with acites to us over the duration of the study. Also the medications taken prior to the admission might have affected the results to some extent. A multicentre, well-designed study with larger group of patient is recommended, keeping our study as bedrock for further development and research in this area.

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