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Original Article

Evaluation of Serum C-Reactive Protein in Diagnosis of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis of Liver and Ascites

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Abstract

Spontaneous Bacterial Peritonitis (SBP), an infection of ascitic fluid without demonstrable intra-abdominal origin and it is a complication of cirrhosis of liver, with a reported mortality of 30% to 50% in adults. The counts of polymorphonuclear leucocytes (PMN) in ascitic fluid ≥ 250/mm² demonstrably confirms the diagnosis of SBP and the patients immediately need treatment with antibiotics irrespective of culture results. Serum C- reactive protein (CRP) is a reliable predictor of SBP and a marker that can be measured in several laboratories. The aim of this study was to estimate serum C-reactive protein levels as a diagnostic tool for evaluation of SBP in patients with liver cirrhosis and ascites. This cross-sectional study was conducted among 90 adult patients diagnosed as cirrhosis of liver with ascites in the Department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka during the period November 2017 to March 2019. Half of the patients were at their productive age (≤30 to 50 years) and others were above 50 years with mean age of 50.5 years; where male female ratio was about 2.5:1. The study found that more than one-fifth (21.1%) of the patients had SBP positive (SBP group) and their mean serum CRP was found 84.59±39.66mg/L; on the other hand rest of the patients were SBP negative (non-SBP group) with mean serum CRP was 15.02 ± 18.34 mg/L. The mean total WBC count and neutrophil count in ascitic fluid were found 2565 ± 3439/mm³ and 1255 ± 1708/mm³ in SBP patients; where 178 ± 149/mm³ and 46 ± 38/ mm³ in non-SBP patients respectively. At the serum CRP cut-off level of 41.5 mg/L, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 89.5%, 94.4%, 81% and 97.1% respectively. In the diagnosis of SBP based on PMN 2250/mm³, the accuracy of the test result was 93.3% and based on ascitic fluid culture results it was 78.9%. It is vital to assess the utility of CRP in diagnosis of SBP in cirrhosis of liver with ascites. At the optimal cut-off level of 41.5 mg/L, the serum CRP value had the good sensitivity (89.5%), specificity (94.4%), and AUC-ROC (0.969) in diagnosis of SBP. Large scale analytical studies on cirrhotic patients with ascites are encouraged to establish the optimum cut-off value of CRP for the diagnosis of SBP.

Keywords: *CRP, cirrhosis of liver, spontaneous bacterial peritonitis*

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INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is defined as an infection of ascitic fluid without a proven intra-abdominal source of infection.[3, 18, 25, 33] Spontaneous bacterial peritonitis (SBP) is an important cause of morbidity and mortality in cirrhosis of liver with ascites. According to studies, the prevalence of SBP in patients with cirrhosis varies from 7% to 30% per year.[1,23,29,69-88,90] In another study the prevalence of SBP in hospitalized patients with liver cirrhosis and ascites was high, ranging between 10% and 30%.[106] In-hospital mortality rates from SBP range between 30% and 50%, but a rapid detection and treatment of this disease leads to significant reduction in the mortality rate to less than 10%.[49] The typical presentation of SBP are fever and generalized abdominal pain.[45] or may lead to the development of hepatic encephalopathy and renal failure.[68] The SBP is suspected

in patients with liver cirrhosis and ascites when they present with symptoms such as acute abdominal pain, fever, and/or altered mental status. However, some patients may be asymptomatic and the SBP is detected by diagnostic paracentesis and study of the ascitic fluid after admission to the hospital for another reason like hematemesis, melena, hepatorenal syndrome and/or hepatic encephalopathy.[12,13]

Hepatic dysfunction results in impaired defenses against bacteria, and associated with structural and functional modifications in the intestinal mucosa that result in an increase in the permeability to bacteria and bacteria-derived products, which worsens over time as the disease progresses.[9]

SBP occurs when a bacterial infection spreads to the ascitic fluid through the gut wall or lymphatics but less commonly via hematogenous spread in absence of a recognized intra- abdominal source of bacterial infection or malignancy.[112] SBP is a major complication of liver cirrhosis and ascites and is considered the most frequent bacterial infection in patients with liver cirrhosis.[19]

SBP is diagnosed on the basis of ≥250 polymorphonuclear leukocytes (PMN) /mm^3 of ascitic fluid irrespective of a positive ascitic fluid culture results and an absence of intra-abdominal source of infection[100] and to begin antibiotics without waiting for culture report.[56,1,23,29,69-88,90] This valid diagnostic tool of SBP has high false negative results.[53] This procedure is operator-dependent, lysis of PMNs can occur during transport to the laboratory, and that explains the presence of false-negative results. Ascitic fluid culture is less sensitive and this conventional method detects bacteria in only 42%-65% of patients[1,23,29,69-88,90] and also time consuming. Alternative methods using automated PMN counting,[11] reagent strips (urine dipsticks),[50] or ascitic lactoferrin[53] have been developed; unfortunately, their diagnostic accuracies are limited and their use depend on availability of laboratory personnel and reagents from the commercial source.[67]

Some authors reported that serum C-reactive protein (CRP) level may also be used as an alternative test for the diagnosis of SBP. CRP is an acute phase reactant which binds to different substrates. It activates the complements, takes part in cytokine secretion, and increases the phagocytic activity of leucocytes. Serum CRP level has been reported to be a reliable predictor of SBP.[55] This marker is one of the most common clinical and inflammatory indicators that can be measured in any laboratory.[52,95] High serum levels of CRP in children with SBP were found [61] and serum CRP was a useful marker in the early detection of SBP with high sensitivity and high negative predictive value.[101] Conventional diagnosis of SBP by detecting the number of PMN in ascitic fluid is laborious and operator dependent having inter-observer variation. Serum CRP is a cheap, relatively noninvasive, simple to perform and can be measured in any laboratory. Some studies from different countries also mentioned that serum CRP had high sensitivity and specificity for early diagnosis of SBP.

MATRIALS AND METHODS

This cross-sectional study was conducted among 90 adult patients who were admitted in the Gastroenterology Department, BSMMU, Dhaka and diagnosed as cirrhosis of liver with ascites during the period November 2017 to March 2019. Ethical clearance was obtained from Institutional Review Board (IRB), BSMMU. Both written and verbal consent were taken from patients prior to enroll into the study. Diagnosis of cirrhosis was confirmed from clinical, laboratory and ultrasonographic findings. Their clinical history, examination and initial investigation report was noted in the standard data sheet. Blood samples were send for complete blood count, prothrombin time, serum creatinine, albumin, bilirubin, liver enzymes and serum CRP. Quantitative CRP was measured by the automated analyzer, Beckman Coulter-AU680. Abdominal paracentesis was done under all aseptic precautions. Laboratory analysis of the ascitic fluid was performed without delay including total and differential cell counts, total protein levels and culture sensitivity test. PMN cell count was performed by a traditional hematological method with an optical light microscope in a manual counting chamber. This method is presently considered the "gold standard" for the evaluation of ascitic fluid PMN count (Riggio *et al.*, 2009). Ten (10) ml of ascitic fluid sample was inoculated in blood culture bottles at bedside for culture and sensitivity test. Diagnosis of SBP was based on PMN cell count ≥250/mm^3 in ascitic fluid irrespective of a positive ascitic fluid culture result. The values of serum CRP were compared with asctic fluid PMN count, ascitic fluid culture results and both. All the tests were done at department of biochemistry, department of clinical pathology and department of microbiology of BSMMU, Dhaka, Bangladesh.

Data processing and analysis:

Statistical analysis of the results being obtained by using windows based computer software devised with Statistical

Packages for Social Sciences (SPSS) version 22. After compilation, data were presented in the form of tables, figures and charts, as necessary. Numerical variables were expressed as mean and standard deviation, whereas categorical variables were counted with perc Categorical variables were analyzed by Chi-squa Significance of CRP in SBP was done by Mann Whi test. Fisher's exact test was done for significance of among SBP patients. Validity test was done to calcul diagnostic utility of CRP in diagnosing SBP. P value than 0.05 was considered statistically significant.

RESULTS

This cross-sectional study was conducted in the Department of Gastroenterology, BSMMU, Dhaka, from November 2017 to March 2019. A total of 90 cirrhotic patients with ascites were included in this study.

Table I shows age-group distribution of patients with cirrhosis of liver and ascites, it was observed that 30% of the patients belongs to age 51-60 years, the mean age of patients was 50.5 years with SD of ±14.3 years. The age range of the patient was from 19 to 95 years.

Table- I: Distribution of the study patients according to age group (n=90)

Age (years)	Frequency (n)	Percentage (%)
≤30	8	8.9
31 - 40	18	20.0
41 - 50	19	21.1
51 - 60	27	30.0
>60	18	20.0
Mean ± SD (years) (Age range)	50.5 ± 14.3(19-95)	

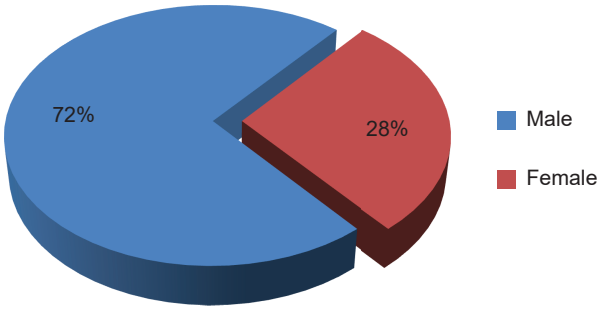

Figure 1: Pie chart showing sex distribution of the patients.

Figure- 1 illastrates the distribution of sex of the patients, it was observed that 72% of theme were male and the male female ratio was about 2.5:1.

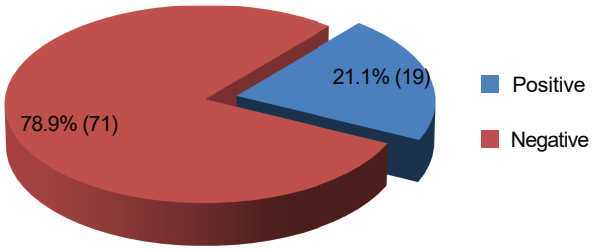

Figure 2: Pie chart showing distribution of patients with SBP positive and negative cases.

Figure- 2 shows the distribution of patients with SBP, among the patients, it was observed that 21.1% of the patients were SBP positive.

Table II shows presenting complaints of SBP patients. It was observed that 15(78.9%) had fever, 15(78.9%) had abdominal pain, 3(15.8%) SBP patients were presented with altered level of consciousness, one (5.3%) presented with haematemesis and 3(15.8) were presented with melena and 10.6% had SBP without any symptom.

Table- II: Presenting complaints of the SBP patients (n=19)

Presenting illness	Spontaneous bacterial peritonitis (SBP) Positive (n=19)
Fever	15 (78.9%)
Abdominal pain	15 (78.9%)
Altered level of consciousness	3 (15.8%)
Haematemesis	1 (5.3%)
Malaena	3 (15.8%)
Asymptomatic	2 (10.6%)

Table- III states the distribution of underlying causes of cirrhosis among the patients, 68.9% of the patient were related to chronic hepatitis B virus infection. Among the positive cases of SBP 15 (78.9%) and among the negative cases 47(66.2%) had had chronic hepatitis B virus infection. Among the patients 10 (11.1%) were related to chronic hepatitis C infection and none them had SBP.

Table III: Underlying cause of cirrhosis of liver of the study subjects (n=90)

	Spontaneous bacterial peritonitis (SBP)	
Causes of cirrhosis	Positive (n=19) (%)	Negative (n=71) (%)
HBV	15 (78.9)	47 (66.2)
HCV	0 (0.0)	10 (14.1)
Wilson's disease	0 (0.0)	1 (1.4)
NASH	0 (0.0)	1 (1.4)
Cryptogenic	4 (21.1)	12 (16.9)

Table IV shows clinical examination findings of the study patients, it was observed that 16 (84.2%) patients in SBP group and 59 (83.1%) in non-SBP group had anemia. There were 14 (73.3%) patients in SBP group and 53 (74.6%) patients in non-SBP group had leukonychia. There were 14 (73.7%) patients in SBP group and 44 (62.0%) patients in non-SBP group had palmar erythema. Other findings are shown in the table below.

Table IV: Clinical examination findings of the study patients (n=90)

General examination	Spontaneous bacterial peritonitis (SBP)		
	Positive (n=19)	Negative (n=71)	p-value
Anaemia	16 (84.2)	59 (83.1)	1.000#
Jaundice	7 (36.8)	16 (22.5)	0.241#
Leukonychia	14 (73.7)	53 (74.6)	1.000#
Clubbing	1 (5.3)	0 (0.0)	0.211#
Palmar erythema	14 (73.7)	44 (62.0)	0.343*
Spider	7 (36.8)	12 (16.9)	0.119#
Gynaecomastia	7 (36.8)	29 (40.8)	0.752*
Oedema	5 (26.3)	20 (28.2)	0.873*
Palpable liver	2 (10.5)	5 (7.0)	0.636#
Palpable spleen	5 (26.3)	25 (35.2)	0.465*
Testicular atrophy (male)	12 (75.0)	29 (40.8)	0.255*

*Chi-square test and #Fisher's Exact test was done to measure the level of significance

Table VI shows the culture result of the ascitic fluid of the study patients. There were 19 patients with SBP among them 2(10.5%) patients were culture positive and 17(89.5%) patients with SBP were culture negative. Of the two patients with culture positive SBP, one was *E. coli* and another was positive for *Klebsiella species*. The culture results were significant among the SBP patients (p=0.043).

Table- VI: Spontaneous bacterial peritonitis (SBP) according to ascitic fluid culture report (n=90)

Culture	Spontaneous bacterial peritonitis (SBP)		
	Positive (n=19) (%)	Negative (n=71) (%)	p-value
Positive	2 (10.5)	0 (0.0)	0.043s
Negative	17 (89.5)	71 (100.0)	

s= significant
Fisher's Exact test was done to measure the level of significance

Table VII shows the sensitivity and specificity of CRP at different level. At a cut-off value of 41.5 mg/L, the serum CRP value had optimal sensitivity of 89.5% and optimal specificity of 94.4% and the Youden's Index was 0.83. In this study patients had taken serum CRP of 41.5 mg/L as cut-off value.

Table- VII: Sensitivity and specificity of CRP at different serum level diagnosis of SBP in study patients (n=90)

Serum CRP (mg/L)	Sensitivity (%)	Specificity (%)	Youden's Index
36.34	89.5	85.9	0.754
37.24	89.5	87.3	0.768
37.90	89.5	88.7	0.782
38.40	89.5	90.1	0.796
39.90	89.5	93.0	0.824
41.50	**89.5**	**94.4**	**0.838**
44.29	84.2	94.4	0.786
48.42	84.2	95.8	0.800

Table VIII shows the validity test results of serum CRP at a cut off level of 41.5 mg/L in the diagnosis of SBP by ascitic fluid PMN count, which shows the sensitivity of 89.5%, specificity of 94.4%. The positive predictive value was 81% and negative predictive value was 97.1%. The accuracy of the test result was 93.3%.

Table- VIII: Validity test of CRP at a cut off value of 41.5 mg/L in diagnosis of SBP by ascitic fluid PMN count in study patients (n=90)

Validity Indices	%	95% CI	
		Min	Max
Sensitivity	89.5	70.5	98.0
Specificity	94.4	89.3	96.6
PPV	81.0	63.8	88.6
NPV	97.1	91.9	99.4
Accuracy	93.3	85.3	96.9

PPV= Positive Predictive Value
NPV= Negative Predictive Value

Table IX shows the validity test results of serum CRP at a cut-off level of 41.5 mg/L in the diagnosis of SBP by ascitic fluid culture, which shows the sensitivity of 100%, specificity of 78.4%. The positive predictive value was 9.5% and negative predictive value was 100%. The accuracy of the test result was 78.9%.

Table- IX: Validity test of CRP at a cut off value of 41.5 mg/L in diagnosis of SBP by ascitic fluid culture in study patients (n=90)

Validity Indices	%	95% CI	
		Min	Max
Sensitivity	100.0	20.1	100.0
Specificity	78.4	76.6	78.4
PPV	9.5	1.9	9.5
NPV	100.0	97.7	100.0
Accuracy	78.9	75.3	78.9

PPV= Positive Predictive Value
NPV= Negative Predictive Value

Table X shows the validity test results of serum CRP at cut-off level of 41.5 mg/L in the diagnosis of SBP by both ascitic fluid culture and PMN count, which shows the sensitivity of 89.5%, specificity of 94.4%. The positive predictive value was 81% and negative predictive value was 97.1%. The accuracy of the test result was 93.3%.

Tabl-X: Validity test of CRP at a cut off value of 41.5 mg/L in diagnosis of spontaneous bacterial peritonitis (by both ascitic fluid culture and PMN count) in study patients. (n=90)

Validity Indices	%	95% CI	
		Min	Max
Sensitivity	89.5	70.5	98.0
Specificity	94.4	89.3	96.6
PPV	81.0	63.8	88.6
NPV	97.1	91.9	99.4
Accuracy	93.3	85.3	96.9

PPV= Positive Predictive Value
NPV= Negative Predictive Value

ROC (Receiver Operating Characteristic) curve:

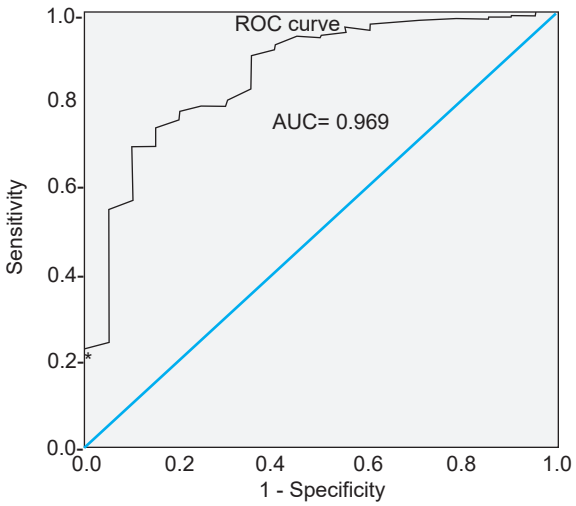

Figure 3: Area under ROC curve showing 0.969 with 95% CI, (0.909-1.000), (P <0.001).

Figure- 3 shows the ROC curve was generated by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) at different cut-off points. The figure shows AUC score of 0.969, which is close to 1. It indicates that serum CRP at a cut-off level of 41.5 mg/L have higher accuracy in diagnosing SBP in the study patients with high significance (p-value <0.001).

DISCUSSION

This cross-sectional study enrolled 90 patients with cirrhosis of liver and ascites; among the patients, 19 patients had SBP according to ascitic fluid PMN count ≥

250/mm^3. The most common clinical presentation was fever and abdominal pain (each 78.9%), altered mental status (15.8%), upper GIT bleeding (21.1%) while 10.6% of patients were asymptomatic. These results were consistent with the study conducted by [1,23,29,69-88,90] in which fever was the most common presenting feature (67%), followed by abdominal pain (60%), abdominal tenderness (42%) and encephalopathy (57%). Bandy and Tuttle, in 2008 reported that as many as 30% of patients with paracentesis-proven SBP may be completely asymptomatic.

The finding of ascitic fluid protein concentration in SBP patients were almost similar to that reported by.[98] They have found mean ascitic fluid protein 9.3± 4.4gm/l, whereas this study found mean ascitic fluid protein 10.97±04.04gm/L in SBP patients. Ascitic fluid analysis in study patients at admission by Syed *et al.* 2007 showed that, the mean ascitic fluid protein was slightly higher in non-SBP group than SBP group (12± 7.5gm/l vs 11±7.2gm/l). In this study the mean ascitic fluid protein in patient of non- SBP group was also higher than SBP group (13.25 ± 5.62 gm/L vs 10.97 ± 4.04gm/L). It may be due to the difference in immune status as well as etiology of cirrhosis in patients (due to HBV and HCV infection), compared to other studies (alcoholic cirrhosis). Runyon, B.A, (1986) had demonstrated that cirrhotic patients with ascitic protein concentrations below 1 g/dl were 10 times more likely to develop SBP than individuals with higher concentration.

Conventional diagnosis of SBP by detecting the number of PMN in ascitic fluid is laborious and operator dependent having inter-observer variation. It is not available everywhere especially in small hospitals with poor laboratory facilities,[66,39,41,42] implied that serum CRP determination can be used to detect bacterial infection in liver cirrhosis patients; Tsiakalos *et al.* (2009) found that CRP, ferritin and β2-microglobulin, significantly increased when cirrhotic patients are affected by bacterial infections, irrespective of the underlying cause of cirrhosis. Our results do suggest that measurement of serum CRP may be useful for excluding the possibility SBP in cirrhotic patients.

The serum CRP level in cirrhosis with ascites seems to be a reliable test to identify SBP, because our study showed the statistically significant difference of its levels between the SBP group and non-SBP group; as mean CRP level 84.59mg/L vs 15.02mg/L (P<0.001), as well as its high diagnostic sensitivity, specificity and accuracy (89.5%, 94.4%, and 93.3% respectively) at a cut-off level of 41.5mg/L. These finding are similar to that of several other previous studies.[8,52,95] The increase in the CRP levels can be partially attributed to its independent production regulation by interleukin-6 and its insensitivity to hepatocyte growth factor[24] or by other cell types such as alveolar [9,16,115] and renal cells.[32] The contrast result was explained by, Le Moine *et al.* in 1994 found CRP to have weak predictive power for infection in patients with decompensated cirrhosis but the production of CRP is reduced, but not abolished, even in patients with advanced liver [52,95]

In this study, at a cut-off value of 41.5mg/L the serum CRP level showed 89.5% sensitivity, 94.4% specificity, 81% PPV, 97.1% NPV and accuracy of 93.3% for detecting SBP. No significant difference was observed between PMN count and both PMN and culture results in terms of diagnostic efficacy of CRP. But sensitivity, specificity, PPV, NPV and diagnostic accuracy of serum CRP in diagnosing SBP based on ascitic fluid culture results were 100%, 78.4%, 9.5%, 100% and 78.9% respectively, with low specificity, PPV and accuracy when compared with PMN alone or with both PMN and culture results. Study conducted on 150 cirrhotic patients with ascites showed 88.43% sensitivity, 84.32% specificity, 85.48% PPV, 90.32% NPV and 85.63% accuracy of serum CRP in diagnosing SBP when compared with ascitic fluid culture[34]. This may be due to large sample size, more culture positivity among study subjects and the use of higher cut-off level of serum CRP.

There are variable cut-off level of CRP level in different previous studies[67] had shown that at a cut-off value of 30 mg/dl, the serum CRP was 96% specific and 90% sensitive for detecting SBP[39,41,42], at a cut-off value of 20 mg/L, the serum CRP had sensitivity of 80.39%, specificity of 80.77% and accuracy of 80.62%). Likewise, the optimal diagnostic cut-off value of CRP was 16.15 mg/L in chronic severe hepatitis B patients with SBP, with sensitivity of 64% and specificity of 95% [26,114] and optimal cut-off value of CRP that can be used for the diagnosis was 10.5 mg/L with sensitivity and specifity of 91% and 97% respectively.[103] Therefore, it is necessary to find a new cut-off value to discriminate infection as well as SBP in patients of cirrhosis with ascites. Study had suggested that the threshold should be moved to 55.8 mg/L, because above these levels, it has almost the similar sensitivity (79%), but much better specificity (96%) and diagnostic accuracy (92%)[103].

CONCLUSION

It is vital to assess the utility of CRP in diagnosis of SBP in cirrhosis with ascites. In previous clinical studies, CRP proved to be effective marker of bacterial infections in patients with liver diseases, but they had diverse diagnostic accuracies at different cut-off values. In this study, CRP at the optimal cut-off value at 41.5 mg/L had the good sensitivity (89.5%), specificity (94.4%), and AUROC (0.969) in diagnosing SBP patients. Larger samples and more homogeneous groups of cirrhotic patients with SBP is need for further studies in order to confirm our results and to establish the optimal cut-off level of CRP for the diagnosis of SBP.

Limitation

The sample size of the study was small.

All patients were collected in this study from a single tertiary level hospital which does not reflect the whole country so, current study suffered from lack of multi-centric patients.

Recommendation

There is a need of large sample study.

The optimal cutoff level of CRP needs to be reached from an independent cohort of patients with SBP.

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