An evaluation of calprotectin in ascitic fluid as a marker for spontaneous bacterial peritonitis diagnosis in cirrhotic patients

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Abstract:

Background: Spontaneous Bacterial Peritonitis (SBP) occurs when sterile ascitic fluids become contaminated with bacteria without an inflammatory lesion or gastrointestinal perforation. **Aim:** To estimate the efficacy of ascitic fluid calprotectin as a possible diagnostic marker for SBP, which occurs in patients with cirrhosis. **Patients and methods:** The study involved fifty patients with ascites and cirrhosis at the internal medicine department of Benha University Hospital. Two groups were included: Group (1) included forty cases who, regardless of the results of ascitic fluid culture, were diagnosed with SBP based on a rise in polymorphonuclear leukocytes (PMNLs) count in ascites 250 cells/mm3 or more in the absence of secondary peritonitis. Ten cases in a group (2) serve as the control group since they show no evidence of SBP. **Results:** In terms of age, gender, smoking status, diabetes mellitus, hypertension, liver shrinkage, and ascites, there wasn't statistically significant variance among the two groups of cases. Calprotectin & platelets showed a statistically significant positive correlation. In order to diagnose SBP, ROC analysis was conducted on calprotectin. A significant AUC of 0.753 was observed, accompanied by a P-value of 0.014 and a ninety-five percentage of confidence interval varying from 0.604 to 0.901. The best cut-off was > 33 ng/ml, at which sensitivity, specificity, PPV, and NPV were 42.5 percent, 100 percent,100 percent, and 30.3 percent, respectively. **Conclusion:** Calprotectin is crucial for diagnosing and managing SBP, especially in cases with cirrhosis, and serves as a fast clinical test.

Keywords: Calprotectin, Ascites, Cirrhosis, SBP, Prognosis.

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Introduction:

Cirrhosis progression and a poor prognosis are both indicated by the presence of ascites, which is a serious complication of the disease [(1)]. With no signs of gastrointestinal perforation & intraabdominal inflammatory lesion (e.g., cholecystitis, acute pancreatitis, abscess), the etiology of SBP, an acute bacterial infection of ascites, is hypothesized to be a bacterial infection of formerly sterile ascitic fluids. The predominant etiology of ascitic fluid infections is intestinal bacteria[(2)]. The death rate among cases who have SBP varies between forty to seventy percent. Patients who recovered from their initial episode of Spontaneous Bacterial Peritonitis (SBP) exhibited a lowered survival rate of fifteen percent compared to cirrhotic patients without a history of SBP. Rapid management of SBP upon admission may significantly reduce mortality [(3)]. There is a correlation between

the production of inflammatory mediators and the SBP. Interleukin 6 (IL-6) and tumor necrosis factor (TNF-) are two types of proinflammatory cytokines that are secreted by patients who have sustained hepatic injuries. These cytokines can be found in both the blood and the ascites of these patients [(4)]. The non-invasive measurement of calprotectin as a biomarker has been utilized to detect inflammation in the gastrointestinal tract. Calprotectin which is a 36 kilodalton calcium & zinc binding protein with antimicrobial activity, is completely observed in neutrophils. The influx of neutrophils is proportional to its concentration in bodily fluids. Levels of calprotectin can be determined using the ELISA method. The measurement of calprotectin in ascites is strongly correlated with the presence of a polymorphonuclear leukocyte (PMNL) count that reliably signifies a level of 250 cells/mm or more, according to the findings of Burri *et al.*, who used this as a standard marker for detecting Spontaneous Bacterial Peritonitis during their research [(5, 6)].

Patients who have cirrhosis and ascites can have bacterial DNA found in their serum and ascitic fluid, despite the fact that it is not possible to culture viable organisms in these circumstances. Due to this, patients who have cirrhosis are at risk of passing away [(7)]. When compared to patients whose protein levels are higher than one g/dL, those whose ascitic fluid protein levels are below one g/dL have a tenfold increased risk of progressing SBP during the duration of their illness [(8)].

The objective of the research was to estimate the diagnostic value of ascitic fluid calprotectin as a marker for SBP in cases who had cirrhosis.

Patients and Methods:

This research was performed on fifty cases who have cirrhosis & ascites and were hospitalized to the internal medicine department of Benha University Hospital. Two groups of cases were established: Group (1) included forty cases who, regardless to the results of ascitic fluid culture, were diagnosed with SBP based on an increase in the count of polymorphonuclear leukocytes (PMNLs) in ascites that is equal to or greater than two hundred and fifty cells/mm^3 with no signs of secondary peritonitis. Ten cases in group (2) serve as the control group since they show no evidence of SBP.

Inclusion criteria: Patients with ascites and cirrhosis were admitted. Both genders are incorporated.

Exclusion criteria: Cases who have any of the following: Abdominal malignancy, recent abdominal surgery, colorectal carcinoma, [hepatocellular carcinoma (HCC), Intra-abdominal infected lesions, hematological, gastric carcinoma, pancreatic carcinoma, cholangio-carcinoma]**,** individuals who have a history of ulcerative colitis or Crohn's disease, both of which are inflammatory bowel diseases, cases who are suffering from heart failure (HF), and patients who have autoimmune disorders weren't included.

The following information was gathered from each patient upon admission:

Initial assessment:

Complete full history was taken which includes: (Residential, occupational, and medical history and special habits).

Investigations including Routine Laboratory Tests.

Examination of ascetic fluid & paracentesis including: The count of white blood cells (WBC) and (PMN) in ascites, LDH, albumin, glucose & serum ascites albumin gradient.

Radiological investigations including: Abdominal & pelvic Ultrasonography.

The enzyme-linked immunosorbent assay (ELISA) was utilized to determine

the concentration of calprotectin in ascitic fluid: Twenty milliliters of ascitic fluid and three milliliters of venous blood were withdrawn. Evaluations were performed on samples of serum and plasma. While the patient was supine and under local anesthesia with lidocaine, twenty milliliters of ascitic fluid were obtained through the process of paracentesis using a sterile needle with a gauge of twenty. This was done under completely aseptic conditions in the right or left lower quadrant. A portion of the specimen was then directly referred to the laboratory for analysis of differential leukocyte counts (PMNLs), bacterial culture & sensitivity testing. After centrifuging the remaining portion of the ascitic fluid, which was approximately three milliliters, for fifteen minutes, the supernatant was transported to 3 sterile eppendorf tubes & then allowed to be stored at a temperature of minus twenty degrees Celsius. An analysis using ELISA was carried out in order to ascertain the levels of Calprotectin. Samples of ascitic fluid were withdrawn from the SBP group for the purpose of analyzing the levels of calprotectin. Calprotectin (DEH 325 Calprotectin human ELISA kit; Demeditech Diagnostics, GMbH, KielWellsee, Germany) Kits were utilized in order to measure the concentrations of the substance in ascitic fluid in accordance with the instructions provided by the manufacturer [(9)].

Administrative and Ethical Design: The official authorization was granted by the department of internal medicine at Benha University Hospital. The approval was granted by the Institutional Research Board (IRB), which is the faculty of medicine's ethical committee.

Statistical Analysis:

The process of managing information and analysis of statistics was conducted using SPSS version 25, which was used. (Armonk, New York, United States). Using the Shapiro-Wilk test & direct visualization of information (for both), we were able to determine whether or not the quantifiable information were normal. The numerical information were then briefed as standard means and deviations or medians and ranges. In order to summarize categorical data, percentages and numbers were used. The independent t-test and the Mann-Whitney U test were used, respectively, in comparising of quantitative data among the studied groups. These tests were utilized for numerical variables that were normally distributed and those that were not normally distributed. On the basis of the requirements, either the Fisher's exact test or the Chi-square test was used to compare categorical data. The use of ROC analysis was carried out to diagnose SBP with calprotectin. Calculations, including diagnostic indices, the best cut-off point, and (AUC) with confidence level of of ninety five percent were performed. A correlation analysis was carried out with the help of Spearman's correlation. Every statistical test was conducted with 2 sides. P values that were fewer than 0.05 were supposed to be statistically significant.

Results:

There weren’t significant differences among both groups related to age (P-value = 0.136), gender (P-value = 1.0), smoking (P-value = 0.053), diabetes mellitus (P-value = 0.44), and hypertension (P-value = 0.864). All patients in both groups showed rural residence and HCV. **Table (1)**

Table 1: Demographic data in the two groups.

		Group I (n = 40)	Group II (n = 10)	P-value
Age (years)	Mean ±SD	62 ±6	59 ±7	0.136
Gender	Males n (%)	32 (80.0)	8 (80.0)	1.0
	Females n (%)	8 (20.0)	2 (20.0)	
Rural residence	n (%)	40 (100.0)	10 (100.0)	-
Smoking	n (%)	8 (20.0)	5 (50.0)	0.053
Diabetes mellitus	n (%)	11 (27.5)	4 (40.0)	0.44
Hypertension	n (%)	9 (22.5)	2 (20.0)	0.864
HCV	n (%)	40 (100.0)	10 (100.0)	-

Independent t-test was used for age. Chi-square test was used for categorical data, HCV means Hepatitis C virus

Fever was significantly greater in group I (70%) than group II (20.0%); P-value was 0.004. And, hepatic encephalopathy was significantly more in group I (67.5) than group II (10.0%); P-value was 0.001. No significant differences were reported regarding hematemesis, melena, and nausea & vomiting. P-values were 0.363, 0.629 & 0.2, respectively. All patients in the two groups reported abdominal pain. **Table (2)**

Table 2: Clinical presentation in the two groups.

		Group I (n = 40)	Group II (n = 10)	P-value
Fever	n (%)	28 (70.0)	2 (20.0)	0.004
Abdominal pain	n (%)	40 (100.0)	10 (100.0)	-
Hepatic encephalopathy	n (%)	27 (67.5)	1 (10.0)	0.001
Hematemesis	n (%)	1 (2.5)	1 (10.0)	0.363
Melena	n (%)	11 (27.5)	2 (20.0)	0.629
Nausea & vomiting	n (%)	0 (0.0)	1 (10.0)	0.2
Diarrhea	n (%)	0 (0.0)	0 (0.0)	-

Chi-square or Fisher's exact test was used

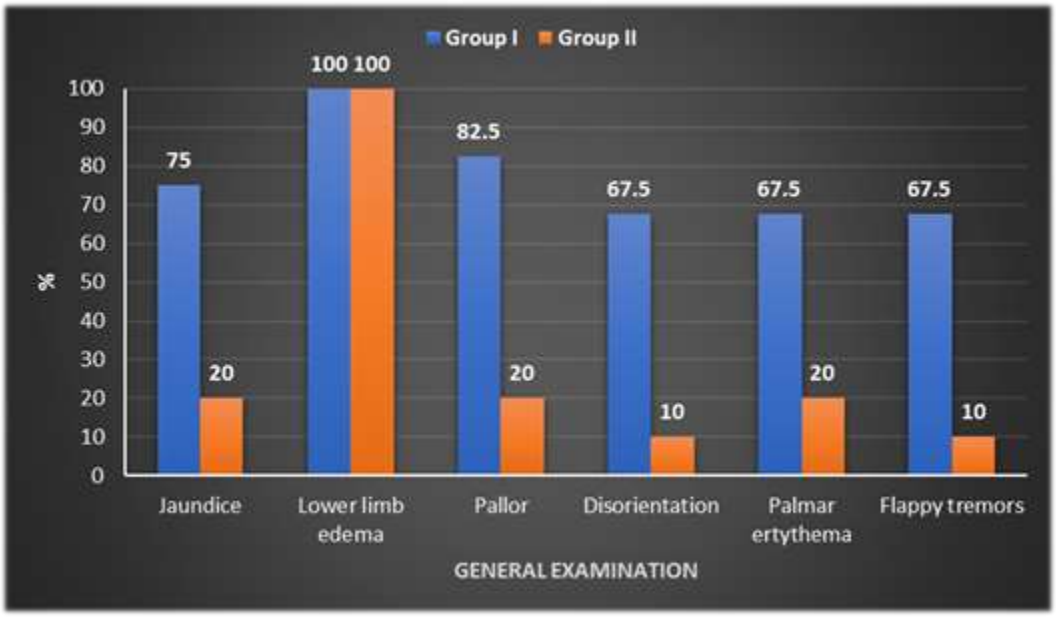

Figure 1: General examination in the two groups

There weren't any significant differences among both groups according to shrunken liver (P-value = 1) and ascites (P-value = 0.205). All patients showed course echo-pattern and splenomegaly. **Table (3)**

Table 3: Ultrasound results in the two groups.

			Group I (n = 40)	**Group II (n = 10)**	**P-value**
Shrunken liver	n (%)		1 (2.5)	0 (0.0)	1.0
Course echo-pattern	n (%)		40 (100.0)	10 (100.0)	-
Splenomegaly	n (%)		40 (100.0)	10 (100.0)	-
Ascites	Moderate	n (%)	10 (25.0)	2 (20.0)	0.205
	Severe	n (%)	22 (55.0)	3 (30.0)	
	Tense	n (%)	8 (20.0)	5 (50.0)	

Chi-square or Fisher's exact test was used

Child C classification was significantly greater in group I (77.5%) than group II (30.0%); P-value was 0.004. **Table (4)**

Table 4: Child-Paugh score in the two groups.

			Group I (n = 40)	**Group II (n = 10)**	**P-value**
Child-Pough	B	n (%)	9 (22.5)	7 (70.0)	0.004
	C	n (%)	31 (77.5)	3 (30.0)	

Chi-square test was used

In group I, there was a significant positive correlation among calprotectin & platelets (r = 0.359 & P-value 0.023). In group II, calprotectin didn't significantly correlate with other research parameters. **Table (5)**

Table 5: Correlation between calprotectin and other parameters in the two groups.

	Group I		**Group II**	
	r	**P-value**	**r**	**P-value**
Age (years)	0.111	0.495	-0.298	0.403
Hb (g/dl)	-0.003	0.987	-0.215	0.55
WBCs (10^3 cell/cmm)	-0.088	0.588	-0.59	0.073
Platelets (10^3 cell/cmm)	.359*	0.023	-0.116	0.75
ALT (IU/l)	-0.191	0.237	0.188	0.602
AST (IU/l)	0.034	0.833	0.03	0.934
Total bilirubin (mdl)g/	-0.237	0.141	-0.141	0.697
Direct bilirubin (mg/dl)	-0.028	0.865	-0.311	0.382
Albumin (g/dl)	0.105	0.521	0.511	0.132
INR	-0.268	0.094	-0.2	0.579
Urea (mg/dl)	0.007	0.965	0.085	0.815
Creatinine (mg/dl)	-0.118	0.467	0.128	0.725
TLC (CELL/ul)	-0.286	0.074	-0.006	0.987

Spearman's correlation was used, r: correlation coefficient, * Significant

For the purpose of diagnosing SBP, ROC analysis was performed on calprotectin. With a confidence interval of ninety five percentage that ranged from 0.604 to 0.901, it presented (AUC) of 0.753 (P-value = 0.014). The most effective threshold was greater than thirty three ng/ml, at any point the sensitivity, specificity, PPV, and NPV were respectively 42.5%, 100%, and 100%. **Table (6)**

Table 6: ROC analysis for calprotectin in diagnosing spontenous bacterial peritonitis.

ROC characteristics	
AUC (95% CI)	0.753 (0.604 – 0.901)
Best cutoff	> 33
Sensitivity	42.5%
Specificity	100%
PPV	100%
NPV	30.3%
P-value	0.014

PPV means Positive predictive value, AUC means Area Under Curve, NPV means Negative predictive value, 95% CI: 95% confidence interval

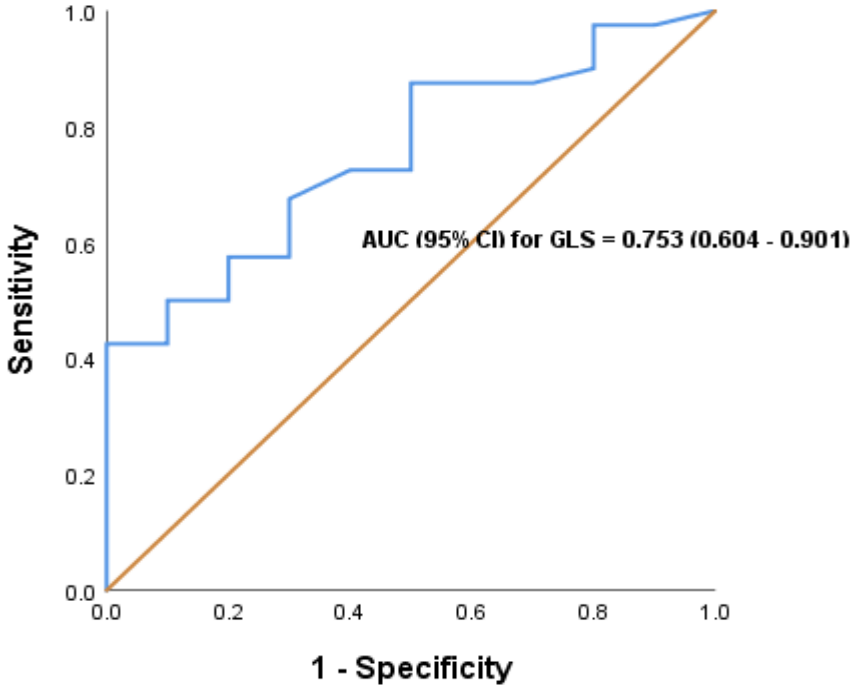

Figure 2: ROC analysis for calprotectin in diagnosing SBP

Discussion:

Cirrhosis is a late-stage liver disease which occurs when fibrosis replaces healthy tissue [(10)]. In patients who have portal hypertension and liver cirrhosis, a SBP is an ascitic fluid infection [(11)].

There was a poor prognosis related to the appearance of spontaneous bacterial peritonitis, with hospital death ranging from ten percent to fifty percent. Therefore, all patients with spontaneous bacterial peritonitis must be evaluated for liver transplantation. Intravenous albumin and antibiotics should be started as soon as possible [(12)].

Within our study regarding age among the studied groups, there wasn't statistically significant variance, the mean age was 62±6 years in group of patients with evidence of SBP and 59±7 years in group of patients without evidence of SBP (P-value = 0.136). Regarding gender, among the two studied groups there wasn't statistically significant variance (P-value = 1.0). Regarding smoking, there wasn't statistically significant variance among both studied groups (P-value = 0.053). And, Regarding diabetes mellitus (P-value = 0.44), and hypertension (P-value = 0.864). every case in both groups showed rural residence and HCV.

Similar results were demonstrated by **Abdel Rahman *et al.*** [(13)] Patients' average age was 55.25 ± 7.89 years, but majority males (n = 51, 63.8%), anti-HCV antibodies were positive in 76.3 percentage of the cases.

In agree with our study **Abdel-Razik *et al.*** [(14)], reported no significant variance in terms of the gender and age among SBP and non-SBP patients.

The fever of alcoholic hepatitis, in which the neutrophil count in the ascitic fluid is normal, is distinguished from that of spontaneous bacterial peritonitis. Abdominal pain can be constant and vary from tense ascites; changes in mental state can be mild and noticeable mainly to those

who are close to the patient. Tenderness is a common symptom. In cases of severe illness, where the prognosis may be terrible, paralytic ileus, hypothermia, and hypotension are common. 13% of patients have no signs or symptoms. Patients who are hospitalized and have been diagnosed with ascites are required to undergo a "diagnostic tap." [15].

Regarding fever there was significantly greater in a group of cases with evidence of spontaneous bacterial peritonitis (70%) than group of cases without evidence of SBP (20.0%); (P-value =0.004). Regarding hepatic encephalopathy, there was a statistically significant rise in hepatic encephalopathy in the group of cases with evidence of SBP (67.5%) than the control group (10.0%); (P-value = 0.001). Regarding hematemesis, melena, and nausea & vomiting there wasn't statistically significant variance among the studied groups P-values were 0.363, 0.629, and 0.2, respectively. Every patient in the two groups reported abdominal pain.

Contrary to our results were the results of **Weil *et al.*** [16], hepatic encephalopathy in a group of cases with evidence of SBP was only 8 patients from 36 with percentages (22.2%) while hepatic encephalopathy in a group of patients without evidence of SBP was 36 patients from 200 with percentages (18%) and (P-value = 0.54). and only 10 patients from 36 with evidence of SBP suffered from abdominal pain with percentages (27.8%); while 33 patients from 200 without evidence of SBP suffered from abdominal pain with percentages (16.6%) and (P-value = 0.11).

Our study shows high statistical significance in the group of patients with evidence of SBP Regarding jaundice (75%), pallor (82.5%), disorientation (67.5%), palmar erythema (67.5%), and flappy tremors (67.5%) compared to the control group (20%, 20%, 10%, 20%, and 10%, respectively). All patients in both groups reported lower limb edema.

Similar data had been recorded by **Lata *et al.*** [17], who noted that symptoms & signs of spontaneous bacterial peritonitis include nausea, disorientation, chills, jaundice, palmar erythema, pallor, flappy tremors, altered mental status, general malaise, worsening ascites & tenderness.

Detecting neutrophil counts greater than two hundred and fifty /μL with ascitic fluid calprotectin may aid in the identification of SBP. This bedside test is simple to perform and plays a critical role in facilitating prompt management [5].

In gastroenterology, the Childe-Turcotte-Bo or Childe standards classification is utilized to estimate the prognosis of chronic liver disease, of which cirrhosis is particularly concerning. According to the sum of 5 clinical measures of liver dysfunction. One to three points are deducted for each measurement, depending on the disease's severity [18].

Regarding Child C classification was significantly more in cases with signs of spontaneous bacterial peritonitis (77.5%) in comparison with the control group (30.0%); the P-value was 0.004. The same results were demonstrated by **Kaplan *et al.*** [19], who noted that Child C classification records a high level in cases with signs of SBP as an indicator of chronic liver disease.

Regarding correlation among calprotectin and other parameters in both groups, there was a significant positive correlation among calprotectin & platelets in cases with signs of SBP (r = 0.359); (P-value = 0.023). while in the control group, calprotectin showed no significant correlation with other study parameters (Age, ALT, AST, Hb, WBCs, Platelets, Total bilirubin, Creatinine, INR, Direct bilirubin, Albumin, Urea, and TLC).

In agreement with our research, **Larsen *et al.*** [20] documented a positive correlation among Calprotectin levels and platelet aggregation as determined by the Multiplate Analyzer (r=0.12, p=0.01). Furthermore, Calprotectin exhibited a weakly positive correlation with AA-induced platelet aggregation as also detected via the Multiplate Analyzer. A correlation between calprotectin and collagen-induced platelet aggregation as measured via the Multiplate Analyzer was not statistically significant.

Additionally, **Tepel *et al.*** [21] discovered that urinary calprotectin is a non-invasive early predictor of immediate renal allograft injury following the transplantation of the kidney**.**

Regarding ROC analysis, it was conducted for calprotectin in diagnosing Spontaneous bacterial peritonitis. It showed a significant AUC of 0.753 (P-value = 0.014), The confidence interval for the ninety-five percent confidence level ranged from 0.604 to 0.901. The best cut-off was > 33 nanogram per milli, at which sensitivity, specificity, PPV, and NPV were 42.5%, 100%, 100%, and 30.3%, respectively.

Abdel Rahman *et al.* [13] reported in a recent study that the cutoff value of calprotectin for the diagnosis of spontaneous bacterial peritonitis was determined through the utilization of receiver operating characteristic curve analysis. Ascitic calprotectin which was more than two ng/mL had ninty percentage of sensitivity, ninty two point five percentage of specificity, ninty two point three percentage of positive predictive value and ninty point two percentag of NPV (AUC 0.963, 95% C.I 0.895–0.992, P = 0.001). As an indicator for the diagnosis of SBP, ascitic calprotectin is useful; the ascitic leucocyte esterase test was positive in ninety-five percentage of patients with SBP, compared to two point five percentage of patients without SBP. The ascitic calprotectin concentration exceeding two ng/mL demonstrated a specificity of ninty two point five %, a positive predictive value of ninty two point three %, and a negative predictive rate of ninty point two percent. Independent predictors of spontaneous bacterial peritonitis include MELD, CRP, hsCRP, and ascitic calprotectin [13]**.**

Along with our study when **Fernandes *et al.*** [22] examined eighty eight cases, forty one of them had spontaneous bacterial peritonitis. They comprised the majority of alcoholic males. There was an increase in ascitic calprotectin levels. By ROC, a cutoff value of 1.57 microgram per milliliters was determined to have a sensitivity of 87.8 percent, specificity of 97.9 percent, PPV of 97.3 percent, and NPV of 90.2 percent**.**

Conclusion:

Calprotectin makes up around 60% of white blood cell proteins. Calprotectin may be useful in detecting white blood cells exceeding 250 cells/mm3 and is essential in the diagnosis of SBP and this serves as a quick clinical test in the management of SBP. Based on our findings, When cirrhotic cases present with SBP, calprotectin is used as a diagnostic guide.

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