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Ascitic Fluid Calprotectin as a Diagnostic Marker of Spontaneous Bacterial Peritonitis in Patients with Liver Cirrhosis

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ABSTRACT
Background: Spontaneous bacterial peritonitis (SBP), a life-threatening infection in patients with advanced liver cirrhosis, is traditionally diagnosed by a high white blood cell count (polymorphonuclear leukocyte count (PMN) > 250/μL) in ascitic fluid. However, this method can be slow. **Objective:** This study explores ascitic fluid calprotectin as a potentially faster and more accurate diagnostic tool.**Patients and Methods:** Ninety patients with decompensated liver cirrhosis (45 with confirmed SBP and 45 without SBP) were included. Ascitic fluid calprotectin levels were measured in all participants.
Results: SBP patients had significantly higher calprotectin levels than the non-SBP group. Additionally, calprotectin levels correlated with white blood cell counts and other inflammatory markers in the ascitic fluid. Using a cut-off value of 433.7 ng/ml, calprotectin achieved a sensitivity of 73.3% and a specificity of 85.1% for detecting SBP.
Conclusion: Ascitic fluid calprotectin shows promise as a reliable and potentially faster method for diagnosing SBP in patients with cirrhosis. It could serve as a valuable addition to existing diagnostic tools.
Keywords: Spontaneous bacterial peritonitis; Calprotectin; Ascites; Liver cirrhosis.

INTRODUCTION

Within ten years of being diagnosed with about 60% of people with compensated liver cirrhosis experience ascites [(1)]. It is linked to a poor prognosis and high death rate, which rises to 50% in two years and 40% in one year [(2)]. People who have serious liver cirrhosis often get spontaneous bacterial peritonitis (SBP), a quick bacterial infection of the ascitic fluid [(3)].

SBP was formerly documented 10% to 20% of patients who are referred to the hospital have ascites; however, this prevalence is thought to be reduced currently due to antibiotic prophylaxis, even though the rate of antibiotic-resistant organisms has grown [(4)]. Because many of these patients are asymptomatic, a diagnostic paracentesis ought to be carried out on all ascites patients at the time of admission to rule out the existence of SBP by detecting absolute polymorphonuclear leukocyte count (PMN) (≥ 250 cells/mm3) in the ascitic fluid [(5)].

To catch a bad bacteria and send antibiotics to the right place, cultures must be done [(6)]. It is essential to identify SBP early and start antibiotic treatment rapidly. Alternatively, PMN counting that is automated [(7)], reagent strips (urine dipsticks) [(8)] and ascitic lactoferrin [(9)] have been made, but they can only be used if there are enough lab workers and widely available chemicals and parts, and their diagnostic accuracy is poor. Consequently, there is still a clinical need for a quick and accurate way to diagnose SBP.

Calprotectin is a mammalian antimicrobial protein that was initially discovered in the 1980s, and it works by sequestering zinc [(10)]; It is a protein that binds zinc and calcium and is almost always found in neutrophils. The amount of this protein in body fluids is linked to the number of neutrophils that are present [(11)]. Calprotectin in ascitic fluid accurately predicts a PMN count of >250/μL, which could be a valuable marker for detecting SBP, particularly when utilizing a basic bedside testing apparatus [(12)].

There is a quantitative correlation between Neutrophils moving into the digestive system and calprotectin being found in feces [(13)]. It is accepted as a reliable indicator of intestinal inflammation since it is released during cell activation and death [(14)].

Calprotectin may be a helpful diagnostic tool for determining the start and course of hepatic encephalopathy as well as SBP, given that the gastrointestinal tracts of individuals with cirrhosis exhibit many changes to the mucosal barrier, including neutrophil infiltrates [(15)]. It has been suggested that the quick bedside test is just as good for finding out if someone has inflammatory bowel disease. It has been made possible to quickly measure calprotectin in feces. The results of this test were compared to those of the well-known enzyme-linked immunosorbent assay (ELISA) method and found to be highly consistent [(16)]. This quick test that can be done at the bedside could help find out how much calprotectin is in the ascitic fluid to help figure out PMN levels and SBP state [(17)].

Our study aimed to examine calprotectin in ascitic fluid as a valid diagnostic sign for finding SBP in people with cirrhosis who also have ascites.

PATIENTS AND METHODOLOGY

For this observational study that is prospective, we enrolled ninety patients above 18 years old with cirrhotic ascites diagnosed clinically and proved by ultrasonography with no history of renal insufficiency, evidence of hepatocellular carcinoma, heart failure, or inflammatory bowel disease. All patients were taken to the coronary and

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gastroenterology center in Damietta for gastroenterology and liver surgery (DCGC), and were clinically suspected of having SBP (abdominal pain, tenderness, fevers, chills, nausea, vomiting, general malaise, altered mental status, and or worsening of ascites) [18] in the period from May 2021 to November 2022.

Every patient underwent a thorough history taking, a clinical examination, and the following laboratory tests; a complete blood picture, liver function assessments, measurement of serum albumin, bilirubin, INR, ALT and AST, complete urine analysis, blood urea, blood creatinine and CRP levels, ascitic fluid tests, and diagnostic paracentesis for the following: total protein and albumin, WBC and its differential count, LDH, culture and sensitivity test of ascitic fluid, and calprotectin level. All enrolled patients underwent diagnostic paracentesis, routinely done for all patients admitted with ascites. In order to diagnose SBP, a 60 cm ascitic fluid sample was divided into three lab tubes and subjected to ascitic fluid culture. The study used an enzyme-linked immunosorbent assay (ELISA) with the Quantum Blue ®Reader from Bühlmann Laboratories (Switzerland) to measure calprotectin amounts as well as total and differential leukocyte cell counts. Being told that you have spontaneous bacterial peritonitis (SBP) is confirmed when the absolute polymorphonuclear (PMN) count surpasses a certain threshold > 250/μL [19,20].

Ethical considerations

The procedures were done in line with the institutional and/or national study committee's ethical standards, as well as the 1964 Helsinki Declaration and any updates to it, or similar ethical standards. The project was approved by the Faculty of Medicine, Helwan University's study Ethics Committee for human subject study (Serial: 22-2021). The dataset used in the study was completely anonymised. All study participants signed an informed consent before being enrolled in the study.

Statistical methods

The statistical analyses were conducted using the SPSS software package, version 19.0, which was made by SPSS Inc. in Chicago, IL, USA. A P-value less than 0.05 means that the data were statistically significant. Quantitative data were presented as mean and standard deviation (SD) and were compared by independent t-test or Mann-Whitney U test. Qualitative data were presented as frequency and percentage and were compared by Chi-Square test. ROC curve was also used.

RESULTS

People in the SBP group were 63.2 years old on average, while people in the non-SBP group were 61.3 years old on average. General characteristics and clinical presentation are shown in table (1).

Table (1): Baseline, Sociodemographic and Clinical data

	Data	Non-SBP group (N=45)		SBP group (N=45)		Significance Test	P value
Age (mean± SD years)		61.3 ± 9.25		63.20 ± 8.20		t= -1.001	0.319
Sex	**Males**	30	66.7%	28	62.2%	χ^2=0.194	0.660
	Females	15	33.3%	17	37.8%		
Occupation	**Working**	17	37.8%	12	26.7%	χ^2=1.272	0.259
	Not	28	62.2%	33	73.3%		
Residence	**Rural**	15	33.3%	21	46.7%	χ^2=1.667	0.197
	Urban	30	66.7%	24	53.3%		
Alcohol intake	**No**	45	100%	45	100%	χ^2= 0	1
	Yes	0	0%	0	0%		
Smoking	**No**	37	82.2%	34	75.6%	χ^2=0.600	0.438
	Yes	8	17.8%	11	24.4%		
History of blood transfusion	**No**	34	75.6%	26	57.8%	χ^2= 3.20	0.074
	Yes	11	24.4%	19	42.2%		
History of bilharziasis	**No**	37	82.2%	37	82.2%	χ^2= 0	1
	Clinical						
Abdominal pain	**No**	28	62.2%	22	48.9%	χ^2= 1.620	0.203
	Yes	17	37.8%	23	51.1%		
Jaundice	**No**	23	51.1%	19	42.2%	χ^2= 0.714	0.398
	Yes	22	48.9%	26	57.8%		
GIT bleeding	**No**	14	31.1%	14	31.1%	χ^2= 0	1
	Yes	31	68.9%	31	68.9%		
Disturbed conscious level	**No**	29	64.4%	14	31.1%	χ^2= 10.02	0.002*
	Yes	16	35.6%	31	68.9%		

GIT: gastrointestinal tract), *: Significant difference, T: Independent samples t-test, χ^2: Chi square test.

The serum laboratory parameters were statistically comparable. The two groups were not significantly different from each other, except for albumin, prothrombin time, and CRP. Serum albumin showed a significant decrease in association with SBP. Conversely, the other two parameters were significantly increased in the SBP group. Most of the ultrasonographic parameters were statistically comparable between the two groups, apart from the degree of ascites (p = 0.008). The incidence of marked ascites was more encountered in association with SBP. No patients had hepatic focal lesions, and all patients had patent portal vein on Doppler assessment. CTP score was significantly higher in SBP compared to the non-SBP group. There was no difference between the groups in the MELD or uMELD scores (Table 2).

Table (2): Baseline assessment of the studied patients included evaluation of liver and renal function, as well as liver cirrhosis severity using Child-Pough and MELD scores.

Renal and liver function	Non-SBP group (N=45)	SBP group (N=45)	Significance Test	P value
Creatinine (mg/dL) (mean± SD)	1.46 ± 0.92	1.47 ± 0.02	z= - 0.125	0.891
ALT (U/L) (mean± SD)	80.82 ± 7.27	57.47 ± 5.79	z= -1.695	0.097
AST (U/L) (mean± SD)	115.60 ± 10.52	128.07 ± 10.34	z= - 0.194	0.846
Serum albumin (g/dl) (mean± SD)	2.77 ± 0.68	2.32 ± 0.65	t=3.239	**0.002***
Total Bilirubin (µmol/L) (mean± SD)	5.02 ± 1.83	4.67 ± 1.38	z=-0.428	0.669
Direct Bilirubin (µmol/L) (mean± SD)	3.54 ± 0.77	3.08 ± 0.48	z= -0.504	0.614
INR (mean± SD)	1.53 ± 0.29	1.60 ± 0.34	t= -0.629	0.531
PT (pc) (mean± SD)	16.08 ± 4.01	17.91 ± 3.09	t= -2.371	**0.020***
CRP (mg/L) (mean± SD)	21.36 ± 4.93	36.51 ± 2.23	z= -3.784	< **0.001***
Child-Pough Score (mean± SD)	9.84 ± 2.44	10.96 ± 1.51	t= -2.559	**0.011***
MELD Score (mean± SD)	18.07 ± 3.78	19.98 ± 4.16	Z= -1.633	0.102
uMELD Score: (mean± SD)	21.24 ± 3.56	23.60 ± 4.37	Z= -1.827	0.068

*: Significant difference, T: Independent samples t-test, Z: Mann-Whitney u-test.

No important difference was found between the two study groups in any of the CBC values (p > 0.05). The average levels of hemoglobin were 11 and 10.11 gm/dl, and the average levels of white blood cells were of 9.98 and $10.2x10^3$/ml in the non-SBP and SBP groups, respectively. Additionally, the mean values of platelets were 182.11 and $161.5x10^3$/ml in the same two groups, respectively. Fasting blood glucose came in at 128.56 and 134.98 mg/dl on average in the same study groups, but there was no statistically significant difference (p = 0.750). Not a single case in this study tested positive for HBV. However, HCV was positive in 55.6% and 66.7% of cases in the non-SBP and SBP groups, respectively (p = 0.280); the rest could be due to cryptogenic cirrhosis.

Total ascitic leucocytic and the number of PMN cells significantly increased when SBP was present. On the other hand, ascitic albumin levels were much lower in people with SBP. Both the ascitic glucose gradient and the serum ascites albumin gradient were statistically comparable between the two groups (Table 3).

Table (3): Ascitic fluid analysis in studied groups.

Ascitic Fluid Analysis	Non-SBP group (N=45)	SBP group (N=45)	Significance Test	P value
Total leucocyte count (mean± SD)	294 ± 15.64	1677.56 ± 314.47	Z = - 8.009	< **0.001***
Polymorph nuclear leucocytes (mean± SD)	134.22 ±7.51	1087.56 ± 1620	Z = - 8.197	< **0.001***
Ascitic albumin (mean± SD)	0.85 ±0.21	0.54 ± 0.14	Z = - 5.342	< **0.001***
Ascitic glucose (mean± SD)	115.18 ± 26.43	135.17 ± 8.04	Z = - 1.005	0.315
Serum ascitic albumin gradient (SAAG) (mean± SD)	2 ±0.14	1.77 ± 0.16	Z = - 1.802	0.072

*: Significant difference, Z: Mann-Whitney u-test

Ascitic calprotectin had mean values of 376.06 and 613.28 ng/ml in the non-SBP group and SBP group, respectively ($p < 0.001$), indicating a significant increase in association with SBP (Figure 1).

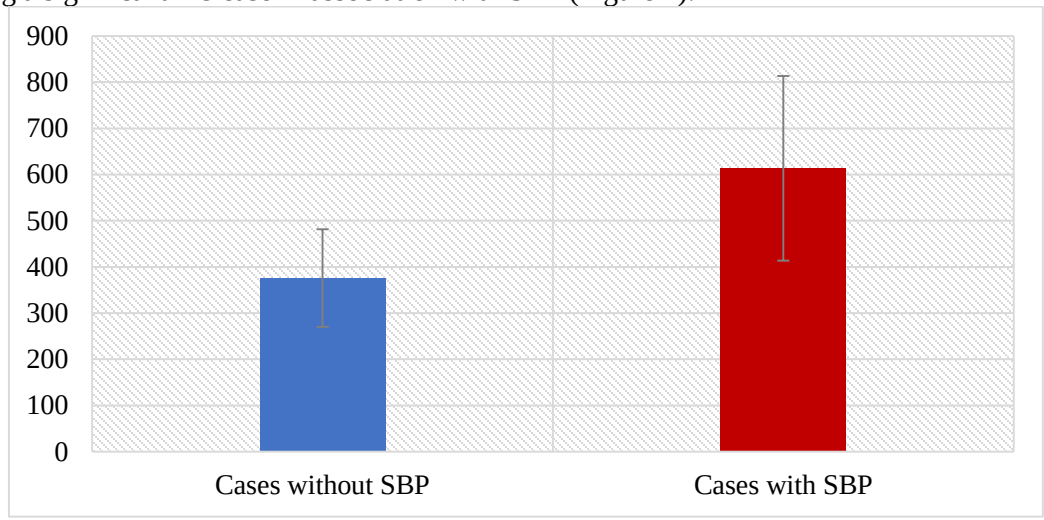

Figure (1): Ascitic fluid calprotectin level in the two studied groups

Ascitic fluid calprotectin had a significant positive correlation with TLC and PMNs, while it had a strong negative relationship with both ascitic albumin and SAAG. Calprotectin did not have a strong relationship with glucose levels in ascitic fluid (Table 4).

Table (4): Correlation between ascitic fluid calprotectin level and other ascitic biomarkers

Correlation of *ascitic calprotectin level* with:	Correlation Coefficient (r)	P value
TLC	0.551	< **0.001***
PMNs	0.554	< **0.001***
Ascitic fluid albumin	-0.364	< **0.001***
Ascitic fluid glucose	0.005	0.961
SAAG	-0.210	**0.047***

*: Significant difference.

Using a cut-off point of 433.7 ng/ml, ascitic calprotectin had sensitivity and specificity of 73.3% and 85.1%, respectively, for detecting patients with SBP (Figure 2).

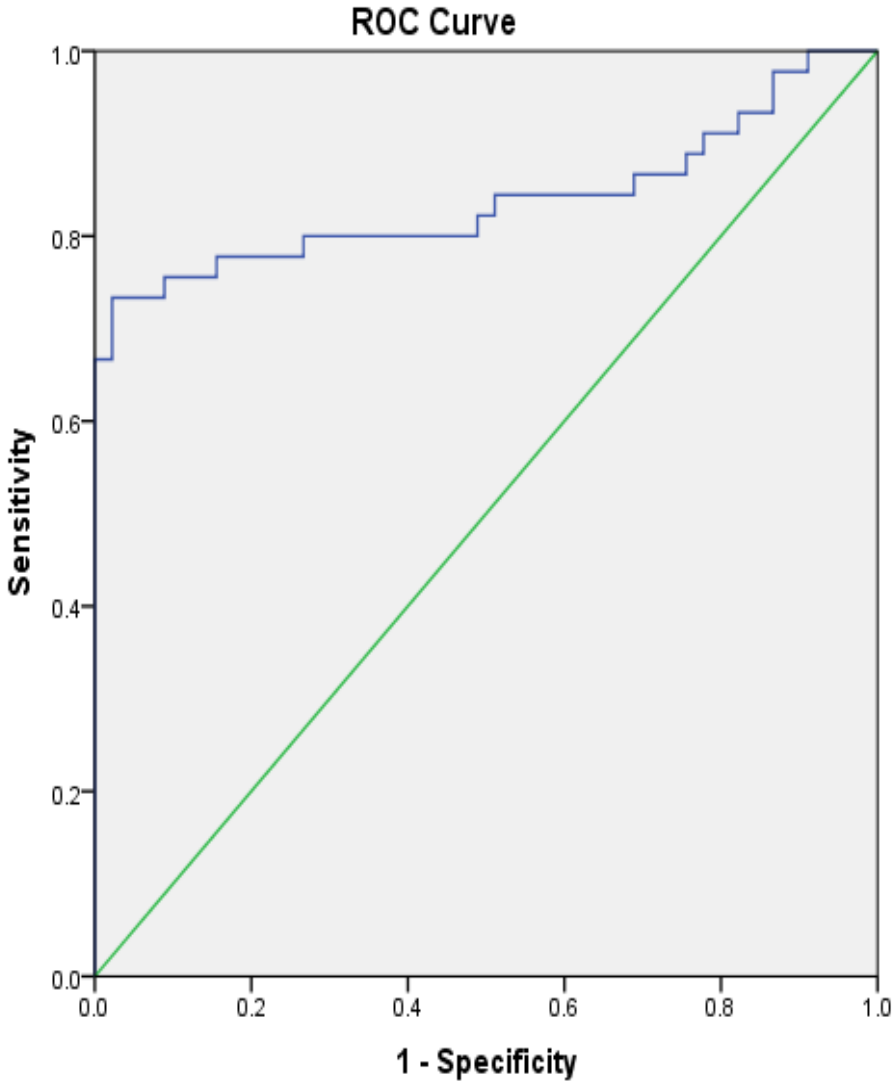

Figure (2) ROC curve analysis for ascitic fluid calprotectin as a marker for SBP.

DISCUSSION

A PMN count of more than 250/µL in ascitic fluid that doesn't come from an illness inside the abdomen was used to diagnose SBP [7]. The count and differential of ascitic fluid leucocytic cells are low-cost and simple to accomplish by hand using light microscope, but the diagnosis is often not made for a while. As a result, an automatic PMN counter was deployed, although the diagnostic accuracy was limited [21]. Therefore, there is a need for a fast and accurate method of diagnosing SBP [22].

The current study showed that there were big changes between the two groups when it came to serum (S.) albumin, PT, CRP, and ascitic fluid Albumin. Regarding lower S. albumin in the SBP group, albumin is synthesized in the liver. In decompensated cirrhosis, impaired liver function reduces albumin production, leading to lower levels in both groups. However, SBP can further worsen liver function and increase protein loss through inflammation, causing a steeper decline in S. albumin. The SBP group had more albumin than the non-SBP group.

Also, PT reflects the extrinsic coagulation pathway. Inflammation associated with SBP disrupts coagulation factors, leading to prolonged PT more in the SBP group than in the non-SBP group. This could explain prolonged PT in the SBP group [23,24]. However, ascitic fluid albumin reflects intravascular albumin concentration and capillary integrity. In SBP, inflammation damages the lining of the blood vessels in the abdomen. This damage makes it easier for albumin to leak out of the bloodstream and into the ascitic fluid. However, due to the nature of inflammation in SBP, the body can't refill albumin in the ascitic fluid very well. This leads to decreased overall albumin concentration within the ascitic fluid compared to patients without SBP.

On the other hand, CRP is a non-specific inflammatory marker. SBP causes significant inflammation, resulting in elevated CRP levels compared to the non-SBP group [24,25]. However, notably, the mean CRP level was elevated even in patients without SBP. This observation aligns with the understanding that CRP is a general sign of inflammation and doesn't show what kind of illness someone has. It's important to remember that people with decompensated liver cirrhosis often experience compromised immune function, which could lead to subclinical infections contributing to mildly elevated CRP levels [26].

The current study's ascitic fluid along with SBP, calprotectin levels rose by a large amount. with mean values in the non-SBP and SBP groups being 376.06 and 613.28 ng/ml, respectively ($P < 0.001$). Calprotectin function is unknown; however, it has been demonstrated to have antibacterial properties. Calprotectin stops the spread of E. coli, S. aureus, Staphylococcus epidermidis, Klebsiella spp., and Candida spp., but only at concentrations lower than those found in the blood of people who have bacteremia, which may be present in some circumstances. Killing occurs at dosages that are two to four times higher than the lowest inhibitory limits [27]. In an earlier study by **Elbanna *et al.***, it was discovered that people with spontaneous bacterial peritonitis (SBP) had much higher amounts of ascitic calprotectin [879.8 $\pm$ 67.5] than people who did not have SBP. [534.2 $\pm$ 59.3 [p<0.01] [28]. **Abdel-Razik *et al.*** validated our results, showing that the median values of ascitic calprotectin were 762.6 and 270.7 ng/ml in the SBP and non-SBP groups, respectively ($p < 0.001$) [29]. **Nabiel *et al.*** reported that the same ascitic marker had mean values of 647.33 and 277.97 ng/ml in the SBP and non-SBP groups, respectively ($p < 0.001$) [30].

Ali and Mohamed reported that ascitic calprotectin showed a significant rise with the development of SBP ($p < 0.001$). It had mean values of 569.15 and 237.64 ng/ml in the SBP and non-SBP groups, respectively [31]. All previous studies confirmed our findings regarding ascitic calprotectin in association with SBP.

In the current study, using a cut-off point of 433.7 ng/ml, ascitic calprotectin had sensitivity and specificity of 73.3% and 85.1%, respectively, for detecting patients with SBP. In a study by **Fernandes and his colleagues**, they found that ascitic fluid calprotectin had a high sensitivity (87.8%) and specificity (97.9%) for finding SBP (AUC 0.916, 95% CI: 0.847–0.986, $P \leq 0.001$). Positive predictive scores were 97.3% and negative predicted scores were 90.2%. Even though the test showed promise, it could still be better. The test had a high amount of specificity—85.1% to be exact. If the calprotectin amount is above 433.7 ng/ml, this means that the test was positive, which indicates the existence of SBP. This can be valuable in ruling out SBP for patients with concerning symptoms. However, the sensitivity (73.3%) was not perfect. Nearly a quarter of patients with SBP might have calprotectin levels below the cut-off, potentially leading to missed diagnoses. Additionally, the optimal cut-off point may need further evaluation [32]. **Burri *et al.*** [21] determined that calprotectin is a dependable predictor of SBP. The ELISA method had an area under the curve (AUC) of 0.977 (95% CI 0.933–0.995), while the point of care testing (POCT) had an AUC of 0.982 (95% CI 0.942–0.997). It was possible to diagnose SBP with a high level of accuracy (95% for ELISA and 89.2% for POCT) and sensitivity (100% for ELISA and 84.7%) when a threshold of 630 µg/ml was used. The results from **Abdel-Razik *et al.*** were similar (85.2% sensitivity and 95.4% specificity) when they used an ELISA technique to measure calprotectin in ascitic fluid at a level of 445 ng/ml [29]. Other authors reported that the 375 ng/ml cut-off value had sensitivity and specificity of 87.5% and 82.1%, respectively [30]. Moreover, **Selim *et al.*** reported that a 620 ng/ml cut-off value had 95.45% for precision and 90.91% for sensitivity [22].

The current study found that ascitic fluid calprotectin was significantly linked to TLC and PMNs, while it had a significant negative correlation with ascitic albumin and serum-ascites albumin gradient (SAAG). It is not clear how calprotectin is connected to the amount of glucose in ascitic fluid. There was a link between the amount of calprotectin in the ascitic fluid and C-reactive protein (CRP) ($r = 0.578$, $P < 0.001$), the number of PMN cells in the ascitic fluid ($r = 0.801$, $P < 0.001$), and the amount of LDH in the ascitic fluid ($r = 0.607$, $P < 0.001$). It was discovered that there was no link between calprotectin in ascitic fluid and blood leukocytes, ascitic protein, or albumin [32]. A study by **Selim *et al.*** found a strong link between ascitic calprotectin and MELD score, ascitic TLC, ascitic PMNs, and total leukocyte count. Conversely, it exhibited a strong negative connection with the levels of albumin in both serum and ascitic fluid [22]. **Elbanna *et al.*** found a strong association between the levels of ascitic calprotectin and the total count of white blood cells in ascitic fluid [p=<0.01] [28]. Despite some heterogenicity in the previous correlations, ascitic calprotectin has a strong association with other inflammatory biomarkers like CRP, PMNs, and TLC.

In the current study, the calprotectin in the ascitic fluid was assessed utilizing the ELISA tests and tests that can be done at the point of care. This study looked at a number of factors and diagnostic methods that can be used instead of counting cells by hand. The current study had some limitations. The first is its nature as a study that only looked at one center and had a small sample size. The second is that the prognostic value of calprotectin as a marker of SBP, as well as its value in monitoring treatment response, should be further evaluated.

CONCLUSION

The study suggests ascitic fluid calprotectin has the potential and can be used to find people with cirrhosis and ascites who have spontaneous bacterial peritonitis (SBP). While a 433.7 ng/ml cut-off yielded reasonable sensitivity (73.3%) and specificity (85.1%), limitations remain. Further research is needed to refine its use, but calprotectin may become a valuable addition to existing methods like neutrophil count for a more comprehensive SBP diagnosis.

DECLARATIONS

- **Availability of data and materials:** The data substantiating the findings of this study can be obtained by contacting the corresponding author. The data ares inaccessible to the public owing to privacy or ethical constraints.
- **Competing interests:** None of the authors have competing interests.
- **Funding:** This is a non-funded work.
- **Authors contribution:** The study was designed by MEK and ME. AS and AEF gathered the data. MEK and ME examined the data. AS authored the initial version of the manuscript. The final version of the text was reviewed and approved by all authors.

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