Original Article

Procalcitonin and C-reactive protein in the diagnosis of spontaneous bacterial peritonitis

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Background: Spontaneous bacterial peritonitis (SBP) is a serious complication of cirrhosis and is associated with high morbidity and mortality. Rapid institution of appropriate antibiotics is central to the improved patient outcome. Correctly obtaining ascites fluid for analysis has several technical and logistic limitations resulting in overuse of empiric antibiotics when patients are admitted to the hospital with suspected SBP. Procalcitonin and C-reactive protein (CRP) are non-invasive markers of infection. We conducted a study to illustrate the role of these markers in making the diagnosis of SBP in patients with cirrhosis.

Methods: A total of 45 patients were enrolled in this prospective cohort study, 14 (31.1%) of which were found to have SBP. Ascitic fluid neutrophils, serum procalcitonin and CRP levels were measured prior to initiation of antibiotics and these parameters were compared between the two groups. Area under receiver operator characteristic (AUROC) curves were used to assess the diagnostic accuracy of procalcitonin and CRP in this population. We defined neutrocytic SBP group as a combination of patients who had classic SBP (positive ascitic culture and >250 neutrophils/mm^3) and culture-negative neutrocytic ascites.

Results: Serum procalcitonin (2.81±2.59 *vs.* 0.43±0.48 ng/mL; P=0.0032), serum CRP (60.30±44.48 *vs.* 22.2±23.28; P=0.0055) and ascitic fluid neutrophil levels (49.23±30.90 *vs.* 16.7±20.39; P=0.0064) were significantly higher in SBP group than non-SBP group. AUROC for procalcitonin (cut-off >2.0 ng/mL) was 0.75 (95% CI, 0.61–0.88), CRP (cut-off >3.0 mg/L) was 0.55 (95% CI, 0.43–0.68) and for procalcitonin combined with CRP was 0.76 (95% CI, 0.61–0.90) for diagnosing all-cause SBP. In a subgroup analysis of patients with neutrocytic SBP, AUROC for procalcitonin was 0.88 (95% CI, 0.74–1.00), CRP was 0.62 (95% CI, 0.45–0.79) and for procalcitonin combined with CRP was 0.93 (95% CI, 0.81–1.00). Addition of CRP to procalcitonin did not significantly change the AUROC for diagnosis of SBP.

Conclusions: Serum procalcitonin could be used as an adjunctive non-invasive biomarker in diagnosing SBP with a high degree of accuracy in cirrhotic patients. Addition of CRP does not seem to significantly increase the diagnostic accuracy of procalcitonin.

Keywords: Procalcitonin; peritonitis; liver cirrhosis; C-reactive protein (CRP); diagnosis

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Introduction

Spontaneous bacterial peritonitis (SBP) is one of the turning points in the natural history of progression of cirrhosis which heralds the onset of decompensated disease. It is associated with a high incidence of morbidity and mortality (up to 20–30%) as it puts cirrhotic patients at risk of developing hepatic encephalopathy, renal failure, acidosis and shock (1). Prompt initiation of antibiotics to treat SBP is the cornerstone of optimal therapy as it improves patient outcomes and survival (2). Primary prophylaxis with antibiotics should be instituted in high-risk patients (e.g., cirrhotics with low protein ascites, gastrointestinal hemorrhage) and secondary prophylaxis for those with a prior history of SBP (3,4).

Practice guidelines from various medical societies recommend doing a paracentesis in order to make a diagnosis of SBP based on ascitic fluid neutrophil count prior to initiation of antibiotics (5,6). Given that the process of paracentesis requires skill, expertise in specimen handling and time delay associated with obtaining ascitic fluid cell count, many physicians in busy office practices in the United States initiate antibiotics based on clinical suspicion alone which adds to the problem of growing antibiotic resistance from overuse of unwarranted antibiotics. Alternatively, the diagnosis of SBP can be entirely missed if clinical suspicion is low and paracentesis is overlooked. In high volume emergency rooms and busy outpatient clinics throughout the country, availability of a quick, reliable, non-invasive marker for SBP would help crucial decision-making regarding need for paracentesis and promote appropriate antibiotic use.

Procalcitonin (PCT), which is widely used as a marker of bacterial infection in various clinical conditions (e.g., pneumonia, meningitis, bacterial gastroenteritis, septic shock) has also been studied in the setting of SBP and has been found to accurately predict the presence of SBP when present at elevated levels (7-17) (*Table 1*). Procalcitonin has been studied alone or in combination with other inflammatory markers such as TNF-alpha, IL-6, lipocalin/NGAL, MIP-1 beta and has been shown to be a sensitive and specific marker for the diagnosis of SBP (7,13,18) (*Table 1*). Similarly, CRP which is an acute phase reactant too has been found to be elevated in patients with SBP (19-21). CRP is a chemokine which is secreted by liver and can be elevated in a wide variety of clinical conditions including infection, connective tissue disorders, malignancies and autoimmune conditions.

To the best of our knowledge, ours is the first prospective study from the United States describing the role of procalcitonin alone or in combination with CRP in diagnosing patients with SBP while adding to the growing body of evidence that non-invasive markers may have a role in the diagnosis of this entity.

We aimed to assess the efficacy of serum procalcitonin level and CRP in predicting the presence of SBP.

Methods

Patient selection

This was a prospective cohort study where cirrhotic patients with suspected SBP admitted to Methodist University Hospital in Memphis, Tennessee, USA between September 2012 and March 2013 were consecutively enrolled in the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by The Institutional Review Board of Methodist University Hospital, Memphis, Tennessee, USA (IRB approval number: 12-02006-XP), with exemption for informed consent.

All subjects in the study met the following inclusion criteria: (I) cirrhosis with ascites; (II) clinical suspicion of SBP, based at the minimum on: large volume ascites and new abdominal pain; (III) ascitic fluid WBC count and culture obtained before the use of antibiotics at admission serum PCT and CRP measurements; (IV) absence of infection in other organs or sites or those already on antibiotics.

Paracentesis and procalcitonin, CRP estimation

We developed a protocol, at the Methodist University Hospital Transplant Institute, for the measurement of serum procalcitonin (normal range: 0.5–2.0 ng/mL) and serum CRP (normal range: 0.5–3.0 mg/L) at the time of hospital admission, prior to administering antibiotics. At our center, paracentesis is performed using aseptic technique and ascitic fluid is inoculated into aerobic and anaerobic blood culture bottles at bedside routinely. Fluid specimen is then sent off promptly (within 1 hour) to the laboratory for ascitic fluid analysis.

Ascitic fluid (AF) was collected from hospitalized patients using sterile method and cultured in blood culture bottles, according to the guidelines of the Infectious Diseases Society of America. Bacterial identification and antimicrobial susceptibility testing were carried out as

Table 1 Studies examining the role of serum procalcitonin in diagnosis of SBP

Author, year, country	# of patients	Underlying disease	Procalcitonin testing method	Cut-off value (ng/mL)	Sensitivity (%)	Specificity (%)
Viallon *et al.* (in 2000), France	61	Cirrhosis	LUMItest	0.75	95	98
Spahr *et al.* (in 2001), Switzerland	20	Cirrhosis	LUMItest	0.5	50	90
Connert *et al.* (in 2003), Germany	100	Cirrhosis	LUMItest	0.58	92	78
Yuan *et al.* (in 2013), China	84	Hepatitis B	Diasorin	0.48	95	79
Cekin *et al.* (in 2013), Turkey	101	Cirrhosis	–	0.42	78	75
Wu J *et al.* (in 2014), China	362	Cirrhosis	–	0.462	83.7	94.9
Lesinska *et al.* (in 2014), Poland	32	Cirrhosis	LUMItest	–	–	–
Gharabaghi *et al.* (in 2015), Iran	33	Cirrhosis	–	0.5	75	92
Cai *et al.* (in 2015), China	78	Cirrhosis	ELFA VIDAS	2.0	68.8	94.2
Wu H *et al.* (in 2016), China	88	Cirrhosis	ECLIA Cobas	0.78	77.5	60.4
Abdel-Razik *et al.* (in 2016), Egypt	79	Cirrhosis	ELISA RayBio	0.94	94.3	91.8

SBP, spontaneous bacterial peritonitis.

Table 2 Spontaneous bacterial peritonitis and its variants

SBP types	PMN ≥250 µL	Culture
Classic SBP	+	+
CNNA	+	–
MNB	–	+
Sterile	–	–

CNNA, culture-negative neutrocytic ascites; MNB, monomicrobial non-neutrocytic bacterascites; PMN, polymorphonuclear cells; SBP, spontaneous bacterial peritonitis.

per standard protocol. Based on the results of ascitic fluid PMN count and culture results, patients were classified into 4 groups: classic SBP (WBC count ≥500/mm^3 and PMN >250/mm^3 in AF with a positive bacterial culture), culture-negative neutrocytic ascites (CNNA; WBC count ≥500/mm^3 and PMN >250/mm^3 in AF but negative culture), monomicrobial non-neutrocytic bacterascites (MNB; AF with a positive bacterial culture/positive gram stain and WBC count <500/mm^3 and PMN <250/mm^3). Finally, sterile ascites was defined when there were <250 neutrophils/microliter and ascitic fluid culture was negative (*Table 2*). A contaminant was defined as a non-pathogenic microorganism that was isolated from ascitic fluid culture. For the purpose of this study, we included variants of classic SBP, CNNA and MNB all under the category of SBP. We also did a subgroup analysis of 'neutrocytic ascites' which included classic SBP and CNNA.

Etiology of cirrhosis was recorded with respect to HBV, HCV, alcoholic, autoimmune cirrhosis and other conditions. Clinical data were obtained retrospectively by thorough review of the patients' medical charts and included age, presence of ascites, encephalopathy, recent episode of variceal bleeding, bacteremia, AST, ALT, total bilirubin, prothrombin activity (PTA) and other variables.

Statistical analysis

Baseline recipient characteristics were summarized for both patients with SBP and patients without SBP. Mean ± standard deviation (SD) was used for continuous variables, and count with percentages was used for categorical variables. Continuous variables were compared using the Wilcoxon Rank Sum test and categorical variables were analyzed with the Chi-square test or Fisher exact test. The level of procalcitonin and CRP was plotted for SBP and non-SBP patients respectively. The AUROC curve for procalcitonin and CRP were plotted to assess the accuracy of diagnosing SBP.

All analyses were conducted using SAS 9.4 (SAS, Cary, NC) software.

Two-sided P value was considered statistically significant when <0.05.

Table 3 Baseline demographics of all patients (n=45)

Patient characteristics	All patients (n=45)	SBP (n=14)	No SBP (n=31)	P value (two sided)
Demographic				
Age (years) mean ± SD	53.8±10.5	53.6±12.9	53.96±9.4	0.62
Gender (male), n (%)	35 (77.7)	12 (85.7)	23 (74.19)	0.47
Race/ethnicity, n (%)				0.31
Caucasian	31	8 (57.1)	23 (74.19)	
African American	11	4 (28.6)	7 (22.6)	
Hispanics	3	2 (14.3)	1 (3.23)	
Etiology of cirrhosis, n (%)				0.80
Alcohol	16 (35.56)	4 (28.6)	12 (38.8)	
Fulminant Hepatic failure	2 (4.44)	1 (7.14)	1 (3.23)	
Hep C	20 (44.44)	8 (57.1)	12 (38.8)	
NASH	3 (6.66)	1 (7.14)	2 (6.46)	
PBC	2 (4.44)	0 (0.00)	2 (6.46)	
PSC	2 (4.44)	0 (0.00)	2 (6.46)	
MELD Score mean ± SD	20.8±6.5	21.5±5.0	20.41±7.16	0.35
Ascitic fluid analysis mean ± SD				
WBC	556.93±1,437.20	1,461.64±2,371	148.3±196.3	0.001
Neutrophil	30.35±29.72	49.23±30.90	16.7±20.39	0.007
Lymphocyte	55.45±28.51	47.20±36.00	57.88±26.75	0.49
Procalcitonin level (ng/dL), mean ± SD	1.17±1.84	2.81±2.59	0.43±0.48	0.003
CRP, mean ± SD	32.42±34.34	60.30±44.48	22.20±23.28	0.007

CRP, C-reactive protein; Hep C, hepatitis C; MELD, model for end stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis; SD, standard deviation; WBC, white blood cell count.

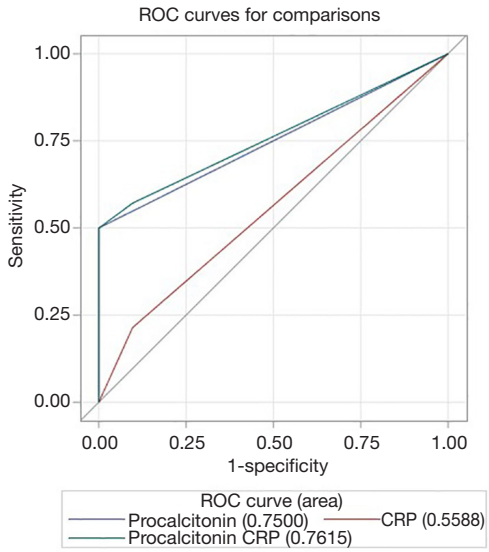
Results

A total of 45 patients with a mean age (± SD) of 53.8±10.5 years with a mean model for end stage liver disease (MELD) score of 20.8±6.5 were enrolled. Patient population comprised of 31 (68.8% Caucasian), 11 (24.4% African-American) and 3 (6.66% Hispanic) subjects. Most common etiology of underlying cirrhosis was hepatitis C (44%) followed by alcohol-induced cirrhosis (35%) and non-alcoholic steatohepatitis (NASH) (6.6%).

Baseline demographics of patients included in the study are shown in *Table 3*.

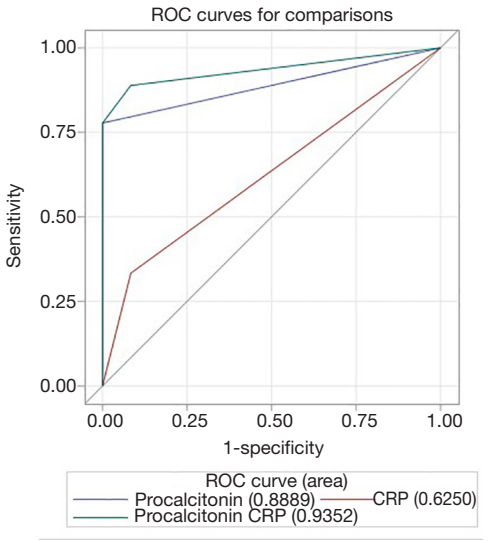
Patients were divided into two groups: those with SBP (n=14) and those without SBP (n=31). There were no statistically significant differences in age, gender, race/ethnicity, etiology of cirrhosis or MELD score (21.5±5.0 *vs.* 20.41±7.16; P=0.35, *Table 3*) between the two groups. Differences in serum procalcitonin level (2.81±2.59 *vs.* 0.43±0.48; P=0.003, *Table 3*), serum CRP level (60.30±44.48 *vs.* 22.20±23.28; P=0.007) and ascitic fluid neutrophil counts (49.23±30.90 *vs.* 16.7±20.39; P=0.007) were highly statistically significant between patients with SBP and those without SBP (*Table 3*, *Figures 1*,*2*).

Of the 14 patients diagnosed with SBP, 4 (28.6%) were found to have classic SBP, 5 (35.7%) had CNNA and remaining 5 (35.7%) had MNB. Of the patients with positive ascitic fluid cultures, most common isolated pathogen was *E. Coli* (44%) followed by *Staphylococcus epidermidis* (33%), group D *Streptococcus* (11%) and



ROC association statistics	Area	95% Wald confidence limits
Procalcitonin	0.75	0.61–0.88
CRP	0.55	0.43–0.68
Procalcitonin & CRP	0.76	0.61–0.90

Figure 1 Comparison of ROC curves showing AUROC for procalcitonin, CRP, and combined effect of procalcitonin-CRP in predicting 'all cause SBP'. ROC, receiver operator characteristics; AUROC, area under receiver operator characteristic; CRP, C-reactive protein; SBP, spontaneous bacterial peritonitis.



ROC association statistics	Area	95% Wald confidence limits
Procalcitonin	0.88	0.74–1.00
CRP	0.62	0.45–0.79
Procalcitonin & CRP	0.93	0.81–1.00

Figure 2 Comparison of ROC curves showing AUROC for procalcitonin, CRP, and combined effect of procalcitonin/CRP in predicting 'neutrocytic SBP'. ROC, receiver operator characteristics; AUROC, area under receiver operator characteristic; CRP, C-reactive protein; SBP, spontaneous bacterial peritonitis.

Streptococcus viridans (11%).

Three out of four patients with classic SBP and 4 out of 5 patients with CNNA were found to have elevated procalcitonin (cut-off 2.0 ng/mL) while all 5 patients with MNB had normal procalcitonin levels (P=0.0476). All 31 patients without SBP had procalcitonin within normal range (≤2 ng/mL).

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of procalcitonin in diagnosing "all SBP" (including classic SBP, CNNA and MNB) and neutrocytic SBP (classic SBP and CNNA) are shown in *Tables 4,5*. These values for CRP in diagnosing "all SBP" and neutrocytic SBP are shown in *Tables 6,7* respectively.

CRP, at a cut-off value of 3 mg/L, alone, was not helpful in distinguishing SBP from non-SBP. Though difference in CRP level was statistically significant between the two groups (60.30±44.48 *vs.* 22.2±23.28; P=0.007), they were >3 mg/L in an overwhelming majority of patients (95%) irrespective of presence or absence of SBP.

AUROC for diagnosing "all cause SBP" for procalcitonin alone was 0.75 (95% CI, 0.61–0.88), CRP alone was 0.55 (95% CI, 0.43–0.68) and for procalcitonin combined with CRP was 0.76 (95% CI, 0.61–0.90) (*Figure 1*). Procalcitonin was an even better test for diagnosing "neutrocytic SBP" as AUROC for procalcitonin alone was 0.88 (95% CI, 0.74–1.00), CRP alone was 0.62 (95% CI, 0.45–0.79) and for procalcitonin combined with CRP was 0.93 (95% CI, 0.81–1.00) (*Figure 2*). As evident from AUROC curves, addition of CRP did not significantly improve the diagnostic yield of procalcitonin in making the diagnosis of SBP. Though AUROC for CRP marginally improved when a much higher cut-off was used for CRP (e.g., >40 mg/L), it still fared poorly when compared to the diagnostic accuracy of

Table 4 Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of procalcitonin in predicting all SBP (includes classic SBP, CNNA, and MNB)

PCT	All SBP		PPV	NPV	Sensitivity	Specificity	Accuracy
	Yes	No					
>2 (positive)	7 (TP)	0 (FP)	100%	82%	50%	100%	84.4%
≤2 (negative)	7 (FN)	31 (TN)					

PPV: TP/(TP + FP); NPV: TN/(TN+FN); sensitivity: TP/(TP + FN); specificity: TN/(TN + FP); accuracy: (TP + TN)/(TP + FP + FN + TN). CNNA, culture negative neutrocytic ascites; FN, false negative; FP, false positive; MNB, monomicrobial non-neutrocytic bacterascites; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; SBP, spontaneous bacterial peritonitis; TN, true negative; TP, true positive.

Table 5 Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of procalcitonin in predicting neutrocytic SBP (includes classic SBP and CNNA)

PCT	Neutrocytic SBP		PPV	NPV	Sensitivity	Specificity	Accuracy
	Yes	No					
>2 (positive)	7 (TP)	0 (FP)	100%	95%	78%	100%	95.5%
≤2 (negative)	2 (FN)	36 (TN)					

PPV: TP/(TP + FP); NPV: TN/(TN+FN); sensitivity: TP/(TP + FN); specificity: TN/(TN + FP); accuracy: (TP + TN)/(TP + FP + FN + TN). CNNA, culture negative neutrocytic ascites; FN, false negative; FP, false positive; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value; SBP, spontaneous bacterial peritonitis; TN, true negative; TP, true positive.

Table 6 Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of CRP in predicting all SBP (includes classic SBP, CNNA, and MNB)

PCT	All SBP		PPV	NPV	Sensitivity	Specificity	Accuracy
	Yes	No					
>3 (positive)	11 (TP)	29 (FP)	27.5%	100%	100%	6.5%	30.9%
≤3 (negative)	0 (FN)	2 (TN)					

PPV: TP/(TP + FP); NPV: TN/(TN+FN); sensitivity: TP/(TP + FN); specificity: TN/(TN + FP); accuracy: (TP + TN)/(TP + FP + FN + TN). CNNA, culture negative neutrocytic ascites; CRP, C-reactive protein; FN, false negative; FP, false positive; MNB, monomicrobial non-neutrocytic bacterascites; NPV, negative predictive value; PPV, positive predictive value; SBP, spontaneous bacterial peritonitis; TN, true negative; TP, true positive.

Table 7 Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of CRP in predicting neutrocytic SBP (includes classic SBP and CNNA)

PCT	Neutrocytic SBP		PPV	NPV	Sensitivity	Specificity	Accuracy
	Yes	No					
>3 (positive)	6 (TP)	34 (FP)	15%	100%	100%	5.56%	19.05%
≤3 (negative)	0 (FN)	2 (TN)					

PPV: TP/(TP + FP); NPV: TN/(TN+FN); sensitivity: TP/(TP + FN); specificity: TN/(TN + FP); accuracy: (TP + TN)/(TP + FP + FN + TN). CNNA, culture negative neutrocytic ascites; CRP, C-reactive protein; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; SBP, spontaneous bacterial peritonitis; TN, true negative; TP, true positive.

procalcitonin.

Discussion

SBP is a common but serious complication of cirrhosis which jeopardizes patient survival as it increases the risk of developing hepatic encephalopathy, gastrointestinal bleeding, renal failure and septic shock (6). It is hypothesized that SBP occurs due to cirrhosis-associated-immune-dysfunction mediated bacterial translocation which is a result of impaired opsonization activity of ascitic fluid, diminished reticulo-endothelial activity, increased intestinal permeability, poor gut motility, decreased phagocytic activity and activation of inflammatory cytokines (22). Most common pathogens that translocate and thus cause SBP include *E. Coli*, *Klebsiella pneumoniae*, *Enterobacter spp*., *Enterococcus spp*. and others.

Ascitic fluid analysis is an essential part of making the diagnosis of SBP. However, obtaining and analyzing ascitic fluid by doing paracentesis itself is fraught with its own set of challenges. Given the time required to perform a paracentesis and the need for ultrasound machine to minimize the risk of bowel perforation, many physicians are reluctant to incorporate this procedure in their busy clinic practices. As most cirrhotic patients have coagulopathy and some degree of thrombocytopenia, many physicians are hesitant to do this procedure despite the strong evidence of the safety of paracentesis in face of these laboratory abnormalities (6,23-25). Proper handling of ascitic fluid is of paramount importance. As bacterial culture is usually desired, at least 10–20 mL of ascitic fluid should be collected during diagnostic paracentesis (26) and promptly inoculated into blood culture bottles at the bedside as taking ascitic fluid-filled syringe to laboratory has been shown to lower the sensitivity of bacterial detection in the specimen (6,27). Though ascites-specific dipstick based on leukocyte esterase for detecting SBP has been developed (6,28), it is not in widespread use and thus diagnosis of SBP still depends on manual cell count which is laborious, time-consuming and introduces operator-bias. Thus, given these challenges associated with diagnostic paracentesis, it would be desirable to have a widely available, non-invasive test with rapid turnaround time and high sensitivity/positive predictive value which can help make an accurate diagnosis of SBP.

Procalcitonin, a precursor of thyroid hormone calcitonin, is a 116 amino acid protein which was first found to be associated with clinically significant infections in humans approximately 25 years ago (29). Although it is most widely used as a surrogate marker of bacterial infection, it has also been found to be elevated in a variety of other non-infectious conditions such as burns (29), postoperative state (30), neuroendocrine tumors of lung and gastrointestinal tract (31,32), hemophagocytic lymph histiocytosis (33) and various other types of cancers (34). Procalcitonin is secreted by almost all parenchymal tissues in the body in response to TNF-alpha during bacterial infection and begins to rise within 4 hours of bacterial infection (11,35). It has a long half-life of 25–30 hours and is undetectable in healthy individuals.

Procalcitonin has been studied in the setting of SBP and serum procalcitonin values have almost invariably been found to be significantly higher in patients with SBP than those without it with the exception of study done by Lesinska *et al.* (7-18) (*Table 1*). In a recent meta-analysis, procalcitonin was found to have a sensitivity of 0.82 and specificity of 0.86 with AUROC of 0.92 for diagnosis of SBP (16). Procalcitonin levels in patients with culture positive SBP versus culture negative SBP (CNNA) were variable where some studies reported statistically significantly elevated procalcitonin in the former group (10) while others did not (9).

MNB patients often pose challenge in a clinical situation when pretest probability of SBP is high but neutrophil count is low in fluid studies. We often wonder if it is a false result related to sample contamination or is it an attenuated response due to weakened immune system, unrecognized outpatient prophylactic antibiotic use or a characteristic unique to certain bacteria. Due to these reasons, we also performed subgroup testing excluding MNB patients and comparing only neutrocytic ascites (classic SBP and CNNA) versus controls which showed even higher sensitivity and specificity of procalcitonin in diagnosing SBP. All our 5 MNB patients had normal procalcitonin levels, suggesting possible contamination or subclinical infection.

C-reactive protein (CRP) is an acute phase reactant of hepatic origin which is secreted in response to IL-6 during systemic inflammatory response (11). It may be elevated in a wide variety of conditions such as infections, collagen vascular diseases, cancers, coronary artery disease, obstructive sleep apnea and others. Both serum and ascitic fluid CRP levels have been studied and found to be elevated in patients with SBP (20,21,36) though some studies did not find any significant difference in CRP levels in patients with SBP and those without it (14). Levels of hs-CRP correlated with increased mortality in patients with SBP (19). A

cutoff of 10 mg/L was suggested for CRP (AUC: 0.93) in a large study of patients with cirrhosis associated bacterial infections (37).

There have been a few studies that looked at combining procalcitonin and CRP in making the diagnosis of SBP and they have been well summarized in the meta-analysis done by Lin *et al.* (9). They reported pooled sensitivity and specificity for procalcitonin to be 79% (95% CI: 64–89%) and 89% (95% CI: 82–94%) respectively. Pooled sensitivity and specificity for CRP was 77% (95% CI: 69–84%) and 85% (95% CI: 76–90%) (11). It concluded that positive likelihood ratio for procalcitonin was high enough for it to qualify as a rule-in test (11). Correspondingly, negative likelihood ratio for CRP was low enough for it to be accepted as a rule-out test (11).

The limitation of the current study is its small sample size that may have led to potential selection bias. Unmeasured confounding variables, and missingness in the data may have potentially influenced the diagnostic accuracy of the procalcitonin and CRP. Additionally, the time of collection since the onset of SBP, duration of illness, severity of underlying liver disease, and associated comorbidities could have a potential influence on the accuracy of results. These confounders may need to be assessed in a larger prospective study. In conclusion, while ascitic fluid neutrophil count still remains the gold standard, results of our study suggest that procalcitonin may be a helpful adjunct in making the diagnosis of SBP in patients with decompensated cirrhosis. In our study, we did not find any significant increase in diagnostic accuracy for SBP when CRP is added to procalcitonin.

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Footnote

Data Sharing Statement: Available at https://tgh.amegroups.com/article/view/10.21037/tgh-19-297/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-19-297/coif). SKS reports grants from Gilead Sciences, Conatus Pharma, Intercept Pharma, Genfit, Bayer, Exact Sciences, Biotest, Shire NASH and Enanta, outside the submitted work; he reports Speaker's Bureau from Intercept Pharma, Alexion and Dova, outside the submitted work; he is on Advisory Board of Bayer and Biotest, outside the submitted work. SKS serves as an Editor-in-Chief of *Translational Gastroenterology and Hepatology*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Institutional Review Board of Methodist University Hospital, Memphis, Tennessee, USA (IRB approval number: 12-02006-XP) with exemption for informed consent.

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