Evaluation of A Novel Index That Incorporates Both Neutrophil-Lymphocyte Ratio and C-Reactive Protein for The Detection of Spontaneous Bacterial Peritonitis

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ABSTRACT
Background: Diagnosing spontaneous bacterial peritonitis (SBP) requires a high clinical index of suspicion because the clinical presentation varies widely. Early detection and treatment of SBP are crucial for improving survival rates. Minimally invasive markers such as blood neutrophil-lymphocyte ratio (NLR) and serum C-reactive protein (CRP) could be helpful to clinicians in identifying SBP patients.
Objective: This study aimed to assess the diagnostic efficacy of integrating measurements of NLR and CRP as a minimally invasive approach for detecting SBP.
Patients and methods: This was a cross-sectional study that included 124 cirrhosis-related ascites patients admitted to the Alexandria Main University Hospital in the Department of Internal Medicine. Participants with ≥ 250 neutrophil cells/mm^3 in ascitic fluid were defined as the SBP group (50 patients). In contrast, those with less than 250 neutrophil cells/mm^3 in ascitic fluid and negative ascitic cultures were the non-SBP group (74 participants).
Results: There was a substantially elevated blood NLR and CRP in SBP patients ($p<0.001$). Analyzed separately, NLR exceeding 3.16 offered a sensitivity of 76% and specificity of 97.3%, whereas CRP above 45.6 mg/L yielded a sensitivity of 84% and specificity of 91.8%. Our new index "NLR x $\sqrt{CRP}$" at a cutoff > 18.28 significantly improved diagnostic precision, with a better sensitivity of 94.0% and specificity of 94.59%.
Conclusions: The use of "NLR x $\sqrt{CRP}$ index" at a cutoff > 18.28 introduces an innovative, efficient, economical, and minimally invasive strategy for the diagnosis of SBP.
Keywords: Spontaneous bacterial peritonitis, Inflammatory markers, C-Reactive protein, Neutrophil-Lymphocyte ratio.

INTRODUCTION

Ascites is a substantial complication of advanced liver dysfunction, which ranks as the principal reason for hospital admissions among patients with cirrhosis. Infections of ascitic fluid in individuals with cirrhosis escalate the risk of mortality by up to four times [1]. Spontaneous Bacterial Peritonitis (SBP), a prevalent and severe infection in this demographic, occurs in 10% to 30% of these patients upon hospitalization [2].

Around 50% of patients are diagnosed with SBP upon admission, whereas it develops in the remaining patients during their hospitalization [3]. The etiology of SBP is linked to alterations in the gut microbiota, bacterial translocation, and increased intestinal permeability [4].

Furthermore, compromised immune function among patients who have advanced cirrhosis significantly contributes to the disease's progression [5]. Given the nonspecific clinical manifestations of SBP and its variability across different stages of liver disease, the diagnosis primarily relies on laboratory and microbiological evaluations. Diagnostic paracentesis and subsequent analysis of ascitic fluid are deemed the definitive methods for confirming or excluding SBP in cirrhotic patients [6]. However, this diagnostic procedure comes with some risks, such as visceral perforation, hemoperitoneum, secondary peritonitis, site of infection, abdominal wall hematoma, and persistent leakage, which is the one that happens most often [7].

Elevations in C-reactive protein (CRP) levels within the bloodstream indicate inflammatory or necrotic lesions within the body [8]. It is posited that during bacterial infections, macrophages secrete cytokines (such as tumor necrosis factor, interleukin-1, and interleukin-6) that stimulate hepatocytes for CRP production [8]. The neutrophil-lymphocyte ratio (NLR), which shows how the body's immune and inflammatory systems work together, is a key indicator for figuring out how balanced they are [9]. Furthermore, platelet indices, CRP levels, and total leukocyte counts were found to be good markers to tell if ascitic fluid is infected [10]. Consequently, we propose that NLR offers a valuable diagnostic method for detecting SBP when integrated with CRP levels.

PATIENTS AND METHODS

This was a cross-sectional study. The software MedCalc 18.2.1 was utilized to calculate the required sample size for the study. This calculation was based on the areas under the ROC curves (AUC) of the combined NLR and CRP in predicting SBP of 0.89, with an alpha error of 5% and a statistical power of 80%. The calculated sample size was rounded to 114 patients, but the study ultimately included a total of 124 patients.

Patients with cirrhosis-related ascites who were admitted to Alexandria Main University Hospital's Hepatobiliary Unit in the Department of Internal Medicine were included in this study. Clinical suspicion of SBP comprised either local manifestations of peritonitis like tenderness in the abdomen, abdominal pain, vomiting and ileus or systemic inflammation signs: fever or hypothermia, chills, change in white blood cell count, hepatic encephalopathy, deteriorating liver function, shock, worsening renal function and gastrointestinal hemorrhage. Ascitic fluid samples were obtained from all hospitalized patients with cirrhotic ascites [11].

Exclusion criteria: Patients who had secondary bacterial peritonitis, tuberculous and malignant, or pancreatic ascites. Patients who had trauma, surgery, cancer, or any concurrent infections affecting their white blood cells or CRP levels (such as urinary tract or pulmonary infections).

Subjects were subjected to the following: Comprehensive history collection, physical examination, abdominal ultrasonography, laboratory tests, routine diagnostic paracentesis, and ascitic fluid analysis. All subjects were evaluated regarding the following:

1. **Clinical evaluation** of local manifestations of peritonitis or systemic inflammation signs.

2. **Abdominal ultrasonography** was used to assess liver echo pattern and size and the presence of cirrhosis and ascites.

3. **Routine laboratory investigations** included the following:
   a. **Complete blood picture.**
   b. **Liver test profile:** serum aspartate and alanine aminotransferase (AST and ALT, respectively), serum albumin, serum bilirubin, and INR.
   c. **Renal function tests:** serum creatinine and urea.
   d. **Serum electrolytes:** sodium and potassium.
   e. **Serum CRP**.

4. **Ascitic fluid sampling for:**
   a. **Chemical analysis** (total proteins, glucose, and lactate dehydrogenase).
   b. **Counting of neutrophils:** to determine the total and differential leukocytic counts.
   c. **Ascitic fluid cultures:** Ascitic fluid inoculation (10 ml) in 2 blood culture bottles was performed at the bedside in all patients.

According to international guidelines, SBP was diagnosed when the ascitic fluid polymorphonuclear neutrophil (PMN) count was $\geq$ 250/mm^3 without alternative peritonitis causes. The study included both culture-positive SBP cases and those with culture-negative neutrocytic ascites. Participants with less than 250 neutrophil cells per mm^3 in ascitic fluid with culture-negative ascitic fluid were designated as the non-SBP group.

Statistical analysis

The collected data was wrangled, coded, and analyzed using the SPSS software (Armonk, NY: IBM Corp., version 25.0) and MedCalc (version 18.2.1), with the Kolmogorov-Smirnov test verifying continuous data distribution normality. Categorical variables were expressed as frequency and percentage and the Chi-square test was used to test the relationship between categorical variables. Quantitative variables were described using either mean $\pm$ standard deviation (SD) (for normally distributed) or median with interquartile range (for non-normally distributed). Independent-Samples t-test (for parametric) or Mann-Whitney U test (for non-parametric) were used to estimate the relation between continuous variables as appropriate. A logistic regression analysis of laboratory predictors affecting the presence of SBP as an outcome was conducted. Odds ratios and 95% confidence intervals (OR, 95% CI) were reported. We used Receiver Operating Characteristic (ROC) curve analysis to test NLR, CRP, and a new index (NLR x $\sqrt{CRP}$ index) for their ability to discriminate between patients with and without SBP. Their AUC were compared, and cutoff values were determined according to the Youden index. Statistical significance was considered at $p \leq 0.05$.

Ethical approval: The Ethical Committee of Alexandria University approved the study's protocol on October 21, 2021 (Serial No.: 0201652, IRB No.: 00012098). We ensured compliance with the 1975 Declaration of Helsinki provisions and Good Clinical Practice guidelines. Informed consents were obtained from all subjects included in the study.

RESULTS

The present study involved 124 cirrhotic patients with ascites, 50 (40.32%) were identified with SBP, while the remaining 74 (59.76%) were the non-SBP group. Table (1) presented clinical, laboratory, and demographic information. Both groups had no statistically significant difference regarding age or gender. Fever, abdominal pain, AKI, peripheral blood leucocyte and neutrophil counts, blood NLR, serum CRP and creatinine differed significantly between the groups. Hemoglobin concentration, platelet count, blood lymphocyte count, INR, serum AST, ALT, albumin, bilirubin, and protein did not differ significantly.

Table 1: Clinical and biochemical characteristics of patients with SBP versus non-SBP group

	SBP (n = 50)	Non-SBP (n = 74)	Statistical test	P value
Age (y), Median (IQR)	61.00 (54.75-65.00)	60.00 (53.75-65.00)	$U = 1692.0$	0.420
Gender				
Males, (N.%)	37 (74.0%)	46 (62.2%)	$U = 1631.0$	0.171
Females, (N.%)	13 (26.0%)	28 (37.8%)		
Fever, (N.%)	28 (56%)	0	-	-
Abdominal pain, (N.%)	28 (56%)	7 (9.5%)	$U = 989.0$	< 0.001*
AKI	19 (38.0%)	14 (18.9%)	$U = 1497.0$	0.019*
Hemoglobin (g/dL), Mean ± SD	10.36 ± 1.89	10.36 ± 1.79	$t = -0.018$	0.985
Platelet count (x10³/cm³), Median (IQR)	126.00 (96.25-155.00)	115.00 (87.75-135.50)	$U = 1608.0$	0.218
White blood cell count (x10³/cm³), Median (IQR)	8.48 (6.19-12.64)	5.88 (4.69-7.91)	$U = 1036.5$	< 0.001*
Neutrophils (x10³/cm³), Median (IQR)	6.15 (4.44-8.94)	3.86 (2.99-4.88)	$U = 841.0$	< 0.001*
Lymphocytes (x10³/cm³), Median (IQR)	1.55 (1.08-2.07)	1.60 (1.24-2.21)	$U = 1731.0$	0.544
NLR, Median ± IQR	3.90 (3.23-4.88)	2.38 (2.08-2.71)	$U = 206.5$	< 0.001*
CRP (mg/L), Median (IQR)	67.45 (47.10-92.51)	24.95 (16.10-36.97)	$U = 234.5$	< 0.001*
Serum AST (U/L), Median (IQR)	56.50 (42.00-67.50)	49.50 (42.75-57.00)	$U = 1503.0$	0.077
Serum ALT (U/L), Median (IQR)	33.50 (25.00-41.75)	30.00 (26.00-37.50)	$U = 1657.0$	0.325
Serum Albumin (g/dL), Mean ± SD	2.70 ± 0.44	2.75 ± 0.36	$t = -0.694$	0.489
Serum total bilirubin (mg/dL), Median (IQR)	2.81 (1.67-3.87)	2.43 (1.69-3.34)	$U = 1593.5$	0.191
Serum direct bilirubin (mg/dL), Median (IQR)	0.98 (0.60-1.72)	0.85 (0.60-1.32)	$U = 1638.0$	0.280
Serum Total protein (g/dL), Mean ± SD	6.50 ± 0.66	6.76 ± 0.91	$t = -1.855$	0.066
INR, Mean ± SD	1.69 ± 0.29	1.58 ± 0.38	$t = 1.844$	0.068
Serum Creatinine (mg/dL), Median (IQR)	1.21 (1.07-1.93)	1.14 (.98-1.28)	$U = 1440.5$	0.037*

AKI, Acute kidney injury; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-reactive protein; INR, International normalization ratio; IQR, Interquartile range; NLR, Neutrophil-lymphocyte ratio; SBP, Spontaneous bacterial peritonitis; SD, Standard deviation. *U*: Mann Whitney *U* test. *t:* Independent-Samples *t*-test.   *: Statistically significant at $P \leq 0.05$.

Table (2) showed a logistic regression analysis of parameters affecting SBP.

Table 2: Logistic regression analysis of parameters affecting SBP

Independent variables	OR	95% CI for OR		
		Lower	Upper	P
Constant	0.000			**0.002***
White blood cell count	1.593	1.073	2.363	**0.021***
NLR	52.933	3.810	735.370	**0.003***
CRP	1.271	1.044	1.549	**0.017***
Serum total bilirubin	2.198	0.073	66.625	0.651
Serum direct bilirubin	0.085	0.000	261.669	0.548
AST	1.133	1.023	1.255	**0.017***
Creatinine	0.806	0.018	36.968	0.912

The sensitivity of the model is 92.7%

AST, Aspartate aminotransferase; CI, Confidence interval; CRP, C-reactive protein; NLR, Neutrophil-lymphocyte ratio; OR, Odds ratio; SBP, Spontaneous bacterial peritonitis.

We found that the best values for diagnosing SBP for NLR were: Cut off > 3.16 mg/L, sensitivity of 76.0%, specificity of 97.3% and AUC of 0.944. For CRP were: Cut off > 45.6 mg/L, sensitivity of 84.0%, specificity of 94.59%, and AUC of 0.937 (Figure 1). When both CRP and NLR were used as "NLR x √CRP index," it showed superiority to either of them alone. At a cutoff > 18.28, the index can predict SBP with 94.0% sensitivity, 94.59% specificity, and an AUC of 0.979. It also had 94.4% overall accuracy, 92.2% positive predictive value (PPV), and 95.9% negative predictive value (NPV) (Table 3).

Table 3: Diagnostic performance of laboratory markers in differentiation between SBP and non-SBP groups

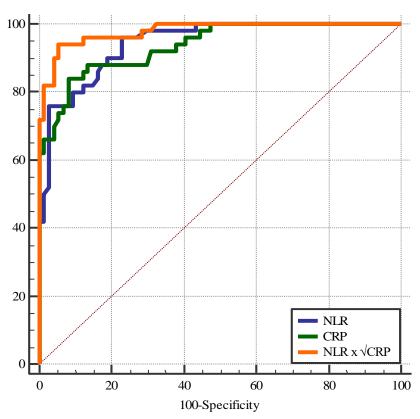|	AUC (95% CI)	Cut off	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	Accuracy	p
NLR	0.944 (0.888 – 0.977)	>3.16	76.0 (61.8 – 86.9)	97.3 (90.6 – 99.7)	95.0 (82.8 – 98.7)	85.7 (78.5 – 90.8)	88.7%	**<0.001** *
CRP	0.937 (0.878 – 0.972)	>45.6	84.0 (70.9 – 92.8)	91.89 (83.2 – 97.0)	87.5 (76.3 – 93.8)	89.5 (81.8 – 94.2)	88.7%	**<0.001** *
NLR + CRP	0.945 (0.908– 0. 982)	>49.99	82.0 (68.56– 91.42)	94.59 (86.7– 98.5)	91.1 (79.6– 96.4)	88.6 (81.1– 93.3)	89.52%	**<0.001** *
NLR x √CRP	0.979 (0.935 – 0.996)	>18.28	94.0 (83.5 – 98.7)	94.59 (86.7 – 98.5)	92.2 (81.9 – 96.8)	95.9 (88.6 – 98.6)	94.4%	**<0.001** *

Fig (1): ROC curve of NLR, CRP and NLR x √CRP.

DISCUSSION

SBP represents a significant and hazardous complication among patients with cirrhosis and ascites, characterized by high rates of recurrence and mortality and an overall poor prognosis [12]. Prompt and accurate diagnosis followed by immediate treatment constitutes the foundational approach in SBP management. The diagnostic criteria for SBP include the identification of an elevated PMN count ≥ 250 cells/mm³ in ascitic fluid, regardless of the positivity of bacterial ascitic cultures, in the absence of any surgically amendable intra-abdominal sources of infection [13]. Alterations in plasma protein levels and CRP, which is predominantly synthesized in the liver, represent the acute phase response, indicative of infection onset [14]. Elevations in CRP levels can occur in response to various conditions, including burns, trauma, cancer, and myocardial infarction, making CRP and other inflammatory markers, such as white blood cells, essential for diagnosing and monitoring numerous infectious diseases and pathological states [15]. Additionally, in the absence of infection, people with cirrhosis naturally have higher baseline CRP levels than non-cirrhotic individuals (12.1±14.4 mg/L vs. 5.9±4.9 mg/L) [16].

NLR serves as an indicator of subclinical inflammation, and alterations in this ratio may point to the presence of early stages of severe infection [17]. This pattern might be attributed to the persistence of infection sources, leading to neutrophil proliferation and lymphocyte suppression through sepsis-induced apoptosis [18]. Neutrophils are pivotal in the innate immune response to infectious injuries, while lymphocytes are central to the adaptive immune system, playing a crucial role in regulating inflammatory responses [19, 20]. The continuous depletion of lymphocytes can result in immune suppression and the failure to resolve inflammation. Therefore, the dynamics between neutrophil proliferation and lymphocyte reduction, driven by ongoing infection and its incomplete clearance, underscore the complex interplay between the innate and adaptive immune responses in severe infections [21]. Patients suffering from trauma and those fitting the criteria for systemic inflammatory response syndrome were found to have persistent neutrophilia and lymphopenia [22].

We found that NLR at a cutoff > 3.16 had a sensitivity of 76.0% and a specificity of 97.3%, while CRP at a cutoff > 45.6 mg/L had a sensitivity of 84.0% and a specificity of 91.89%. Several recent studies have focused on the role of inflammatory markers such as CRP and NLR in diagnosing SBP [23–25]. CRP, a general marker for inflammation, has been identified as an important marker of infection in hospitalized individuals with cirrhosis [25]. A study conducted by **Huynh et al.** [26]

validated a new simple scoring system for predicting SBP in patients suffering from cirrhotic ascites. The study found that mean platelet volume (MPV), CRP level, and NLR were independent variables associated with SBP. The ROC curve showed that serum CRP could diagnose SBP at a cutoff value > 42.4 mg/L, with a specificity of 98% and a sensitivity of 85% for diagnosing SBP (AUC = 0.92; p<0.001). However, the study also emphasized that these markers cannot replace the need for diagnostic paracentesis, which is the gold standard for diagnosing SBP.

Another study validated the diagnostic accuracy of NLR and MPV in cirrhotic patients with SBP. The study found that patients with SBP had significantly higher NLR and MPV than patients without SBP. At a cutoff value of 5.6, the NLR had an AUC of 0.872, a PPV of 68%, an NPV of 87%, and an accuracy of 80% for detecting SBP. It was 78% sensitive and 81% specific. Compared to utilizing NLR alone, the combination of NLR and MPV did not significantly improve diagnostic value [24]. A prospective study of 100 cirrhotic patients with ascites found that blood NLR > 3.38 had an 80% specificity and 94% sensitivity for the diagnosis of SBP. However, it was also found that hsCRP has a blunted rise in patients with cirrhosis and SBP, making it unreliable as a diagnostic test. The group without SBP showed moderately elevated hsCRP with a mean of 17.46 ± 6.19 mg/L [27].

A case-control study included a total of 60 cirrhotic decompensated patients. It assessed the validity of diagnostic paracentesis using combined blood NLR and CRP as a minimally invasive predictor for early diagnosis of SBP. The study found that a blood NLR > 2.9 can be used for SBP diagnosis in cirrhotic patients with a specificity of 88%, a sensitivity of 95%, an NPV of 90%, a PPV of 92%, an AUC of 0.85, and an accuracy of 92%. A CRP level > 15 mg/L could diagnose SBP with a sensitivity and specificity of 85% and 90%, respectively, NPV of 88%, PPV of 90%, AUC of 0.80, and accuracy of 90%. It was also found that a combination of NLR and CRP at a cutoff > 22.6 had a sensitivity and specificity of 86% and 91%, respectively, in SBP diagnosis among cirrhotic patients [28]. In another study, the sensitivity and specificity of blood NLR > 2.89 were 80.3% and 88.9%, respectively, for SBP diagnosis [29].

It was shown by **Jeedigunta and colleagues** [30] that a blood NLR > 3.32 can predict SBP among patients with ascites with a sensitivity of 86%, a specificity of 70%, and an AUC of 87.6 (P<0.001). **Awad et al.** [23] found that NLR levels > 3.5 can distinguish between SBP patients and controls with 100% sensitivity, 42.86% specificity, 63.6% PPV, and 100% NPV. CRP can distinguish between patients and controls at a cutoff level of > 43.3 mg/L, with 77.14% sensitivity, 62.86%

specificity, 62.86% PPV, and 73.3% NPV. A meta-analysis that included 14 studies revealed higher levels of NLR in cirrhotic individuals who developed SBP than those who did not [31]. Moreover, a study proposed a novel blood bioscore called "the PEC index," created by combining measurements of procalcitonin (PCT), erythrocyte sedimentation rate, and CRP. After ruling out other infections, the study suggested that the PEC index could provide a precise, minimally invasive diagnosis of SBP. The sensitivity of CRP at a cutoff value > 21.0 mg/L was 93.33%, while this low cutoff resulted in a very low specificity of 51.67% (AUC = 0.736) [32]. Another study revealed that the sensitivity and specificity of monocyte chemotactic protein-1 were higher than PCT and CRP in the diagnosis of SBP. CRP at a cutoff point > 11.2 mg/L had sensitivity and specificity of 52.5 and 64.3, respectively, with an AUC of 0.562 [33]. **Baweja et al.** [27] found that CRP alone may not be a reliable SBP diagnosis marker.

This study points to the possible importance of our new index, "NLR x √CRP," for SBP diagnosis, which showed a better AUC of 0.979 (95% CI: 0.935–0.996) at a cutoff > 18.28, with 94.0% sensitivity, 94.59% specificity, 92.2% PPV, 95.9% NPV, and an overall accuracy of 94.4%. The sensitivity, NPV, and accuracy of our index were much higher than what was found in previous studies when NLR or CRP markers were used separately. Our results point to the promising role of integrating NLR and CRP levels in "NLR x √CRP index" as a minimally invasive marker for diagnosing SBP. It can also help detect bacterial infections other than SBP. Research conducted by **Lee et al.** [34] highlights the potential diagnostic value of NLR, akin to CRP, in assessing the severity of pneumonia patients, noting an association between elevated NLR and an increased likelihood of requiring intensive care admission. The present study offers a straightforward, minimally invasive, and cost-effective method for SBP detection utilizing routine laboratory assessments. Integrating NLR and CRP measurements in our "NLR x √CRP index" not only facilitates the early diagnosis of SBP but also aids in preemptive management strategies, potentially diminishing the risk of further complications.

Application of this novel index may help in the management of SBP. According to the guidelines, patients with cirrhosis and ascites who were hospitalized should undergo diagnostic paracentesis. However, sometimes paracentesis may be delayed or even not performed, especially in primary care settings where the expertise may not be available, which can delay the start of treatment and have a deleterious impact on the prognosis. Therefore, recent studies have focused on evaluating minimally invasive parameters that can help predict SBP, which needs urgent antibiotic therapy, if rapid and secure paracentesis is not feasible or there is inadequate experience with this procedure [35]. The present work may be limited by its single-center setting and sample size, which may hinder the generalizability of the findings. Future research is recommended to validate the diagnostic equation in larger, multicenter cohorts, diverse populations, and different clinical settings. Further studies should also explore the application of the diagnostic formula in conjunction with other diagnostic modalities.

Conclusion: The novel index "NLR x √CRP" can introduce an innovative, efficient, economical, and minimally invasive strategy for diagnosing SBP. Its implementation in clinical settings could significantly improve the early diagnosis and management of this life-threatening condition, ultimately enhancing patient outcomes.

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