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Can combined blood neutrophil to lymphocyte ratio and C-reactive protein be used for diagnosis of spontaneous bacterial peritonitis?

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ABSTRACT

Background and objective: Spontaneous bacterial peritonitis (SBP) is diagnosed by the presence of ≥250 polymorphonuclear neutrophils (PMN)/mm^3 in the ascites and the absence of surgically treatable cause of intra-abdominal infection. Blood neutrophil lymphocytic ratio (NLR) is an inexpensive and simple test for inflammation. C-reactive protein (CRP) is an inflammatory marker used for the diagnosis and follow-up of many diseases and morbidities. We aimed to evaluate the clinical utility of combined blood NLR and CRP as a non-invasive test for SBP diagnosis.

Methods: Blood NLR was calculated, and CRP value determined in 180 cirrhotic patients with ascites (126 with and 54 without SBP). Sensitivity and specificity of combined blood NLR and CRP values for SBP diagnosis were estimated by receiver operator characteristic curve.

Results: Both blood NLR and CRP values were significantly higher in SBP ($p < 0.001$). For SBP diagnosis, a blood NLR of >2.89 had a sensitivity 80.3% and specificity 88.9%. CRP >11.3 mg/dL had a sensitivity 88.9% and specificity 92.6%. In logistic regression analysis, combined blood NLR and CRP had a sensitivity 95.1% and specificity 96.3% at the same cut off values.

Conclusions: Combined NLR and CRP could be used as a novel, simple, low-cost, non-invasive test for SBP diagnosis.

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KEYWORDS
Neutrophil to lymphocyte ratio; C-reactive protein; spontaneous bacterial peritonitis

Introduction

Ascites, a major complication of decompensated liver disease, is the most common cause of hospitalisation in the cirrhotic patient. Bacterial infections of ascites in the cirrhotic patients increase mortality up to fourfold [1–3].

Spontaneous bacterial peritonitis (SBP) is a serious common form of infection in cirrhotic ascitic patients [4–6]. Its prevalence among the hospitalised group of those patients varies from 10 to 30%. About half have SBP at admission, the other half develop SBP during hospitalisation [7]. SBP is a consequence of qualitative and quantitative changes in microbiota of the gut, bacterial translocation and increased permeability of the intestine [8]. Also, the impairments of the immune system observed in advanced cirrhotic patients play an important role [9]. As signs and symptoms of SBP are non-specific and the presentation varies according to the stage of the disease, diagnosis depends mainly on the laboratory and microbiological tests. Paracentesis and laboratory examination of the ascitic fluid is considered the gold standard test to confirm or rule out the diagnosis of SBP in cirrhotic patients [10]. The diagnostic paracentesis risks include: visceral perforation, haemoperitoneum, peritonitis, local infection at the site of paracentesis, abdominal wall haematoma and persistent leak, which is the most common complication [11,12].

C-reactive protein (CRP) is increased in the blood when there is an inflammatory lesion or histologically necrotic lesion in the living body [13]. Serum CRP is thought to be synthesised only in hepatocytes by the induction of cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor produced by macrophages at the time of bacterial infection [14,15] . The blood neutrophil lymphocyte ratio (NLR) is an important index for the balance of the inflammatory and immune systems, reflecting systemic inflammation responses [16]. Platelet indices, CRP and total white blood cell counts are reported to predict ascites fluid infection [17]. Therefore, we hypothesised that NLR, alone and in combination with CRP, provides clinically valuable diagnostic criteria for SBP diagnosis.

Patients and methods

The study included 180 patients were recruited from Mansoura University Hospitals; Tropical Medicine

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Department and Gastroenterology and Hepatology unit. Patients were included had a clinical and radiological diagnosis of portal hypertension and ascites. Exclusion criteria were ascites without cirrhosis (e.g. malignant ascites), patients with immunocompromised state, sepsis, secondary bacterial peritonitis due to any surgical cause, receipt of antibiotics prior to hospitalisation or under prophylactic antibiotics for SBP, diabetes mellitus, hyperlipidemia, clinically overt hypo- or hyperthyroidism, peripheral vascular disease, hypertension or heart failure and major cardiac problems, autoimmune diseases or neoplastic disorders, haematological disorders on anticoagulant medications, and patients with unrelated infection that may influence the levels of blood WBC or CRP, e.g. skin and chest infection. Patients were subjected to history taking, general examination, physical and ultrasonographic abdominal examination, laboratory assessment, routine diagnostic paracentesis and analysis of ascitic fluid.

Fifteen ml of ascitic fluid was taken under complete aseptic technique, from a puncture site, by paracentesis. About 10 ml was immediately inoculated in bedside aerobic and anaerobic blood culture bottles. The remaining amount of ascitic fluid was sent for biochemical and cytological examination in tubes containing EDTA and analysed within 3 h of aspiration. Total proteins and glucose levels, part of this ascitic fluid, was analyzed after centrifugation in the laboratory for 3 min. A smear prepared from the deposit was stained with Gram stain. The total and differential leukocyte counts were determined the uncentrifuged portion.

Inoculated blood cultures were incubated for 3 successive days at 37 °C with subculture on blood, chocolate and MacConkey agars. Bacteriological examination and sensitivity to antimicrobials were performed using standard procedures. According to international guidelines, SBP was diagnosed if the polymorph nuclear neutrophil (PMN) cell count in the ascitic fluid is ≥250/mm^3 in the absence of other causes of peritonitis [18]. Therefore, patients with culture-positive and culture-negative neutrocytic ascites (CNNA) were considered as cases. At the time of paracentesis, the laboratory tests, including total leukocyte count, liver function tests, prothrombin time, activated partial thromboplastin time, blood sugar, creatinine, urea, alpha-feto protein and carcinoembryonic antigen were performed. NLR (neutrophil count divided by the number of lymphocytes; neutrophil lymphocyte ratio was calculated). CRP was assessed by particle-enhanced immunoturbidimetric assay (C-reactive protein (Roche Diagnostics).

Cirrhosis was diagnosed on a clinical basis, laboratory tests, sonographic findings and endoscopic evidence. Patients with a neutrophil cell count in ascitic fluid *I* < 250 cells/mm^3 and a culture-negative ascites fluid were assigned as the control group. The protocol was approved by the Mansoura University Ethical Committee. A written informed consent was obtained from all patients provided before participation in any protocol-specific procedures. The study was conducted in accordance with the Helsinki Declaration guidelines.

Data were analyzed using the SPSS (statistical package for social science) computer program version 20. The normality of the distribution was checked by Kolmogorov–Smirnov test. Numerical variables were expressed as mean, standard deviation, or median, interquartile range. For comparison between two groups, *t* test (for parametric) or Mann–Whitney test (for non-parametric) was used. The cut-off point was chosen as the point with the highest sensitivity and specificity rates using receiver operator characteristics (ROC) curve. A *p*-value < 0.05 was considered statistically significant.

Results

Of the 180 patients with liver cirrhosis and ascites, 126 patients had SBP (70%), leaving 54 patients (30%) as controls free of SBP. Clinical, laboratory and demographic details are shown in Table 1. The two groups were matched for age, sex, hepatorenal syndrome, rupture oesophageal varices and hepatic encephalopathy and viral infections. NLR, CRP, creatinine, bilirubin and AST differed between the groups. No significant differences were found in platelets, haemoglobin concentration, PT, ALT and serum albumin.

Among the 126 patients with SBP, 50 (39.7%) were culture positive (Table 2). No significant differences were found between culture-positive and culture-negative SBP regarding, age, sex, HRS, ROV, HCV related cirrhosis,

Table 1. Clinical and biochemical characteristic of patients with SBP vs. non-spontaneous bacterial peritonitis patients.

	SBP	Not SBP	
	(*N* = 126)	(*N* = 54)	*P* value
Age (years)	55.6 ± 9	54.3 ± 4.3	0.313
Sex (m/f)	84/42	24/30	0.03
HBV (N&%)	36 (28.6%)	10 (18.5%)	0.155
HCV (N&%)	90 (71.4%)	44(81.5%)	0.156
HRS (N&%)	24(19.0%)	12 (22.2%)	0.70
ROV (N&%)	32 (25.4%)	12 (22.2%)	0.72
HE (N&%)	98 (77.8%)	48 (88.9%)	0.19
Fever (N&%)	70(55.6%)	0	–
Abdominal pain (N&%)	68 (54.8%)	0	–
Platelets (10^9/L)	89 ± 35	98 ± 53	0.181
Haemoglobin (g/L)	104 ± 20	101 ± 22	0.372
WBCC (10^9/L)	12.5 ± 6.3	11.5 ± 6.2	0.328
NLR	4.5 (3.2–8.7)	2.1 (1.6–2.6)	>0.001
CRP (mg/dL)	48 (12–90)	3.74 (2.3–5.2)	>0.001
Creatinine (μmol/L)	124(80–186)	115 (62–106)	0.001
Bilirubin (μmol/L)	60 (31–108)	20 (12–70)	0.012
PT seconds	13.9 ± 2.8	13.4 ± 2.6	0.26
ALT (U/L)	31(21–42)	36 (20–56)	0.35
AST (U/L)	63 (38–96)	31 (22–95)	0.028
Albumin (g/L)	23.6 ± 6.3	24.1 ± 6.3	0.626

Notes: HBV: hepatitis B virus; HCV: hepatitis C virus; HRS: hepatorenal syndrome; ROV: rupture oesophageal varices; HE: hepatic encephalopathy; WBCC: white blood cell count; NLR: blood neutrophil lymphocytic ratio; CRP: C-reactive protein PT: prothrombin time (Reference value 12 s); ALT: alanine transaminase; AST: aspartate transaminase; IQR: Inter quartile range. Numerical data mean (SD) or median (IQR).

fever and abdominal pain, and numerous biochemical parameters. There was a significant increase of HE-and HBV-related cirrhosis in patients with culture-negative SBP vs. culture-positive SBP (both $p = 0.03$ and $p = 0.03$). In patients with culture-positive SBP, there were a significant elevation of platelet count, vs. culture-negative SBP ($p < 0.01$).

Table 2. Clinical and biochemical characteristic of culture-positive vs. culture-negative spontaneous bacterial peritonitis patients.

	Culture-positive ($n = 50$)	Culture-negative ($n = 76$)	*P* value
Age (years)	56.6 ± 9.8	55.0 ± 8.4	0.33
Sex: m/f	30/20	54/22	0.19
HBV (N&%)	4(8.0%)	18(23.7%)	0.03
HCV (N&%)	40 (80.0%)	50(65.8%)	0.08
HRS (N&%)	6(12.0%)	18 (23.7%)	0.10
ROV (N&%)	14(28.0%)	18 (23.7%)	0.59
HE (N&%)	34(68.0%)	64(84.2%)	0.03
Fever (N&%)	32(64.0%)	38(50.0%)	0.12
Abdominal pain (N&%)	32(64.0%)	36(48.6%)	0.09
Platelet (10^9/L)	113 ± 89	81 ± 46	<0.01
HB (g/L)	103 ± 22	104 ± 19	0.67
WBC (10^9/L)	12.9 ± 8.1	11.4 ± 7.4	0.29
NLR	5.3 (3.6–8.7)	4.1 (3.2–8.5)	0.23
CRP(mg/dL)	48 (12–90)	48.0 (24–48)	0.34
Creatinine (µmol/L)	142(50–160)	151(80–186)	0.11
Bilirubin (µmol/L)	50(29–85)	70(31–108)	0.21
PT (seconds)	13.8 ± 2.7	13.5 ± 2.5	0.52
ALT (U/L)	32 (21–37)	30 (22–42)	0.35
AST (U/L)	68 (29–96)	61 (38–62)	0.94
ALBUMIN (g/L)	24 ± 6.6	23.3 ± 6.1	0.54

Notes: HBV: hepatitis B virus; HCV: hepatitis C virus; HRS: hepatorenal syndrome; ROV: rupture oesophageal varices; HE: hepatic encephalopathy; WBCC: white blood cell count; NLR: blood neutrophil lymphocytic ratio; CRP: C-reactive protein PT: prothrombin time(Reference value 12 s); ALT: alanine transaminase; AST: aspartate transaminase; IQR: Inter quartile range. Numerical data mean (SD) or median (IQR).

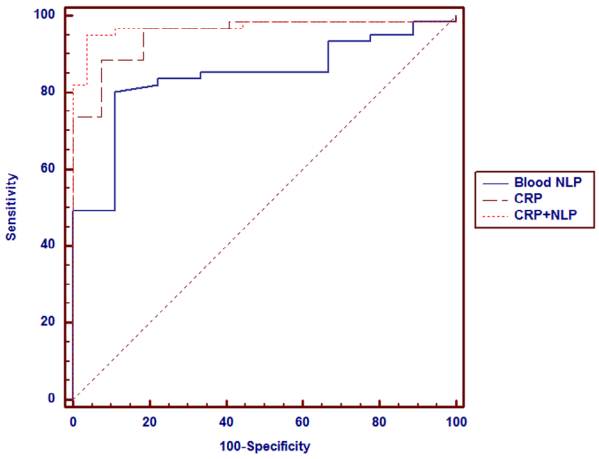

Figure 1. Receiver operator characteristics curves for CRP (dashed line), NLR (solid line) and both indices combined (dotted line).

The ROC curve analysis demonstrated that a cut-off value of >2.89 for NLR and 11.3 mg/dL for CRP had optimum discriminative power (Figure 1). Table 3 shows AUC, sensitivity, specificity, positive and negative predictive values, and accuracy. All indices were superior when both CRP and NLR were combined.

Discussion

SBP is a frequent hazardous event in patients with cirrhosis and ascites, with high recurrence, mortality rates and poor prognosis [19]. Rapid diagnosis and treatment are the cornerstones in the management of SBP. Diagnosis of SBP based on positive ascitic fluid bacterial cultures and the detection of an elevated absolute fluid PMN count in the ascites (≥250/mm^3) in the absence of an evident surgically treatable intra-abdominal cause of infection [20]. The acute phase response is one of the earliest signs of infection and includes the changes in the levels of many plasma proteins, such as CRP, synthesised almost exclusively in the liver [14]. CRP rises in the case of burns, trauma, cancer and myocardial infarction. Inflammatory markers, such as white blood cells and CRP, are used for the diagnosis and follow-up of many diseases and morbidities [21].

We found that, in patients with SBP, CRP was significantly higher compared to non-SBP, but there was no significant difference in patients with culture-positive SBP vs. culture-negative SBP. A previous study concluded that the level of CRP alone is not an accurate marker for the diagnosis of SBP [22]. Pieri et al. found that the basic level of CRP in patients with cirrhosis is higher than in patients without cirrhosis, but when infection occurs, the more serious the potential liver dysfunction, the lower the increase in CRP [23]. Janum et al. concluded that the power of CRP for infection prediction is weak in patients with advanced cirrhosis [24]. We also found that in patients with SBP, NLR was significantly higher compared to non-SBP, whereas NLR showed no significant difference in patients with culture-positive SBP versus culture-negative SBP. In agreement with our study, many previous studies have shown the clinical usefulness of NLR as useful indicator for bacterial infection [14,25]. Malka et al. have concluded that NLR as a useful prognostic marker for various tumours, but its usefulness in gram-negative bacterial infections is lacking [26]. A recent study concluded that the NLR is higher in patients with CHC with HOMA-insulin resistance (IR) > 3 and advanced fibrosis. This ratio can be used as a new

Table 3. Level and area under ROC of NLR, CRP and combined NLP with CRP for detection Spontaneous bacterial peritonitis.

	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Blood NLR (>2.89)	0.84 ± 0.04	80.3	88.9	94.4	65.8	82.8
CRP (>11.3)	0.95 ± 0.02	88.9	92.6	96.6	78.1	90.0
NLP + CRP	0.97 ± 0.02	95.1	96.3	98.4	89.7	95.6

Notes: NLR: blood neutrophil lymphocytic ratio; CRP: C-reactive protein; AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value.

non-invasive marker to predict IR and advanced disease [27]. NLR has been used in various clinical situations. Previous studies have shown that NLR is an effective tool in predicting infections, cardiovascular disease and type 2 diabetes [28–30]. Heffernan et al. found the presence of persistent neutrophilia and lymphopenia in trauma patients and patients who had the criteria for the systemic inflammatory response syndrome [31].

NLR is a marker of subclinical inflammation. The initial stages of severe infection may be diagnosed by increased neutrophils and decreased lymphocyte counts in the peripheral blood sample [25]. This could be explained by increased numbers of neutrophil implied that source of infection was not eradicated, which induced depression of lymphocyte. Evidence is growing that neutrophil is the key cellular component of host defence in the innate immune system against infectious injury, while lymphocyte is considered as the major cellular line of the adaptive immune system. Lymphocyte plays a key role in the regulation of inflammatory response, and their loss due to continuous sepsis-induced apoptosis may lead to the immune system suppression and non-resolution of inflammation [31,32]. Taken together, the sustainability of infection and the incomplete eradication of source of infection are responsible for the increase of neutrophils production by the medulla and decrease lymphocyte counts by apoptosis and other mechanisms.

Combined NLR and CRP can be used as a novel non-invasive test for SBP diagnosis. Lee et al. found that NLR might have diagnostic utilities such as CRP in evaluation of severity of patients with pneumonia, where higher NLR increased the risk of intensive care unit treatment of pneumonia patients [33]. This study represents an advance in biomedical science because it shows that the combined NLR and CRP (which requires only routine laboratory tests) could be used as a novel, simple, low-cost, non-invasive test for SBP diagnosis which helps its early management to reduce the incidence of subsequent complications.

Summary table

What is known about this subject

- SBP is a serious common form of infection in cirrhotic ascitic patients.
- Paracentesis and laboratory examination of the ascitic fluid are considered the gold standard test to confirm or rule out the diagnosis of SBP.
- Non-invasive methods focusing on blood markers are common.

What this paper adds

- Combined NLR (at the cut of >2.89) and CRP (at the cut of >11.3 mg/dl) offer superior diagnostic power for SBP than either test alone, so can be used as a novel non-invasive test for SBP diagnosis.

Disclosure statement

No potential conflict of interest was reported by the authors.

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