Opinion

Non-Invasive Methods for the Prediction of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis

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Abstract: Spontaneous bacterial peritonitis (SBP) is a potentially fatal complication in patients with liver cirrhosis. Early diagnosis and prompt treatment of SBP are vital to shorten hospital stays and reduce mortality. According to society guidelines, patients with cirrhosis and ascites who are admitted to the hospital should have diagnostic paracentesis. However, for various reasons, paracentesis may be delayed or not performed. Therefore, recent research has focused on identifying non-invasive parameters useful in SBP prediction which require urgent antibiotic therapy if rapid and secure paracentesis is not possible or there is insufficient experience with this method. In this review, we discuss the non-invasive methods available to predict SBP.

Keywords: spontaneous bacterial peritonitis; ascites; cirrhosis; predictors; neutrophil-lymphocyte ratio; Wehmeyer's scoring system

1. Introduction

Spontaneous bacterial peritonitis (SBP) is an infection of the ascitic fluid that occurs in the absence of perforation of a hollow viscus or an intra-abdominal inflammatory focus, such as an abscess, acute pancreatitis or cholecystitis [1]. Together with urinary tract infections, SBP represents the most common type of infection in patients with cirrhosis, followed by pneumonia, soft tissue infections, and spontaneous bacteremia [2]. When first described, the mortality of SBP exceeded 90%. However, with early recognition of the disease and prompt and appropriate antibiotic therapy, mortality has been reduced to around 20–30% [1,3]. Because the clinical presentation of SBP is heterogeneous and delay in starting antibiotic treatment is associated with substantially increased mortality [4], according to society guidelines, a diagnostic paracentesis should be carried out as soon as a patient with cirrhosis, and ascites is admitted urgently to the hospital for any reason, even if there are no symptoms that point to an infection [1,3,5]. However, paracentesis may be delayed or not performed for various reasons (weekend hospitalization, multiple comorbidities, primary care hospital, private hospital, patient refusal) [6]. Delayed recognition and treatment of SBP of even a few hours are associated with an increased risk of death [4].

A history of SBP [7], variceal hemorrhage [8], and usage of proton pump inhibitors [9] are well-known clinical risk factors for developing SBP. However, there is disagreement about the evidence that is currently available regarding the prediction of SBP by standard laboratory testing. This review discusses non-invasive methods for SBP prediction in patients with cirrhosis, which are suitable for physicians who receive patients with cirrhosis and ascites to be able to quickly stratify the risk of SBP and have an appropriate management attitude. Especially if a quick and safe paracentesis is not available or if there is a lack of experience with this procedure.

2. Serum Biomarkers

2.1. Procalcitonin

Procalcitonin (PCT), a precursor of calcitonin, is a serum biomarker that helps distinguish bacterial infection from other causes of infection or inflammation. Procalcitonin levels in the blood of healthy individuals are below the limit of detection of clinical assays, and the level of procalcitonin rises in response to a pro-inflammatory stimulus, especially of bacterial origin [10]. The value of PCT in predicting SBP has been demonstrated in several studies. The value of PCT in the early detection of bacterial infection in cirrhosis is controversial, especially in predicting SBP [11–13]. In 2013, Su D. H. et al. performed a meta-analysis of PCT, including 181 episodes of suspected infection, which yielded pooled sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios of 86%, 80%, 7.73 and 0.14, respectively, suggesting PCT as a diagnostic aid for SBP with moderate to high accuracy [14]. In another study in 2015, a study of Yang Y. conducted a meta-analysis including 742 patients across 17 studies showed that PCT at a cut-off of 0.42–0.76 ng/mL had a sensitivity of 82% and specificity of 86% for predicting SBP [15].

Based on the results of the present meta-analysis, serum PCT levels can be used to assist clinicians in the rapid and accurate diagnosis of SBP. At present, there are still not many studies on this issue; therefore, more large, prospective, well-designed studies are needed to assess the diagnostic accuracy of PCT in SBP due to cirrhosis.

2.2. C-Reactive Protein

C-reactive protein (CRP) is a notable biochemical marker of inflammation due to a range of causes, including infectious diseases and noninfectious inflammatory disorders, and has likewise been demonstrated to be engaged with a few immunological functions [16,17]. Previous research has been done in a variety of clinical settings on the utility of CRP values in the diagnosis of infection [18]. According to several studies, the CRP cut-off level for cirrhotic patients' infection diagnosis should be between 2.0 and 8.0 mg/dL [13,19,20]. Patients with cirrhosis typically have higher basal CRP levels than those without cirrhosis, but when infection strikes those patients who have more severe underlying liver failure as well as cirrhosis, the lower CRP level rises. Therefore, in individuals with severe cirrhosis, CRP's ability to predict infection is poor [21].

The optimal CRP cut-off value, according to a retrospective investigation of 78 patients, was 15.53 ng/mL. CRP had a 75% sensitivity and a 61.2% specificity for patients with liver cirrhosis with SBP, respectively (area under the curve (AUC): 0.613, CI 95%: 0.532–0.724, $p < 0.01$). Serum PCT levels, on the other hand, appear to have several advantages over the conventional methods in the early detection of SBP in advanced liver cirrhosis, while CRP in SBP patients does not seem to provide sufficient diagnostic accuracy [22]. Cekin studied 101 patients and found that serum PCT may be a more accurate diagnostic marker than CRP in patients with liver cirrhosis-related ascites [23].

2.3. Homocysteine

Homocysteine (Hcy) is an amino acid found in all cells in small amounts; it is an essential metabolite of methionine, and about 80% of the Hcy is protein-bound, mainly to albumins [24]. The metabolism of Hcy is largely controlled by the liver [25]. A recent study assessed the efficacy of serum Hcy concentration for the diagnosis of SBP. In this study, SBP patients had significantly higher blood levels of Hcy than the other group and at a cut-off value of 17.79 µmol/L, serum homocysteine may provide a reliable and non-invasive diagnostic marker for all varieties of SBP, as shown by its 89.3% specificity and 95.1% sensitivity for identifying SBP (area under the ROC curve (AUC): 0.932) [26]. However, the sample size was small, and larger studies are required to estimate this marker in various clinical settings and define a reliable cut-off.

2.4. Interferon-γ-Induced Protein

Interferon-γ-induced protein (IP-10) is a member of the Cys-X-Cys (CXC) family, a sub-family of cytokines. It is a proinflammatory chemokine that is mostly produced by residing and infiltrating cells in inflamed tissues in response to bacterial or viral pathogens [27,28]. In patients with cirrhosis, tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6], and chemokines are released into the blood and ascitic fluid in cirrhotic patients in response to hepatic damage. [29]. According to a prospective study of 477 cirrhotic patients with ascites, serum IP-10 had an AUC of 0.912, 91% sensitivity, and 89% specificity for diagnosing SBP at a cut-off value of 1915 pg/mL. In cirrhotic patients with SBP, there was a positive connection between serum IP-10 and other proinflammatory cytokines (TNF-α and IL-6). This could be an indication of persistent systemic inflammatory reactions [30]. However, the results of this study cannot be generalized to all patients with liver cirrhosis because it included all patients with ascites, regardless of the underlying cause; thus, the results cannot be generalized to all patients with liver cirrhosis. Further studies with a stricter design are needed to establish a reliable cut-off for serum IP-10 for the diagnosis of SBP.

3. Hematological Indices

3.1. Neutrophil-to-Lymphocyte Ratio

The blood neutrophil-lymphocyte ratio (NLR) is a crucial parameter for the balance of the inflammatory and immune systems, reflecting responses to systemic inflammation [31]. In patients with decompensated liver cirrhosis, NLR is a non-invasive marker that can be used to predict the occurrence of hospital infections [32]. NLR is a predictor of SBP that can be utilized in combination with other markers. According to Mousa et al., blood NLR > 2.89 had an 80.3% sensitivity and 88.9% specificity for diagnosing SBP, while blood NLR and CRP combined (cut-off 11.3 mg/dL) had a 95.1% sensitivity and 96.3% specificity [33]. Another study in the Romanian population demonstrated the good accuracy of the SBP diagnosis using a model based on NLR and erythrocyte sedimentation rate, and at a cut-off value of >2.4, the NLR's sensitivity and specificity were 98.61% and 81.94%, respectively [34]. However, it was a single-center retrospective study, and other data are contradictory in terms of the cut-off value.

3.2. Mean Platelet Volume

Platelets are thought to be a significant source of prothrombotic chemicals linked to inflammatory indicators and are involved in the initiation and spread of vascular and inflammatory disorders [35,36]. The hemostatic and pro-inflammatory effects of larger platelets are consequently more effectively exerted since they contain more granules [37]. As a result, it is suggested that the mean platelet volume (MPV) is a measure of platelet activation and function [38]. Ahmed Abdel-Razik showed that MPV has 95.9% sensitivity and 91.7% specificity for identifying SBP at a cut-off value of 8.77 fL [39]. A later study showed that a cut-off MPV value of 8.3 fL better distinguishes between cirrhotic patients with SBP and those without infection [40]. Two recent studies also showed the ability of MPV at cut-off 9.8 and 10.45 fL to predict SBP despite differences in cut-off point and sensitivity and specificity between studies [41,42].

From the results of the studies, it can be seen that MPV is the earliest laboratory test that can provide a rapid diagnostic tool for SBP, even before performing ascitic fluid sampling and examination.

4. Models for Prediction of SBP

Although single tests have shown some value in predicting SBP, their studies have been small and inconsistent. In order to predict SBP in patients with cirrhotic ascites, prediction scores in conjunction with clinical and laboratory indicators are therefore being developed. Therefore, several scoring systems have been developed recently.

4.1. Scoring System including Age, CRP, and Platelet Count

In 2014, a Wehmeyer study's study showed that platelet count of less than 100.000/μL, age greater than 60, and CRP greater than 60 mg/L were independent predictors of SBP [43]. The authors suggested a new, straightforward scoring system for SBP prognosis that took into account age, platelet count, and CRP (thrombocytopenia and age are both given one point, while CRP is given two points; Table 1). The simple scoring system had an 81.8% positive predictive value with a 98.8% specificity for the diagnosis of SBP (score ≥ 3) and an 87.9% sensitivity with a 93.5% negative predictive value at a threshold of one point [43].

Table 1. Wehmeyer's Scoring system for the diagnosis of SBP [43].

Parameter	"Cut-Off"	Scoring Points
Age	>60 years	1
Platelet count	≤100,000/μL	1
C-reactive protein	>60 mg/L	2

In 2018, a study was conducted in Egypt to evaluate a scoring system's cut-off values, including age, CRP level, and platelet count. Age, platelet count, and CRP level were found to be the independent predictors of SBP by multivariate analysis, according to the author's modification of the scoring system (the CRP value was given one point if it was between 13.5 and 30 mg/L, two points if it was between 30 and 60 mg/L, and three points if it was higher than 60 mg/L). The findings indicated that scores of four or five were reliable indicators of SBP (Table 2). On the other hand, scores of zero or one might be used to rule out the diagnosis of SBP [44].

Table 2. Modified Wehmeyer's SBP scoring system and the incidence of SBP [44].

SBP Scoring System	SBP Negative (%)	SBP Positive (%)
0	100	0
1	94.5	5.5
2	72.4	27.6
3	25	75
4	15.4	84.6
5	0	100

4.2. Mansoura Simple Scoring System

The Mansoura simple scoring system attempts to provide a straightforward scoring system by acknowledging the value and efficacy of NLR and MPV levels as well as clinical factors that predict SBP in cirrhotic ascites. The Tropical Medicine Department at Mansoura University conducted this retrospective cohort research between August 2011 and May 2018. According to the study's findings, the independent predictors of SBP were the age of at least 55 years, MPV of at least 8.5 fL, NLR of at least 2.5, and CRP of at least 40 mg/LA scoring system using these four factors (age, MPV, NLR, and CRP each receiving one point, while CRP receiving two points; Table 3) produced results with a specificity of 98.2% and a positive predictive value for the diagnosis of SBP of 88.1% (score ≥ 4). The negative predictive value was 97.5%, with a sensitivity of 92.9% at a threshold of one point (Table 4) [45].

Table 3. Mansoura scoring system.

Parameter	"Cut-Off"	Scoring Points
Age	≥55 years	1
MPV	≥8.5 fl	1
NLR	≥2.5	1
CRP	≥40 mg/L	2

Table 4. Diagnostic validity of the scoring system at various cut-offs.

Cut-Off	Specificity (%)	Sensitivity (%)	NPV (%)	PPV (%)
1	30.8	88.2	95.1	14.8
2	60.8	79.4	95.6	21.6
3	97.1	58.7	92.4	79.4
4	97.8	55.8	90.8	85.3
5	100	14.7	89.6	100

NPV, negative predictive value; PPV, positive predictive value.

This scoring system is easy to use, readily available, non-invasive, and reliable. It involves basic data that are collected when patients with cirrhotic ascites are admitted to the hospital. This scoring system would enable physicians to accurately differentiate between patients with and without SBP and to quickly start antibiotic treatment. However, this study's scoring system has one limitation in that it fails to diagnose SBP in patients who got 1 or 2 points [45].

4.3. PEC Index

Although the average estimate of serum PCT's sensitivity and specificity for the diagnosis of SBP in several clinical studies were shown to be relatively good [15], this performance was insufficient to produce a reliable, acceptable diagnosis. In 2020, Elsadek tried combining the measurement of serum PCT with those of serum ESR and CRP to create a new serum index for SBP diagnosis known as the PEC index. The PEC index was calculated using the formula [PEC index = PCT × (ESR + CRP)]. This formula was chosen based on statistical evidence following several iterations of various formulas. This was done to achieve a more dependable diagnostic accuracy of PCT.

The authors found that patients with SBP had a serum PEC index that was significantly higher than that of patients with sterile ascites. PEC index has sensitivity and specificity of 98.33% and 96.67%, respectively, at a cut-off value of 20, with an AUC of 0.97 and a 95% confidence interval (CI) of 0.940 to 0.99 [46]. In cirrhotic patients with ascites, the new serum PEC index is sufficient to provide a highly reliable non-invasive diagnosis of SBP. However, this is only the first study with a small sample size. There is a need for larger studies that evaluate the diagnostic value of the PEC index in SBP and compare it to other serum biomarkers.

5. Conclusions

In summary, Infections are common in liver cirrhosis patients, and SBP is one of the most prevalent, with varying frequency but a significant fatality rate. One of the most crucial factors in treating this significant consequence of decompensated liver cirrhosis is early detection. Finding non-invasive, affordable, and simple-to-implement parameters related to SBP that have a predictive role is essential. However, need to be kept in mind these methods cannot completely replace paracentesis; more studies are needed to determine whether non-invasive methods are sufficiently accurate to identify the development of SBP in cirrhosis.

The use of non-invasive methods for the prediction of SBP (Table 5) shows promise and will continue to become more important. In particular, scoring systems, which are simple, available, non-invasive, and reliable and involve easy parameters collected at hospital admission of cirrhotic ascites cases, help physicians start treatment without delay to avoid any complications (Figure 1). These initiatives and areas of uncertainty should be the focus of future research.

Table 5. Test characteristics for non-invasive prediction SBP.

Non-Invasive Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR (+)	LR (−)	AUROC
PCT [15]	79–87	82%–89			4.94	0.22	0.92
CRP [22]	75	61.2					0.613
Hcy [26]	95.1	89.3	68.2	99.2			0.932
IP-10 [30]	91	89	97	95			0.912
NLR [34]	98.61	81.94					0.963
MPV [40]	84	82	83	84			0.9
Wehmeyer's Scoring system [43]	29.4	100	100	83.1			0.68
Mansoura simple scoring system [45]	55.8	97.8	85.3	90.8			0.795
PEC Index [46]	98.33	96.67					0.977

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUROC, the area under the receiver operating characteristic.
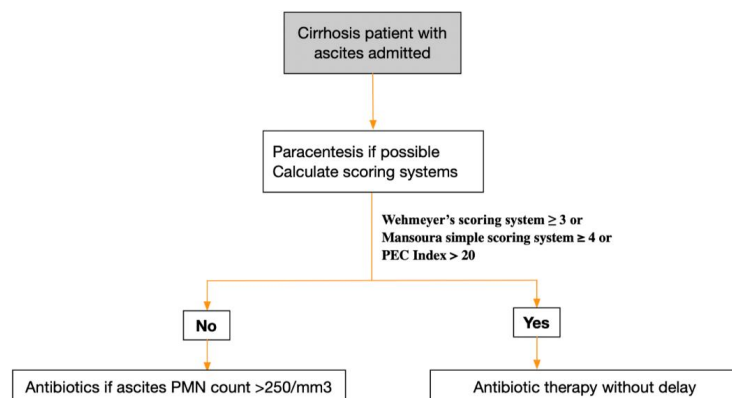
Figure 1. Proposed algorithm for the non-invasive prediction of SBP assessment to risk stratify patients using scoring systems. Patients with ascites cirrhosis admitted to hospital. Excluded patients who: (1) had received antibiotic and/or prophylaxis for SBP before admission, (2) had bacterial infection other than SBP. Wehmeyer's scoring system [43]; the Mansoura simple scoring system [45]. PEC Index [46]. PMN: polymorphonuclear leukocyte.

Conflicts of Interest: Authors declare no conflict of interest for this article.

Abbreviations

SBP: Spontaneous bacterial peritonitis; PCT: Procalcitonin; CRP: C-reactive protein; Hcy: Homocysteine; IP-10: Interferon-γ-induced protein; NLR: The blood neutrophil-lymphocyte ratio; MPV: the mean platelet volume

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