

# A Quick Screening Model for Symptomatic Bacterascites in Cirrhosis

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## ABSTRACT

**Background:** Diagnosis of spontaneous bacterial peritonitis in cirrhosis can be made when a patient has an ascites polymorphonuclear leukocyte count  $\geq 250/\text{mm}^3$ . However, symptomatic bacterascites, which is a variant of spontaneous bacterial peritonitis with signs of infection but an ascites polymorphonuclear leukocyte count  $< 250/\text{mm}^3$ , cannot be confirmed until the time-consuming ascites culture becomes positive. Currently, early indicators for symptomatic bacterascites remain undetermined. **Aims:** To develop a quick screening model for early detection of symptomatic bacterascites in cirrhosis. **Materials and Methods:** Data on patients with cirrhotic ascites from two hospitals (from 2010 to 2014) were collected retrospectively. Patients with symptomatic bacterascites were enrolled in the case group and compared with patients without any infection in the control group. Logistic regression analysis was used to build a model for screening symptomatic bacterascites, and a receiver operating characteristics curve was used to assess the model. **Results:** In total, 103 patients were enrolled in the case group and 204 patients were enrolled in the control group. A screening model was constructed based on body temperature, abdominal tenderness, blood neutrophil percentage, blood total bilirubin, prothrombin time, and ascites nucleated leukocyte count. The area under the receiver operating characteristic curve was 0.939; a screening score of 0.328 was the best cutoff value. **Conclusion:** Patients with suspected symptomatic bacterascites can be quickly screened according to the developed model, and a screening score  $\geq 0.328$  indicates symptomatic bacterascites.

**Key Words:** Cirrhosis, spontaneous bacterial peritonitis, symptomatic bacterascites

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Spontaneous bacterial peritonitis (SBP) is a severe complication of decompensated cirrhosis, and the in-hospital mortality for SBP ranges from 21.3% to 37%.<sup>[1-3]</sup> Bacterial translocation is the major cause of SBP; therefore, no intra-abdominal source of infection can be found.<sup>[4,5]</sup> Ascites culture is the gold standard for SBP diagnosis, and a high ascites polymorphonuclear leukocyte (PMN) count is accepted as an early indicator of SBP.<sup>[6,7]</sup> An ascites PMN count  $\geq 250/\text{mm}^3$  is considered to indicate empirical antibiotic therapy based on the current guidelines.<sup>[6,7]</sup> However, in clinical practice, this standard may lead to misdiagnosis in certain cases.

Symptomatic bacterascites (SB) is a variant of SBP with signs of infection but an ascites PMN count  $< 250/\text{mm}^3$ , and it can be only confirmed by a positive ascites culture.<sup>[8,9]</sup> SB is common in clinical practice accounting for 63% of SBP episodes and leads to a high mortality rate of 48.4%.<sup>[8]</sup> According to current guideline,<sup>[6]</sup> SB should be treated with antibiotics. Therefore, early detection of SB is important for both patients and physicians. Apparently, the threshold of ascites PMN count mentioned above is not useful for the diagnosis of SB, and ascites culture always takes several days;<sup>[10]</sup> therefore, it is difficult to diagnose SB as soon as it appears.

To date, early indicators for SB have not been determined. Although reagent strips have been tested for detecting

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SB, the results are unsatisfactory.<sup>[9]</sup> The current guideline suggests that patients with ascites PMN counts  $<250/\text{mm}^3$  and signs of infection should be treated with antibiotics while awaiting culture results,<sup>[7]</sup> which can be considered as management for SB. However, the “signs of infection” include several clinical manifestations only and no objective laboratory indices; therefore, this strategy would be implemented subjectively, leading to the abuse of antibiotics or delays in treatment. Worse still, ascites infection can manifest as diarrhea, hepatic encephalopathy, renal inadequacy, gastrointestinal hemorrhage, or other symptoms.<sup>[6]</sup> These different manifestations seem unrelated to ascites infection, which makes SB difficult to be detected in time. Therefore, we aim to create a quick screening model for the early detection of patients with SB using a retrospective case–control study.

## MATERIALS AND METHODS

### Study population

We performed a retrospective, two-center and case–control study in which inpatients with cirrhotic ascites at the First Affiliated Hospital of Nanchang University and the Infectious Disease Hospital of Nanchang University were enrolled between January 2010 and December 2014. The diagnosis of cirrhosis was based on clinical, laboratory, and imaging findings.<sup>[11]</sup> Ascites was confirmed by abdominal paracentesis.

### Diagnostic criteria

According to previous researches,<sup>[8,9]</sup> the diagnosis of SB was based on a positive ascitic fluid culture in association with an ascites PMN count  $<250/\text{mm}^3$  and suspicious signs of SBP. As described in the guidelines (American Association for the Study of Liver Diseases and European Association for the Study of the Liver),<sup>[6,7]</sup> suspicious signs of SBP included local symptoms and/or signs of peritonitis (eg, abdominal pain, abdominal tenderness, vomiting, diarrhea, and ileus), signs of systemic inflammation (eg, hyper- or hypothermia, chills, peripheral leukocytosis, tachycardia, and/or tachypnea), worsening of liver function, hepatic encephalopathy, shock, renal failure, gastrointestinal bleeding, and acidosis.

### Case and control group definitions

Subjects of the case group met the following criteria: (1) Patients with SB; (2) no antibiotics were administered in the two weeks prior to the presentation of SB; and (3) no intra-abdominal or extra-abdominal source of infection. Subjects of the control group met the following criteria: (1) Patients without any infection; (2) no antibiotics were administered in the two weeks prior to be enrolled; (3) PMN count  $<250/\text{mm}^3$  in an ascites sample, which was also negative for bacteria; and (4) discharged with improved condition including remission of symptoms, significant

ascites reduction and stabilization, and improved blood biochemical indices without antibiotic treatment.

The infection mentioned above was defined by the necessity of antibiotic intervention. To achieve a patient sample as representative as possible of the actual clinical situation, no exclusion criteria regarding concurrent diseases or nonantibiotic treatments were implemented.

### Data collection

General information and candidate indicators of SB were reviewed. The former included gender, age, concurrent diseases, liver cancer, and cirrhosis etiology, and the latter included life signs (body temperature, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure), local signs (abdominal pain, abdominal tenderness, abdominal rebound pain, vomiting, diarrhea, and ileus), clinical events (chills, shock, hepatic encephalopathy and gastrointestinal bleeding), hematological indices (white blood cell count, neutrophil percentage, prothrombin time and levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, bicarbonate, urea nitrogen, and creatinine), and ascites examination (nucleated leukocyte count, polymorphonuclear leukocyte count, and percentage of polymorphonuclear leukocytes). Candidate indicators were chosen based on the description of suspicious signs of SBP in the guidelines<sup>[6,7]</sup> and clinical judgment. Child–Pugh scores<sup>[12]</sup> were calculated and classified.

Candidate indicators were gathered on the day when ascites samples were collected for the control and case groups but before antibiotic administration for the case group. If the indicators were repeatedly measured, only the first measurements were recorded. If a patient experienced more than one event that met the inclusion criteria, only data for the first event were included in the analysis.

### Statistical analysis

Quantitative variables that were normally distributed are expressed as mean  $\pm$  SD, and those that were abnormally distributed are expressed as (median [interquartile range]) (M [IQR]). The quantitative variables were compared using the *t*-test or the rank sum test. Qualitative variables were expressed as percentages and compared using the Chi-square test or Fisher’s exact test. Binary logistic regression was used for the multivariate analysis. A screening model for SB was created from the candidate indicators that were significant in the multivariate analysis. To reduce the risk for overfitting the screening model, it was stated that the ratio of candidate variables to the number of observed events should be 1:5 or less, in final model.<sup>[13]</sup> The model was assessed using a receiver operating characteristics (ROC) curve that was applied to all patients in the current study. The cutoff value

that resulted in the highest Youden's index was chosen as the optimal cutoff value. Significance was established at  $P < 0.05$ . Data analysis was performed using SPSS 19.0 software. As this study was exploratory in design, sample size and power of the test were not estimated formally.

## RESULTS

### Patient characteristics

The clinical features of the patients are reported in Table 1. A total of 307 patients (65 from the First Affiliated Hospital of Nanchang University and 242 from the Infectious Disease Hospital of Nanchang University) were enrolled and then divided into the case group (103 patients) and the control group (204 patients). There were more male than female patients (74.8% vs. 25.2% and 71.1% vs. 28.9% for the case

and control groups, respectively), and the most common etiology of cirrhosis was hepatitis B in both groups (75.7% vs. 71.1%). Differences in gender, age, concurrent diseases, presence of liver cancer, and etiology of cirrhosis between the two groups were not significant ( $P > 0.05$ ). Child-Pugh score and class were significantly different between the two groups ( $P < 0.05$ ).

### Univariate analysis of candidate indicators for symptomatic bacterascites

The candidate indicators of SB are outlined in Tables 2 and 3, which show that the incidences of abdominal pain, abdominal tenderness, and abdominal rebound pain were significantly higher in the SB patients than in the controls (13.6% vs. 3.4%, 46.6% vs. 5.9%, and 34% vs. 2.5%, respectively,  $P < 0.001$ ). Although the ascites nucleated leukocyte count and PMN count of the SB patients were low, their median values were still significantly higher than those of the control group (200 vs. 100 and 70.3 vs. 24, respectively,  $P < 0.001$ ). Other significant candidate indicators were body temperature, chills, hepatic encephalopathy, white blood cell count, blood neutrophil percentage, blood total bilirubin, prothrombin time, blood urea nitrogen, blood creatinine, and ascites polymorphonuclear leukocyte percentage ( $P \leq 0.002$ ). No patients experienced shock or ileus during this study.

### Multivariate analysis of candidate indicators for symptomatic bacterascites

Indicators that were significant in the univariate analysis were further examined by multivariate analysis, and the results are shown in Table 4. Body temperature, abdominal tenderness (yes = 1, no = 0), blood neutrophil percentage, blood total bilirubin, prothrombin time, and ascites nucleated leukocyte count were significantly related to SB ( $P < 0.05$ ).

### Construction and assessment of screening model for symptomatic bacterascites

The screening score (SS) of SB for individual patients can be calculated by combining the values of six indicators with the regression coefficients reported in Table 4 as follows:  $SS = \exp(\text{logit}(SS)) / (1 + \exp(\text{logit}(SS)))$ , where  $\text{logit}(SS) = -50.325 + 1.09 \times \text{body temperature} + 2.103 \times \text{abdominal tenderness (yes = 1, no = 0)} + 0.048 \times \text{blood neutrophil percentage} + 0.008 \times \text{blood total bilirubin} + 0.069 \times \text{prothrombin time} + 0.013 \times \text{ascites nucleated leukocyte count}$ . For example, for a hypothetical patient with a body temperature of 37.9°C, abdominal tenderness, blood neutrophil percentage of 60.6%, blood total bilirubin of 28.1  $\mu\text{mol/L}$ , prothrombin time of 16.4 seconds and ascites nucleated leukocyte count of 260/ $\text{mm}^3$ , the SS would be calculated as follows:  $\text{Logit}(SS) = -50.325 + 1.09 \times 37.9 + 2.103 \times 1 + 0.048 \times 60.6 + 0.008 \times 28.1 + 0.069 \times 16.4 + 0.013 \times 260 = 0.734$ ;  $SS = \exp(0.734) / (1 + \exp(0.734)) = 0.676$ .

**Table 1: Clinical features of patients in both groups**

Characteristics	Case group (n=103)	Control group (n=204)	Statistics	P
Gender (male), n(%)	77 (74.8)	145 (71.1)	$\chi^2=0.463$	0.496
Age (years), median (IQR)	52 (41–58)	51 (43–61)	$Z=-0.709$	0.478
Etiology of cirrhosis, n(%)				
Hepatitis B	78 (75.7)	145 (71.1)	No statistic	0.162
Hepatitis C	1 (1.0)	6 (2.9)		
Alcohol	6 (5.8)	7 (3.4)		
Schistosomiasis	2 (1.9)	6 (2.9)		
Primary biliary	1 (1.0)	0 (0)		
Secondary biliary	1 (1.0)	0 (0)		
Multiple*	12 (11.7)	25 (12.3)		
Cryptogenic	2 (1.9)	15 (7.4)		
Liver cancer, n(%)	13 (12.6)	18 (8.8)	$\chi^2=1.087$	0.297
Concurrent diseases, n(%)				
CHD	3 (2.9)	4 (2.0)	No statistic	0.990
T2DM	5 (4.9)	10 (4.9)		
Hypertension	3 (2.9)	6 (2.9)		
COPD	1 (1.0)	3 (1.5)		
CKD	2 (1.9)	6 (2.9)		
Multiple*	3 (2.9)	9 (4.4)		
No	86 (83.5)	166 (81.4)		
Child-Pugh class, n(%)				
A	1 (1.0)	7 (3.4)	$\chi^2=36.93$	<0.001
B	25 (24.3)	118 (57.9)		
C	77 (74.7)	79 (38.7)		
Child-Pugh score, (mean±SD)	10.97±1.92	9.09±1.81	$t=-8.388$	<0.001

\*Two or more etiologies were listed, †Two or more diseases were listed. CHD: Coronary heart disease, T2DM: Type 2 diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, IQR: Interquartile range, SD: Standard deviation

**Table 2: Univariate analysis of candidate indicators for symptomatic bacterascites**

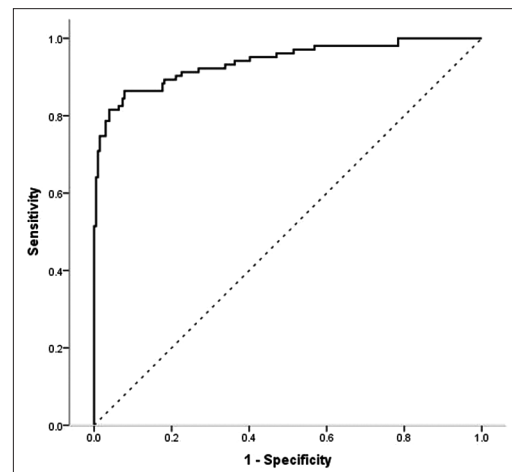
Candidate indicators	Case group (n=103)	Control group (n=204)	Statistics	P
<b>Life signs</b>				
Body temperature (°C), median (IQR)	36.9 (36.5-38)	36.6 (36.5-36.9)	Z=-5.652	<0.001
HR (beats/min), median (IQR)	84 (77-91)	82.5 (76-90)	Z=-0.551	0.582
RR (breaths/min), median (IQR)	20 (18-20)	20 (19-20)	Z=-0.623	0.533
SBP (mmHg), median (IQR)	110 (101-120)	113.5 (105.3-122)	Z=-1.122	0.262
DBP (mmHg), median (IQR)	70 (65-72)	70 (65-73.8)	Z=-1.144	0.253
<b>Hematological indices</b>				
WBC ( $\times 10^9/L$ ), median (IQR)	6.8 (4.3-10.1)	3.5 (2.5-4.5)	Z=-8.017	<0.001
NEUT%, median (IQR)	74.1 (62.7-81.4)	59.9 (49.8-68.1)	Z=-7.438	<0.001
ALT (u/L), median (IQR)	60 (32-100)	55 (31-88)	Z=-1.018	0.309
AST (u/L), median (IQR)	93 (52-146)	80 (48-127.3)	Z=-1.439	0.150
TB ( $\mu\text{mol/L}$ ), median (IQR)	57.4 (31.9-190.7)	29.2 (18.6-43.9)	Z=-6.231	<0.001
ALB (g/L), (mean $\pm$ SD)	26.87 $\pm$ 4.94	27.75 $\pm$ 5.35	t=-1.406	0.161
PT (s), median (IQR)	22.3 (17.4-29.6)	17.7 (15.3-21.1)	Z=-5.287	<0.001
HCO <sub>3</sub> <sup>-</sup> (mmol/L), median (IQR)	21.6 (19.3-23.8)	22.2 (20.5-24.6)	Z=-1.867	0.062
UN (mmol/L), median (IQR)	6 (4.7-9.3)	4.8 (3.6-6.5)	Z=-4.802	<0.001
Creatinine ( $\mu\text{mol/L}$ ), median (IQR)	76 (60-93)	61 (53-82)	Z=-3.538	<0.001
<b>Ascites examination</b>				
Nucleated leukocyte count (/mm <sup>3</sup> ), median (IQR)	200 (130-270)	100 (60-160)	Z=-7.715	<0.001
PMN count (/mm <sup>3</sup> ), median (IQR)	70.3 (41.8-113.1)	24 (14.1-45.5)	Z=-8.926	<0.001
PMN%, median (IQR)	36 (30-45)	26 (16.3-33.8)	Z=-6.394	<0.001

HR: Heart rate, RR: Respiratory rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WBC: White blood cells; NEUT%: Neutrophil percentage, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TB: Total bilirubin, ALB: Albumin, PT: Prothrombin time, HCO<sub>3</sub><sup>-</sup>: Bicarbonate, UN: Urea nitrogen, PMN: Polymorphonuclear leukocyte, PMN%: Percentage of polymorphonuclear leukocytes, IQR: Interquartile range, SD: Standard deviation

**Table 3: Univariate analysis of candidate indicators for symptomatic bacterascites**

Candidate indicators	Case group (n=103)	Control group (n=204)	Statistics ( $\chi^2$ )	P
<b>Local signs</b>				
Abdominal pain, n(%)	14 (13.6)	7 (3.4)	11.089	0.001
Abdominal tenderness, n(%)	48 (46.6)	12 (5.9)	72.171	<0.001
Abdominal rebound pain, n(%)	35 (34.0)	5 (2.5)	60.044	<0.001
Vomiting, n(%)	5 (4.9)	7 (3.4)	0.087	0.768
Diarrhea, n(%)	7 (6.8)	20 (9.8)	0.772	0.380
<b>Clinical events</b>				
Hepatic encephalopathy, n(%)	9 (8.7)	2 (1.0)	9.783	0.002
Gastrointestinal bleeding, n(%)	8 (7.8)	12 (5.9)	0.399	0.528
Chills, n(%)	9 (8.7)	1 (0.5)	12.273	<0.001

The screening scores of all patients enrolled in this study were calculated. A ROC curve for this screening model was constructed, and the area under the curve (AUC) was 0.939 ([95% CI, 0.908–0.970],  $P < 0.001$ , Figure 1). According to the maximum Youden's index, the optimal cutoff value of SS was 0.328, and it had a sensitivity of 86.4% and a specificity of 92.2%.



**Figure 1:** Receiver operating characteristic curve of the screening model for symptomatic bacterascites. Note: X-axis, 1-specificity; Y-axis, sensitivity; dashed line, reference line; solid curve, receiver operating characteristic curve of the screening model for symptomatic bacterascites, with an area under the curve was 0.939 ([95% confidence interval, 0.908–0.970],  $P < 0.001$ )

## DISCUSSION

Ascites PMN count, ascitic fluid lactoferrin, serum procalcitonin, and other indicators have been reported to be useful for the early diagnosis of SBP.<sup>[6,14,15]</sup> However,

**Table 4: Multivariate analysis of candidate indicators for symptomatic bacterascites**

Indicators	Regression coefficient	OR	95% CI	P
Body temperature (°C)	1.090	2.974	1.412-6.261	0.004
Abdominal tenderness (yes=1, no=0)	2.106	8.219	2.418-27.943	0.001
Blood neutrophil percentage	0.048	1.049	1.010-1.090	0.014
Blood total bilirubin (µmol/L)	0.008	1.008	1.002-1.015	0.016
Prothrombin time (s)	0.069	1.072	1.007-1.141	0.029
Ascites nucleated leukocyte count (/mm <sup>3</sup> )	0.013	1.013	1.001-1.026	0.041
Constant	-50.325	<0.001	NA	<0.001

OR: Odds ratio, CI: Confidence interval, NA: Not available

these methods were all tested in patients with ascites PMN counts  $\geq 250/\text{mm}^3$ ; thus, whether they are suitable for the screening of SB is still unknown. Ascites bacteria can be quickly detected by identification of bacterial 16S rRNA and by Raman spectroscopy,<sup>[16,17]</sup> which seem to be good techniques for diagnosing SB. Regrettably, these techniques are not recommended by the current guidelines.<sup>[6,7]</sup> In the absence of effective indicators or means, the model generated in this study, with integrated factors including clinical manifestations and laboratory examinations for the screening of SB, would be useful.

According to a previous study, abdominal tenderness is common in patients with SBP.<sup>[18]</sup> Wallerstedt *et al.* concluded that paying particular attention to abdominal tenderness may be the best way to become aware of the possible development of SBP.<sup>[19]</sup> In this study, as a binary variable, abdominal tenderness had a large odds ratio, suggesting that positive abdominal signs are reliable indicators of SB when other effective indicators are not available. Presumably, abdominal rebound tenderness is also an important indicator of SB in clinical practice; however, it was not included in this model.

It has been reported that most patients with SBP have elevated body temperature.<sup>[18]</sup> Similarly, in this study, among the continuous variables included in the model, body temperature had the largest odds ratio, which indicates that increased temperature is a powerful indicator of ascites infection. As a special pathophysiological characteristic, hypersplenism is common in decompensated liver cirrhosis and occurs with a low baseline of white blood cell count, which may not exceed the upper limit of normal even under stimulation by bacterial infection.<sup>[20,21]</sup> This finding can mislead physicians attempting to determine whether infection is present; therefore, the blood neutrophil

percentage, which is minimally impacted by hypersplenism, was recommended as a good substitute for white blood cell count in this study for the detection of infection.

Because an ascites PMN count cutoff value of  $\geq 250/\text{mm}^3$  is not capable of identifying SB, the ascites PMN count was not used in our screening model and was replaced by the ascites nucleated leukocyte count. In addition, Link *et al.* reported that an ascites nucleated leukocyte count lower than  $1000/\text{mm}^3$  was unlikely to indicate SBP, with a negative predictive value of 95.5%.<sup>[22]</sup> Therefore, we hypothesize that it is feasible to determine an ascites nucleated leukocyte count cutoff value for the early detection of SB.

Generally, abnormal blood total bilirubin and prothrombin time values have not been regarded as direct indicators of SBP but rather as results or risk factors for SBP.<sup>[23]</sup> However, these two indices were included in our screening model, as they were found to be significant indicators of SB in this study. A possible explanation may be that whether antibiotic treatment is warranted partially depends on the extent of liver function damage, and patients of suspected SB with worsening liver function cannot afford a fatal strike resulting from a missed diagnosis or delayed treatment. In other words, antibiotics should be used more readily in particular situations, such as when liver function deteriorates rapidly without an explicit cause.

Gastrointestinal bleeding is not exclusive to SB and was rejected by the univariate analysis in this study. Nevertheless, the current guideline suggests that patients with cirrhosis that are experiencing gastrointestinal bleeding should be treated with short-term (maximum 7 days) antibiotic prophylaxis (Class I, Level A) regardless of whether they have a bacterial infection.<sup>[12]</sup> So cirrhotic patients with suspected SB and gastrointestinal bleeding should receive antibiotic therapy directly.

## CONCLUSION

We identified several convenient indicators and developed a screening model for SB. Patients with suspected SB can be quickly screened according to the developed model, and a screening score  $\geq 0.328$  may be considered to indicate SB. Further studies are needed to validate this screening model and its rationality.

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## Conflicts of interest

There are no conflicts of interest.

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