A novel score-based approach by using routine laboratory tests for accurate diagnosis of spontaneous bacterial peritonitis (SBP) in cirrhotic patients

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Abstract

Summary
Background: Spontaneous Bacterial Peritonitis (SBP) poses a significant risk to cirrhosis patients with ascites, emphasizing the critical need for early detection and intervention. This retrospective observational study spanning a decade aimed to devise predictive models for SBP using routine laboratory tests. Additionally, it aimed to propose a novel scoring system to aid SBP diagnosis.

Methods: Data analysis encompassed 229 adult cirrhotic patients hospitalized for ascites between 2012 and 2021. Exclusions eliminated cases of secondary ascites unrelated to liver cirrhosis. Patients were categorized into SBP-positive (n=110) and SBP-negative (n=119) groups. Comparative analysis of demographic details and various laboratory indicators (Neutrophil-to-Lymphocyte Ratio (NLR), Mean Platelet Volume (MPV), C-Reactive Protein (CRP), Platelet (PLT), Alanine Transaminase (ALT), Aspartate Amino Transferase (AST), Potassium (K), Sodium (Na), Total Bilirubin (TB) and International Normalized Ratio (INR) was performed between the groups. The study presented effective SBP prediction models for prompt diagnosis and treatment: a multivariate logistic regression model and a simple scoring system.

Findings: The study advocates early diagnosis and rapid treatment for all cirrhotic patients with ascites, regardless of cirrhosis stage. Furthermore, it recommends initiating SBP treatment for patients scoring 2-3 in the proposed scoring system while excluding SBP findings for those scoring zero.
Conclusion: Combining age, sex, and specific laboratory tests (MPV, NLR, CRP, TB, and INR) within random forest models and a simple scoring system enables swift and accurate SBP diagnosis.

1. Introduction

Ascites, a prevalent and severe complication of chronic liver diseases, notably cirrhosis, imposes a significant burden of morbidity and mortality (1). Cirrhosis, characterized by progressive liver tissue fibrosis, stands as a leading cause of liver-related morbidity and mortality globally (2). It commonly originates from chronic liver injuries induced by factors such as viral hepatitis, excessive alcohol intake, nonalcoholic fatty liver disease (NAFLD), autoimmune liver diseases (3-5). During the early stages of cirrhosis, patients might remain asymptomatic or exhibit non-specific symptoms like fatigue, weight loss, and abdominal discomfort. However, disease progression leads to complications like ascites, hepatic encephalopathy, and variceal bleeding (6). Notably, individuals with cirrhosis are more vulnerable to bacterial infections, with up to 35% developing infections post-hospitalization (2). Ascites, the abnormal accumulation of fluid in the abdominal cavity, represents the most common complication of cirrhosis. It develops due to factors such as portal hypertension and renal sodium retention. The onset of ascites significantly impacts the quality of life and prognosis for cirrhotic patients (7). Among the life-threatening infections in cirrhotic patients with ascites, Spontaneous Bacterial Peritonitis (SBP) stands prominent. SBP results from bacterial translocation from the gut to the peritoneum, often due to compromised immune function (8-12). Its classic symptoms include fever and abdominal pain, though these might be absent in some cases (13). Swift diagnosis and treatment are pivotal for SBP, as mortality rates range from 10% to 50%, contingent on various factors (13). Traditional SBP diagnosis relies on ascitic fluid analysis through invasive procedures like paracentesis. To overcome the limitations of invasive testing, research has explored non-invasive markers, including neutrophil-to-lymphocyte ratio (NLR), mean platelet volume (MPV), Platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP). (14-18) This article reviews the critical importance of early diagnosis and management of ascites and SBP in cirrhotic patients, emphasizing non-invasive markers to expedite diagnosis.

2. Scientific Background

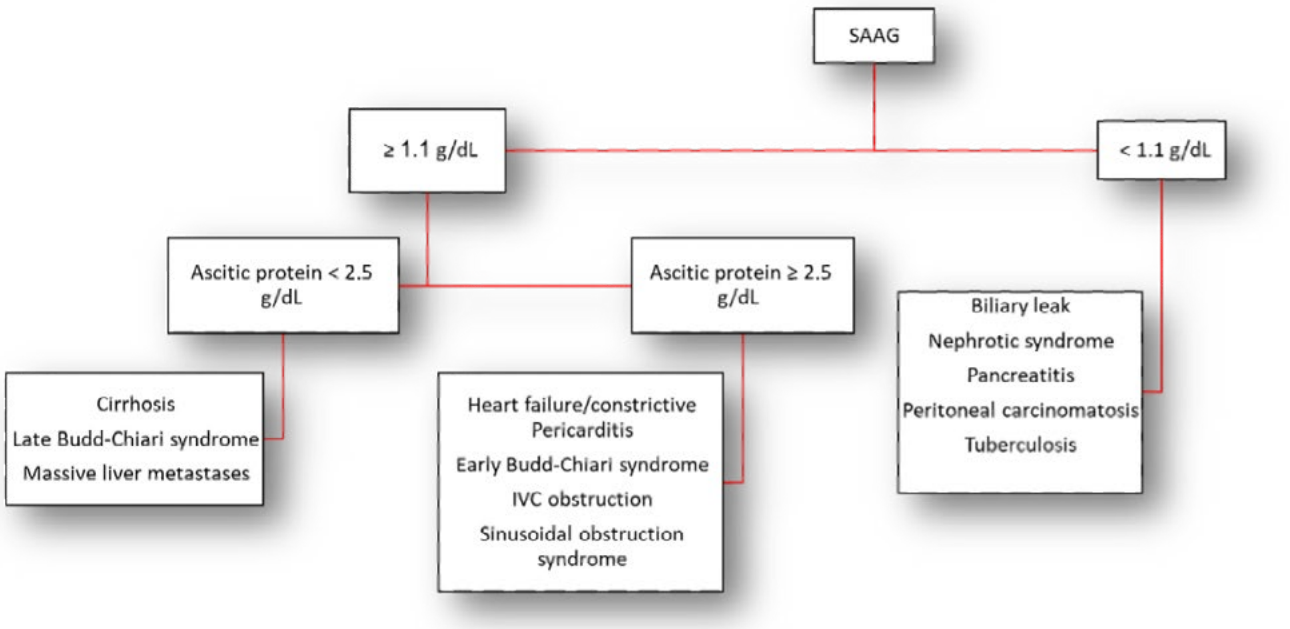
Cirrhosis, marked by liver fibrosis, represents a progressive liver disease with diverse etiologies. Although the liver can function initially despite cirrhosis, disease progression can culminate in liver failure and life-threatening complications (2). These complications encompass ascites, hepatic encephalopathy, and variceal bleeding (3-5). Effective management of cirrhosis involves addressing underlying causes, such as antiviral therapy for viral hepatitis or lifestyle modifications for non-alcoholic fatty liver disease. In advanced stages, liver transplantation might become necessary (3-5) Ascites emerges as a frequent consequence of cirrhosis, affecting approximately 60% of patients within ten years of diagnosis (19). It stems from portal hypertension-induced sodium retention and carries a high mortality rate, particularly when refractory to medical treatment (19). Timely diagnosis and management significantly enhance patient outcomes (7). Diagnosing ascites involves puncturing ascitic fluid to measure albumin levels, neutrophil counts, and culture for infection (20). Ascites etiology can also be discerned based on serum-ascites albumin gradient (SAAG) levels (21).

SBP stands as a common and life-threatening infection in cirrhotic patients with ascites. It correlates with a compromised immune system, bacterial translocation, and systemic inflammation, SBP diagnosis typically relies on invasive procedures like paracentesis (13). Mortality rates for SBP vary, yet early diagnosis and appropriate treatment are pivotal in reducing morbidity and mortality (13). Strategies for SBP prevention encompass prophylactic antibiotics and interventions to diminish bacterial translocation (8-12). Diagnosing SBP often necessitates invasive surgical puncture, leading to potential treatment delays. Therefore, the identification of reliable and non-invasive markers for early diagnosis holds crucial significance (22). Promising markers encompass NLR, MPV, PLR, CRP, total bilirubin, and INR (18, 16-17, 14-15, 23-26). Neutrophil-to-Lymphocyte Ratio (NLR), calculated by dividing the neutrophil count by the lymphocyte count, emerges as an indicator of immune system balance. Elevated NLR exhibits promise in diagnosing SBP (27). Mean Platelet Volume (MPV), associated with platelet activation, has been under study as a potential non-invasive marker for SBP diagnosis, showing promising results (28).C-Reactive Protein (CRP), synthesized during inflammation, has demonstrated diagnostic and prognostic value in SBP detection (22). Elevated INR and bilirubin levels are associated with an increased risk of SBP and higher mortality rates (23-25). Utilizing non-invasive markers like these offers potential benefits in early SBP diagnosis, ensuring timely intervention and improved patient outcomes.

3. Methods

The study employed computer algorithms constructed using fixed codes for diagnoses and laboratory tests. These algorithms aimed to maximize accuracy in extracting data for patients meeting the inclusion criteria. The first step involved gathering diagnoses and demographic data through the medical center's computerized medical record, utilizing one of the described algorithms. Next, the study extracted results from bacteriological laboratory cultures for ascites fluid sent between 2012 and 2021, totaling 408 cultures. Subsequently, patients with creatinine levels exceeding 5 mg/dL (79 patients) were excluded due to dialysis dependency, categorized as secondary ascites. Among the remaining 329 patients, the Serum Ascites Albumin Gradient (SAAG) was calculated using the Kasper et al. model (21) to isolate cases of ascites due to liver cirrhosis. Patients with a SAAG $\geq$ 1.1 and an ascites protein < 2.5 were included. Further data extraction included laboratory test results, demographic information, diagnoses, and background diseases using the established algorithms. This encompassed details such as age, gender, length of hospitalization, days of survival after hospitalization commencement, and mortality within 30 days post-hospitalization. The study population was stratified into two groups: one with a positive diagnosis for Spontaneous Bacterial

Peritonitis (SBP) (N=110) and a control group with a negative SBP diagnosis (N=119). Lastly, a statistical analysis was conducted on the data generated by the algorithms to compare the two study groups. This analysis aimed to evaluate any potential relationships between various laboratory indicators and SBP, employing statistical prediction models outlined in the results chapter. The dataset consisting of 229 samples was split into a training set (172 samples, or 75% of the data) and a testing set (57 samples, or 25% of the data). The training set was used to build the models, while the testing set was reserved for evaluating their performance on unseen data. The R package 'caret' was employed to perform model training and validation.



Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L., Jameson, J. L., & Loscalzo, J. (2019). Preface Harrison's Manual of Medicine. Asia Book Registry.

Figure 1: Etiology of ascites according to SAAG Kasper model values with numerical data (Kasper et al., 2019)

4. Results

4.1 Demographic data

Table 1: Descriptive statistics of the demographic data by the SBP group

	No SBP (N=119)	**SBP (N=110)**	**Total (N=229)**	***p* value**
Age	70.57 (12.06)	69.15 (13.59)	69.89 (12.81)	0.401
Gender				0.059
Female	50 (42.0%)	33 (30.0%)	83 (36.2%)	
Male	69 (58.0%)	77 (70.0%)	146 (63.8%)	

Notes: t-test for independent samples was used to test differences in continuous variables and Fisher exact test for categorical variables.

The SBP group comprised 70% males with a mean age of 69.2 (SD = 13.6), while the group without SBP consisted of 58% males with a mean age of 70.6 (SD = 12.1). As per Table 1, no statistically significant differences in age and gender were observed between the two groups.

4.2 Laboratory data

Table 2: Descriptive statistics of the Laboratory data by the SBP group

	No SBP (N=119)	SBP (N=110)	Total (N=229)	*p* value
Lymphocytes (abs)	1.46 (1.09)	1.35 (0.68)	1.41 (0.91)	0.384
NEUT (abs)	6.06 (2.68)	7.13 (3.98)	6.57 (3.40)	**0.017**
NLR (ratio)	5.11 (3.14)	8.06 (9.59)	6.56 (7.22)	**0.003**
PLT (1000/uL)	210.55 (86.94)	216.15 (99.60)	213.39 (93.39)	0.664
MPV (fL)	9.29 (1.42)	8.81 (1.35)	9.05 (1.40)	**0.016**
CRP (mg/dl)	34.97 (36.26)	43.39 (41.55)	39.61 (39.36)	0.201
ALT (U/l)	29.47 (19.14)	38.07 (42.02)	33.71 (32.68)	0.069
AST (U/l)	36.03 (35.99)	43.76 (53.27)	39.94 (45.59)	0.254
Potassium (mmol/l)	4.35 (0.72)	4.41 (0.62)	4.38 (0.67)	0.490
Sodium (mmol/l)	137.39 (4.50)	137.47 (5.00)	137.43 (4.75)	0.898
TB (mg/dl)	1.71 (1.83)	2.57 (2.75)	2.14 (2.36)	**0.010**
INR (ratio)	1.38 (0.87)	1.71 (1.42)	1.54 (1.18)	**0.039**

Notes: t-test for independent samples was used to test differences in continuous variables. Spontaneous Bacterial Peritonitis (SBP), Neutrophil to lymphocyte ratio (NLR), Mean Platelet Volume (MPV), C-Reactive Protein (CRP), Platelets (PLT), Alanine Trans Aminase (ALT), Aspartate Amino Transferase (AST), Total Bilirubin (TB), International Normalized Ratio (INR).

(7.13 vs. 6.06, p = .017), NLR (8.06 vs. 5.11, p = .003), TB (2.57 vs. 1.71, p = .010) and INR (1.71 vs. 1.38, p = .039), and lower in MPV (8.81 vs. 9.29, p = .016). No statistically significant differences were present in Lymphocytes, PLT, CRP, ALT, AST, Potassium and Sodium.

4.3 Mortality data

Table 3: Descriptive statistics of the mortality data by the SBP group

	No SBP (N=119)	SBP (N=110)	Total (N=229)	*p* value
Length of stay (days)	7.41 (6.82)	9.18 (13.21)	8.27 (10.45)	0.202
30-days mortality (n = 19)	12 (10.1%)	7 (6.4%)	19 (8.3%)	0.308
30-days Survival days (n = 19)	13.42 (8.37)	10.29 (8.40)	12.26 (8.29)	0.443
Survival days (n = 119)	716.53 (851.63)	709.44 (824.93)	713.02 (834.95)	0.963

Notes: t-test for independent samples was used to test differences in continuous variables and Fisher exact test for categorical variables.

4.4 Predictive models for SBP

4.4.1 multivariate logistic regression

A multivariate logistic regression was first performed to predict SBP based on NLR, MPV, INR, TB and the demographic data age and gender (Table 4).

Table 4: logistic regression model for predicting

Predictors	*Odds Ratios*	*95%CI*	*p*
(Intercept)	8.76	5.15 – 19.22	**0.001**
NLR (ratio)	1.09	1.01 – 2.10	**0.013**
MPV (fL)	0.74	0.63 – 0.82	**0.011**
INR (ratio)	1.30	1.14 – 1.50	**0.009**
TB (mg/dl)	1.15	0.95 – 1.96	0.077
Age	0.98	0.90 – 1.87	0.229
Gender [Male]	1.94	0.98 – 5.55	0.055

Neutrophil to lymphocyte ratio (NLR), Mean Platelet Volume (MPV), International Normalized Ratio (INR), Total Bilirubin (TB).

As presented in table 4, the variables NLR (OR = 1.09, 95%CI: 1.01 – 2.10), MPV (OR = 0.74, 95%CI: 0.63 – 0.82), and INR (OR = 1.30, 95%CI: 1.14 – 1.50) were statistically significantly associated with SBP. The global model was significant with R2Tjur = 0.244.

Table 5 presents a summary of the algorithm performances. It indicates that the random forest model exhibited superior performance compared to both the decision tree model and the standard logistic regression when tested on new data. Specifically, the random forest algorithm outperformed the other models across both the experimental and validation groups, The enhanced efficacy of the random forest algorithm can be attributed to its nature as an ensemble of decision trees. By amalgamating multiple trees, this model excels in capturing intricate data patterns and mitigating overfitting, hence showcasing its ability to generalize well to unseen data.

Table 5: Summary of algorithms performance

	Accuracy [95%CI]	Sensitivity	Specificity	NPV	PPV	P [Acc>NIR]	AUC
Testing data							
Logistic regression	67% [52%-81%]	55%	82%	66%	69%	**0.009**	0.67
Decision tree	86% [71%-97%]	77%	84%	72%	80%	**<0.001**	0.79
Random forest	89% [78%-99%]	85%	95%	79%	82%	**<0.001**	0.83
Training data							
Logistic regression	74% [65%-83%]	65%	85%	74%	75%	**0.003**	0.84
Decision tree	88% [83%-95%]	82%	92%	81%	85%	**<0 .001**	0.92
Random forest	100% [97%-100%]	100%	100%	100%	100%	**<0.001**	1.00

Neutrophil to lymphocyte ratio (NLR), Mean Platelet Volume (MPV), International Normalized Ratio (INR), Total Bilirubin (TB).

4.4.2 Scoring system

The scoring system was created by simulating the laboratory results data set to achieve the maximum accuracy in predicting SBP based on three different laboratory indices, where one point is assigned to each value that is above a predefined result cutoff according to the ROC curves of each index: Cutoff TB ≥ 2.375 mg/dl, NLR ≥ 3.438 and CRP ≥ 30 mg/dl.

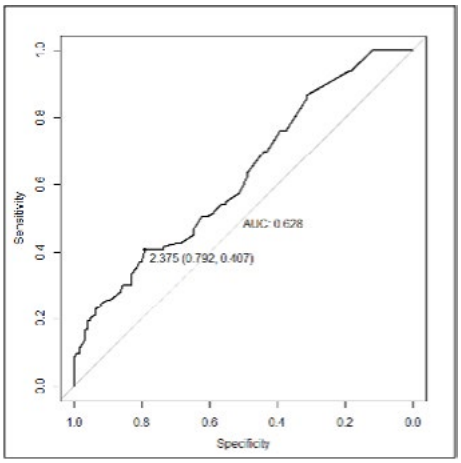


Figure 2A: ROC curve for Total Bilirubin (TB)

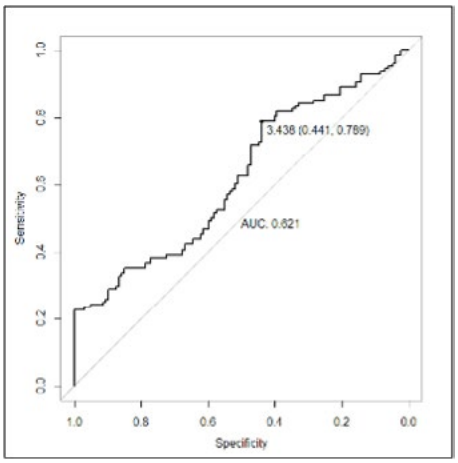


Figure 2B: ROC curve for Neutrophil to lymphocyte ratio (NLR)

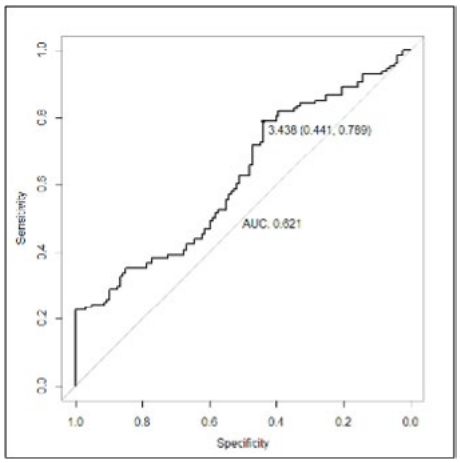


Figure 2C: ROC curve for C-Reactive Protein (CRP)

The ROC curve for the specificity and sensitivity of TB showed that at a score cutoff of TB ≥ 2.375 mg/dl, had a specificity of 79.2% and a sensitivity of 40.7% for predicting SBP (AUC = 0.628; P<0.001). The ROC curve for the specificity and sensitivity of NLR at a Cutoff result of NLR ≥ 3.438, had a specificity of 44.1% and a sensitivity of 78.9% for predicting SBP (AUC = 0.621; P<0.001). The ROC curve for the specificity and sensitivity of CRP showed that at a score cutoff of CRP ≥ 30 mg/dl, had a specificity of 89.3% and a sensitivity of 62% for predicting SBP (AUC = 0.714; P<0.001).

Table 7 presents the distribution of total scores among the study population, ranging from 0 to 3. It illustrates that: 61 patients obtained a score of 0, among whom 59 were negative for SBP, and 2 were positive. This signifies a 97% Negative Predictive Value (NPV) and a 3% Positive Predictive Value (PPV).
70 patients received a score of 1, with 38 testing negative for SBP and 32 testing positive. This shows a 54% NPV and a 46% PPV. 76 patients achieved a score of 2, where 21 were negative for SBP and 55 were positive. This results in a 28% NPV and a 72% PPV. 22 patients obtained a score of 3, among whom 1 was negative for SBP and 21 were positive. This demonstrates a 4% NPV and an impressive 96% PPV.

Table 6: Scoring system for predicting SBP

Lab Variable ≥ cutoff	Scoring points	Else
TB ≥ 2.375	1	0
NLR ≥ 3.438	1	0
CRP ≥ 30	1	0

Table 7: Summary of scoring system performance for the study population

Lab Variable sum of cutoff	No SBP (N=119)	SBP (N=110)	Total (N=229)	NPV	PPV
0	59	2	61	**97%**	3%
1	38	32	70	54%	46%
2	21	55	76	28%	**72%**
3	1	21	22	4%	**96%**

Table 8: The effect of the total score on the risk of having SBP

	SBP		
Predictors	**Odds Ratios**	**CI**	**p**
(Intercept)	0.05	0.01 – 0.17	**<0.001**
sum cat [1]	15.48	4.40 – 98.47	**<0.001**
sum cat [2]	39.81	10.80 – 259.54	**<0.001**
sum cat [3]	399.00	50.63 – 9583.99	**<0.001**
R2 Tjur		0.265	

The results of the scoring model show that the total score has a statistically significant effect on the risk of having SBP ($P < 0.001$). Patients with a score of 1 are 15.48 times more likely to have SPB than patients with a score of 0. Patients with a score of 2 are 39.81 times more likely to have SPB than patients with a score of 0. Patients with a score of 3 are 399 times more likely to have SPB than patients with a score of 0.

5. Discussion

Early detection of Spontaneous Bacterial Peritonitis (SBP) in cirrhotic patients with ascites is vital for effective treatment. Routine lab tests—Neutrophil-to-Lymphocyte Ratio (NLR) (16), Mean Platelet Volume (MPV) (3), C-Reactive Protein (CRP) (9), Total Bilirubin (TB), and International Normalized Ratio (INR) (24)—proved promising in predicting SBP.

NLR emerged as a strong predictor, aligning with prior studies that linked higher NLR values with SBP presence (8,9). In our study, an NLR cutoff of ≥ 3.438 showed significance in detecting SBP (sensitivity: 78.9%, specificity: 44.1%) (8).

MPV, contrary to conventional literature, revealed a significant decrease in SBP patients, aligning with previous studies. (3,16) Similarly, elevated CRP and INR levels were associated with SBP, echoing previous findings of their diagnostic relevance (9,24). TB, less studied in this context, showed potential as a predictor, with a cutoff of ≥ 2.375 mg/dl indicating SBP presence (sensitivity: 40.7%, specificity: 79.2%).

The developed random forest model, leveraging these markers, displayed a high predictive accuracy (sensitivity: 85%, specificity: 95%) in detecting SBP without invasive procedures (29). A scoring system akin to previous models demonstrated effective risk stratification for SBP, correlating scores with SBP probability (30).

The retrospective nature of our single-center study poses limitations in sample size and real-time data. The scoring system's limitations in diagnosing SBP with a single point warrant further refinement, Integration of the random forest model into clinical tools could aid in SBP diagnosis.

To validate findings, prospective studies with larger cohorts are crucial, Implementing the models in diverse medical centers globally could enhance SBP diagnosis and treatment. Recommendations include treating patients scoring 2-3 on the system and considering a prospective study for real-time validation.

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