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Risk stratification of spontaneous bacterial peritonitis in cirrhosis with ascites based on classification and regression tree analysis

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Abstract Risk stratification for spontaneous bacterial peritonitis (SBP) in patients with cirrhosis and ascites helps guide care. Existing prediction models, such as end-stage liver disease (MELD) score, are accurate but controversial in clinical practice. We developed and validated a practical user-friendly bedside tool for SBP risk stratification of patients with cirrhosis and ascites. Using classification and regression tree (CART) analysis, a model was developed for prediction of SBP in cirrhosis with ascites. The CART model was derived on data collected from 676 patients admitted from January 2007 to December 2009 retrospectively, and then was prospectively tested in another independent 198 inpatients between January 2010 and December 2010. The accuracy of CART model was evaluated using the area under the receiver operating characteristic curve. The performance of the model was further validated by comparing its predictive accuracy with that of the MELD score. Furthermore, the model was used to stratify SBP among patients with MELD scores under 15. CART analysis identified four variables for prediction of SBP: creatinine, total bilirubin, prothrombin time and white blood cell count, and three risk groups: low (2.0%), intermediate (27.5–33.3%) and high (60.6–86.4%) risk. The accuracy of CART model (0.881) exceeded that of MELD (0.791). Subjects in the intermediate risk and high risk groups had 22.21-fold (95% confident interval (CI), 9.98–49.45) and 173.50-fold (95% CI, 77.68–634.33) increased risk of SBP, respectively, comparing with the low risk group. Similar results were found when this risk stratification was applied to the validation cohort. Cirrhotic patients with ascites at low, intermediate, and high risk for SBP can be easily identified using CART model, which provides clinicians with a validated, practical bedside tool for SBP risk stratification.

Keywords Prediction · Risk factor · Paracentesis · Subgroup analysis · Model of end-stage liver disease

Abbreviations

A/G	Albumin/globulin ratio
AKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUROC	Area under the receiver operating characteristic curve
CART	Classification and regression tree

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CI	Confident interval
GGT	γ-Glutamyltransferase
HBV	Hepatitis B virus
HE	Hepatic encephalopathy
INR	International normalized ratio
MELD	Model of end-stage liver disease
OR	Odds ratio
PT	Prothrombin time
s	Second
SBP	Spontaneous bacterial peritonitis
Scr	Serum creatinine
TB	Total bilirubin
WBC	White blood cell

Introduction

Spontaneous bacterial peritonitis (SBP) developed ranging from 20 to 30% in patients with cirrhosis and ascites at 1-year follow-up, with a mortality rate of 20–40% [5, 12, 19]. After an episode of SBP, recurrence and mortality rates increased sharply [10]. The available evidence indicated that antibiotic prophylaxis was effective in the prevention of SBP [8, 16]. However, several problems would arise in long-term primary prophylaxis for first episode of SBP. Cost issues aside, appearance of resistant bacteria strains and the risk of subsequent development of SBP caused by resistant organisms should be considered [4, 7]. It is urgent to identify subgroups of cirrhotic patients with ascites who is at high risk of developing first episode of SBP, and can benefit from antibiotic prophylactic therapy.

Several risk indicators of SBP had been proposed in recent years, such as low ascites fluid protein level, platelet count and high serum bilirubin [2, 11, 15]. Moreover, model of end-stage liver disease (MELD) score, which was originally established to evaluate short-term mortality risk in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunt [17], had also been used to assess risk for SBP in patients with cirrhosis [9, 18]. However, clinically practical method of risk stratification of SBP in patients with different combinations of parameters was not well established. Combinations of the variables with optimal cut-off values would be an easier approach in the evaluation of risk for SBP.

Classification and regression tree (CART) analysis belongs to a family of nonparametric regression methods. The CART analysis is a tree-based classification and prediction method that uses recursive partitioning to split the training records into segments with similar output field values. At each split, the best predictor is automatically selected based on the modeling method used and 2 child nodes were generated. In turn, two child nodes may become parent nodes yielding additional child nodes. This process continues until no additional significant variable was detected or the sample size of the subgroup was below 20. As a result, the decision tree models are produced, which are easy to use and understand. It can be used simply to identify patients at different levels of risk by combining different variables. CART analysis had provided accurate prognostic models in different medical areas [3, 13, 21]. However, this method had not been used in the risk assessment of SBP development in cirrhotic patients with ascites.

In this study, CART analysis was used to develop a simple and accurate prediction model for stratifying cirrhotic patients with ascites, according to their risk of developing a first episode of SBP. Furthermore, the novel model would be tested in an independent cohort. Furthermore, we tested how well the new discrimination model could stratify SBP among patients with MELD scores under 15, in which SBP occurrence rate was low.

Patients and methods

Study population for development of CART model (derivation cohort)

Medical records of 1,381 consecutive cirrhotic patients with ascites who underwent diagnostic paracentesis within 48 h of admission to the First Affiliated Hospital of Wenzhou Medical College were reviewed from January 2007 to December 2009. Data concerning demographic information, medical history, clinical characteristics, laboratory values, co-morbidities, and physical exam findings were collected retrospectively. Exclusion criteria were: (1) patients admitted with gastrointestinal hemorrhage, or a previous history of gastrointestinal hemorrhage or SBP, because most of such patients had received antibiotic prophylaxis for SBP [10]; (2) liver cancer; (3) patients who had antibiotic administration within 2 weeks before admission; (4) patients with a potential confounding etiology for ascites unrelated to cirrhosis, such as peritoneal carcinomatosis, pancreatitis, tuberculosis, hemorrhage into ascites, or congestive heart failure; (5) for early identification of patients at risk for SBP, patients with fever, abdominal pain, or hepatic encephalopathy (HE) were excluded from the study; (6) nosocomial-acquired SBP. Seven hundred and five patients were excluded from the analysis: 116 subjects suffered from gastrointestinal hemorrhage, 137 patients had a previous history of SBP, 68 patients had a previous history of gastrointestinal hemorrhage, 132 patients had liver cancer, 58 patients received antibiotic treatment within 2 weeks before admission, 35 patients had confounding etiologies for ascites, 86 patients with fever, abdominal pain, or HE, and 73 patients with nosocomial-acquired SBP. Thus, a

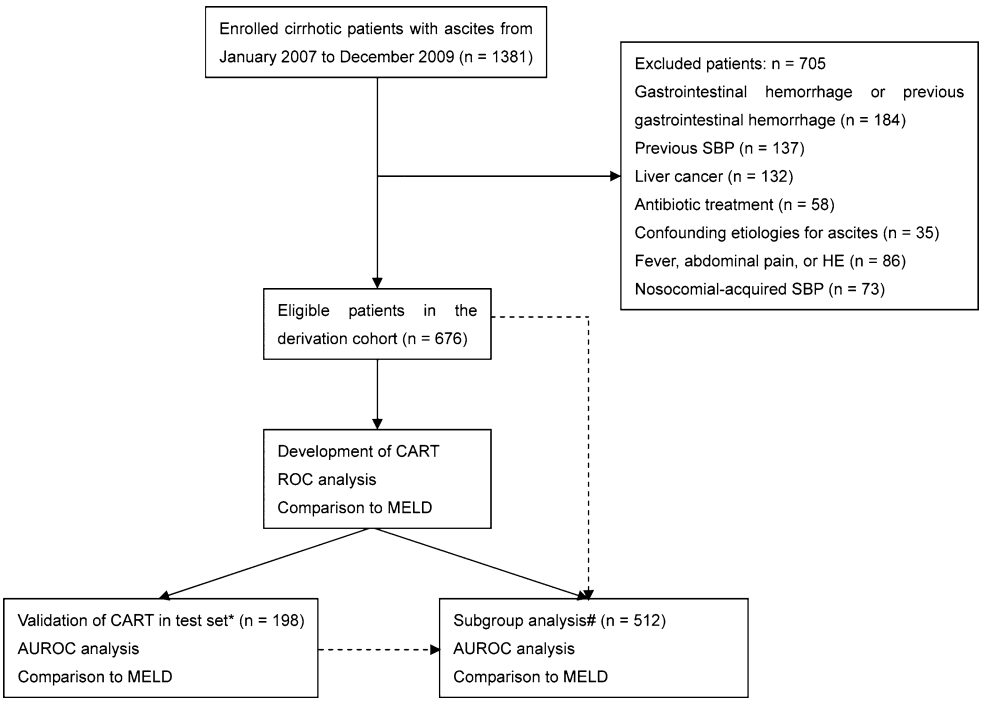

Fig. 1 Flow diagram of patients included in the study. *An independent cohort was prospectively enrolled for the validation of the derived CART model between January 2010 and December 2010. #Patients with MELD scores under 15 in derivation cohort and validation cohort. *Dotted line* showed that the patients in subgroup analysis were selected from derivation cohort and validation cohort. *AUROC* area under the receiver operating characteristic curve, *CART* classification and regression tree, *HE* hepatic encephalopathy, *MELD* model of end-stage liver disease, *SBP* spontaneous bacterial peritonitis

total of 676 eligible patients were included in the derivation cohort. The flow of inclusion and exclusion was shown in Fig. 1. This study was approved by the Ethical Committees of the First Affiliated Hospital of Wenzhou Medical College. All patients provided written informed consent.

Definitions

The diagnosis of cirrhosis was based on the results of the combination of physical, laboratory, and radiologic examination results or endoscopic signs of portal hypertension. Ascites was confirmed by ultrasonography. SBP was defined as polymorphonuclear cells count greater than or equal to 250 per cubic millimeter with or without a positive culture of the ascetic fluid, in the absence of finding suggestive of secondary peritonitis [5]. A community-acquired SBP episode was considered in any case diagnosed during the first 48 h of hospitalization. The diagnosis of liver cancer was made based on computer tomography and/or magnetic resonance imaging and/or hepatic angiogram.

CART analysis

In the study, CART analysis was applied to determine which cirrhotic patients with ascites would develop a first episode of SBP, solely based on the pre-paracentesis objective variables. The terminal subgroups were most homogeneous with respect to the probability of SBP development. Then, cirrhotic patients at low, intermediate, and high risk for SBP were identified according to the rates of SBP of subgroups. SBP occurrence rates for these risk groups and the odds ratios (ORs) and 95% confident interval (CI) between risk groups were determined.

Sample size for the validation cohort

To have an appropriate set for validation, it was planned that the validation set should have at least 5 events (SBP) for each variable included in the model derived from the derivation set [1]. Therefore, an independent cohort which consisted of 198 consecutive cirrhotic patients with ascites underwent diagnostic paracentesis was prospectively enrolled at the First Affiliated Hospital of Wenzhou Medical College between January 2010 and December 2010. The study protocols for these subjects were identical to those used in the development phase. The values of pre-paracentesis variables were taken within 24 h of admission.

CART model validation and comparison

The ability of the derived tree to stratify cirrhotic patients into different risk of SBP was tested in the independent validation cohort. The patients from the validation cohort were allocated to subgroups using the flowchart of the derived CART tree. The patients at low, intermediate, and high risk for SBP were identified and the SBP OR and 95% CI between risk groups were determined. In order to assess model calibration, the correlation between the model derivation and the validation dataset was also calculated. To validate the model further, we compared its performance with that of MELD score using the area under the receiver operating characteristic curve (AUROC) in both cohorts.

MELD score had been proved to be associated with risk for SBP and then was chosen as the reference standard. It was calculated according to the modified Malinchoc formula: $R = 9.57 \times \log_e(\text{creatinine [mg/dl]}) + 3.78 \times \log_e(\text{bilirubin [mg/dl]}) + 11.2 \times \log_e(\text{INR}) + 6.43 \times$ (aetiology: 0 if cholestatic or alcoholic, 1 otherwise).

Subgroup analysis

An important application of the new discrimination model in cirrhosis with ascites was to identify patients at risk for SBP with low MELD scores. We were interested in determining how well the new discrimination model could stratify SBP among patients with MELD scores under 15, in which SBP occurrence rate was low [18]. Therefore, we performed a subgroup analysis in which we applied the new prediction rule exclusively to patients with MELD scores under 15 in derivation cohort and validation cohort.

Statistical analysis

Continuous variables were expressed by mean ± SD and categorical values were described by count and proportions. For comparison of different groups, the Mann–Whitney U test and the χ^2 test were used to compare continuous and categorical variables, respectively. CART analysis was performed using data mining software Clementine version 12.0 (SPSS Inc, Chicago, IL). Additional statistical analysis was performed in SPSS 13.0 software (SPSS Inc, Chicago, IL). ROC curve analysis was computed using MedCalc 10.0 software (Mariakerke, Belgium). For all analyses, a P value of <0.05 was considered statistically significant.

Result

Characteristics of patients in the derivation and validation cohorts

In the derivation cohort, 676 cases were enrolled for CART model development, of which 153 patients (22.6%) had SBP. The mean age was 54.3 ± 10.0 years, 493 were male (72.9%), and hepatitis B virus (HBV) was the most frequent etiology of cirrhosis (64.8%). A total of 198 subjects were prospectively enrolled in the validation cohort. Sixty-nine patients (34.8%) were found to have SBP. The mean age was 53.6 ± 10.6 years, 145 were male (73.2%), and HBV was also the predominant etiology of cirrhosis (57.1%). There was a significant increase in overall SBP occurrence between the derivation and validation cohorts ($P = 0.001$). Distributions for demographic and clinical features between the two cohorts were depicted in Table 1.

CART analysis

Twenty variables were evaluated in this CART analysis, of which the CART method identified serum creatinine (Scr) as the variable of initial split with an optimal cut-off of 79.5 μmol/l. Among patients with Scr lower than 79.5 μmol/l, prothrombin time (PT) was selected as the variable of second split at a discrimination level of 22.95 s (s). The next best predictor of SBP in the lower PT node was total bilirubin (TB) with an optimal cut-off of 72.5 μmol/l. For the node with patients having a Scr level of lower than 79.5 μmol/l, PT of less than 22.95 s, and TB level of lower than 72.5 μmol/l, white blood cell (WBC) counts was selected as additional significant variable, dichotomized at a level of $6.85 \times 10^3/\text{mm}^3$. Among patients with Scr levels higher than 79.5 μmol/l, TB was selected as the next best predictor of SBP and dichotomized at a level of 63.5 μmol/l. Any additional risk nodes involving additional variables could not be generated to offered incremental risk discrimination. Therefore, a total of 6 subgroups of patients were produced by 4 predictive variables selected in this CART analysis: subgroup 1 (Scr $\leq$ 79.5 μmol/l and PT $>$ 22.95 s), subgroup 2 (Scr $>$ 79.5 μmol/l and TB $\leq$ 63.5 μmol/l), subgroup 3 (Scr $>$ 79.5 μmol/l and TB $>$ 63.5 μmol/l), subgroup 4 (Scr $\leq$ 79.5 μmol/l, PT $\leq$ 22.95 s and TB $>$ 72.5 μmol/l), subgroup 5 (Scr $\leq$ 79.5 μmol/l, PT $\leq$ 22.95 s, TB $\leq$ 72.5 μmol/l and WBC $\leq 6.85 \times 10^3/\text{mm}^3$), and subgroup 6 (Scr $\leq$ 79.5 μmol/l, PT $\leq$ 22.95 s, TB $\leq$ 72.5 μmol/l and WBC $> 6.85 \times 10^3/\text{mm}^3$) (Fig. 2).

The probabilities of SBP occurrence for the 6 subgroups were highly distinct. Patients were stratified into 3 risk levels: a low risk group (subgroup 5) with SBP rate of 2.0%, an intermediate risk group (subgroup 2, subgroup 4 and subgroup 6) with the SBP rate ranging from 27.5 to 33.3%, and a high risk group (subgroup 1 and subgroup 3) with SBP rate ranging from 60.6 to 86.4%. Subjects in the intermediate risk and high risk groups had 22.21-fold (95% CI, 9.98–49.45, $P < 0.001$) and 173.50-fold (95% CI, 77.68–634.33, $P < 0.001$) increased rates of SBP, respectively, compared with those in the low risk group (Table 2).

CART tree validation and comparison

The decision tree generated by CART analysis was validated for its ability to risk-stratify patients in the validation cohort of 198 subjects, which was independent of the model building dataset. Each patient was allocated to subgroups according to flowchart of the derived CART tree. The rates of SBP in each subgroup were shown in Supplementary Fig. 1, which were closely correlated with those in the model building dataset ($r^2 = 0.963$) (Fig. 3). This CART tree was also able to stratify patients in the validation cohort into high, intermediate, and low risk. Subjects in the intermediate risk

Table 1 Baseline characteristics of the derivation cohort and validation cohort

Variables	Derivation cohort ($n = 676$)	Validation cohort ($n = 198$)	P value
SBP (%)	153 (22.6)	69 (34.8)	0.001
Demographic			
Age (years)	54.3 ± 10.0	53.6 ± 10.6	0.348
Male gender (%)	493 (72.9)	145 (73.2)	0.933
Etiology of liver disease			
HBV (%)	438 (64.8)	113 (57.1)	0.048
Alcohol (%)	122 (18.1)	41 (20.7)	0.398
HBV + Alcohol (%)	56 (8.3)	26 (13.1)	0.040
Other (%)	60 (8.9)	18 (9.1)	0.926
Laboratory values			
ALT (U/l)	70.49 ± 190.70	85.58 ± 138.57	0.301
AST (U/l)	108.53 ± 278.97	116.47 ± 139.04	0.699
TB (μmol/l)	53.24 ± 58.29	65.49 ± 62.49	0.014
Albumin (g/l)	27.55 ± 5.41	27.49 ± 5.02	0.888
Globulin (g/l)	33.50 ± 8.54	35.15 ± 7.72	0.015
A/G ratio	0.89 ± 0.32	0.82 ± 0.25	0.003
GGT (U/l)	135.48 ± 191.17	134.14 ± 175.56	0.929
AKP (U/l)	134.27 ± 133.62	143.61 ± 103.20	0.365
Scr (μmol/l)	72.22 ± 36.41	83.94 ± 46.85	0.001
Serum sodium (mmol/l)	137.76 ± 4.56	136.23 ± 4.88	<0.001
WBC count ($\times 10^3/mm^3$)	4.83 ± 2.33	5.52 ± 3.28	0.006
Hemoglobin (g/l)	96.28 ± 24.97	104.60 ± 22.28	<0.001
Platelet count ($\times 10^3/mm^3$)	84.57 ± 51.81	77.96 ± 48.37	0.109
PT (s)	18.27 ± 3.49	19.29 ± 3.43	<0.001
Prothrombin activity (%)	59.13 ± 16.04	55.42 ± 14.18	0.003
INR	1.54 ± 0.38	1.63 ± 0.34	0.004
Alpha-fetoprotein (μg/l)	23.15 ± 7.90	25.29 ± 42.99	0.544
MELD score	14.60 ± 5.22	16.47 ± 5.05	<0.001

Continuous values were expressed by mean ± SD, and categorical values were described by count and proportions

A/G albumin/globulin ratio, *AKP* alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* γ-glutamyltransferase, *HBV* hepatitis B virus, *INR* international normalized ratio, *MELD* model for end-stage liver disease, *PT* prothrombin time, *SBP* spontaneous bacterial peritonitis, *Scr* serum creatinine, *TB* total bilirubin, *WBC* white blood cell

and high risk groups had 19.33-fold (95% CI, 5.56–57.09, $P < 0.001$) and 369.75-fold (95% CI, 107.89–2175.98, $P < 0.001$) increased rates of SBP, respectively, compared with those in the low risk group, which were similar to those of the derivation cohort (Table 2).

The performance of the derived CART tree was compared with MELD score. The CART tree had an excellent predictive accuracy, with AUROC significantly better than those of MELD score (0.881 vs. 0.791, $P < 0.001$) (Fig. 4a), and also was reproducible when applied to the validation set (0.924 vs. 0.858, $P = 0.025$) (Fig. 4b).

Subgroup analysis (stratification patients with MELD scores under 15)

There were 512 patients with MELD scores under 15 in the derivation and validation cohorts for subgroup analysis. In these cases, there were 51 patients with SBP (10.0%). The observed patients in this subgroup analysis were stratified into high, intermediate, and low risk according to the CART tree (Supplementary Table 1). This risk tree displayed its reliable ability to identify patients with increased risk of SBP in this subgroup analysis. The AUROCs of the CART tree and MELD score for prediction of SBP in the subgroup analysis were 0.869 and 0.663, respectively ($P < 0.001$) (Fig. 4c).

Discussion

The data from this large single-center cohort indicated that the prevalence of the first episode SBP was not improved in the past few years compared with historical cohorts [14]. In our study, there was a significant increase in overall SBP occurrence in validation cohort. Based on the data presented in Table 1, the difference was mainly owing to the different severity of the disease between the two cohorts; more severe disease was observed in the validation cohort. This would probably be due to higher distribution of the patients with HBV and Alcohol related cirrhosis.

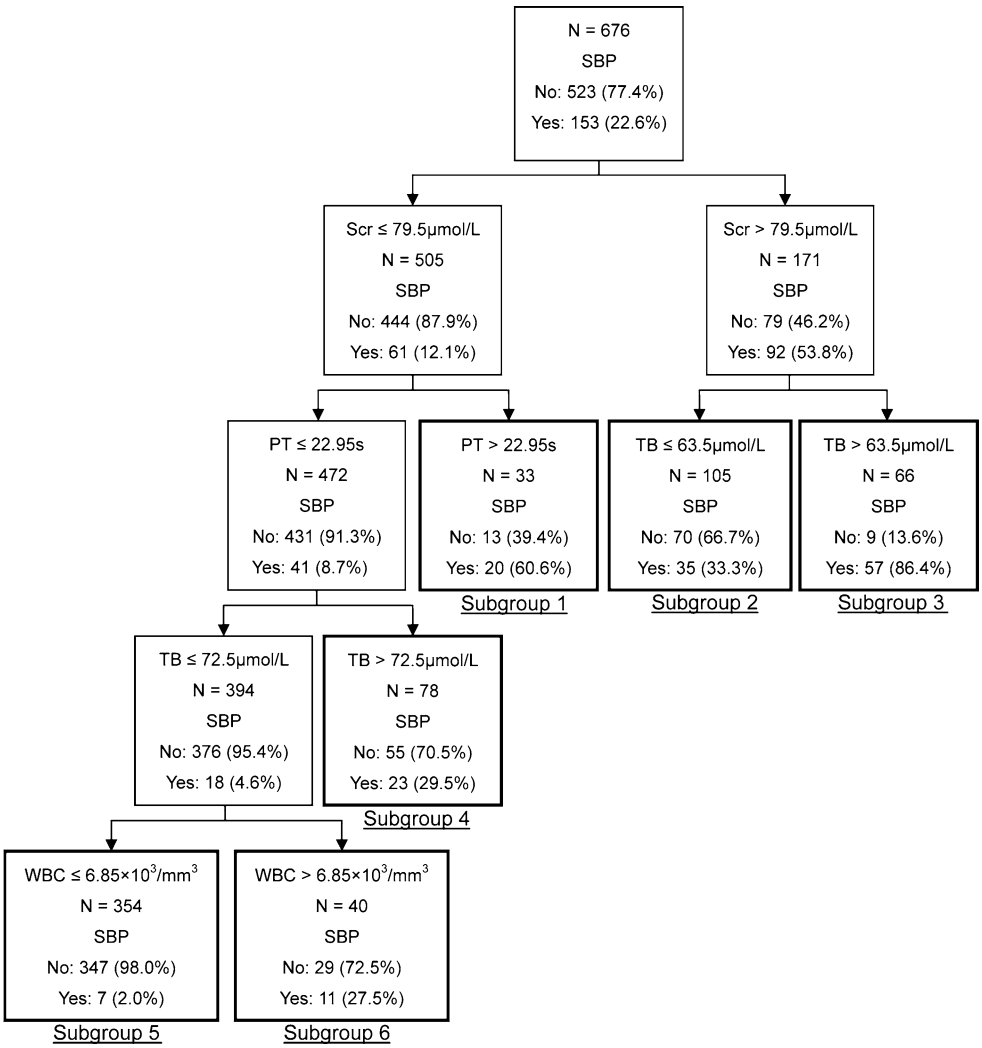

Fig. 2 Predictors of SBP and risk stratification for the derivation cohort. Terminal subgroups of patients discriminated by the analysis were numbered from one to six. *PT* prothrombin time, *SBP* spontaneous bacterial peritonitis, *Scr* serum creatinine, *TB* total bilirubine, *WBC* white blood cell

Table 2 SBP between risk groups

Risk group	Derivation cohort				Validation cohort			
	Number of subjects (%)	SBP (%) (95% CI)	OR (95% CI)	*P* value	Number of subjects (%)	SBP (%) (95% CI)	OR (95% CI)	*P* value
Low risk	354 (53.4)	7 (2.0) (0.6–3.7)	Reference		89 (44.9)	2 (2.2) (0.0–5.6)	Reference	
Intermediate risk	223 (33.0)	69 (30.9) (24.7–36.8)	22.21 (9.98–49.45)	<0.001	52 (26.3)	16 (30.8) (19.2–44.2)	19.33 (5.56–57.09)	<0.001
High risk	99 (14.6)	77 (77.8) (69.7–85.9)	173.50 (77.68–634.33)	<0.001	57 (28.8)	51 (89.5) (80.7–96.5)	369.75 (107.89–2175.98)	<0.001
Total	676 (100)	153 (22.6) (19.7–25.9)	14.50 (7.23–41.84)	<0.001	198 (100)	69 (34.8) (28.3–42.4)	23.27 (8.28–58.07)	<0.001

CI confident interval, *OR* odds ratio, *SBP* spontaneous bacterial peritonitis

Furthermore, the incidence of SBP varied greatly in the different risk groups (low risk group, 2.0–2.2%; high risk group, 57.1–94.0%). Therefore, it was important to identify the patients with high risk of SBP who could benefit from antibiotic prophylactic treatments.

In the present study, we had derived a novel prediction model to assess risk of SBP in cirrhotic patients with ascites. Four laboratory variables were highlighted in the analysis: Scr, TB, PT and WBC count. The patients were classified to 6 subgroups with different probabilities of SBP

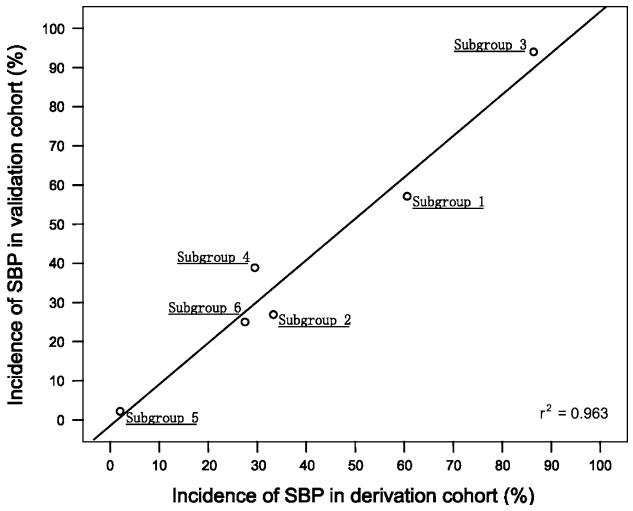

Fig. 3 Consensus analysis for derivation cohort and validation cohort: subgroup-stratified comparison of the SBP rate. The rate of SBP in each subgroup was plotted. The *X* axis represents the model building, and the *Y* axis represents the validation datasets. *SBP* spontaneous bacterial peritonitis

based on these variables. Patients were stratified into 3 risk groups according to the rate of SBP: 2.0% for low risk group, 27.5–33.3% for intermediate risk group and 60.6–86.4% for high risk group, according to the result of CART analysis. Patients could be allocated to specific subgroups by following the flow-chart form. In addition, the reproducibility of the prediction model was validated by an independent prospective cohort, in which some of the characteristics of the patients, such as the rate of SBP and laboratory values, differed from the derivation cohort. Thus, the novel model might have the potential to support decisions making in selecting high risk patients for antibiotic prophylaxis.

In our study, the Scr was selected as the first split variable with 79.5 μmol/l in the CART model. Patients with cirrhosis and ascites had a circulatory dysfunction which played important roles in the pathophysiological processes of renal failure and would be aggravated by infection, such as SBP [6, 20]. Level of Scr would elevate in the process of development of SBP. The finding raised the possibility that improvement of circulatory function accompanying with Scr decreasing in cirrhotic patients with ascites might contribute to decrease the occurrence of the SBP. A large prospective study is needed to be conducted to confirm the hypothesis.

The association between the first SBP episode and liver insufficiency had been proofed in previous studies [2, 9]. In a large series of cirrhotic patients with ascites, increased PT and TB, which were considered as markers of liver dysfunction, were significant and independent predictors of a first SBP episode [2]. In risk analysis of a first community-acquired SBP in cirrhosis with low ascitic fluid protein levels, SBP risk increased with bilirubin concentration above 57.4 μmol/l [11]. Our data showed that PT and TB were selected as the second factors for splitting by CART in patients with Scr $\leq$ 79.5 μmol/l and Scr $>$ 79.5 μmol/l, respectively. In addition, TB was also the third most important predictor for SBP in patients with PT $\leq$ 22.95 s. These findings indicated that antibiotic prophylaxis was needed for patients with severe liver insufficiency.

WBC defending against bacterial infection is usually the first responders to microbial infection. In cirrhotic patients, the spleen frequently enlarges and holds the WBC, reducing the number of these cells in blood. Elevating WBC count may indicate microbial infection. In our study, WBC count ($6.85 \times 10^3/mm^3$) could be a predicator for SBP in selected patients with Scr $\leq$ 79.5 μmol/l, PT $\leq$ 22.95 s and TB $\leq$ 72.5 μmol/l who were at low risk of SBP (4.6 and 4.1% in derivation and validation cohorts, respectively).

In addition to these parameters, other parameters were correlated with SBP in patients with cirrhosis include ascitic fluid opsonic activity, serum albumin, poor nutritional status, serum AST levels, ascitic fluid protein levels [2, 11]. Because multiple risk factors could exist in the same patient, risk factor analysis must consider factors in combination rather than isolation. Although no SBP risk stratification scheme was available for patients with cirrhosis

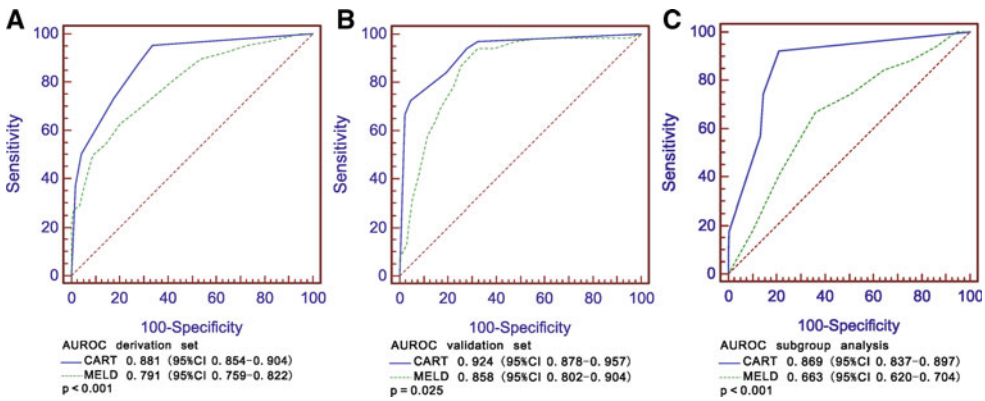

Fig. 4 Comparison of the AUROC for CART Model and MELD score. **a** Derivation set; **b** validation set; **c** subgroup analysis. *AUROC* area under the receiver operating characteristic curve, *CART* classification and regression tree, *CI* confident interval, *MELD* model of end-stage liver disease

and ascites, it had been proofed that increasing MELD score was independently associated with a higher risk of SBP. However, the complexity nature of MELD score had greatly limited its use. The number of variables and mathematical functions involved frequently require access to a computer or an electronic calculator to generate a score and then to determine risk made it impractical for bedside assessment. Similar to multivariate regression analysis, the CART method can detect interactions between variables. Moreover, it yields a decision tree that is relatively easy to apply at the bedside, leading to its potential use in a wide variety of clinical conditions. In current study, an intuitive decision tree (Fig. 2), based on the combined use of four variables (Scr, TB, PT and WBC count), usually available at patient's bedside, allowed an early discrimination of low, intermediate, or high risk groups with clearly distinct rate of SBP. Each of variables could be easily obtained early in the course of general hospital admission. Furthermore, the accuracy of the new prediction model was better than that of the MELD score. The CART model could also accurately identify patients with MELD score below 15.

The validated CART model could be helpful in difficult medical decision making in cirrhotic patients with ascites. Patients stratified to be at the higher risk group should receive a paracentesis and might undergo higher-level monitoring and earlier antibiotic prophylaxis for SBP, while patients judged to be at lower risk group might be reassured and receive less intensive and delayed antibiotic prophylaxis. In addition, the model might be valuable in designing clinical trials involving antibiotic prophylaxis of SBP. It could identify homogeneous patients into uniform groups and balance the risk factors across treatment groups, especially when the outcome of interest is determined by many different variables. For example, patients at high risk for SBP which were selected by CART analysis could be chosen as inclusion subjects in the design of controlled trials.

There were some potential limitations of the current study must be acknowledged. First, the study population came exclusively from a single center and the derivation set were collected retrospectively. The novel model should be validated in the external cohorts prospectively. Second, for early identification of patients with cirrhosis and ascites at risk for SBP, only pre-paracentesis variables were analyzed in this study, and ascitic fluid characteristics, such as ascitic fluid protein level, were not assessed in the current model. Third, data in this study was obtained from inpatients which were at a relatively more advanced stage of the disease and were at higher risk of SBP than outpatients. It would be interesting and necessary to validate the novel model in these patients.

In summary, cirrhotic patients with ascites at low, intermediate, and high risk for SBP can be easily identified using CART model, which provides clinicians with a validated, practical bedside tool for SBP risk stratification.

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Conflict of interest No conflicts of interest exist.

References

1. Altman DG, Vergouwe Y, Royston P, Moons KG (2009) Prognosis and prognostic research: validating a prognostic model. BMJ 338:b605
2. Andreu M, Sola R, Sitges-Serra A, Alia C, Gallen M, Vila MC, Coll S, Oliver MI (1993) Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. Gastroenterology 104:1133–1138
3. Augustin S, Muntaner L, Altamirano JT, Gonzalez A, Saperas E, Dot J, Abu-Suboh M, Armengol JR, Malagelada JR, Esteban R et al (2009) Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. Clin Gastroenterol Hepatol 7:1347–1354
4. Campillo B, Dupeyron C, Richardet JP, Mangeney N, Leluan G (1998) Epidemiology of severe hospital-acquired infections in patients with liver cirrhosis: effect of long-term administration of norfloxacin. Clin Infect Dis 26:1066–1070
5. European Association for the Study of the Liver (2010) EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 53:397–417
6. Fasolato S, Angeli P, Dallagnese L, Maresio G, Zola E, Mazza E, Salinas F, Dona S, Fagiuoli S, Sticca A et al (2007) Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 45:223–229
7. Fernandez J, Navasa M, Gomez J, Colmenero J, Vila J, Arroyo V, Rodes J (2002) Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 35:140–148
8. Fernandez J, Navasa M, Planas R, Montoliu S, Monfort D, Soriano G, Vila C, Pardo A, Quintero E, Vargas V et al (2007) Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 133:818–824
9. Gayatri AA, Suryadharma IG, Purwadi N, Wibawa ID (2007) The relationship between a model of end stage liver disease score (MELD score) and the occurrence of spontaneous bacterial peritonitis in liver cirrhotic patients. Acta Med Indones 39:75–78
10. Ghassemi S, Garcia-Tsao G (2007) Prevention and treatment of infections in patients with cirrhosis. Best Pract Res Clin Gastroenterol 21:77–93
11. Guarner C, Sola R, Soriano G, Andreu M, Novella MT, Vila MC, Sabat M, Coll S, Ortiz J, Gomez C, Balanzo J (1999) Risk of a

first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic fluid protein levels. Gastroenterology 117:414–419
12. Khan J, Pikkarainen P, Karvonen AL, Makela T, Peraaho M, Pehkonen E, Collin P (2009) Ascites: aetiology, mortality and the prevalence of spontaneous bacterial peritonitis. Scand J Gastroenterol 44:970–974
13. Kurosaki M, Sakamoto N, Iwasaki M, Sakamoto M, Suzuki Y, Hiramatsu N, Sugauchi F, Yatsuhashi H, Izumi N (2011) Pretreatment prediction of response to peginterferon plus ribavirin therapy in genotype 1 chronic hepatitis C using data mining analysis. J Gastroenterol 46:401–409
14. Lee JM, Han KH, Ahn SH (2009) Ascites and spontaneous bacterial peritonitis: an Asian perspective. J Gastroenterol Hepatol 24:1494–1503
15. Llach J, Rimola A, Navasa M, Gines P, Salmeron JM, Gines A, Arroyo V, Rodes J (1992) Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration. Hepatology 16:724–727
16. Loomba R, Wesley R, Bain A, Csako G, Pucino F (2009) Role of fluoroquinolones in the primary prophylaxis of spontaneous bacterial peritonitis: meta-analysis. Clin Gastroenterol Hepatol 7:487–493
17. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC (2000) A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 31:864–871
18. Obstein KL, Campbell MS, Reddy KR, Yang YX (2007) Association between model for end-stage liver disease and spontaneous bacterial peritonitis. Am J Gastroenterol 102:2732–2736
19. Runyon BA (2009) Management of adult patients with ascites due to cirrhosis: an update. Hepatology 49:2087–2107
20. Sola E, Gines P (2010) Renal and circulatory dysfunction in cirrhosis: current management and future perspectives. J Hepatol 53:1135–1145
21. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA (2008) The early prediction of mortality in acute pancreatitis: a large population-based study. Gut 57:1698–1703