Original Article

Development and Validation of a Prognostic Model for One-year Survival of Cirrhosis Patients with First-ever Spontaneous Bacterial Peritonitis

Rui-Rui Wang[1,2#] [iD], Hong-Qiu Gu[3,4#] [iD], Ying-Ying Wei[5], Jin-Xiang Yang[6], Yi-Xin Hou[1] [iD], Hui-Min Liu[1] [iD], Zhi-Yun Yang[1] [iD], Xian-Bo Wang[1] [iD] and Yu-Yong Jiang[1*] [iD]

[1]Center of Integrative Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, China; [2]Graduate School, Beijing University of Chinese Medicine, Beijing, China; [3]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [4]National Center for Healthcare Quality Management in Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [5]The first Clinical School, Beijing University of Chinese Medicine, Beijing, China; [6]Department of Gastroenterology, Beijing University of Chinese Medicine Third Affiliated Hospital, Beijing, China

Abstract

Background and Aims: Spontaneous bacterial peritonitis (SBP) is one of the leading causes of death in patients with liver cirrhosis. We aimed to establish a prognostic model to evaluate the 1-year survival of cirrhosis patients after the first episode of SBP. ***Methods:*** A prognostic model was developed based on a retrospective derivation cohort of 309 cirrhosis patients with first-ever SBP and was validated in a separate validation cohort of 141 patients. We used Uno's concordance, calibration curve, and decision curve (DCA) analysis to evaluate the discrimination, calibration, and clinical net benefit of the model. ***Results:*** A total of 59 (19.1%) patients in the derivation cohort and 42 (29.8%) patients in the validation cohort died over the course of 1 year. A prognostic model in nomogram form was developed with predictors including age [hazard ratio (HR): 1.25; 95% confidence interval (CI): 0.92–1.71], total serum bilirubin (HR: 1.66; 95% CI: 1.28–2.14), serum sodium (HR: 0.94; 95% CI: 0.90–0.98), history of hypertension (HR: 2.52; 95% CI: 1.44–4.41) and hepatic encephalopathy (HR: 2.06; 95% CI: 1.13–3.73). The nomogram had a higher concordance (0.79) compared with the model end-stage liver disease (0.67) or Child-Turcotte-Pugh (0.71) score. The nomogram also showed acceptable calibration (calibration slope, 1.12;

Bier score, 0.15±0.21) and optimal clinical net benefit in the validation cohort. ***Conclusions:*** This prediction model developed based on characteristics of first-ever SBP patients may benefit the prediction of patients' 1-year survival.

Introduction

Spontaneous bacterial peritonitis (SBP) is one of the most common types of infections in patients with decompensated liver cirrhosis and a leading cause of acute-on-chronic liver failure in patients with cirrhosis.[1,2] Studies have reported an up to 20% mortality rate for patients after the first episode of SBP, and up to 70% after 1 year.[3] Bacterial infections account for 38% of mortality among patients with cirrhosis.[4] Previous reports on the prognosis for SBP have been focused on risk factors or prediction models for short-term or inpatient outcomes.[5–11] Detection of death within 1 year could aid in delivering proper care and optimizing use of limited resources for treatment. In this study, we aimed to identify independent predictors of 1-year survival in patients after the first episode of SBP in cirrhosis, in order to construct and validate a risk prediction score to assess individual prognosis.

Methods

Derivation and validation cohorts

A total of 2,821 SBP cases occurring between January 2013 and May 2018 were screened for this study. These definite SBP cases were diagnosed at Beijing Ditan Hospital in Chi-

Definite SBP from January 2013 to May 2018（n=2821）

Excluded(n=2351)
Existing SBP before, secondary peritonitis or other infections (n=1153)
Malignant tumor patients(n=651)
Severe heart, kidney or other primary diseases(n=258)
Immunosuppression(n=24)
Mental patients(n=23)
Incomplete clinical data(n=232)
Liver transplantation(10)

Enrolled patients（n=470）

Excluded(n=20)
Uncertain outcome

Enrolled patients who followed up for one year（n=450）

Derivation cohort（SBP from January 2013 to December 2016，n=309）

Validation cohort（SBP from January 2017 to May 2018，n=141）

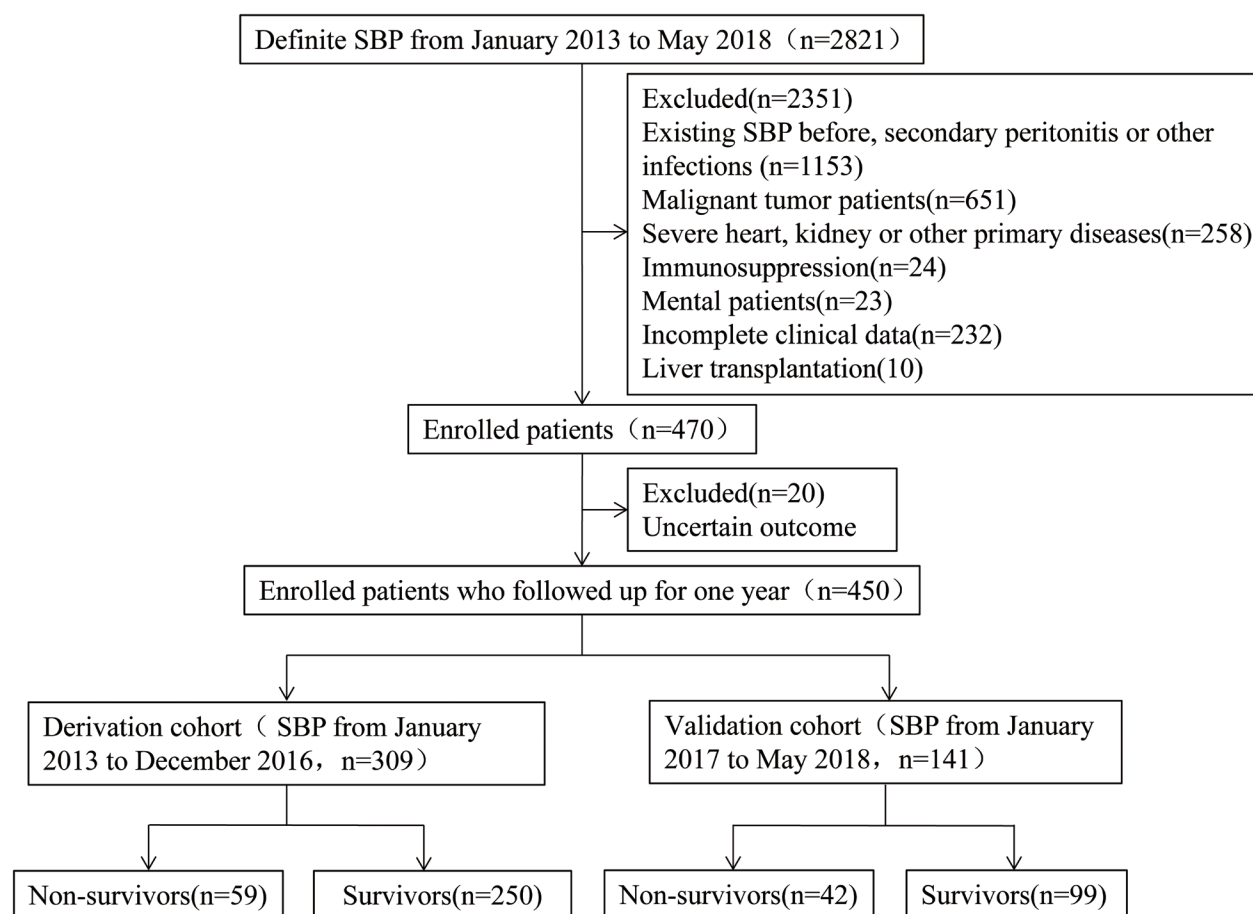Non-survivors(n=59)　Survivors(n=250)　Non-survivors(n=42)　Survivors(n=99)

Fig. 1. Study flow chart for derivation and validation cohort. After exclusion, 450 of the 2821 definite SBP cases were identified in our study. Derivation and validation cohort included 309 and 141 cases, respectively.

na, either at hospital admission or during hospitalization due to liver cirrhosis. Each record was reviewed, abstracted and crosschecked by two clinicians (YXH, HML). The exclusion criteria were as follows: (1) previous SBP; (2) secondary peritonitis or human immunodeficiency virus (HIV) infection; (3) concomitant infections at other sites, such as the lung, urinary tract, or soft tissue; (4) tumor, mental illness, or use of immunosuppressants; (5) severe heart, kidney or other primary diseases; (6) incomplete clinical data; (7) previous liver transplantation or liver transplantation within 1 year following the SBP infection. Only the first episode of SBP was included for each patient. This study was approved by the Ethics Committee of Beijing Ditan Hospital at Capital Medical University.

After exclusion criteria were applied, 450 of the 2,821 definite SBP cases were identified and included in our study. We then divided this cohort into the derivation and validation cohorts using the time point of January 1st, 2017. The 309 cases in the derivation cohort were used for variable selection and risk score development. The patient enrolment flowchart is shown in Figure 1.

Definitions

Liver cirrhosis was defined as any two of the following: clinical signs [spider nevi, ascites, hepatic encephalopathy (HE); compatible laboratory data [total bilirubin (TBIL), albumin (ALB), cholinesterase, international normalized ratio

(INR)]; imaging findings (nodular liver, varices, splenomegaly]; or corroborative histology.

SBP diagnosis was based on Chinese guidelines on the management of ascites and its related complications in cirrhosis,[12] with two conditions. First, there must be at least one of the following: signs or symptoms of acute peritonitis (abdominal pain, abdominal tenderness or rebound pain, increased abdominal muscle tension, vomiting, diarrhea, or intestinal obstruction), signs or symptoms of systemic inflammatory response syndrome (fever or hypothermia, chills, or tachycardia), deteriorated liver function without obvious inducement, HE, shock, refractory ascites, sudden lack of response to diuretics, renal failure, or acute gastrointestinal bleeding. There must also be at least one of the following test abnormalities: ascitic fluid polymorphonuclear cell count $\geq 250 \times 10^9$ cells/mm^3, positive culture of ascites bacteria, or procalcitonin (PCT) > 0.5 ng/mL and excluded infections in other sites.

Model end-stage liver disease (MELD) and Child-Turcotte-Pugh (CTP) scores were calculated according to previously published criteria.[13–15] All definitions and prognostic scores were applied at baseline. The baseline laboratory values were obtained within 3 days when patients were diagnosed as SBP.

Antibiotics and albumin therapy

All patients were treated with antibiotics within 2 weeks.

Due to the retrospective nature of the study, the choice of antibiotics and dosage of ALB were at the discretion of the supervising physician. There were 15 patients in the derivation group whose results in the ascites bacterial culture were positive, and antibiotics were mainly selected according to drug susceptibility. Most of the other patients were recommended cefotaxime, which is an antibiotic similar to the third-generation cephalosporins, or empirical antibiotic therapy according to clinical guidelines.[12,15,16] Additionally, if a patient's serum ALB levels were lower than 30 g/L, they were given an intravenous infusion of human ALB (10 g/day) until serum ALB levels exceeded 30 g/L.

Predictors and outcome

Potential predictive variables that might be associated with the long-term survival in cirrhosis with SBP were collected at hospital admission. These variables include age, sex, etiology of cirrhosis, comorbidities (history of diabetes and hypertension), complications (HE, upper gastrointestinal bleeding, and liver-kidney syndrome), and biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALB, TBIL, serum creatinine (Cr), serum sodium, C-reactive protein (CRP), PCT, platelet (PLT) count, neutrophil count, lymphocyte count, and neutrophil-lymphocyte ratio (NLR). The outcome was survival within 1 year of admission. Follow-up and outcome ascertainment were completed over the telephone by trained study coordinators.

Nomogram development and performance assessment

The final predictors in our prediction model were determined based on prior literature, clinical plausibility, data availability, and backward stepwise selection of all covariates in the Cox model. A nomogram was generated using coefficients of independent predictors of 1-year mortality, which were derived from the multivariable Cox regression. The value of each predictor was allocated a score from 0 to 100. We summed all scores to assign a probability of survival for each patient.

To assess the discrimination of our prediction model, we calculated Uno's concordance statistics and integrated time-dependent area under the curve (IAUC),[17] plotted time-dependent receiver operating characteristic (ROC) curves both for the derivation and validation cohorts, and compared them with models using only the MELD or CTP scores.[18] To evaluate the agreement between predicted and observed probabilities, Brier scores and calibration slopes were calculated and calibration curves were generated. We also performed decision curve analyses (DCA) to compare the benefits of our prediction model with the prediction models using only the MELD or CTP scores.

Statistical analysis

Patient characteristics in each cohort were described using frequencies and percentages for categorical variables or means and standard deviations for continuous variables. To assess the association between predictors and 1-year survival, we used univariate and multivariable Cox proportional hazards models to estimate the hazard ratios (HRs) and corresponding 95% confidence intervals.

All statistical analyses were performed with SAS version 9.4 or R version 3.6.0 (SAS Institute, Cary, NC, USA). A *p*-value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

The derivation and validation cohorts included 309 and 141 patients for analysis, respectively. Patients' demographic, clinical, and laboratory characteristics are summarized in Table 1. The mean age was 51 in the derivation cohort and 59 in the validation cohort. There was a total of 239 (77.3%) patients in the derivation cohort, and 95 (67.4%) patients in the validation cohort were male. The etiology of cirrhosis in the two cohorts was primarily hepatitis B, with 169 (57.4%) cases in the derivation cohort and 50 (35.5%) cases in the validation cohort. A total of 59 (19.1%) patients in the derivation cohort and 42 (29.8%) in the validation cohort died within 1 year.

Univariate and multiple Cox regression analyses

Univariate analysis showed that etiology, TBIL, serum sodium, ALB, Cr, history of hypertension, and HE were significantly correlated with 1-year mortality in the derivation cohort. Independent predictors of death identified using the multivariable Cox regression analyses were hepatitis C (HR: 2.94, 95% CI: 1.10–7.89, *p*=0.0001), TBIL (HR: 1.66, 95% CI: 1.28–2.14, *p*<0.0001), serum sodium (HR: 0.94, 95% CI: 0.90–0.98, *p*=0.0046), history of hypertension (HR:2.52, 95% CI: 1.44–4.41, *p*=0.0012), and HE (HR: 2.06,95% CI: 1.13–3.73, *p*=0.0178). Although age (HR: 1.25, 95% CI: 0.92–1.71, *p*=0.1557) was not identified as a statistically significant predictor in the multivariable Cox model, we included it based on clinical knowledge and evidence from prior literature (Table 2).

Nomogram

The nomogram was established based on age, etiology, history of hypertension, HE, TBIL, and serum sodium (Fig. 2). The probability of 1-year survival can be obtained by reading this nomogram. For example, a 50 year-old (20 points) first-time SBP patient with an etiology of alcohol (12.5 points), no history of hypertension (0 points), no previous history of HE (0 points), TBIL of 12.2 μmol/L (27.5 points), and serum sodium of 140 mmol/L (22.5 points) would have a total nomogram score of 82.5 and a <0.1 probability of 1-year death. In comparison, a 70 year-old (36.25 points) first-time SBP patient with an etiology of hepatitis B (0 points), history of hypertension (33.75 points), previous history of HE (26.25 points), TBIL of 33.1 μmol/L (45 points), and serum sodium of 130 mmol/L (44 points) would have a total nomogram score of 185.25 and a 0.55 probability of 1-year death.

Validation of the prognostic nomogram

Uno's concordance of the nomogram was optimal, with 0.77 (95% CI: 0.74–0.80) in the derivation cohort and 0.79 (95% CI: 0.76–0.82) in the validation cohort. The nomogram also had a higher IAUC than the CTP or MELD model in both cohorts (Fig. 3).

Calibration plots showed that the predicted probability was highly consistent with the actual probability in both cohorts (Fig. 4). The Brier score was 0.12±0.22 in the derivation cohort and 0.15±0.21 in the validation cohort. The calibration slope was 1.05 for the derivation cohort and 1.12 for the validation cohort. In the DCA, our nomogram provided

Table 1. Baseline characteristics of enrolled spontaneous bacterial peritonitis patients in the derivation and validation cohorts

Variables	Derivation cohort, *n*=309	Validation cohort, *n*=141
Age in years	51.9±9.5	59.1±11.4
Male sex	239 (77.3)	95 (67.4)
Diagnosis		
Hepatitis B	169 (54.7)	50 (35.5)
Hepatitis C	21 (6.8)	11 (7.8)
Alcohol	84 (27.2)	44 (31.2)
Other	35 (11.3)	36 (25.5)
Complication		
Diabetes mellitus	69 (22.3)	53 (37.6)
History of hypertension	47 (15.2)	34 (24.1)
HE	56 (18.1)	57 (40.4)
Gastrointestinal hemorrhage	97 (31.4)	50 (35.5)
Hepatorenal syndrome	51 (16.5)	12 (8.5)
ALT in U/L	32.7 (19.1–57.9)	33.8 (19.7–60.5)
AST in U/L	42.5 (28.7–85.5)	27.1 (19.2–42.3)
ALB in g/L	28.5 (25.7–31.1)	28.9 (25.5–32.6)
TBIL in µmol/L	44.6 (22.9–105.7)	36.2 (18.5–97.6)
Cr in µmol/L	69.4 (58.0–89.5)	77.7 (61.2–106.2)
Serum sodium in mmol/L	137.3 (132.7–140.3)	136.0 (133.0–140.1)
Neutrophils count as $\times 10^9$/L	3.8 (2.3–5.7)	3.4 (2.1–5.4)
Lymphocyte count as $\times 10^9$/L	0.8 (0.5–1.3)	0.8 (0.5–1.0)
NLR	4.1 (2.6–7.3)	4.7 (2.7–8.3)
PLT as $\times 10^9$/L	64.0 (45.4–99.4)	71.0 (48.4–98.0)
CRP in mg/L	22.5±26.9	2.8±1.5
PCT in µg/L	3.2±15.0	3.3±8.3
INR	1.5 (1.3–1.8)	1.5 (1.3–2.0)
CTP score	9.8±2.1	9.8±2.6
MELD	12.0±7.5	12.6±9.1

Data in the table are the mean ± standard deviation for continuous variables after calculating the log, and *n* (%), frequency with percentage for categorical variables.

superior net benefit in both cohorts compared to the MELD and CTP score models (Fig. 5).

Discussion

In this study, we established a prognostic model for 1-year survival of patients with first-time SBP under real-world conditions. The performance of this model was satisfactory in terms of discrimination, calibration, and clinical benefit indicators in both the development and validation cohorts. The six variables we used to calculate mortality risk (age, etiology, history of hypertension, serum TBIL level, serum sodium level, and complication of HE) are readily available in most clinical datasets, and as such, this nomogram provides clinicians with an accessible tool to estimate individual patients' risk of death. If the patient's estimated risk is low, the clinician may choose to continue the current treatment, whereas patients estimated to have high risk may require more aggressive treatment.

Previous studies of patients with SBP have focused on predictors of acute or short-term outcomes.[8,10,11] A prior study showed that the mortality rate during hospitalization is high (20% to 43%), and remains high at 1 year after discharge.[6] Our study found a similar prevalence of death within 1 year for first-time SBP patients (19.1%).

This study evaluated a number of independent variables that can be used to predict mortality in patients with SBP, including complications such as HE and upper gastrointestinal bleeding, indicators of infection such as total white blood cells and CRP, and other liver and kidney function indicators, such as AST, TBIL, INR, and Cr.[5,7] Previous studies have shown that MELD and CTP can be used as predictors of death in SBP patients during hospitalization.[10,11,19] However, our study indicates that they are not suitable as independent predictors of long-term prognosis of first-time SBP patients. In addition to the aforementioned common independent variables, we also considered the impact of comorbid hypertension and diabetes, which are two common complications. We found that hypertension was an independent risk factor, suggesting that hemodynamic disorders may play an important role in

Table 2. Univariate and multivariable Cox regression analysis in patients with spontaneous bacterial peritonitis patients from the derivation cohort, *n*=309

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age per 10 years	1.28 (0.96–1.71)	0.0892	1.25 (0.92–1.71)	0.1557
Male sex	0.75 (0.42–1.34)	0.3335		
Diagnosis				
Hepatitis B	1.0 (Reference)		1.0 (Reference)	
Hepatitis C	2.13 (0.78–5.83)	0.1389	2.94 (1.10–7.89)	0.0319
Alcoholic fatty liver	2.38 (1.32–4.28)	0.0038	1.40 (0.74–2.64)	0.3000
Other	2.51 (1.19–5.31)	0.0156	1.96 (0.90–4.29)	0.0922
Complication				
Diabetes mellitus	1.32 (0.75–2.32)	0.3421		
History of hypertension	2.50 (1.43–4.34)	0.0012	2.52 (1.44–4.41)	0.0012
HE	2.46 (1.42–4.26)	0.0013	2.06 (1.13–3.73)	0.0178
Gastrointestinal hemorrhage	1.04 (0.61–1.80)	0.8775		
Hepatorenal syndrome	1.74 (0.95–3.18)	0.0729		
Biochemical parameters				
ALT	1.00 (1.00–1.00)	0.7343		
AST	1.00 (1.00–1.00)	0.7381		
ALB	0.93 (0.89–0.98)	0.0061		
TBIL	1.84 (1.44–2.36)	<0.0001	1.66 (1.28–2.14)	0.0001
Cr	1.01 (1.00–1.02)	0.0035		
Serum sodium	0.93 (0.89–0.96)	<0.0001	0.94 (0.90–0.98)	0.00046
CRP	1.00 (1.00–1.01)	0.3754		
PCT	1.00 (0.99–1.02)	0.9817		
PLT	1.00 (1.00–1.00)	0.6835		
NLR	1.01 (0.97–1.05)	0.6284		
INR	1.98 (1.29–3.03)	0.0019		

the long-term prognosis of SBP patients with cirrhosis. This issue has received little attention in prior literature.

Bacterial infections in advanced liver cirrhosis cause profound changes in systemic hemodynamics, with effects such as peripheral vasodilation, reduced systemic vascular resistance, and reduced responsiveness to vasoconstrictors.[20] As a result, the body needs to increase cardiac output to maintain adequate organ perfusion. However, the cardiac compensation reserve of patients with hypertension may be reduced, resulting in impaired adaptive responses to acute circulatory stress, such as in SBP. At the same time, hypertension is often accompanied by a decrease in renal function, leading to an increased risk of hepatorenal syndrome. A study in Austria showed that non-selective beta-blockers increased the length of hospital stay in cirrhosis patients with SBP and increased the risk of hepatorenal syndrome as well as acute kidney injury.[21] This is related to decreased cardiac output in patients with cirrhosis treated with non-selective beta-blockers. One study in Spain found that serum urea nitrogen, white blood cell count, CTP, and mean arterial blood pressure are independent risk factors for in-hospital mortality in patients with SBP.[10] The aforementioned studies as well as the present study show that hemodynamic disorders significantly affect the prognosis of patients with SBP. Furthermore, hypertension is a component of meta-bolic syndrome. Metabolic syndrome increases the incidence of liver disease-related events by 49%, and those with both metabolic syndrome and hepatitis B infection were more likely to have liver disease-related events.[22] As such, hypertension likely has an important effect on the long-term prognosis of SBP patients with cirrhosis, though the specific mechanism warrants further research and discussion.

Numerous studies have shown that older age is an important factor in the poor prognosis of liver disease.[23–25] This may be related to a decline in immune function, leading to increased sensitivity to infections.[26,27] Several recent studies have found that serum sodium levels are closely related to clinical progress and prognosis, and that the correction of hyponatremia is an integral part of treatment for patients with decompensated liver cirrhosis.[28,29] For example, tolvaptan can effectively improve hyponatremia, thereby improving the prognosis of patients with cirrhosis and ascites.[30] Our study found that hyponatremia is an independent risk factor for death in patients with SBP, which is consistent with findings from previous studies.[31,32] Hyponatremia causes cellular edema, increased intestinal mucosal permeability, bacterial translocation, and also leads to SBP.[33] Moreover, hyponatremia causes cerebral edema, leading to decreased blood volume and induction of hepatorenal syndrome.
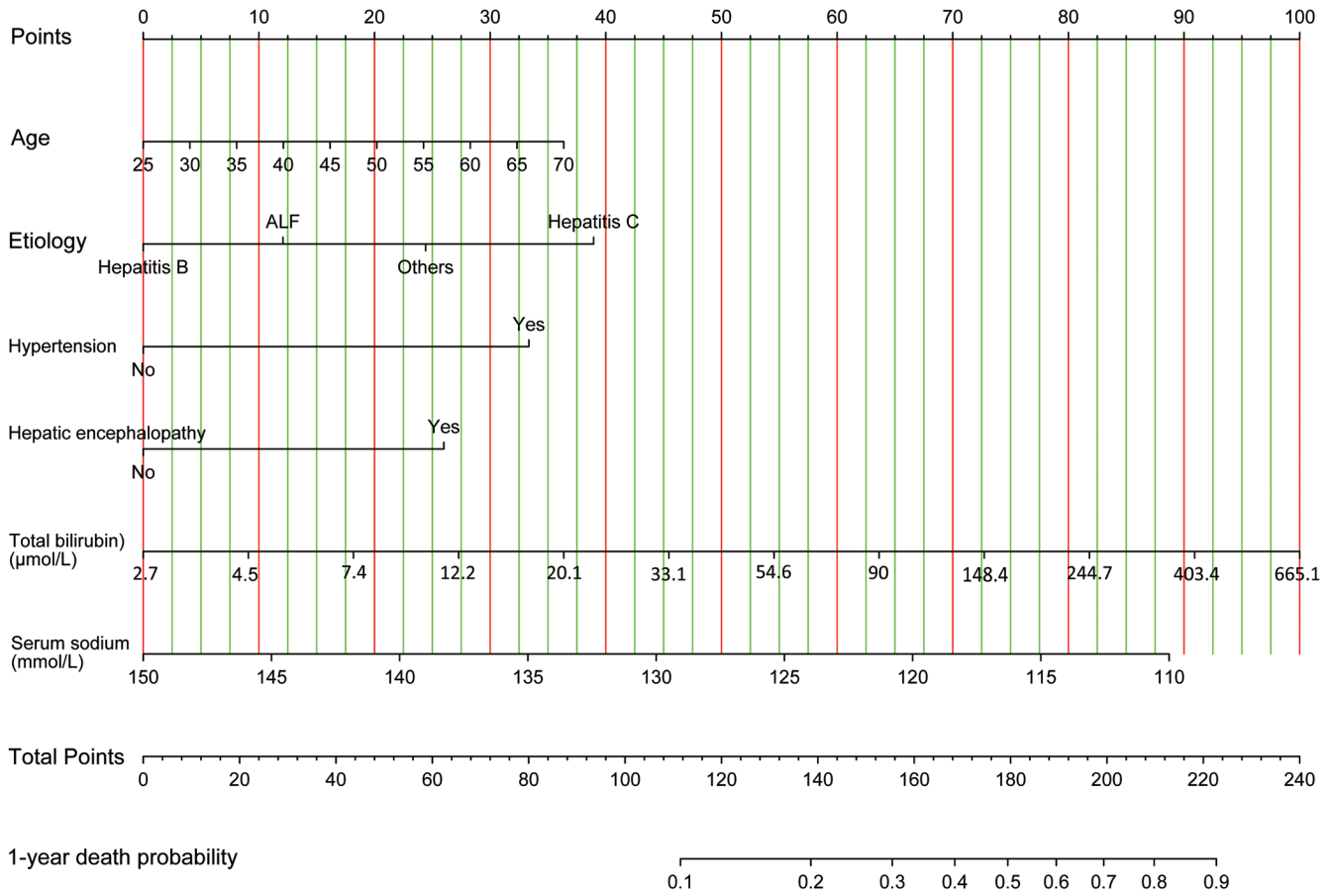
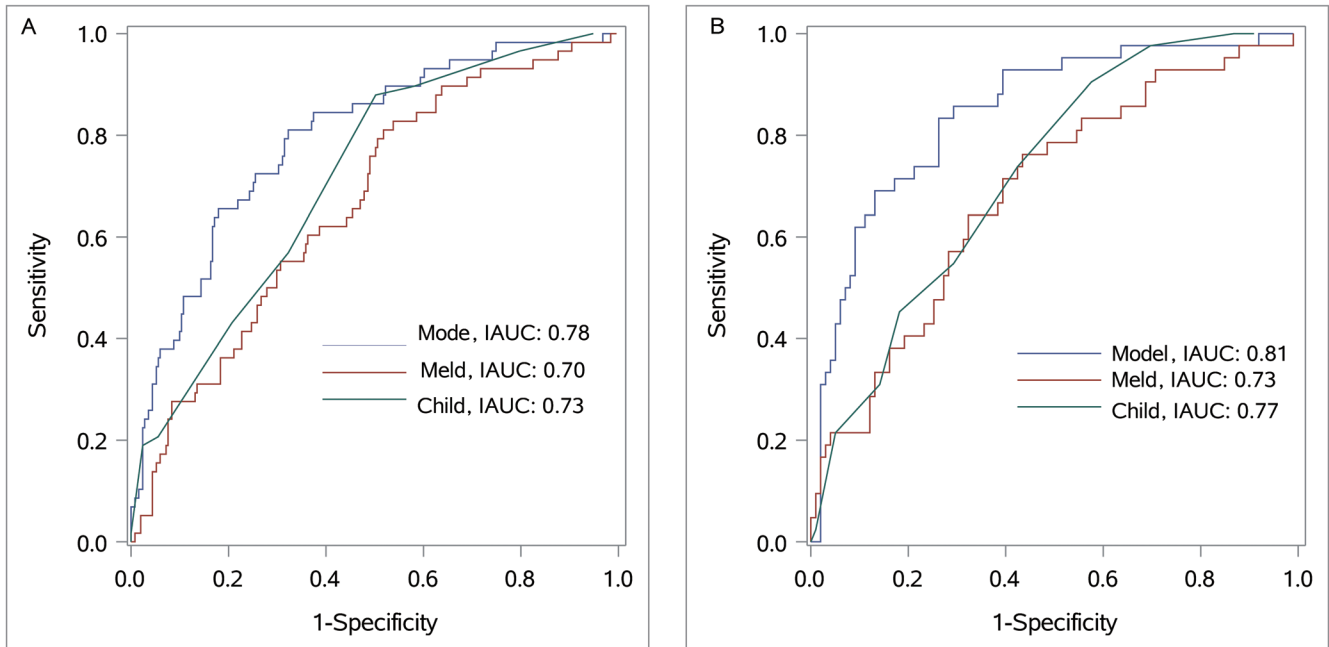**Fig. 2. Nomogram for 1-year survival of cirrhosis patients with first-ever SBP.**

Fig. 3. ROC curves of different models in predicting 1-year prognosis in derivation and validation cohort.
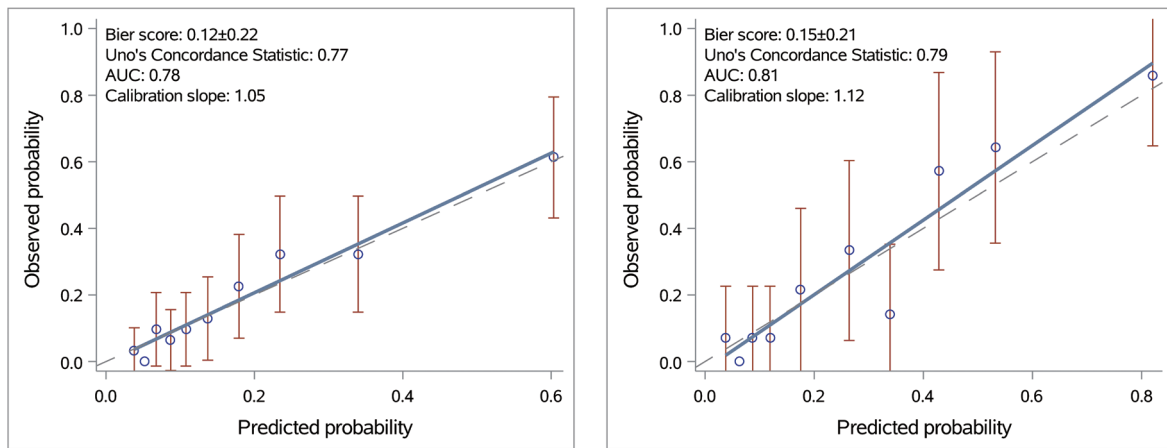
Fig. 4. Calibration curve of overall survival at 1 year for the derivation and validation cohort. Nomogram-predicted probability of survival is plotted on the X-axis, and the actual survival is plotted on the Y-axis. Dashed lines along the 45-degree line through the point of origin represent the perfect calibration models in which the predicted probabilities are identical to the actual probabilities

TBIL is an important indicator for evaluating liver function and is also a major component of the MELD score and the CTP score. HE is another common and serious complication of cirrhosis,[34] reflecting a significant decrease in liver detoxification causing brain dysfunction. Infections such as SBP are an important cause of HE onset,[35,36] which in turn leads to further disease progression.[37] These relationships were corroborated in our study, which identified both TBIL and HE as independent risk factors for cirrhosis and SBP prognosis.

Our study found that compared with hepatitis C, alcohol, and other causes, there was a lower rate of 1-year mortality in cases of SBP caused by the hepatitis B virus (HBV). This may be due to the usage of oral antivirals, such as nucleoside analogs. Previous studies have also supported long-term antiviral therapy to improve CTP scores and prognosis in patients with HBV-related cirrhosis.[38]

Our study included a large number of SBP cases and supports the value of developing similar prediction models in different populations and over different periods of time after the initial SBP episode. However, our study also has several limitations. Generalizability of our findings may be limited

since this is a single-center study in China with cohorts of predominantly HBV-related cirrhosis patients. The diagnostic criteria for SBP patients included in this study were defined by the guidelines for diagnosis and treatment of ascites in cirrhosis in China, which is not completely consistent with guidelines issued by the American Association for the Study of Liver Diseases (AASLD) in 2009 and the European Association for the Study of the Liver (EASL) in 2010.[15,16] Therefore, it is unclear whether our nomogram meets the diagnostic criteria of EASL and AASLD and whether it is suitable for the evaluation of SBP prognosis in other settings. Lastly, because the positive rate of ascites culture and blood culture was low, our findings could not explain the correlation between the type of bacterial infection and patient prognoses. Future studies should aim to further explore this relationship with larger sample sizes.

Conclusions

In this study, univariate and multivariable analyses were
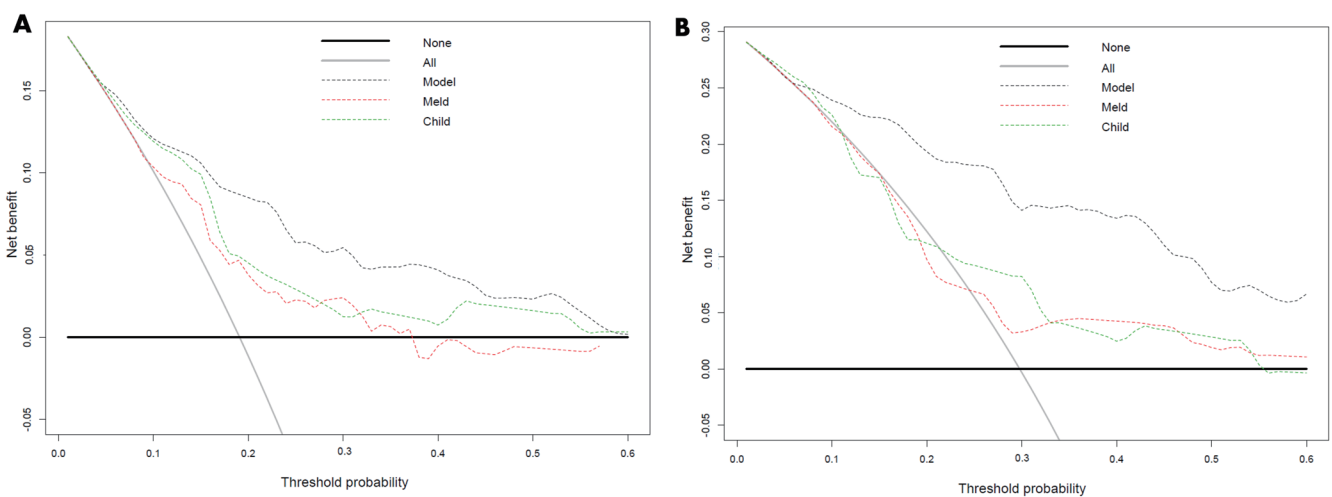

Fig. 5. DCA in the derivation and validation cohort at 1 year. DCA depict the clinical net benefit in pairwise comparisons across the different models. The horizontal solid black line represents the assumption that no patients will experience the event, and the solid gray line represents the assumption that all patients will relapse. In DCA, the nomogram showed superior net benefit compared with other models across a range of threshold probabilities.

performed on SBP patients based on relevant biochemical indices, and a nomogram was established using the multivariable Cox analysis. We found that independent risk factors affecting the prognosis of SBP patients included age, etiology, history of hypertension, serum TBIL level, serum sodium level, and complication of HE. Hypertension was first proposed as an independent factor of SBP but little attention has been paid to it in prior literature. Meanwhile, the long-term prognosis of SBP is closely related to the severity of liver damage. This prediction model performed better than models based on MELD and CTP scores, thus supporting its utility for individualized counseling and clinical treatment.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceived and designed the study (YYJ), acquired and analyzed the data. (RRW, HQG, YYW, JXY, YXH, HML, XBW, ZYY), drafted the manuscript (RRW, HQG), interpreted the findings (YYJ, RRW, HQG, YYW, JXY, YXH, HML, XBW, ZYY), and revised the manuscript (YYJ). All authors read and approved the final version of the manuscript.

Data sharing statement

All data and models generated or used during the study appear in the submitted article.

References

[1] Piano S, Brocca A, Mareso S, Angeli P. Infections complicating cirrhosis. Liver Int 2018;38(Suppl 1):126–133. doi:10.1111/liv.13645.

[2] Mücke MM, Rumyantseva T, Mücke VT, Schwarzkopf K, Joshi S, Kempf VAJ, *et al*. Bacterial infection-triggered acute-on-chronic liver failure is associated with increased mortality. Liver Int 2018;38(4):645–653. doi:10.1111/liv.13568.

[3] Andreu M, Sola R, Sitges-Serra A, Alia C, Gallen M, Vila MC, *et al*. Risk factors for spontaneous bacterial peritonitis in cirrhotic patients with ascites. Gastroenterology 1993;104(4):1133–1138. doi:10.1016/0016-5085(93)90284-j.

[4] Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, *et al*. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010;139(4):1246–1256, 1256.e1-5. doi:10.1053/j.gastro.2010.06.019.

[5] Jun BG, Lee WC, Jang JY, Jeong SW, Kim YD, Cheon GJ, *et al*. Follow-up creatinine level is an important predictive factor of in-hospital mortality in cirrhotic patients with spontaneous bacterial peritonitis. J Korean Med Sci 2018;33(12):e99. doi:10.3346/jkms.2018.33.e99.

[6] Lim KH, Potts JR, Chetwood J, Goubet S, Verma S. Long-term outcomes after hospitalization with spontaneous bacterial peritonitis. J Dig Dis 2015;16(4):228–240. doi:10.1111/1751-2980.12228.

[7] Tsung PC, Ryu SH, Cha IH, Cho HW, Kim JN, Kim YS, *et al*. Predictive factors that influence the survival rates in liver cirrhosis patients with spontaneous bacterial peritonitis. Clin Mol Hepatol 2013;19(2):131–139. doi:10.3350/cmh.2013.19.2.131.

[8] Bal CK, Daman R, Bhatia V. Predictors of fifty days in-hospital mortality in decompensated cirrhosis patients with spontaneous bacterial peritonitis. World J Hepatol 2016;8(12):566–572. doi:10.4254/wjh.v8.i12.566.

[9] Musskopf MI, Fonseca FP, Gass J, de Mattos AZ, John JA, de Mello Brandão

AB. Prognostic factors associated with in-hospital mortality in patients with spontaneous bacterial peritonitis. Ann Hepatol 2012;11(6):915–920. doi:10.1016/S1665-2681(19)31418-8.

[10] Poca M, Alvarado-Tapias E, Concepción M, Pérez-Cameo C, Cañete N, Gich I, *et al*. Predictive model of mortality in patients with spontaneous bacterial peritonitis. Aliment Pharmacol Ther 2016;44(6):629–637. doi:10.1111/apt.13745.

[11] Tandon P, Kumar D, Seo YS, Chang HJ, Chaulk J, Carbonneau M, *et al*. The 22/11 risk prediction model: a validated model for predicting 30-day mortality in patients with cirrhosis and spontaneous bacterial peritonitis. Am J Gastroenterol 2013;108(9):1473–1479. doi:10.1038/ajg.2013.204.

[12] Xu X, Duan Z, Ding H, Li W, Jia J, Wei L, *et al*. Chinese guidelines on the management of ascites and its related complications in cirrhosis. Hepatol Int 2019;13(1):1–21. doi:10.1007/s12072-018-09923-2.

[13] Weiss N, Jalan R, Thabut D. Understanding hepatic encephalopathy. Intensive Care Med 2018;44(2):231–234. doi:10.1007/s00134-017-4845-6.

[14] Wijdicks EF. Hepatic encephalopathy. N Engl J Med 2016;375(17):1660–1670. doi:10.1056/NEJMra1600561.

[15] Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49(6):2087–2107. doi:10.1002/hep.22853.

[16] EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53(3):397–417. doi:10.1016/j.jhep.2010.05.004.

[17] Uno H, Cai T, Pencina MJ, D'Agostino RB, Wei LJ. On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. Stat Med 2011;30(10):1105–1117. doi:10.1002/sim.4154.

[18] Uno H, Cai T, Tian L, Wei LJ. Evaluating prediction rules for *t*-year survivors with censored regression models. Journal of the American Statistical Association 2007;102(478):527–537. doi:10.1198/016214507000000149.

[19] Bal CK, Bhatia V, Daman R. Predictors of fifty days in-hospital mortality in patients with culture negative neutrocytic ascites. BMC Gastroenterol 2017;17(1):64. doi:10.1186/s12876-017-0621-x.

[20] Bellot P, García-Pagán JC, Francés R, Abraldes JG, Navasa M, Pérez-Mateo M, *et al*. Bacterial DNA translocation is associated with systemic circulatory abnormalities and intrahepatic endothelial dysfunction in patients with cirrhosis. Hepatology 2010;52(6):2044–2052. doi:10.1002/hep.23918.

[21] Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, *et al*. Nonselective β blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology 2014;146(7):1680–1690.e1. doi:10.1053/j.gastro.2014.03.005.

[22] Ren W, Wang J, Gao Y, Yang F, Huang W. Metabolic syndrome and liver-related events: a systematic review and meta-analysis. BMC Endocr Disord 2019;19(1):40. doi:10.1186/s12902-019-0366-3.

[23] Faber W, Stockmann M, Schirmer C, Möllerarnd A, Denecke T, Bahra M, *et al*. Significant impact of patient age on outcome after liver resection for HCC in cirrhosis. Eur J Surg Oncol 2014;40(2):208–213. doi:10.1016/j.ejso.2013.10.018.

[24] Kim IH, Kisseleva T, Brenner DA. Aging and liver disease. Curr Opin Gastroenterol 2015;31(3):184–191. doi:10.1097/MOG.0000000000000176.

[25] Floreani A. Liver diseases in the elderly: an update. Dig Dis 2007;25(2):138–143. doi:10.1159/000099478.

[26] Schneider EL. Infectious diseases in the elderly. Ann Intern Med 1983;98(3):395–400. doi:10.7326/0003-4819-98-3-395.

[27] Zeeh J, Platt D. The aging liver: structural and functional changes and their consequences for drug treatment in old age. Gerontology 2002;48(3):121–127. doi:10.1159/000052829.

[28] Prohic D, Mesihovic R, Vanis N, Puhalovic A. Prognostic significance of ascites and serum sodium in patients with low meld scores. Med Arch 2016;70(1):48–52. doi:10.5455/medarh.2016.70.48-52.

[29] John S, Thuluvath PJ. Hyponatremia in cirrhosis: pathophysiology and management. World J Gastroenterol 2015;21(11):3197–3205. doi:10.3748/wjg.v21.i11.3197.

[30] Kogiso T, Kobayashi M, Yamamoto K, Ikarashi Y, Kodama K, Taniai M, *et al*. The outcome of cirrhotic patients with ascites is improved by the normalization of the serum sodium level by tolvaptan. Intern Med 2017;56(22):2993–3001. doi:10.2169/internalmedicine.9033-17.

[31] Egerod Israelsen M, Gluud LL, Krag A. Acute kidney injury and hepatorenal syndrome in cirrhosis. J Gastroenterol Hepatol 2015;30(2):236–243. doi:10.1111/jgh.12709.

[32] Sigal SH. Hyponatremia in cirrhosis. J Hosp Med 2012;7(Suppl 4):S14–S17. doi:10.1002/jhm.1915.

[33] Lee S, Saxinger L, Ma M, Prado V, Fernández J, Kumar D, *et al*. Bacterial infections in acute variceal hemorrhage despite antibiotics-a multicenter study of predictors and clinical impact. United European Gastroenterol J 2017;5(8):1090–1099. doi:10.1177/2050640617704564.

[34] Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002;35(3):716–721. doi:10.1053/jhep.2002.31250.

[35] Bleibel W, Al-Osaimi AM. Hepatic encephalopathy. Saudi J Gastroenterol 2012;18(5):301–309. doi:10.4103/1319-3767.101123.

[36] Córdoba J, Mínguez B. Hepatic encephalopathy. Semin Liver Dis 2008;28(1):70–80. doi:10.1055/s-2008-1040322.

[37] Yu H, Chen Y, Jiang P. Prognostic value of hepatic encephalopathy for survival of patients with liver failure: A systematic review and meta-analysis. Ann Hepatol 2019;18(4):607–612. doi:10.1016/j.aohep.2019.01.006.

[38] Kim CH, Um SH, Seo YS, Jung JY, Kim JD, Yim HJ, *et al*. Prognosis of hepatitis B-related liver cirrhosis in the era of oral nucleos(t)ide analog antiviral agents. J Gastroenterol Hepatol 2012;27(10):1589–1595. doi:10.1111/j.1440-1746.2012.07167.x.