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

Rui-Rui Wang1,2#, Hong-Qiu Gu3,4#, Ying-Ying Wei3, Jin-Xiang Yang6, Yi-Xin Hou1#, Hui-Min Liu1#, Zhi-Yun Yang1#, Xian-Bo Wang1 and Yu-Yong Jiang1*

1Center of Integrative Medicine, Beijing Ditan Hospital, Capital Medical University, Beijing, China; 2Graduate School, Beijing University of Chinese Medicine, Beijing, China; 3China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; 4National Center for Healthcare Quality Management in Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; 5The first Clinical School, Beijing University of Chinese Medicine, Beijing, China; 6Department 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 predicting 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; 1180. Tel: +86-13552175162, E-mail: jyuy11@126.com

Conclusions: This prediction model developed based on characteristics of first-ever SBP patients may benefit the prediction of patients’ 1-year survival. Citation of this article: Wang RR, Gu HQ, Wei YY, Yang JX, Hou YX, Liu HM, et al. Development and validation of a prognostic model for one-year survival of cirrhosis patients with first-ever spontaneous bacterial peritonitis. J Clin Transl Hepatol 2021;9(5):647–654. doi: 10.14218/JCTH.2021.00031.

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-
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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)

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.

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, 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 ≥ 250×10^9 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. 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. Additionally, the third-generation cephalosporins, or empirical antibiotic therapy, 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). 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. 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
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.

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 x10⁹/L      | 3.8 (2.3–5.7)            | 3.4 (2.1–5.4)            |
| Lymphocyte count as x10⁹/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 x10⁹/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.

Previous studies of patients with SBP have focused on predictors of acute or short-term outcomes. A prior study showed that the mortality rate during hospitalization is high (20% to 43%), and remains high at 1 year after discharge. 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. Previous studies have shown that MELD and CTP can be used as predictors of death in SBP patients during hospitalization. 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...
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 metabolic 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.

### 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               |                        |                      |
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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.
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, reflecting a significant decrease in liver detoxification causing brain dysfunction. Infections such as SBP are an important cause of HE onset, which in turn leads to further disease progression. 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.

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. 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
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), interpreted the findings (YYJ, RRW, HQG, YYW, JXY, YKH, HML, XBW, ZYY), drafted the manuscript (RRW, HQG), 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 are provided in the submitted article.

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

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