

RESEARCH ARTICLE

A prognostic model for hepatitis B acute-on-chronic liver failure patients treated using a plasma exchange-centered liver support system

Zhongyang Xie^{1,2} | Laurencia Violetta^{1,2} | Ermei Chen^{1,2} | Kaizhou Huang^{1,2} | Daxian Wu^{1,2} | Xiaowei Xu^{2,3} | Xiaoxi Ouyang^{1,2} | Yalei Zhao^{1,2} | Lanjuan Li^{1,2}

¹State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

²Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Zhejiang University, Hangzhou, China

³Department of Infectious Disease, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Correspondence

Lanjuan Li, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China.
Email: ljli@zju.edu.cn

Funding information

Key research and development project of Department of Science and Technology of Zhejiang Province, Grant/Award Number: 2017C03051; Science Fund for Creative Research Groups of the National Natural Science Foundation of China, Grant/Award Number: 81721091

Abstract

Aim: To determine the prognostic risk factors of patients with hepatitis B virus related acute-on-chronic liver failure (HBV-ACLF) treated with plasma exchange (PE)-based artificial liver support system (ALSS), and create a prognostic predictive model.

Methods: A total of 304 HBV-ACLF patients who received PE-based ALSS were retrospectively analyzed. Potential prognostic factors on admission associated with survival were investigated. Of note, 101 additional patients were analyzed to validate the performance of the prognostic models.

Results: According to 28-day survival, a total of 207 patients who survived and 97 non-survivors were identified in the derivation group. Overall, 268 (88.2%) ACLF cases were caused by reactivation of HBV. Cox proportional hazards regression model revealed that age, total bilirubin, ln (alpha-fetoprotein [AFP]), encephalopathy (HE) score, sodium level, and international normalized ratio (INR) were independent risk factors of short-term prognosis. We built a model named ALSS-prognosis model (APM) to predict the 28-day survival of HBV-ACLF patients with ALSS; the model APM showed potentially better predictive performance for both the derivation and validation groups than MELD, MELD-Na, and CLIF-C ACLF score.

Conclusions: Low AFP was found to be an independent risk factor for high mortality in HBV-ACLF patients treated with PE-based ALSS. We generated a new model containing AFP, namely APM, which showed potentially better prediction performance than MELD, MELD-Na, and CLIF-C ACLF score for short-term outcomes, and could aid physicians in making optimal therapeutic decisions.

KEYWORDS

AFP, ALSS, HBV-ACLF, plasma exchange

Zhongyang Xie and Laurencia Violetta contributed equally to this study.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2019 The Authors. *Journal of Clinical Apheresis* published by Wiley Periodicals, Inc.

1 | INTRODUCTION

With an estimated 130 million carriers and 30 million chronically infected individuals, China has been recognized as a high-prevalence area for hepatitis B virus (HBV).¹ Individuals with chronic HBV are at risk of developing an acute exacerbation leading to acute-on-chronic liver failure (ACLF), which has high short-term mortality.² Liver transplantation (LT) has been associated with long-term survival in these patients. However, donor liver scarcity and socioeconomic challenges have made LT impracticable, thus alternative therapies are required to overcome this unmet need.² Since the late fifties, a variety of artificial liver support systems (ALSSs) have been utilized to treat liver failure. Several studies have shown that ALSSs, in particular plasma exchange (PE), prolong the survival of patients with both ALF and ACLF.³⁻⁵ In addition to rapid elimination of toxic metabolites, PE is also able to replenish beneficial plasma factors, which serves as a bridge to LT by providing a suitable environment for liver recovery.⁶

An accurate prognostic scoring system is necessary to estimate disease severity and accurately appoint ACLF patients to the appropriate management. Various prognostic models including the Model for End-stage Liver Disease (MELD),⁷ MELD-sodium (MELD-Na),⁸ and Chronic Liver Failure-Consortium (CLIF-C) ACLF⁹ score were deemed suitable to predict severity in ACLF patients with HBV etiology.^{9,10} Conversely, due to clinical discrepancies between Eastern and Western ACLF,¹¹ these scores were found to be less sensitive for early

diagnosis of HBV-ACLF compared to the score recently proposed score by the Study of Severe Hepatitis B (COSSH)¹² in China, which was constructed based on a large, multicenter cohort of HBV-related ACLF patients. However, whether these models can be used to evaluate the prognosis of HBV-ACLF patients with ALSS is unknown. For patients receiving ALSS treatment, the factors related to prognostic and curative effects need to be analyzed.

In the present study, we investigated the prognosis, and factors affecting prognosis, in patients with HBV-ACLF treated using PE-based ALSS. Furthermore, we propose a novel model that could predict prognosis in these patients.

2 | MATERIALS AND METHODS

2.1 | Study design

Liver failure patients who received ALSS at our hospital between January 2015 and July 2017 were identified retrospectively. The operating guide for ALSSs was strictly applied to identify patients for ALSS treatment.¹³ Data of all patients were extracted from the electronic medical records system and analyzed anonymously according to the Declaration of Helsinki. This study was approved by the Human Ethics Committee of the First Affiliated Hospital of Zhejiang University.

In the derivation group, a total of 628 patients with chronic hepatitis B (CHB),¹¹ with or without cirrhosis,

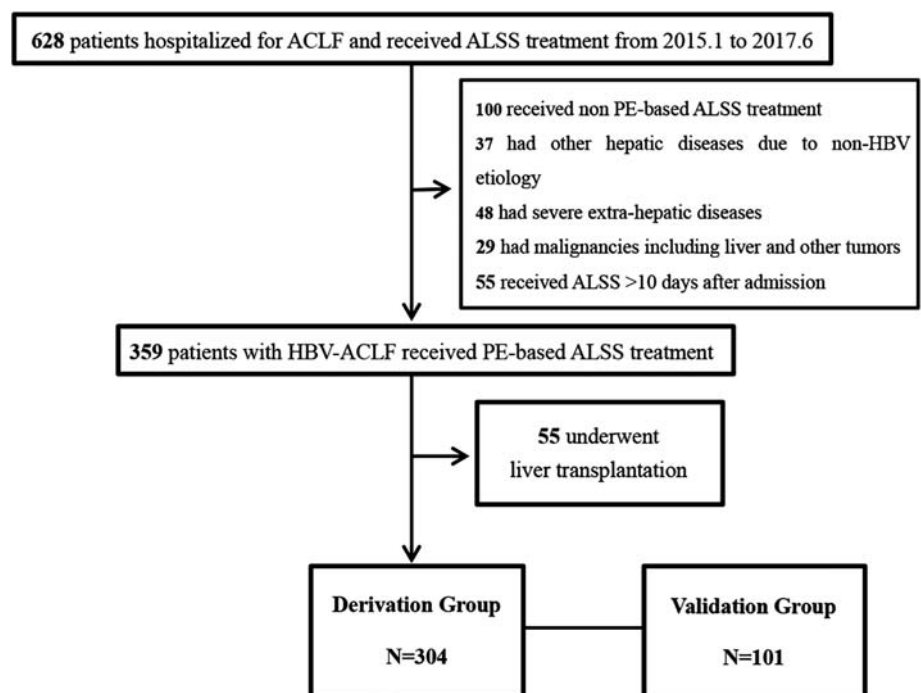


FIGURE 1 Flow chart of inclusion of HBV-ACLF patients with ALSS. HBV-ACLF, HBV related acute-on-chronic liver failure; ALSS, artificial liver support system; PE, plasma exchange; LT, liver transplantation

who met the diagnostic criteria for ACLF were included in the study (Figure 1). Patients with liver failure of non-HBV etiology or co-infection with an additional hepatitis virus ($n = 37$), malignancies ($n = 29$), non-PE-based ALSS ($n = 100$), or severe extra-hepatic diseases ($n = 49$) were excluded from the study. In addition, patients ($n = 55$) who received the first ALSS treatment more than 1 week after admission were excluded. During the course of hospitalization, 55 patients received LT and the remaining 304 patients were enrolled in this study. Our study also included patients who presented without ACLF at admission, but who later developed ACLF prior to the start of ALSS therapy.

Additional 101 patients were enrolled in the validation group between August 2017 and December 2017 from First Affiliated Hospital of Zhejiang University and Shulan (Hangzhou) Hospital; all of them met the aforementioned inclusion and exclusion criteria.

2.2 | Definition and staging

As proposed by the Asian Pacific Association for the Study of the Liver,¹⁴ ACLF was defined as acute liver injury (TB ≥ 5 mg/dL and INR ≥ 1.5) complicated within 4 weeks by ascites and/or hepatic encephalopathy (HE) in patients with previously diagnosed or undiagnosed chronic liver disease.

Assessment of different prognostic models was performed according to different criteria and researches.^{7,8,12,15} Cirrhosis was diagnosed based on previous liver biopsy results, clinical evidence of previous decompensation, laboratory tests, endoscopy (esophageal and gastric varices), and radiological evidence of portal hypertension and/or liver nodularity. Ascites was confirmed by abdominal imaging, paracentesis, and clinical evidence of prior decompensation. West Haven criteria were used for the assessment and grading of HE.¹⁶ Gastrointestinal (GI) bleeding was defined as the presence of blood in the stool or vomit. Common bacterial infections include spontaneous bacterial peritonitis, pulmonary infection, and urinary tract infection.¹⁷

2.3 | Data collection

The baseline characteristics recorded consisted of encephalopathy score (determined clinically), plus laboratory parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), albumin, ferritin, alpha-fetoprotein (AFP), sodium, glucose, creatinine, international normalized ratio (INR), and white blood cell (WBC), hemoglobin, and platelet counts. Furthermore, calculation of MELD, MELD-Na, CLIF-C

ACLF, and COSSH-ACLF scores was performed.^{7,12,15} All data were collected at the time of admission. HBV serology and HBV-DNA were assayed at admission. Any adverse reactions related to ALSS treatment were recorded.

2.4 | Treatment

Circulatory access was established via the patients' femoral vein and PE was performed using the EC-40W membrane separation method (Asahi KASEI Co., Tokyo, Japan). The total exchange volume was 2500 to 3500 mL, which composed 1500 to 2500 mL of fresh frozen plasma (FFP) and 500 to 1000 mL of 5% albumin. FFP was provided by the local Blood Transfusion Service, which was obtained by voluntary blood donation. The PE rate was set to 20 to 25 mL/min with an adjusted blood flow rate of 100 to 130 mL/min. Five milligram of dexamethasone was injected routinely to prevent allergic reactions. Based on the prothrombin time prior to PE, approximately 20 to 60 mg of heparin and 10 to 30 mg of protamine sulfate were administered every session. PE-centered ALSS included the utilization of PE alone or in combination with hemofiltration (HF) or plasma perfusion (PP). HF was performed following PE, which used a BLS816G column (SORIN Group, Como, Italy) at a filtrate flow rate of 50 mL/kg/h for 6 to 8 hours. PP was performed using EC-40W for plasma separation and two adsorption columns (BS330 and HA330-II; Jian Fan, Zhuhai, China) for toxin removal. The methods were performed according to patient condition. HF is suitable for encephalopathy, acute kidney injury, and water-electrolyte imbalance. Bilirubin adsorption is utilized for hyperbilirubinemia with mild coagulation dysfunction (INR < 2). ALSS treatment was performed every 2 to 3 times per week and was discontinued if bleeding or circulatory complications occurred.¹⁸ In total, 873 sessions of ALSS treatment were performed, with an average of two sessions per patient (range: 1-6 sessions per patient).

All patients received standard medical therapy (SMT), including bed rest, adequate nutritional support, and oral antiviral drugs. Complications were also treated, as follows: ascites were treated with sodium and water restriction and/or diuretics, and peritoneocentesis combined with intravenous albumin when necessary; broad-spectrum antibiotics were given initially to patients with bacterial infections and later modified based on culture and/or antibiotic sensitivity results; acute GI bleeding was treated with intravenous somatostatin, pituitrin, proton pump inhibitors, and endoscopic therapy when needed; HE patients received lactulose and L-ornithine aspartate; fluid replacement was applied in patients with low mean arterial pressure and/or vasoconstrictors in

TABLE 1 Clinical characteristics of derivation and validation groups of HBV-ACLF patients treated with PE-based ALSS at admission

| | Derivation group (n = 304) | Validation group (n = 101) | P value |
|-------------------------------------|----------------------------|----------------------------|---------|
| Age | 47.77 ± 11.32 | 42.88 ± 12.073 | <.0001 |
| Gender (female/male) | 36/268 | 11/90 | .796 |
| Hypertension | 40 (13.2) | 14 (13.9) | .857 |
| Diabetes | 24 (7.9) | 5 (5.0) | .321 |
| Alcohol | 76 (25.0) | 29 (28.7) | .461 |
| Smoking | 115 (37.8) | 32 (31.7) | .266 |
| Cirrhosis | 128 (42.1) | 48 (47.5) | .3432 |
| Precipitating event | | | |
| HBV-reactivation | 268 (88.2) | 90 (89.0) | .741 |
| Spontaneous reactivation | 211 (69.4) | 68 (67.3) | |
| NUC cessation | 41 (13.5) | 16 (15.8) | |
| NUC resistance | 16 (5.3) | 6 (5.9) | |
| Infection | 34 (11.2) | 8 (7.9) | |
| Others | 2 (0.7) | 3 (3.0) | |
| HBeAg positive | 124 (40.8) | 50 (49.5) | .126 |
| HBeAb positive | 198 (65.1) | 50 (49.5) | .005 |
| Lg(HBV-DNA) | 5 (3, 6) | 4 (3, 6) | .583 |
| Complications | | | |
| HE | 25 (8.2) | 27 (26.7) | <.0001 |
| Ascites | 88 (36.2) | 56 (55.4) | .24 |
| GI bleeding | 9 (3.0) | 4 (4.0) | <.0001 |
| Bacterial infection | 39 (16) | 34 (33.7) | .007 |
| MELD score | 22.71 (19.8, 25.56) | 23.9 (21.5, 28.06) | .006 |
| MELD-Na score | 23.04 (20.3, 26.28) | 24.29 (21.65, 29) | .009 |
| CLIF-C ACLF score | 40.11 (36.18, 43.9) | 39.89 (35.4, 45.98) | .468 |
| COSSH ACLF score | 5.97 (5.51, 6.48) | 6.14 (5.65, 6.93) | .049 |
| Laboratory data | | | |
| ALT (U/L) | 462 (211, 956) | 271 (118, 718) | .164 |
| AST (U/L) | 313 (137, 639) | 215 (93, 456) | .385 |
| TB (μmol/L) | 19.33 (15.5, 25.63) | 20.47 (15.64, 23.8) | .744 |
| ALP(U/L) | 138 (115, 166) | 127 (113, 149) | .015 |
| GGT (U/L) | 86 (63, 130) | 88 (58, 133) | .96 |
| Albumin (g/dL) | 32.2 (29.8, 35.1) | 33.2 (30.8, 35.6) | .011 |
| Sodium (mmol/L) | 138 (136, 140) | 138 (135.5, 140) | .834 |
| Creatinine (μmol/L) | 0.72 (0.62, 0.85) | 0.70 (0.60, 0.83) | .157 |
| INR | 1.99 (1.7, 2.54) | 2.39 (1.94, 2.91) | <.0001 |
| WBC (10 ⁹ /L) | 6.8 (5.4, 9.1) | 7 (5.6, 8.9) | .068 |
| Hemoglobin (g/L) | 137.5 (123.25, 149) | 133 (116, 143) | .348 |
| Platelet count (10 ⁹ /L) | 124 (87, 157) | 111 (82, 155) | .556 |
| Ferritin (μg/L) | 3196 (1705, 6438) | 2805 (1499, 5375) | .894 |
| Alpha fetoprotein (μg/L) | 95 (38, 245) | 88 (35, 261) | .763 |

Note: Data are expressed as mean ± SD, median with interquartile range (p25, p75) or number of patients (percentages). ALP, phosphatase alkaline; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CLIF-C ACLF, European Association for the Study of Chronic Liver Failure; COSSH-ACLF, Chinese Group on the Study of Severe Hepatitis B; GGT, gamma-glutamyl transpeptidase; GI, gastrointestinal; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; NUC, nucleoside analogs; WBC, white blood cell count.

TABLE 2 Univariate and multivariate analysis between survival and non-survival groups

| Variables | Univariate Cox regression | | | | Multivariate Cox regression | | | |
|--------------------------|---------------------------|-------|-----------------------|-------|-----------------------------|-------|---------------------|-------|
| | B | SE | HR (95% CI) | P | B | SE | OR (95% CI) | P |
| Clinical characteristics | | | | | | | | |
| Gender | 0.081 | 0.308 | 1.085 (0.593-1.985) | .792 | | | | |
| Age | 0.023 | 0.009 | 1.024 (1.006-1.042) | .010 | 0.030 | 0.009 | 1.03 (1.012-1.049) | .001 |
| Alcohol | 0.149 | 0.207 | 1.161 (0.774-1.742) | .471 | | | | |
| Hypertension | 0.539 | 0.256 | 1.715 (1.038-2.832) | .035 | | | | |
| Diabetes | 0.428 | 0.320 | 1.535 (0.819-2.875) | .181 | | | | |
| Cirrhosis | -0.002 | 0.206 | 0.998 (0.667-1.494) | .994 | | | | |
| Decompensation history | -0.048 | 0.369 | 0.954 (0.463-1.966) | .898 | | | | |
| Ascites | 0.243 | 0.204 | 1.276 (0.856-1.901) | .232 | | | | |
| GI bleeding | 0.364 | 0.511 | 1.439 (0.529-3.914) | .476 | | | | |
| Infection | 0.445 | 0.261 | 1.56 (0.935-2.604) | .089 | | | | |
| HE score | 0.973 | 0.189 | 2.645 (1.827-3.829) | <.001 | 0.834 | 0.216 | 2.303 (1.509-3.515) | <.001 |
| Laboratory parameters | | | | | | | | |
| HBeAg positive | -0.070 | 0.208 | 0.933 (0.62-1.402) | .737 | | | | |
| HBeAb positive | 0.093 | 0.216 | 1.097 (0.719-1.676) | .667 | | | | |
| Ig(HBV-DNA) | 0.086 | 0.051 | 1.09 (0.986-1.204) | .093 | | | | |
| ALT | 0.000 | 0.000 | 1.000 (0.9996-1.0002) | .687 | | | | |
| AST | 0.000 | 0.000 | 1.000 (0.9996-1.0003) | .816 | | | | |
| TB | 0.054 | 0.013 | 1.056 (1.029-1.083) | <.001 | 0.087 | 0.014 | 1.091 (1.062-1.120) | <.001 |
| ALB | 0.002 | 0.003 | 1.002 (0.995-1.008) | .633 | | | | |
| ALP | 0.003 | 0.002 | 1.003 (0.999-1.007) | .096 | | | | |
| GGT | 0.000 | 0.001 | 1.000 (0.997-1.003) | .980 | | | | |
| ln(AFP) | -0.300 | 0.068 | 0.741 (0.648-0.847) | <.001 | -0.219 | 0.077 | 0.804 (0.691-0.935) | .005 |
| ln(Ferritin) | 0.311 | 0.117 | 1.364 (1.086-1.715) | .008 | | | | |
| Creatinine | 0.070 | 0.179 | 1.073 (0.756-1.523) | .694 | | | | |
| BUN | 0.020 | 0.009 | 1.02 (1.003-1.038) | .025 | | | | |
| Sodium | -0.076 | 0.022 | 0.927 (0.888-0.967) | .001 | -0.045 | 0.02 | 0.956 (0.920-0.993) | .021 |
| INR | 1.045 | 0.154 | 2.842 (2.100-3.847) | <.001 | 0.895 | 0.16 | 2.447 (1.788-3.349) | <.001 |
| FIB | -0.386 | 0.239 | 0.680 (0.425-1.086) | .107 | | | | |
| Hemoglobin | 0.005 | 0.006 | 1.005 (0.994-1.016) | .401 | | | | |
| WBC | 0.075 | 0.024 | 1.077 (1.029-1.128) | .002 | | | | |
| PLT | -0.001 | 0.002 | 0.999 (0.995-1.003) | .551 | | | | |
| Prognostic score | | | | | | | | |
| MELD | 0.134 | 0.022 | 1.143 (1.095-1.193) | <.001 | | | | |
| MELD-Na | 0.091 | 0.012 | 1.095 (1.069-1.122) | <.001 | | | | |
| CLIF-C ACLF | 0.132 | 0.018 | 1.141 (1.101-1.183) | <.001 | | | | |
| COSSH-ACLF | 1.244 | 0.130 | 3.47 (2.692-4.474) | <.001 | | | | |

Abbreviations: AFP, alpha fetoprotein; ALB, albumin; ALP, phosphatase alkaline; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CLIF-C ACLF, European Association for the Study of Chronic Liver Failure; COSSH-ACLF, Chinese Group on the Study of Severe Hepatitis B; FIB, fibrinogen; GGT, gamma-glutamyl transpeptidase; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; PLT, platelets; TB, total bilirubin; WBC, white blood cell count.

those with circulatory dysfunction; and persistent low-flow oxygen therapy (2-4 L/min) was administered to patients with a PaO₂ < 80 mm Hg, with mechanical ventilation provided when severe respiratory dysfunction occurred.

2.5 | Statistical analysis

All data were analyzed using the SPSS software (ver. 22.0; SPSS Inc., Chicago, Illinois). Continuous variables were expressed as the mean ± SD or median (p25, p75) and were compared using Student's *t* test, Mann-Whitney *U* test, or Wilcoxon rank-sum test, and categorical variables by χ^2 test. Survival rates were estimated by Kaplan-Meier analysis and compared by the log-rank test. Patients who received LT were censored at the time of survival analysis. Potential predictors of prognosis were identified by univariate and multivariate analysis using the Cox proportional hazards regression model. Multivariate logistic regression was used to establish the new model and the performance of the prognostic scores was assessed by comparison of receiver operating characteristic (ROC) curves using the *z* test (DeLong's method). A *P* value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

Table 1 summarized the clinical characteristics of derivation (n = 304) and validation groups (n = 101) of HBV-

ACLF treated with PE-based ALSS. In the presented cohort, majority of the patients had HBV reactivation (88.2% in derivation group, 89% in validation group) as the cause of ACLF due to spontaneous reactivation, cessation of nucleoside analogs (NUCs) or development of antiviral resistance in patients who had previously started oral NUCs. There was no significant difference in gender distribution, risk factors, the presence of cirrhosis, precipitating events, HBV-DNA level, ascites, CLIF-C ACLF score, and majority of the lab parameters at baseline between the two groups.

The age (*P* < .0001), number of HBeAb positive patients (*P* = .005), presence of GI bleeding (*P* < .0001), bacterial infection (*P* = .007), and level of ALP (*P* = .015) were significantly higher in the derivation group than in the validation group. Meanwhile, the number of patients presented with HE (<.0001), the MELD (*P* = .006), MELD-Na score (*P* = .009) and COSSH-ACLF score (*P* = .049), albumin level (*P* = .011), and INR value

TABLE 3 AUROC of single prognostic factors

| Variables | AUROC | SE | 95% CI |
|-----------|-------|--------|-------------|
| ln(AFP) | 0.649 | 0.0344 | 0.593-0.703 |
| INR | 0.653 | 0.0358 | 0.596-0.707 |
| TB | 0.627 | 0.0363 | 0.570-0.682 |
| Age | 0.592 | 0.0346 | 0.535-0.648 |
| HE score | 0.568 | 0.0205 | 0.510-0.625 |
| Sodium | 0.575 | 0.036 | 0.517-0.631 |

Abbreviations: AFP, alpha fetoprotein; AUROC, area under the receiver operating characteristic curves; HE, hepatic encephalopathy; INR, international normalized ratio; TB, total bilirubin.

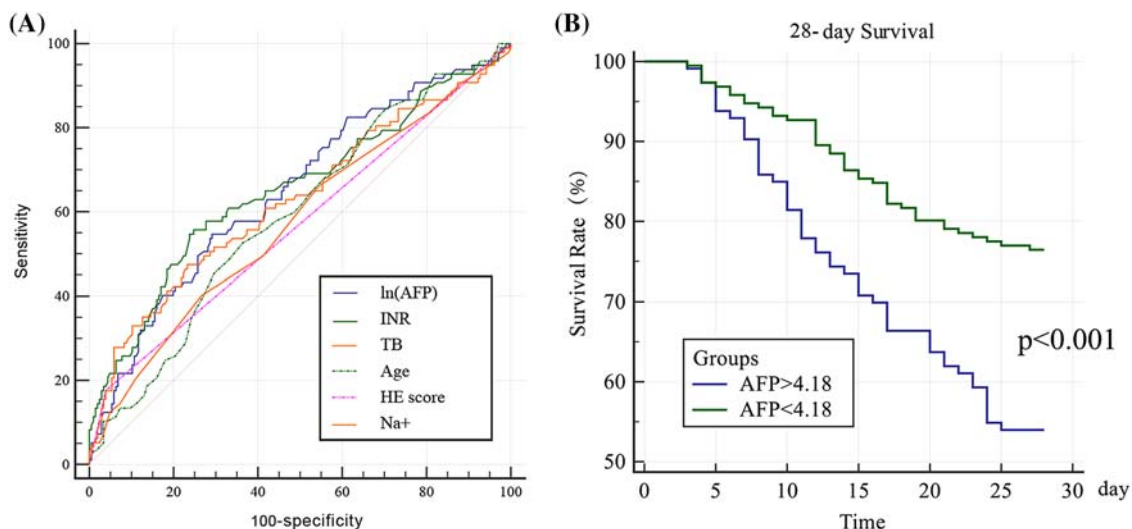


FIGURE 2 Receiver operating characteristic curves of single prognostic factor (A) and Kaplan-Meier curve of the high-AFP group (ln(AFP) > 4.18) and low-AFP group (ln(AFP) ≤ 4.18)

TABLE 4 Comparison of the predictive value of prognostic scoring systems for HBV-ACLF patients with PE-based ALSS

| Model | Derivation group | | | Derivation group | | | Validation group | | |
|-------------|------------------|-----------------|--------------|------------------|--------------|---------|------------------|-------------|---------|
| | Sensitivity (%) | Specificity (%) | Cutoff value | AUROC | 95% CI | P value | AUROC | 95% CI | P value |
| APM | 73.2 | 71.5 | 2.56 | 0.790 | 0.740-0.834 | | 0.747 | 0.651-0.828 | |
| MELD | 49.48 | 81.16 | 24.8 | 0.666 | 0.610-0.7219 | .0003 | 0.667 | 0.566-0.757 | .0648 |
| MELD-Na | 52.58 | 77.29 | 24.8 | 0.685 | 0.629-0.736 | .001 | 0.645 | 0.543-0.737 | .0308 |
| CLIF-C ACLF | 61.86 | 74.40 | 41.99 | 0.726 | 0.673-0.776 | .0184 | 0.694 | 0.595-0.782 | .3367 |
| COSSH-ACLF | 84.54 | 55.56 | 5.88 | 0.759 | 0.706-0.806 | .1292 | 0.718 | 0.620-0.803 | .4948 |

Abbreviations: APM: $0.042 \times \text{age} + \text{TB (mg/dL)} \times 0.094 + 1.228 \times \text{INR} - 0.473 \times \ln[\text{AFP } (\mu\text{g/L})]$. AUROC, area under the receiver operating characteristic curves; MELD, Model for End-stage Liver Disease; COSSH-ACLF, Chinese Group on the Study of Severe Hepatitis B; CLIF-C ACLF, European Association for the Study of Chronic Liver Failure.

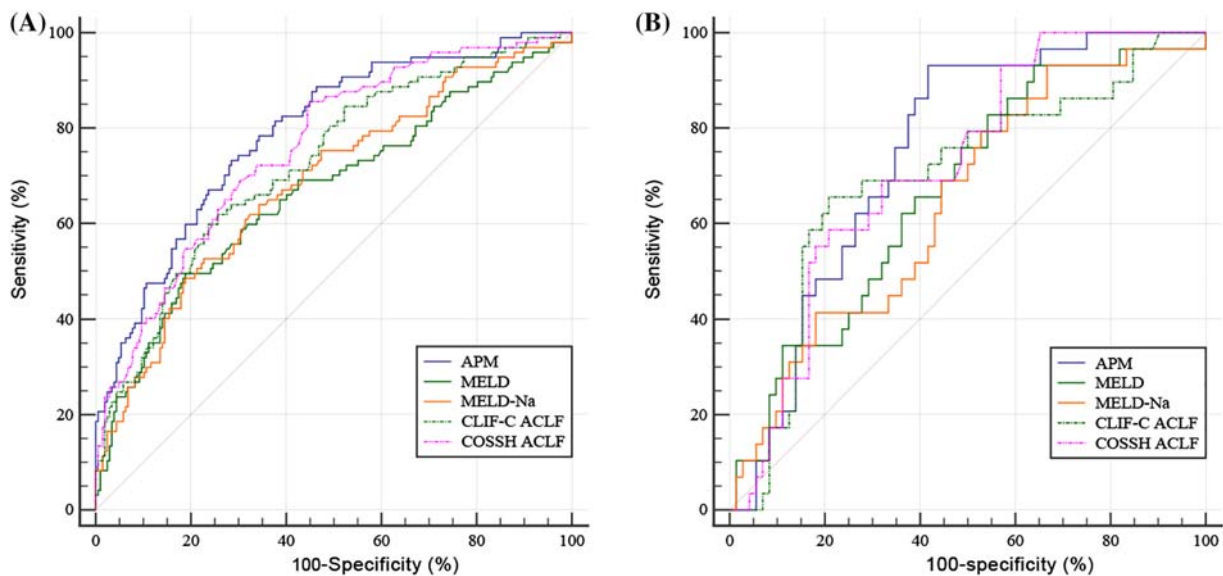


FIGURE 3 Receiver operating characteristic (ROC) curves illustrating the ability of different prognostic models in derivation (A) and validation (B) groups to predict the 28-day mortality of HBV-ACLF patients receiving ALSS. APM: $0.042 \times \text{age} + \text{TB (mg/dL)} \times 0.094 + 1.228 \times \text{INR} - 0.473 \times \ln[\text{AFP } (\mu\text{g/L})]$

($P < .0001$) were significantly less in the derivation group compared to the validation group.

3.2 | Analysis of prognostic factors of HBV-ACLF patients with PE-based ALSS

According to survival at day 28, patients were allocated into survival and non-survival groups (Table S1). Patients in the survivor group were significantly younger, had significantly less incidence of HE ($P < .0001$), had substantially lower levels of TB ($P < .001$), INR ($P < .001$), D-dimer ($P < .001$), ferritin ($P = .015$) and WBC counts ($P < .001$), as well as lower MELD, MELD-Na, CLIF-C ACLF and COSSH-ACLF scores (all $P < .0001$), but had higher AFP levels ($P < .001$) at admission compared to HBV-ACLF patients who did not survive.

Table 2 showed that by univariate analysis, the age, hypertension, HE score, TB, $\ln(\text{AFP})$, $\ln(\text{ferritin})$, BUN, sodium, INR, WBC count, and all prognostic scores (MELD, MELD-Na, CLIF-C ACLF, COSSH-ACLF) were significantly associated with mortality. Among them, AFP and ferritin were identified as new prognostic markers. Correlation analysis revealed a negative correlation between AFP and AST levels ($r = -.219$; $P = .0001$; Figure S1A) and a positive correlation between ferritin with ALT ($r = .334$, $P < .001$) and AST levels ($r = .309$, $P < .001$; Figure S1B,C). Furthermore, multivariate analysis revealed that age, HE score, TB, $\ln(\text{AFP})$, sodium, and INR were independently associated with prognosis at day 28.

Then, we further analyzed the prognostic value of $\ln(\text{AFP})$. ROC curve showed that $\ln(\text{AFP})$ had the second largest AUROC, superior to TB, HE score, age, and

sodium (Figure 2A and Table 3). According to the cutoff value, patients in the derivation group were divided into low AFP group ($\ln(\text{AFP}) < 4.18$) and high AFP group ($\ln(\text{AFP}) > 4.18$). Kaplan-Meier curve revealed that high AFP group had significantly higher 28-day survival rate than low AFP group ($P < .001$, Figure 2B).

3.3 | Establishment and validation of a new prognostic model containing AFP

Using logistic regression model, we generated a new prognostic model, the ALSS-prognosis model (APM), using a four factor multivariate logistic regression: $0.042 \times \text{age} + \text{TB} (\text{mg/dL}) \times 0.094 + 1.228 \times \text{INR} - 0.473 \times \ln[\text{AFP} (\mu\text{g/L})]$. The predictive values of the different models are illustrated in Table 4 and Figure 3. APM demonstrated a significantly higher AUROC (0.790) compared to MELD (AUROC = 0.666, $P = .0003$), MELD-Na (AUROC = 0.685, $P = .001$), and CLIF-C ACLF (AUROC = 0.726, $P = .0184$), but not compared to COSSH-ACLF (AUROC = 0.759, $P = .1292$) for the derivation group.

The established models were further verified in the validation group. Consistent with the derivation group, APM had the highest AUROC value among all prognostic models. As a result of the small sample size in the verification group, APM was significantly different to MELD-Na ($P = .0308$), but no significant difference was observed compared to MELD, CLIF-C ACLF, and COSSH-ACLF.

4 | DISCUSSION

Despite the introduction to antivirals, patients with HBV-ACLF have poor survival owing to HBV reactivation and the development of antiviral resistance.¹⁹ HBV-ACLF has become one of the most common indications for LT at our center, but liver donor shortage necessitates the need for alternative therapy. PE has been widely used in China due to its ability to rapidly remove over-accumulated toxic materials and replace beneficial plasma substances.^{20,21} Although PE alone is useful, combining PE with other purification methods is even more effective.^{22,23} It was reported that if MELD score could be reduced prior LT, the prognosis of HBV-ACLF could be improved.²⁴ Previous studies have reported that treatment with PE-based ALSS could significantly lowered serum bilirubin, liver enzyme levels and INR, as well as improved MELD score in HBV-ACLF patients.^{5,18} These effects from PE might help to reduce the metabolic burden and promote the

regeneration of hepatocytes, thus prolonging the survival of patients. Xu et al²⁵ also demonstrated the importance of ALSS in terms of providing additional time for HBV-ACLF patients awaiting LT.

Although several previous prognostic models for ACLF have been derived and verified among eastern and western countries, no specific model for prediction of HBV-ACLF patients who received ALSS treatment has previously been published in any detail. In this study, we used MELD, MELD-Na, CLIF-C ACLF, and COSSH-ACLF to predict the short-term prognosis on this group of patients. The COSSH-ACLF¹² scoring system was established specifically for ACLF patients with HBV etiology, with liver and coagulation failure as the most common types of organ failures, which explained the low serum creatinine values of patients in the current study. Its prognostic value for HBV-ACLF patients receiving ALSS have been confirmed in our study. This score was consistent with unique characteristics of ACLF that include hyperbilirubinemia (TB), coagulopathy (INR), and multiple OF (systemic organ failure assessment [SOFA]), which enrolled seven evaluation indicators in total. MELD was previously used to evaluate the curative effects of ALSS,²⁶ but in our study, the AUROC only reached 0.666, which was the lowest among the models we used for evaluating prognosis.

In this study, we found that high AFP levels were associated with improved outcomes in HBV-ACLF patients receiving ALSS. AFP has been widely used as a clinical biomarker of chronic liver diseases and hepatic malignancy.²⁷ Huang et al²⁸ suggested that AFP is a marker of liver regeneration, whereby a high AFP was associated with greater hepatocyte regeneration and favorable outcomes in patients with HBV-ACLF. Kakisaka et al²⁹ suggested that serum AFP level may reflect the induction of liver progenitor cells in acute liver failure patients, and the persistent induction of liver progenitor cells may be needed for a recovery from liver failure. These findings suggested that patients with high AFP had greater regeneration activity and thus a better response to ALSS. Luo et al³⁰ combined MELD with AFP, HE, WBC, and age to generate a new prognostic model to predict the prognosis of HBV-ACLF patients. This model performed a higher AUROC than MELD, MELD-Na, and iMELD. Nonetheless, the modified MELD as described by Luo et al requires the input of a large number of independent factors, making it complicated and difficult to use in routine clinical practice.

The new model APM was generated to predict the outcome of patients with HBV-ACLF treated with PE-based ALSS. It was superior in comparison to the other

models for predicting the 28-day mortality, as demonstrated by the AUROC. With a cutoff value of 2.56, APM significantly surpassed the predictive value of the other models, except for COSSH-ACLF. Then, we evaluated its performance in a validation group containing 101 patients from two different hospitals. Similarly as in the derivation group, APM performed highest AUROC than other models. Although our APM model did not demonstrate a significant advantage compared to the COSSH-ACLF scoring system in derivation group, our model only included four factors, making it significantly more convenient to calculate and apply in the clinical setting. Our APM could be a useful tool to assist clinicians in deciding if ALSS treatment is beneficial for a given patient with HBV-ACLF; ALSS offers minimal benefit to patients with a score above 2.56 and LT should be used for management of those patients.

Our study had some limitations. First, it used a retrospective design and data were only collected for patients with HBV-ACLF from a single medical center. Second, no comparison was performed with patients who only received conventional medical treatment. Although our new model offered better prognostic prediction efficiency, it can only be applied to HBV-ACLF patients receiving additional ALSS therapy. Whether this model can be applied to other etiologies of ACLF requires further validation in randomized controlled trials involving multiple centers that include more heterogeneous groups of ACLF patients.

5 | CONCLUSIONS

In our study, low serum AFP level was found to be an independent risk factor for high mortality in HBV-ACLF patients with PE-based ALSS. We have proposed a new prognostic prediction model containing AFP, namely APM, which was superior for predicting short-term outcomes and may aid physicians in choosing the best therapeutic management method.

REFERENCES

- Liu J, Fan D. Hepatitis B in China. *Lancet*. 2007;369:1582-1583.
- Sarin SK, Choudhury A. Acute-on-chronic liver failure: terminology, mechanisms and management. *Nat Rev Gastroenterol Hepatol*. 2016;13:131-149.
- Larsen FS, Schmidt LE, Bernsmeier C, et al. High-volume plasma exchange in patients with acute liver failure: an open randomised controlled trial. *J Hepatol*. 2016;64:69-78.
- Yue MW, Yang LH, Yang JH, Xu Y, Yang J, Song GB. The effect of plasma exchange on entecavir-treated chronic hepatitis B patients with hepatic de-compensation and acute-on-chronic liver failure. *Hepatol Int*. 2016;10:462-469.
- Yu JW, Sun LJ, Zhao YH, Li SC. Prediction value of model for end-stage liver disease scoring system on prognosis in patients with acute-on-chronic hepatitis B liver failure after plasma exchange and lamivudine treatment. *J Gastroenterol Hepatol*. 2008;23(8pt1):1242-1249.
- Maiwall R, Moreau R. Plasma exchange for acute on chronic liver failure: is there a light at the end of the tunnel? *Hepatol Int*. 2016;10:387-389.
- Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464-470.
- Biggins SW, Kim WR, Terrault NA, et al. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology*. 2006;130:1652-1660.
- Li N, Huang C, Yu KK, Lu Q, Shi GF, Zheng JM. Validation of prognostic scores to predict short-term mortality in patients with HBV-related acute-on-chronic liver failure. *Medicine (Baltimore)*. 2017;96:e6802.
- Wu J, Li YY, Hu JH, et al. Differential characteristics and prognosis of patients with hepatitis B virus-related acute-on-chronic liver failure defined by European Association for the Study of the Liver—chronic liver failure criteria. *Hepatol Res*. 2018;48:153-164.
- Li H, Chen LY, Zhang N n, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to Hepatitis B. *Sci Rep*. 2016;6:25487.
- Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *Gut*. 2018;67:2181-2191.
- Artificial Liver Group Chinese Association of Infectious and Parasitic Diseases. Operating guide for artificial liver support system. *Zhonghua Gan Zang Bing Za Zhi*. 2002;10:329-332.
- Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL). *Hepatol Int*. 2009;3:269-282.
- Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426-1437.e1-9.
- Blei AT, Cordoba J. Hepatic encephalopathy. *Am J Gastroenterol*. 2001;96:1968-1976.
- Yin S, Wang SJ, Gu WY, Zhang Y, Chen LY, Li H. Risk of different precipitating events for progressing to acute-on-chronic liver failure in HBV-related cirrhotic patients. *J Dig Dis*. 2017;18:292-301.
- Chen JJ, Huang JR, Yang Q, et al. Plasma exchange-centered artificial liver support system in hepatitis B virus-related acute-on-chronic liver failure: a nationwide prospective multicenter study in China. *Hepatobiliary Pancreat Dis Int*. 2016;15:275-281.
- Zoulum F, Locarnini S, Hepatitis B. Virus resistance to nucleos(t)ide analogues. *Gastroenterology*. 2009;137:1593-608.e1-2.
- Li LJ, Zhang YM, Liu XL, et al. Artificial liver support system in China: a review over the last 30 years. *Ther Apher Dial*. 2006;10:160-167.
- Stenbøg P, Busk T, Larsen FS. Efficacy of liver assisting in patients with hepatic encephalopathy with special focus on plasma exchange. *Metab Brain Dis*. 2013;28:333-335.

22. Sadahiro T, Hirasawa H, Oda S, et al. Usefulness of plasma exchange plus continuous hemodiafiltration to reduce adverse effects associated with plasma exchange in patients with acute liver failure. *Crit Care Med*. 2001;29:1386-1392.
23. Zhou PQ, Zheng SP, Yu M, He SS, Weng ZH. Prognosis of acute-on-chronic liver failure patients treated with artificial liver support system. *World J Gastroenterol*. 2015;21:9614-9622.
24. Ling Q, Xu X, Wei Q, et al. Downgrading MELD improves the outcomes after liver transplantation in patients with acute-on-chronic hepatitis B liver failure. *PLoS One*. 2012;7:e30322.
25. Xu X, Liu X, Ling Q, et al. Artificial liver support system combined with liver transplantation in the treatment of patients with acute-on-chronic liver failure. *PLoS One*. 2013;8:e58738.
26. Xia Q, Dai X, Zhang Y, et al. A modified MELD model for Chinese pre-ACLF and ACLF patients and it reveals poor prognosis in pre-ACLF patients. *PLoS One*. 2013;8:e64379.
27. Eleftheriou N, Heathcote J, Thomas HC, Sherlock S. Serum alpha-fetoprotein levels in patients with acute and chronic liver disease. Relation to hepatocellular regeneration and development of primary liver cell carcinoma. *J Clin Pathol*. 1977;30:704-708.
28. Huang GQ, Xie YY, Zhu PW, et al. Stratified alpha-fetoprotein pattern accurately predicts mortality in patients with acute-on-chronic hepatitis B liver failure. *Expert Rev Gastroenterol Hepatol*. 2018;12:295-302.
29. Kakisaka K, Kataoka K, Onodera M, et al. Alpha-fetoprotein: a biomarker for the recruitment of progenitor cells in the liver in patients with acute liver injury or failure. *Hepatol Res*. 2015;45:E12-E20.
30. Luo Y, Xu Y, Li M, Xie Y, Gong G. A new multiparameter integrated MELD model for prognosis of HBV-related acute-on-chronic liver failure. *Medicine (Baltimore)*. 2016;95:e4696.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Xie Z, Violetta L, Chen E, et al. A prognostic model for hepatitis B acute-on-chronic liver failure patients treated using a plasma exchange-centered liver support system. *J Clin Apher*. 2020;35:94–103. <https://doi.org/10.1002/jca.21762>