OBJECTIVE: To investigate the impact of the baseline status of patients with hepatitis B virus-associated acute-on-chronic liver failure on short-term outcomes.

METHODS: A retrospective study was conducted that included a total of 138 patients with hepatitis B virus-associated acute-on-chronic liver failure admitted to the Department of Infectious Diseases, Taihe Hospital, Hubei University of Medicine, from November 2013 to October 2016. The patients were divided into a poor prognosis group (74 patients) and a good prognosis group (64 patients) based on the disease outcome. General information, clinical indicators and prognostic scores of the patients’ baseline status were analyzed, and a prediction model was established accordingly.

RESULTS: Elder age, treatment with artificial liver support systems and the frequency of such treatments, high levels of white blood cells, neutrophils, neutrophil count/lymphocyte count ratio, alanine aminotransferase, gamma-glutamyl transferase, total bilirubin, urea, and prognostic scores as well as low levels of albumin and sodium were all significantly associated with the short-term outcomes of hepatitis B virus-associated acute-on-chronic liver failure. The predictive model showed that logit ($p$) = 3.068 + 1.003 neutrophil count/lymphocyte count ratio - 0.892 gamma-glutamyl transferase - 1.138 albumin - 1.364 sodium + 1.651 artificial liver support therapy.

CONCLUSION: The neutrophil count/lymphocyte count ratio and serum levels of gamma-glutamyl transferase, albumin and sodium were independent risk factors predicting short-term outcomes of hepatitis B virus-associated acute-on-chronic liver failure, and the administration of multiple treatments with artificial liver support therapy during the early stage is conducive to improved short-term outcomes.

KEYWORDS: Hepatitis B Virus; Acute-on-Chronic Liver Failure; Prognosis.
therapy can temporarily replace part of the liver function and prevent further exacerbation of liver failure by removing toxic substances and metabolites from the serum, improving the microenvironment for liver cell regeneration and liver function repair. However, the efficacy of artificial liver support therapy for liver failure remains controversial (5-7).

The early identification, accurate diagnosis and prognostic evaluation of ACLF can provide a guiding basis for active and effective treatment. Therefore, a better understanding of prognostic factors and more precise prognostic evaluation systems for ACLF are in urgent need. A variety of factors can affect the progression and prognosis of ACLF. Many prognostic scoring systems are available for predicting the outcomes of ACLF, including the Child-Turcotte-Pugh (CTP) system, the model for end-stage liver disease (MELD) and the MELD-sodium (MELD-Na). Each scoring system has certain limitations given that not all of the influencing factors can be included in the individual assessment. The integrated MELD (iMELD) is a new scoring system that features the addition of two independent ACLF prognostic risk factors, age and serum Na levels, to the MELD scoring system (8). In addition, the albumin-bilirubin (ALBI) grading system is a recently developed scoring system to assess liver function (9). Several studies have compared the predictive ability of different scoring systems in ACLF (10-12). Comparisons of the predictive abilities of the CTP, MELD, MELD-Na, iMELD and ALBI scoring systems for the prognosis of HBV-ACLF are rarely reported. Attempts to analyze the impact of clinical parameters and the combined prognostic abilities of these parameters on ACLF prognosis have provided inconsistent results due to differences in study subjects, study phases and follow-up periods (13-15). The integration of general information, clinical indicators and a prognostic scoring system may better predict the short-term outcomes of patients with HBV-ACLF.

In this study, a retrospective investigation was carried out in HBV-ACLF patients admitted to the Department of Infectious Diseases, Taihe Hospital, Hubei University of Medicine from November 2013 to October 2016. General patient information, laboratory indicators and prognostic scores at baseline of HBV-ACLF patients with different prognoses were analyzed, and the factors that influenced the short-term outcomes of HBV-ACLF were investigated.

**PATIENTS AND METHODS**

**Patient selection**

Based on the clinical data in the medical record system of Taihe Hospital, Hubei University of Medicine, a retrospective analysis was conducted in patients admitted to the Department of Infectious Diseases from November 2013 to October 2016 who met the criteria of HBV-ACLF during their hospitalization. The data from the medical records of the selected patients were input in the form of case reports and verified with the clinical data system in our hospital. All of the patients were given comprehensive supportive treatment of internal medicine after admission to the hospital, including anti-viral therapy with nucleoside analogs. Artificial liver support therapy was optional based on the patient’s condition and willingness. The end point of the observation in this study was the time of discharge or in-hospital death of the patient. The study protocol was approved by the Ethics Committee of Taihe Hospital, Hubei University of Medicine.

**Inclusion and exclusion criteria**

The diagnostic criteria for HBV-ACLF were based on the “Guidelines for the Prevention and Treatment of Chronic Hepatitis B” of China issued in 2015 and the “Guidelines for Diagnosis and Treatment of Liver Failure (2012 Edition)” of China. The exclusion criteria included patients complicated with other forms of viral hepatitis, alcoholic liver disease, autoimmune liver disease, drug-induced liver injury, associated tumors or severe organ disease other than hepatitis B.

**General information**

The general information included gender, age, with/without (w/wo) liver cirrhosis, rebound after withdrawal of anti-viral drugs, complication with ascites at admission and the acceptance and frequency of artificial liver support therapy. All of this information was retrieved from the medical record system of Taihe Hospital.

**Clinical indicators**

The following measurements were performed using venous blood collected on the first day of admission or on the morning following admission: baseline white blood cell count (WBC), absolute neutrophil count (NE), absolute lymphocyte count (LY), NE:LY ratio (NE/LY), platelet count (PLT), levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), albumin (Alb), total bilirubin (TBil), urea (Urea), and creatinine (Cr), prothrombin time (PT), prothrombin activity (PTA), activated partial thromboplastin time (APTT), the international normalized ratio (INR) and serum Na levels. All results were retrieved from the clinical database.

**Prognostic score**

The prognostic scoring systems included the CTP, MELD, MELD-Na, iMELD and ALBI. The CTP score is the cumulative result of the scores for five items (ascites, hepatic encephalopathy, TBil, Alb and PT extension time), with 1-3 points for each item and a maximum of 15 points (16, 17). The equation for the MELD score is as follows: MELD = 3.7 × LN (TBil [mg/dL]) + 11.2 LN (INR) + 9.6 LN (Cr [mg/dL]) + 6.4 × cause (0 for cholestatic or alcoholic liver diseases and 1 for all others); the result is a rounded integer (18). The equation for the MELD-Na score is as follows: MELD + 1.59 × (135 - Na), wherein Na is 135 mmol/L if Na > 135 mmol/L and 120 mmol/L if Na < 120 mmol/L (19). The equation for the iMELD score is as follows: MELD + (0.3 × Age) · (0.7 × Na) + 100 (8). The equation for the ALBI score is as follows: [log10TBil [μmol/L] × 0.66] + (Alb [g/L] × - 0.085) (9).

**Prognostic criteria**

The prognostic criteria in this study were based on the ACLF clinical improvement criteria in “Guidelines for Diagnosis and Treatment of Liver Failure (2012 Edition)” of China (2). A good prognostic needs to meet all of the following conditions simultaneously: 1) the clinical symptoms are significantly improved and hepatic encephalopathy has disappeared; 2) signs of jaundice and ascites are significantly improved; and 3) liver function is significantly improved (TBil <5 ULN, PTA >40%). The patients who died, whose condition became more advanced, and those who still experienced ACLF were included in the poor prognosis group.
Data processing
All data included in this study were retrieved from the electronic medical record system of Taihe Hospital and validated using the clinical data system. Cases with missing or incomplete data, such as AFP data, were not included in the study.

Statistical analysis
Statistical Package for the Social Sciences (SPSS) 17.0 software was used for the statistical analysis. The measurement data were first tested for a normal distribution. Data that showed a normal distribution were represented as \( \bar{x} \pm s \) and were analyzed using the t-test. The data that were not normally distributed were represented as medians (\( P_{25} \) and \( P_{75} \)) and analyzed using the nonparametric rank sum test. The count data among different groups were analyzed using the \( \chi^2 \) test. The area under the receiver operating characteristic (ROC) curve was used to assess the predictive power of the five scoring systems for the prognosis of HBV-ACLF, and the cut-off value of the continuous variable was calculated. The method of likelihood-ratio-forward-selection in non-conditional binary logistic regression analysis was used to obtain the independent risk factors and to establish a predictive model. The threshold used for statistical significance was \( p < 0.05 \).

### RESULTS

Case enrollment
A total of 171 patients with HBV-ACLF were admitted to the department of infectious disease of Taihe Hospital from November 2013 to October 2016. A total of 138 patients were selected according to the inclusion and exclusion criteria, including 111 males and 27 females with an average age of 45.80 ± 11.01 years. There were 74 cases in the poor prognosis group, accounting for 53.6%, and 64 cases in the good prognosis group, accounting for 46.4%. Of the cases in the poor prognosis group, 59 cases showed ACLF; 15 cases were in the pre-ACLF state at admission. In the good prognosis group, the corresponding numbers were 45 cases and 19 cases, respectively (Figure 1).

General information of the patients
The average age of the patients in the poor prognosis group was significantly higher than that in the good prognosis group (48.08 ± 9.08 years vs. 43.16 ± 12.44 years, \( p = 0.01 \)). The number of patients who received artificial liver support therapy and the frequencies of artificial liver support therapy in the good prognosis group, accounting for 46.4%. Of the cases in the poor prognosis group, 59 cases showed ACLF; 15 cases were in the pre-ACLF state at admission. In the good prognosis group, the corresponding numbers were 45 cases and 19 cases, respectively (Figure 1).

### Table 1 - General information of the patients.

|                      | Good prognosis | Poor prognosis | \( t^* \) value | \( p \) value |
|----------------------|----------------|----------------|-----------------|--------------|
| Age (years)          | 43.16 ± 12.44  | 48.08 ± 9.08   | 2.621           | 0.010        |
| Gender (male/female) | 52/12          | 59/15          | 0.05            | 0.822        |
| W/wo liver cirrhosis | 19/45          | 32/42          | 2.707           | 0.100        |
| W/wo drug-withdrawal rebound | 6/5       | 10/22          | 1.035           | 0.309        |
| W/wo ascites         | 41/23          | 55/19          | 1.707           | 0.191        |
| W/wo ALST            | 54/10          | 36/38          | 19.31           | 0.000        |
| Number of treatments | 1.62 (0.79, 2.55) | 0.64 (0, 1.61) | -4.422         | 0.000        |

Note: W/wo indicates with/without; ALST is the abbreviation of artificial liver support therapy.

---

**Figure 1 - Case screening and enrollment. No statistically significant difference was observed between the poor prognosis group and the good prognosis group in terms of disease stage at admission.**
The baseline clinical indicators for HBV-ACLF patients with different prognoses

The WBC, NE, NE/LY, ALT, GGT, TBil and Urea scores/levels were significantly higher in the poor prognosis group ($p<0.05$), while the Alb and Na levels in the good prognosis group ($p<0.01$). There were no statistically significant differences between the two groups in terms of the other clinical indicators, including LY, PLT, AST, Cr, PT, APTT and INR (Table 2).

High CTP, MELD, MELD-Na, iMELD and ALBI scores all predict poor short-term outcomes for HBV-ACLF patients

Compared with the patients with a good prognosis, the patients with a poor prognosis showed significantly higher scores for the CTP, MELD, MELD-Na, iMELD and ALBI prognostic systems ($p<0.05$) (Table 3). The prognosis of HBV-ACLF was well predicted by these five types of prognostic scores. The areas under the ROC curves of the CTP, MELD, MELD-Na, iMELD and ALBI prognostic systems were 0.672, 0.641, 0.656, 0.699, and 0.682, respectively (Table 4, Figure 2).

Independent prognostic factors and novel prediction model for HBV-ACLF

The different measures of general patient information, clinical indicators and prognostic scores at baseline for the two groups were assigned corresponding values for non-conditional binary logistic regression analysis. The cut-off values of the continuous variables were calculated using the area under the ROC curve (Tables 5 and 6) to establish the following prediction model: logit ($p$) = 3.068 + 1.003/NE/LY - 0.892/GGT - 1.138/Alb - 1.364/Na + 1.651/Artificial liver support therapy. The area under the ROC curve was 0.656, with a specificity of 64.1% and sensitivity of 62.2%. NE/LY, GGT, Alb, Na and artificial liver support therapy were the independent factors influencing the short-term outcomes of HBV-ACLF (Table 7).

### Table 2 - Clinical indicators of the baseline status of the patients.

| Indicator | Good prognosis | Poor prognosis | Statistics value | $p$ value |
|-----------|----------------|----------------|------------------|-----------|
| WBC ($\times 10^{12}/L$) | 5.31 (4.12, 6.79) | 6.40 (4.48, 9.07) | Z = -2.291 | 0.022 |
| NE ($\times 10^{12}/L$) | 3.16 (2.28, 4.99) | 4.03 (2.86, 6.57) | Z = -2.248 | 0.025 |
| LY ($\times 10^{12}/L$) | 1.13 (0.84, 1.43) | 1.21 (0.63) | Z = -0.566 | 0.572 |
| NE/LY | 2.70 (1.79, 5.37) | 3.96 (2.93, 6.69) | Z = -2.517 | 0.012 |
| PLT ($\times 10^{12}/L$) | 88.0 (65.25, 125.67) | 85.0 (46.0, 122.33) | Z = -1.087 | 0.277 |
| ALT (U/L) | 507.5 (175.5, 902.0) | 198.0 (81.0, 674.0) | Z = -2.589 | 0.01 |
| GGT (U/L) | 289.5 (124.0, 767.5) | 210.0 (95.67, 424.0) | Z = -1.543 | 0.123 |
| Alb (g/L) | 108.5 (62.5, 159.5) | 66.0 (47.0, 125.0) | Z = -2.735 | 0.006 |
| TBil (mmol/L) | 33.74 ± 5.174 | 30.71 ± 5.56 | Z = -3.30 | 0.001 |
| Urea (mmol/L) | 234.24 ± 106.27 | 301.62 ± 144.45 | Z = -2.147 | 0.042 |
| Cr (mmol/L) | 4.17 (2.98, 5.44) | 4.54 (3.54, 7.52) | Z = -2.002 | 0.045 |
| Na (mmol/L) | 55.75 (42.7, 77.95) | 56.95 (42.7, 85.5) | Z = -0.431 | 0.666 |
| PT (s) | 138.91 (42.7, 77.95) | 136.07 (63.3) | Z = -3.136 | 0.002 |
| PTA (%) | 22.45 ± 18.5 | 25.0 ± 18.6 (30.9) | Z = -1.738 | 0.082 |
| INR | 52.83 ± 14.70 | 56.33 ± 18.69 | t = 1.231 | 0.22 |
| ALBI score | 1.98 ± 0.62 | 2.05 (1.6, 2.72) | t = 3.639 | 0.000 |

Note: Normally distributed data are represented as $\bar{x} \pm s$. Non-normally distributed data are represented as medians ($P_{25}$ and $P_{75}$).

### Table 3 - Prognostic scores of the patients at baseline.

| Prognostic score | Good prognosis | Poor prognosis | Statistics value | $p$ value |
|------------------|----------------|----------------|------------------|-----------|
| CTP score | 10.11 ± 1.78 | 11.2 ± 1.68 | t = 3.706 | 0.000 |
| MELD score | 18.08 ± 7.10 | 21.58 ± 7.39 | t = 2.828 | 0.005 |
| MELD-Na score | 18.95 ± 7.7 | 24.18 ± 10.11 | t = 3.573 | 0.000 |
| iMELD score | 33.79 ± 9.15 | 40.75 ± 9.90 | t = 4.268 | 0.000 |
| ALBI score | -1.34 ± 0.52 | -1.01 ± 0.54 | t = 3.639 | 0.000 |

### Table 4 - Comparison of the five types of prognostic scores.

| Area | Sensitivity (%) | Specificity (%) | Std. error | Asymptotic Sig. | 95% C.I. |
|------|----------------|-----------------|------------|----------------|---------|
| CTP  | 0.672 | 47.3 | 79.7 | 0.045 | 0.000 | 0.593 | 0.761 |
| MELD | 0.641 | 56.8 | 71.9 | 0.047 | 0.004 | 0.549 | 0.733 |
| MELD-Na | 0.656 | 41.9 | 85.9 | 0.046 | 0.002 | 0.565 | 0.746 |
| iMELD | 0.699 | 74.3 | 62.5 | 0.045 | 0.000 | 0.611 | 0.786 |
| ALBI | 0.682 | 62.2 | 67.2 | 0.045 | 0.000 | 0.594 | 0.771 |
| Logit(p) | 0.656 | 62.2 | 64.1 | 0.046 | 0.002 | 0.565 | 0.746 |

The baseline clinical indicators for HBV-ACLF patients with different prognoses

The WBC, NE, NE/LY, ALT, GGT, TBil and Urea scores/levels were significantly higher in the poor prognosis group ($p<0.05$), while the Alb and Na levels in the good prognosis group were significantly higher than in the poor prognosis group ($p<0.01$). There were no statistically significant differences between the two groups in terms of the other clinical indicators, including LY, PLT, AST, Cr, PT, APTT and INR (Table 2).

High CTP, MELD, MELD-Na, iMELD and ALBI scores all predict poor short-term outcomes for HBV-ACLF patients

Compared with the patients with a good prognosis, the patients with a poor prognosis showed significantly higher scores for the CTP, MELD, MELD-Na, iMELD and ALBI prognostic systems ($p<0.05$) (Table 3). The prognosis of HBV-ACLF was well predicted by these five types of prognostic scores. The areas under the ROC curves of the CTP, MELD, MELD-Na, iMELD and ALBI prognostic systems were 0.672, 0.641, 0.656, 0.699, and 0.682, respectively (Table 4, Figure 2).

Independent prognostic factors and novel prediction model for HBV-ACLF

The different measures of general patient information, clinical indicators and prognostic scores at baseline for the two groups were assigned corresponding values for non-conditional binary logistic regression analysis. The cut-off values of the continuous variables were calculated using the area under the ROC curve (Tables 5 and 6) to establish the following prediction model: logit ($p$) = 3.068 + 1.003/NE/LY - 0.892/GGT - 1.138/Alb - 1.364/Na + 1.651/artificial liver support therapy. The area under the ROC curve was 0.656, with a specificity of 64.1% and sensitivity of 62.2%. NE/LY, GGT, Alb, Na and artificial liver support therapy were the independent factors influencing the short-term outcomes of HBV-ACLF (Table 7).
DISCUSSION

HBV-ACLF is a common fatal clinical disease characterized by a large number of necrotic liver cells, a complex pathological mechanism and rapid progression. The results of this study showed that many factors are closely related to the short-term outcomes of this condition.

Age has been shown to be closely related to the severity of liver diseases and serves as an independent prognostic factor for end-stage liver disease (8, 20). Studies have found that the short-term mortality rate of patients with ACLF is positively correlated with patient age (21). In this study, the average age of the patients with a poor prognosis was significantly higher than that in the patients with a good prognosis, suggesting that age is an important prognostic factor in HBV-ACLF.

As an important supportive treatment measure for the recovery of liver function, artificial liver support can significantly improve the short-term outcomes of this condition. However, the impact of artificial liver support therapy on long-term survival is uncertain (6). Considering that the above results are for different types of artificial liver support therapy and different periods of application, plasma replacement therapy was primarily applied in this study. The number of patients who received artificial liver support therapy and the frequency of this therapy were significantly higher in the good prognosis group than in the poor prognosis group. Moreover, artificial liver support therapy was an independent factor for the short-term outcomes of HBV-ACLF. Therefore, the early active implementation of treatment combined with artificial liver support therapy can significantly improve the short-term outcomes of patients with HBV-ACLF.

WBC, NE and the NE/LY ratio are often associated with the short-term outcomes of patients with HBV-ACLF. In this study, the WBC, NE count and NE/LY ratio are also important prognostic factors for HBV-ACLF. In this study, the WBC, NE count and NE/LY ratio were significantly higher than those of the patients with a good prognosis, suggesting that, in addition to WBC, a high NE count and NE/LY ratio are also important prognostic factors for HBV-ACLF.

Table 5 - Area under the ROC curve and the cut-off value of each variable.

| Source of the Curve | Cut-off value | c-statistic | 95% CI Lower | 95% CI Upper |
|---------------------|---------------|-------------|--------------|--------------|
| Age                 | 43.5          | 0.643       | 0.549        | 0.738        |
| WBC                 | 6.75          | 0.613       | 0.52         | 0.707        |
| NE                  | 5.635         | 0.611       | 0.517        | 0.705        |
| NE/LY               | 2.947         | 0.624       | 0.53         | 0.719        |
| ALT                 | 127.5         | 0.372       | 0.279        | 0.465        |
| GGT                 | 76            | 0.365       | 0.272        | 0.457        |
| Alb                 | 34.85         | 0.343       | 0.252        | 0.435        |
| TBil                | 251.2         | 0.632       | 0.54         | 0.725        |
| Urea                | 6.365         | 0.599       | 0.505        | 0.693        |
| Na                  | 136.3         | 0.361       | 0.268        | 0.454        |
| CTP                 | 11.5          | 0.672       | 0.593        | 0.761        |
| MELD                | 21.448        | 0.641       | 0.549        | 0.731        |
| MELD-Na             | 25.636        | 0.656       | 0.565        | 0.746        |
| iMELD               | 34.705        | 0.699       | 0.611        | 0.786        |
| ALBI                | -1.119        | 0.682       | 0.594        | 0.771        |

Table 6 - Variable assignment.

| Variable               | Assignment | Prognosis |
|------------------------|------------|-----------|
| Age                    | ≤ 43.5     | Good      |
| WBC                    | ≤ 6.75     | Good      |
| NE                     | ≤ 5.635    | Good      |
| NE/LY                  | ≥ 2.947    | Poor      |
| ALT                    | ≤ 127.5    | Poor      |
| GGT                    | ≤ 76       | Poor      |
| Alb                    | ≤ 34.85    | Poor      |
| TBil                   | ≤ 251.2    | Poor      |
| Urea                   | ≤ 6.365    | Poor      |
| Na                     | ≤ 136.3    | Poor      |
| MELD                   | ≤ 21.448   | Poor      |
| MELD-Na                | ≤ 25.636   | Poor      |
| iMELD                  | ≤ 34.705   | Poor      |
| CTP                    | ≤ 11.5     | Poor      |
| ALBI                   | ≤ -1.119   | Poor      |
| Artificial liver support therapy (ALST) | No        | Good      |

Figure 2 - ROC curves for CTP, MELD, MELD-Na, iMELD, ALBI score and logit (p) curve.
Table 7 - Logistic regression analysis results.

|            | B    | SE   | Wald | Sig  | Exp(B) | 95% CI for Exp(B) |
|------------|------|------|------|------|--------|------------------|
|            | Lower| Upper|      |      |        |                  |
| NE/LY      | 1.003| 0.444| 5.109| 0.024| 2.728  | 1.003 - 6.512    |
| GGT        | -0.892| 0.428| 4.338| 0.037| 0.41   | 0.177 - 0.949    |
| Alb        | -1.138| 0.511| 4.951| 0.026| 0.321  | 0.118 - 0.873    |
| Na         | -1.364| 0.455| 8.979| 0.003| 0.256  | 0.105 - 0.624    |
| Artificial liver support therapy | 1.651 | 0.473 | 12.161 | 0.000 | 5.21   | 2.06 - 13.174    |
| Constant term | 3.068 | 1.441 | 4.535 | 0.033| 21.489 |                  |

synthesis of proteins and coagulation factors decreases, resulting in decreased Alb levels and the development of coagulation disorders. In the present study, liver function and coagulation function were abnormal in both groups, and the levels of ALT, GGT, TBil and Alb all showed significant differences between the two groups. Of these measures, GGT and Alb were independent risk factors for poor prognosis of HBV-ACLF. However, a comparison of the baseline PTA of the patients in the two groups showed a significance level of \( p = 0.05 \). Therefore, this difference was not considered statistically significant. Baseline PTA may be related to the patient’s stage of disease at admission. Because the majority of patients in this study had reached the ACLF stage at admission, with PTA ≤ 40%, the difference between the two groups was small. Changes and differences in coagulation can be further investigated and analyzed at different times and over different observation periods.

Ascites, hyponatremia and hepatorrenal syndrome are common complications of ACLF. Complications such as refractory ascites, hyponatremia and renal injury are often interrelated and may continuously degenerate (2). In this study, the serum Na levels of patients in the poor prognosis group were significantly lower than those of the patients with a good prognosis. Low Na levels were an independent risk factor for poor prognosis of HBV-ACLF; this finding is consistent with the results of the studies of Zhang et al (15) and Shi et al (24). The results suggest that electrolytes should be closely monitored and electrolyte imbalances should be corrected during HBV-ACLF treatment.

In conclusion, a variety of factors can affect the prognosis of HBV-ACLF. Higher age, high WBC, NE, NE/LY, and artificial liver support therapy were shown to be important factors that affect the short-term outcomes of HBV-ACLF as well. In addition to the indexes of liver function, complications such as infection were also included in this model. Thus, the novel predictive model was extremely suitable for ACLF patients in the end stage with multiple complications, especially those with extremely elevated INR, and this circumstance was restricted in evaluations using the iMELD, MELD-Na, and MELD scores.

Differences in study subjects, study phases and sample sizes may lead to different results. Although this study was a comprehensive study of factors that contribute to the short-term outcomes of HBV-ACLF, it had some limitations. First, all patients were enrolled from a single center, which may not reflect regional influences on the prognosis. Secondly, alpha fetoprotein and a history of antiviral therapy were not examined in this study. Lastly, only short-term outcomes were analyzed. Multi-center studies over different observation periods are required to further research HBV-ACLF and to provide a better theoretical basis for its clinical diagnosis and treatment.

In conclusion, a variety of factors can affect the prognosis of HBV-ACLF patients. Older age, high WBC, NE, NE/LY, and TBil levels, renal dysfunction, hyponatremia, hypoprothrombinemia and high prognostic scores at baseline often suggest a poor prognosis. For patients with HBV-ACLF, within the context of anti-viral treatment and comprehensive internal medicine treatment, infection control should be strengthened and the stability of the patient’s lab values, including the electrolyte balance, should be maintained. In addition, early active treatment combined with artificial liver support therapy is recommended. Further studies are needed to enhance our understanding of HBV-ACLF pathogenesis and reduce its morbidity and mortality.

**ACKNOWLEDGMENTS**

This work was partly supported by the National Natural Science Foundation of China (81541140), Natural Science Foundation of Hubei Province.
of China (2014CBB645), Research and Development Project of the Science and Technology Plan of Hubei Province (2011BCB030), Foundation for Innovative Research Team of Huabei University of Medicine (2014CXG05) and the Key Program for Precision Medicine of Taihe Hospital (2016JZ05).

**AUTHOR CONTRIBUTIONS**

Lei Q, Ke C, Chen Y, Luo J and Meng Z conceived and designed the study. Lei Q, Ao K, Zhang Y, Ma D, Ding D were responsible for the data collection. Lei Q analyzed the data and wrote the manuscript. Meng Z was responsible for the manuscript final revision.

**REFERENCES**

1. Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Garcia-Tsao G, et al. Acute-on-chronic liver failure. J Hepatol. 2012;57(6):1336-48, http://dx.doi.org/10.1016/j.jhep.2012.06.026.
2. Liver Failure And Artificial Liver Group CSOI, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Diseases and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. [Diagnostic and treatment guidelines for liver failure (2012 version)]. Zhonghua Gan Zang Bing Za Zhi. 2013;21(3):177-83.
3. Ye YN, Cao ZL. [Three shock hypotheses that may induce liver failure]. Zhonghua Gan Zang Bing Za Zhi. 2009;17(8):638-40.
4. Liu XY, Peng F, Pan YJ, Chen J. Advanced therapeutic strategies for HBV-related acute-on-chronic liver failure. Hepatobiliary Pancreat Dis Int. 2015;14(4):354-60, http://dx.doi.org/10.1016/S1499-3872(15)60338-1.
5. Vaid A, Chweich H, Balk IM, Jaber BL. Molecular adsorbent recirculating system as artificial support therapy for liver failure: a meta-analysis. ASAIO J. 2012;58(1):51-9, http://dx.doi.org/10.1097/MAT.0b013e318238d077.
6. Shen Y, Wang XL, Wang B, Shao JC, Liu YM, Qin Y, et al. Survival Benefits With Artificial Liver Support System for Acute-On-Chronic Liver Failure: A Time Series-Based Meta-Analysis. Medicine (Baltimore). 2016;95(3):e2506, http://dx.doi.org/10.1097/MD.0000000000002506.
7. Chen JJ, Huang JR, Yang Q, Xu XW, Liu XL, Hou SK, 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(3):275-81, http://dx.doi.org/10.1016/S1499-3872(16)60084-X.
8. Luca A, Angermann B, Bertolini G, Koenig F, Vizzini G, Ploner M, et al. An integrated MELD model including serum sodium and urine albumin improves the prediction of early mortality in patients with cirrhosis. Liver Transpl. 2007;13(8):1174-80, http://dx.doi.org/10.1002/lt.21197.
9. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550-8, http://dx.doi.org/10.1200/JCO.2014.57.9151.
10. Li C, You S, Liu H, Liu W, Wan Z, Tang G, et al. [The value of the baseline MELD scores, MELD-Na scores and iMELD scores in short-term prognosis in hepatitis B virus related acute-on-chronic liver failure patients]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2016;38(8):650-2, http://dx.doi.org/10.3760/cma.j.issn.2095-4352.2014.08.003.
11. Shen Y, Liu YM, Wang B, Zhu YG, Wang YY, Wang XL, et al. External validation and comparison of six prognostic models in a prospective cohort of HBV-ACLF in China. Ann Hepatol. 2016;15(2):234-45.
12. Peng Y, Qi X, Tang S, Deng H, Li J, Ning Z, et al. Child-Pugh, MELD, and ALBI scores for predicting the in-hospital mortality in cirrhotic patients with acute-on-chronic liver failure. Expert Rev Gastroenterol Hepatol. 2016;10(8):971-80, http://dx.doi.org/10.1586/17474126.2016.117778.
13. Li C, Lyu S, Zhu B, Wan ZH, Liu WS, Gao L, et al. [Risk factors for short-term outcome of patients with HBV-related acute-on-chronic liver failure]. Zhonghua Gan Zang Bing Za Zhi. 2016;24(3):207-13.
14. Huang K, Hu JH, Wang HF, He WP, Chen J, Duan XZ, et al. Survival and prognostic factors in hepatitis B virus-related acute-on-chronic liver failure. World J Gastroenterol. 2011;17(29):3448-52, http://dx.doi.org/10.3748/wjg.v17.i29.3448.
15. Zhang Q, Guo X, Zhao S, Pang X, Wang Y, Zhang Y, et al. Prognostic performance of clinical indices and model scorings for acute-on-chronic liver failure: A study of 164 patients. Exp Ther Med. 2016;11(4):1348-54, http://dx.doi.org/10.3892/etm.2016.3037.
16. Child CG, Turzotte JC. Surgery and portal hypertension. Major Probil Clin Surg. 1964;1:1-85.
17. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transsection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9, http://dx.doi.org/10.1093/bjsg/60.8.646.
18. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kossberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464-70, http://dx.doi.org/10.1053/jhep.2001.22172.
19. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology. 2006;130(6):1652-60, http://dx.doi.org/10.1053/j.gastro.2006.02.010.
20. Qin G, Shao JC, Wang B, Shen Y, Zheng J, Liu XJ, et al. Artificial liver support system improves short- and long-term outcomes of patients with HBV-associated acute-on-chronic liver failure: a single-center experience. Medicine (Baltimore). 2014;93(28):e338, http://dx.doi.org/10.1097/MD.0000000000000338.
21. Qin G, Shao JC, Zhu YC, Xu AD, Yao JH, Wang XL, et al. Population-representative Incidence of Acute-On-Chronic Liver Failure: A Prospective Cross-Sectional Study. J Clin Gastroenterol. 2016;50(8):670-5, http://dx.doi.org/10.1097/MG.0000000000000338.
22. Nochaj, RS Ahmad S. Infections in Liver Disease. Crit Care Clin. 2016;32(3):411-24, http://dx.doi.org/10.1016/j.ccc.2016.03.008.
23. Sole C, Sola E, Morales-Ruiz M, Fernandez G, Huelin P, Grauera I, et al. Characterization of Inflammatory Response in Acute-On-Chronic Liver Failure and Relationship with Prognosis. Sci Rep. 2016;6:32341, http://dx.doi.org/10.1038/srep32341.
24. Shi QJ, Cai YJ, Lin Z, Dong J, Wu JM, Wang XD, et al. Development and validation of a prognostic nomogram for acute-on-chronic hepatitis B liver failure. J Gastroenterol Hepatol. 2017;32(2):497-505, http://dx.doi.org/10.1111/j.1345-7256.2016.07004.x.