Research Article

Prediction and Risk Factors for Prognosis of Cirrhotic Patients with Hepatic Encephalopathy

Ying Peng, Qinglin Wei, Yun Liu, Zhenyu Wu, Hongjia Zhang, Hongbo Wu, and Jin Chai

1Cholestatic Liver Diseases Center and Department of Gastroenterology, The First Affiliated Hospital of Army Medical University, Chongqing, China
2Department of Gastroenterology, The First Affiliated Hospital of Army Medical University, Chongqing, China
3Department of Gastroenterology, The Seventh Medical Center of PLA General Hospital, Beijing 100700, China

Correspondence should be addressed to Hongbo Wu; doc_whb@163.com and Jin Chai; jin.chai@cldcsw.org

Received 2 July 2021; Revised 23 September 2021; Accepted 4 October 2021; Published 18 October 2021

Academic Editor: Fariborz Mansour-ghanaei

Copyright © 2021 Ying Peng et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background and Aims. Hepatic encephalopathy (HE) is characterized by recurrence and poor quality of life. Acute-on-chronic liver failure (ACLF) mainly occurs in patients with chronic liver diseases and often presents with HE. Several predictive models have been proposed to predict the outcomes of these patients. Our study is aimed at identifying associated risk factors and the prognostic accuracies of predictive models in HE patients with or without ACLF. Methods. Patients with liver cirrhosis were retrospectively enrolled. Risk factors were evaluated by multivariate regression analyses. The predictive capabilities of models were calculated using the receiver operating characteristic (ROC) curve analyses and compared by the DeLong tests. Outcomes were defined as in-hospital mortality, HE severity, and ACLF occurrence. Results. In multivariate regression analyses, serum biomarkers neutrophil and total bilirubin (TBIL) were independently correlated with in-hospital death. Alanine aminotransferase (ALT) and blood urea nitrogen (BUN) were independent serum biomarkers associated with HE severity. Hemoglobin, TBIL, BUN, and international normalized ratio (INR) were significant indicators associated with ACLF incidence. For prediction of in-hospital mortality, Child-Pugh was superior to the others in the whole patients, while NLR showed the best capability in the ACLF group. Conclusion. In cirrhotic patients present with HE, BUN is a risk factor associated with HE severity and ACLF incidence. Child-Pugh and NLR scores may be effective prognosticators in patients with HE.

1. Introduction

Hepatic encephalopathy (HE) is one of the most severe complications of liver cirrhosis, which is also responsible for the major cause of admissions and high mortality in cirrhotic patients. HE has been classified into five grades consisting of progressive stages of mental disorders based on the West Haven criterion. To avoid subjective prejudice, HE is presently classified into two types, covert hepatic encephalopathy (CHE) and overt hepatic encephalopathy (OHE), according to its severity [1]. It has been reported that HE affects more than one-third of cirrhotic patients, of which OHE is irreversible and accounts for more than 30% to 50% of these patients [2].

It has been proven that the occurrence of HE is strongly associated with previous episodic HE in hospitalized cirrhotic patients. Patients manifesting with HE will have a higher risk of progression to acute-on-chronic liver failure (ACLF) and result in poor prognosis in comparison to those without [3]. ACLF, characterized by organ failures and high short-term mortality, will substantially increase the economic burden and medical utilization of patients with chronic liver diseases [4]. To this end, identifying and diagnosing HE patients at an early stage and better prognostication are essential for reducing healthcare burden and mortality.

Various models for monitoring and predicting outcomes in patients with liver diseases have been proposed and
validated. However, there is no consensus on which model should be chosen when applying to different populations. Child-Pugh and the model for end-stage liver disease (MELD) score, the well-known prognostic tools of liver function, have been widely used for the prediction of patients with liver diseases. Biggins et al. have conducted a prospective multicenter study enrolling patients with end-stage liver diseases. Originated from the MELD algorithm, they proposed a new score, the model for end-stage liver disease-sodium (MELD-Na), the predictive ability of which was more accurate than that of MELD [5]. The albumin-bilirubin (ALBI) score was initially validated to assess the outcome of patients with hepatocellular carcinoma (HCC), and its effectiveness has been confirmed by relevant studies [6–8]. The neutrophil to lymphocyte ratio (NLR) score, an indicator representing inflammation, has been widely used as a predictive tool for various diseases [9–11].

Few studies have compared the predictive capabilities of the above scores. The previous study explored the prognostic factors correlated with 180 cirrhotic patients presenting with HE who were admitted in the medical intensive care unit (ICU). The researchers found that systolic blood pressure < 90 mmHg, total WBC > 12000 n/mm^3, and use of mechanical ventilation were significant risk factors for mortality. However, SAPS II, Acute Physiology and Chronic Health Evaluation II (APACHE II), Child-Pugh, and GCS had no significant difference between survivors and nonsurvivors [12]. Therefore, we conduct a retrospective study to investigate the accuracies of Child-Pugh, MELD, MELD-Na, ALBI, and NLR scores in predicting in-hospital mortality of cirrhotic patients with HE with or without ACLF. We also detected the associated risk factors for the severity of HE, and the occurrence of ACLF and in-hospital death.

2. Patients and Methods

All patients admitted to the First Affiliated Hospital of Army Medical University from January 2016 to August 2020 were searched through an electronic medical record database. We retrospectively selected patients who were diagnosed with liver cirrhosis and manifested with HE.

The exclusion criteria were as follows: (1) patients with readmissions, (2) patients with HCC or other malignancies, (3) patients with primary neurological diseases or mental disorders, and (4) patients without completed data.

Demographic data, medical history, comorbidities, clinical presentation, laboratory tests, grades of HE, presenting with or without ACLF, and in-hospital mortality were reviewed. HE was classified according to the West Haven criteria. Child-Pugh, MELD, MELD-Na, NLR, and ALBI scores were calculated in all groups. To explore the factors associated with the severity of HE, serum laboratory indicators and noninvasive prognostic models were compared with patients with a low grade (I or II) and high grade (III or IV). HE often occurs in the setting of ACLF and leads to short-term survival; thus, we further detected the characteristics in association with ACLF and in-hospital death. The accuracies of Child-Pugh, MELD, MELD-Na, NLR, and ALBI scores in the prediction of in-hospital death were compared in all the populations and the ACLF patients. The clinical research was authorized by the Ethics Committee Board of Southwest Hospital (KY2020202).

Child-Pugh score calculation consists of total bilirubin, albumin, INR, ascites, and HE. Child-Pugh is classified into A (5-6), B (7-9), and C (10-15) grades [13–15].

\[
\text{MELD}[14] = 9.57 \times \log_{10} (\text{creatinine} \text{ (mg/dl)}) + 3.78 \times \log_{10} (\text{bilirubin} \text{ (mg/dl)}) + 11.2 \times \log_{10} (\text{INR}) + 6.43
\]

The creatinine value >4 is set to 4, the minimum value of the three variables is set to 1. The maximum score is limited to 40.

\[
\text{MELD} - \text{Na}[5] = \text{MELD} + 1.59 \times (135 - \text{Na} \text{ (mmol/L)})
\]

The value of serum Na ranges from 120 to 135.

\[
\text{ALBI}[7] = -0.085 \times (\text{albumin} \text{ (g/L)}) + 0.66 \times \log_{10} (\text{bilirubin} \text{ (μmol/L)})
\]

ALBI score is divided into three grades: ≤−2.6 (grade 1); >−2.6 and ≤−1.39 (grade 2); >−1.39 (grade 3).

\[
\text{NLR}[15] = \frac{\text{neutrophil count}}{\text{lymphocyte count}}.
\]

2.1. Statistical Analysis. Continuous data were shown as mean ± standard deviation (SD) or median (interquartile range). Categorical data were shown as frequency (percentage). Comparisons between normally distributed continuous data were used by Student’s independent t-test, while non-normal distributed data were used by the Mann-Whitney U test. Categorical data were compared using the chi-square test or Fisher’s exact test. Logistic regression models were used to identify risk factors for HE severity, ACLF incidence, and hospitalized death. Analyses were performed on SPSS version 23.0. The predictive capabilities of scores were calculated using the receiver operating characteristic (ROC) curve analyses. The areas under the ROC curves (AUCs) with 95% confidence intervals (CIs) were compared by the DeLong tests. The cut-off value, sensitivity, specificity, positive likelihood ratio (LR), and negative LR, positive predictive value (PV), and negative PV were also presented. ROC analyses were performed by using MedCalc version 11.4.2.0. A two-sided p value < 0.05 was considered significantly different.

3. Results

3.1. Baseline Characteristics of the Whole Patients. A total of 304 patients were eligible for this study after exclusion. Among the whole patients, 242 patients were male (79.6%). The predominant etiology of liver cirrhosis was HBV infection (65.5%), and the second was alcohol abuse (14.5%). Regrettably, ammonia was only collected in 198 patients. The number of patients presenting with HE grade I/II and
Table 1: Comparative data of survivors versus nonsurvivors.

| Variable                          | Survivors (n = 240) | Nonsurvivors (n = 64) | p value |
|-----------------------------------|---------------------|-----------------------|---------|
| No. of patients (n)               | Median (IQR)        | Median (IQR)          |         |
| Gender (male, %)                  | 189 (78.8)          | 53 (82.8)             | 0.923   |
| Age (years)                       | 52.0 ± 12.1         | 52.7 ± 11.2           | 0.668   |
| Vital signs                       |                     |                       |         |
| Systolic blood pressure (mmHg)    | 117.4 ± 16.7        | 118.3 ± 16.7          | 0.701   |
| Diastolic blood pressure (mmHg)   | 69.4 ± 11.0         | 71.3 ± 12.5           | 0.251   |
| Heart rate (b.p.m.)               | 87.4 ± 14.7         | 85.7 ± 12.8           | 0.390   |
| Etiologies of liver diseases, n (%) |                   |                       | 0.424   |
| HBV                               | 153 (63.7)          | 46 (71.9)             |         |
| HCV                               | 5 (2.1)             | 0 (0)                 |         |
| Alcohol                           | 37 (15.4)           | 7 (10.9)              |         |
| HBV+HCV                           | 1 (0.4)             | 0 (0)                 |         |
| HBV+alcohol                       | 8 (3.3)             | 3 (4.7)               |         |
| HCV+alcohol                       | 3 (1.3)             | 0 (0)                 |         |
| DILI                              | 1 (0.4)             | 0 (0)                 |         |
| AIH                               | 3 (1.3)             | 2 (3.1)               |         |
| PBC+AIH                           | 2 (0.8)             | 1 (1.6)               |         |
| HBV+AIH                           | 1 (0.4)             | 0 (0)                 |         |
| HBV+DILI                          | 2 (0.8)             | 0 (0)                 |         |
| Unknown                           | 24 (10.0)           | 5 (7.8)               |         |
| Laboratory tests                  |                     |                       |         |
| WBC (10^3/μL)                     | 6.9 ± 4.5           | 9.8 ± 6.4             | <0.001* |
| RBC (10^3/μL)                     | 3.1 ± 0.9           | 3.1 ± 1.1             | 0.748   |
| Hemoglobin (g/L)                  | 100.5 ± 26.9        | 101.2 ± 30.9          | 0.864   |
| Platelet (10^9/L)                 | 82.1 ± 54.1         | 81.1 ± 53.9           | 0.611   |
| Neutrophil (10^9/L)               | 4.9 ± 3.7           | 7.8 ± 6.0             | <0.001* |
| Lymphocyte (10^9/L)               | 1.2 ± 1.0           | 1.3 ± 1.3             | 0.818   |
| TBIL (μmol/L)                     | 197.7 ± 190.2       | 332.8 ± 220.3         | <0.001* |
| DBIL (μmol/L)                     | 113.0 ± 118.1       | 195.3 ± 138.7         | <0.001* |
| IBIL (μmol/L)                     | 80.4 ± 78.5         | 141.9 ± 98.9          | <0.001* |
| Albumin (g/L)                     | 29.8 ± 5.1          | 29.6 ± 5.0            | 0.748   |
| ALT (U/L)                         | 186.3 ± 427.6       | 292.9 ± 477.2         | 0.001*  |
| AST (U/L)                         | 202.2 ± 423.7       | 359.2 ± 471.0         | <0.001* |
| ALP (U/L)                         | 145.4 ± 81.3        | 131.0 ± 67.7          | 0.250   |
| Variable                        | Survivors (n=240) | Nonsurvivors (n=64) | p value |
|--------------------------------|-------------------|---------------------|---------|
|                                | No. of patients (n) | Mean ± SD or no. (%) | Median (IQR) | No. of patients (n) | Mean ± SD or no. (%) | Median (IQR) |
| GGT (U/L)                      | 240               | 87.6 ± 113.7        | 54.0 (30.2-99.0) | 64               | 102.9 ± 100.6        | 68.5 (41.3-128.8) | 0.076   |
| Blood urea nitrogen (mmol/L)   | 240               | 8.2 ± 6.2           | 6.6 (4.4-9.7)    | 64               | 11.0 ± 8.1           | 9.2 (4.9-14.3)     | 0.005*  |
| Creatinine (μmol/L)            | 240               | 92.2 ± 79.9         | 69.1 (55.0-96.2) | 64               | 112.0 ± 94.0         | 87.3 (60.6-135.7)  | 0.012*  |
| Potassium (mmol/L)             | 240               | 3.9 ± 0.7           | 3.9 (3.4-4.3)    | 63               | 4.0 ± 0.8            | 4.0 (3.6-4.6)      | 0.370   |
| Sodium (mmol/L)                | 240               | 136.3 ± 6.6         | 137.0 (132.0-140.4) | 64             | 134.5 ± 7.8         | 135.3 (129.3-140.8) | 0.061   |
| Calcium (mmol/L)               | 231               | 2.2 ± 0.2           | 2.2 (2.1-2.3)    | 64               | 2.2 ± 0.3           | 2.2 (2.0-2.4)      | 0.477   |
| Ammonia (μmol/L)               | 162               | 59.8 ± 51.7         | 42.0 (27.8-79.3) | 36               | 87.2 ± 73.9         | 66.5 (28.8-116.3)  | 0.031*  |
| PT (second)                    | 240               | 21.9 ± 9.5          | 18.7 (15.4-25.6) | 64               | 27.2 ± 11.3         | 24.6 (18.1-34.7)   | <0.001* |
| APTT (second)                  | 240               | 55.5 ± 21.4         | 51.3 (38.7-69.3) | 64               | 65.6 ± 25.8         | 59.6 (48.8-83.7)   | 0.004*  |
| INR                            | 240               | 1.9 ± 0.9           | 1.6 (1.3-2.2)    | 64               | 2.3 ± 1.0           | 2.2 (1.6-2.8)      | <0.001* |
| Ascites (no/mild/moderate-severe) | 240             | 52/104/84           | 64               | 8/34/22          | 0.066               |
| Hepatic encephalopathy (grades I-II/grades III-IV) | 240 | 199/41             | 64               | 32/32            | 0.545               |
| Child-Pugh score               | 240               | 10.7 ± 2.0          | 11.0 (9.0-12.0)  | 64               | 12.0 ± 1.5          | 12.0 (11.0-13.0)   | <0.001* |
| Child-Pugh class (A/B/C)       | 240               | 5/61/174            | 64               | 0/3/61           | 0.958               |
| ALBI score                     | 240               | 1.2 ± 0.5           | -1.1 (-1.6-(-0.8)) | 64          | -0.9 ± 0.5          | -0.9 (-1.2-(-0.7)) | 0.002*  |
| ALBI grade (1/2/3)             | 240               | 1/86/153            | 64               | 0/13/51          | 0.557               |
| MELD score                     | 240               | 20.9 ± 8.3          | 19.0 (14.0-27.8) | 64               | 24.8 ± 8.2          | 24.5 (20.0-29.8)   | 0.001*  |
| MELD-Na score                  | 240               | 22.3 ± 8.4          | 22.0 (15.0-29.0) | 64               | 26.5 ± 8.0          | 26.0 (21.0-33.0)   | 0.001*  |
| NLR                            | 240               | 5.5 ± 5.5           | 3.7 (2.3-6.6)    | 64               | 9.7 ± 13.3          | 7.4 (3.4-11.1)     | <0.001* |

Abbreviations: AIH: autoimmune hepatitis; ALBI: albumin to bilirubin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; DBIL: direct bilirubin; DILI: drug-induced liver injury; GGT: gamma-glutamyl transpeptidase; HBV: hepatitis B virus; HCV: hepatitis C virus; IBIL: indirect bilirubin; IQR: interquartile range; INR: international normalized ratio; MELD: model for end-stage liver diseases; MELD-Na: model for end-stage liver diseases-sodium; NLR: neutrophil to lymphocyte ratio; PBC: primary biliary cholangitis; PT: prothrombin time; RBC: red blood count; SD: standard deviation; TBIL: total bilirubin; WBC: white blood count. Note: *p value < 0.05.
Table 2: Diagnostic accuracies of Child-Pugh, ALBI, MELD, MELD-Na, and NLR scores.

| Prognostic model | Area under the ROC curve | Criterion value | Sensitivity | Specificity | Positive LR | Negative LR | Positive PV | Negative PV | p value |
|------------------|--------------------------|-----------------|-------------|-------------|-------------|-------------|-------------|-------------|---------|
| The whole patients |
| Child-Pugh | 0.681 (95% CI: 0.626-0.733) | 10.0 | 79.7 | 46.3 | 1.5 | 0.4 | 28.3 | 89.5 | <0.0001* |
| ALBI | 0.615 (95% CI: 0.558-0.670) | -1.3 | 76.6 | 44.2 | 1.4 | 0.5 | 26.8 | 87.6 | 0.0030* |
| MELD | 0.630 (95% CI: 0.573-0.684) | 19.0 | 76.6 | 52.5 | 1.6 | 0.5 | 30.1 | 89.4 | 0.0005* |
| MELD-Na | 0.640 (95% CI: 0.583-0.694) | 20.0 | 81.3 | 45.8 | 1.5 | 0.4 | 28.6 | 90.2 | 0.0002* |
| NLR | 0.664 (95% CI: 0.608-0.717) | 7.2 | 53.1 | 79.2 | 2.6 | 0.6 | 40.5 | 86.4 | <0.0001* |
| ACLF subgroup |
| Child-Pugh | 0.621 (95% CI: 0.533-0.703) | 11.0 | 76.3 | 41.1 | 1.3 | 0.6 | 34.1 | 81.2 | 0.0165* |
| ALBI | 0.578 (95% CI: 0.489-0.663) | -1.3 | 89.5 | 28.4 | 1.3 | 0.4 | 33.3 | 87.1 | 0.1487 |
| MELD | 0.531 (95% CI: 0.443-0.618) | 27.0 | 65.8 | 51.6 | 1.4 | 0.7 | 35.2 | 79.0 | 0.5870 |
| MELD-Na | 0.500 (95% CI: 0.412-0.588) | 27.0 | 52.6 | 59.0 | 1.3 | 0.8 | 33.9 | 75.7 | 0.9963 |
| NLR | 0.701 (95% CI: 0.616-0.778) | 7.2 | 60.5 | 82.1 | 3.4 | 0.5 | 57.5 | 83.9 | 0.0003* |

Abbreviations: ACLF: acute-on-chronic liver failure; ALBI: albumin to bilirubin; CI: confidence interval; HE: hepatic encephalopathy; LR: likelihood ratio; MELD: model for end-stage liver diseases; MELD-Na: model for end-stage liver diseases-sodium; NLR: neutrophil to lymphocyte ratio; PV: predictive value; ROC: receiver operating characteristic. Note: *p value < 0.05.
grade III/IV was 231 and 73, respectively. The mean Child-Pugh, ALBI, MELD, MELD-Na, and NLR scores were 11.0 ± 2.0, −1.1 ± 0.5, 21.8 ± 8.4, 23.2 ± 8.5, and 6.4 ± 8.0, respectively. In-hospital deaths occurred in 64 patients (21.1%).

3.2. Variables Associated with In-Hospital Death. We compared the clinical characteristics between hospitalized survivors and nonsurvivors. Comparative data showed that white blood count (WBC), neutrophil, total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, ammonia, prothrombin time (PT), activated partial thromboplastin time (APTT), international normalized ratio (INR), Child-Pugh, ALBI, MELD, MELD-Na, and NLR scores were statistically different between survivors and nonsurvivors (Table 1). The significantly different characteristics between the two groups were included in the multivariate logistic regression models, which were performed to identify independent risk factors. We precluded DBIL, IBIL, PT, APTT, ammonia (106 patients lacked data of ammonia), and five prognostic models to avoid collinearity. Neutrophil and TBIL were found independently correlated with in-hospital mortality (Table S1).

3.3. Diagnostic Accuracies of Five Models in the Whole Patients. The AUCs of Child-Pugh, ALBI, MELD, MELD-Na, and NLR in the prediction of in-hospital death were 0.681 (95% CI: 0.626-0.733, \( p < 0.0001 \)), 0.615 (95% CI: 0.558-0.670, \( p = 0.003 \)), 0.630 (95% CI: 0.573-0.684, \( p = 0.0005 \)), 0.640 (95% CI: 0.583-0.694, \( p = 0.0002 \)), and 0.664 (95% CI: 0.608-0.717, \( p < 0.0001 \)), respectively (Table 2, Figure 1). The Child-Pugh score showed better predictive performance than the other four models. When compared among these five models, statistical difference was only found between Child-Pugh and ALBI (\( p = 0.031 \)). There were no differences among other comparisons.

3.4. Variables Associated with HE Severity. Deaths occurred in 32 of 231 patients in mild (grade I or II) HE and 32 of 76 patients in severe (grade III or IV) HE groups, respectively, which showed significant differences. Gender, age, vital signs, and etiologies of cirrhosis presented no statistically significant differences between the two groups. Blood routine tests including WBC, red blood count (RBC), and neutrophil were significantly different in comparison. As for the serum liver function tests, TBIL, IBIL, ALT, and AST were significantly different. Besides, significant differences were detected in BUN, ammonia, and patients manifesting with ascites between comparisons of the two groups.
| Variable | HE grade I or II ($n = 231$) | HE grade III or IV ($n = 73$) | $p$ value |
|----------|-----------------------------|-----------------------------|-----------|
| Gender (male, %) | 231 182 (78.8) | 73 60 (82.2) | 0.530 |
| Age (years) | 231 52:4±1 452:0 (44.0-60.0) | 73 51:6±1 373:0 (40.5-62.0) | 0.654 |
| Vital signs | | | |
| Systolic blood pressure (mmHg) | 231 117.1±16.7 116.0 (105.0-127.0) | 73 119.3±16.5 117.0 (104.5-133.0) | 0.310 |
| Diastolic blood pressure (mmHg) | 231 69.7±11.3 68.0 (63.0-75.0) | 73 70.1±11.5 67.0 (61.5-80.0) | 0.828 |
| Heart rate (b.p.m.) | 231 86.4±14.0 85.0 (78.0-93.0) | 73 89.1±15.1 88.0 (78.5-99.0) | 0.168 |
| Etiologies of liver diseases | | | |
| HBV | 153 (66.2) | 46 (63.0) | 0.585 |
| HCV | 4 (1.7) | 1 (1.4) | |
| Alcohol | 30 (13.0) | 14 (19.2) | |
| HBV+HCV | 1 (0.4) | 0 (0) | |
| HBV+alcohol | 7 (3.0) | 4 (5.5) | |
| HCV+alcohol | 3 (1.3) | 0 (0) | |
| DILI | 1 (0.4) | 0 (0) | |
| AIH | 2 (0.9) | 3 (4.1) | |
| PBC+AIH | 3 (1.3) | 0 (0) | |
| HBV+AIH | 1 (0.4) | 0 (0) | |
| HBV+DILI | 2 (0.9) | 0 (0) | |
| Unknown | 24 (10.4) | 5 (6.8) | |
| Laboratory tests | | | |
| WBC ($10^9$/L) | 231 7.2±5.1 5.8 (3.9-9.0) | 73 8.5±4.9 7.5 (4.9-10.3) | 0.008* |
| RBC ($10^12$/L) | 231 3.1±0.9 3.0 (2.5-3.6) | 73 3.3±1.0 3.2 (2.6-4.1) | 0.034* |
| Hemoglobin (g/L) | 230 99.6±26.2 97.0 (80.0-117.0) | 73 104.1±32.0 102.0 (80.0-131.0) | 0.271 |
| Platelet ($10^9$/L) | 230 81.7±53.3 66.0 (46.8-106.3) | 73 82.7±56.5 64.0 (40.0-122.0) | 0.730 |
| Neutrophil ($10^9$/L) | 231 5.2±4.5 3.7 (2.4-6.6) | 73 6.4±4.0 5.7 (3.1-8.8) | 0.004* |
| Lymphocyte ($10^9$/L) | 231 1.2±1.1 0.9 (0.7-1.5) | 73 1.2±0.9 1.0 (0.6-1.5) | 0.853 |
| TBIL (μmol/L) | 231 211.9±197.9 123.5 (44.0-371.5) | 73 270.9±218.1 260.0 (67.3-421.8) | 0.028* |
| DBIL (μmol/L) | 231 123.8±125.9 69.3 (18.3-231.3) | 73 151.1±129.2 146.0 (30.1-236.8) | 0.055 |
| IBIL (μmol/L) | 231 85.1±78.1 51.6 (22.9-137.0) | 73 119.6±106.0 93.0 (34.1-180.8) | 0.015* |
| Albumin (g/L) | 231 29.7±4.9 29.8 (26.4-32.5) | 73 30.0±5.5 29.7 (25.8-34.1) | 0.705 |
| ALT (U/L) | 231 176.8±397.7 42.1 (23.9-100.6) | 73 309.9±543.4 80.3 (33.8-365.8) | 0.002* |
| AST (U/L) | 218 199.9±406.8 68.6 (40.9-157.0) | 67 333.2±511.6 112.1 (49.3-338.8) | 0.015* |
| ALP (U/L) | 231 143.7±79.7 123.0 (95.0-171.0) | 73 138.0±76.2 120.0 (80.5-179.5) | 0.589 |
| Variable                      | No. of patients (n) | HE grade I or II (n = 231) | HE grade III or IV (n = 73) | p value |
|-------------------------------|---------------------|----------------------------|-----------------------------|---------|
|                               |                     | Mean ± SD or no. (%)       | Median (IQR)                |         |
| GGT (U/L)                     | 231                 | 85.3 ± 95.9                | 57.0 (32.0-102.0)           |         |
| Blood urea nitrogen (mmol/L) | 231                 | 8.3 ± 5.9                  | 6.6 (4.4-9.8)               |         |
| Creatinine (μmol/L)           | 231                 | 93.3 ± 81.5                | 70.0 (55.0-100.2)           |         |
| Potassium (mmol/L)            | 223                 | 3.9 ± 0.7                  | 3.9 (3.4-4.3)               |         |
| Sodium (mmol/L)               | 231                 | 136.0 ± 6.6                | 136.0 (131.7-140.0)         |         |
| Calcium (mmol/L)              | 223                 | 2.2 ± 0.2                  | 2.2 (2.1-2.3)               |         |
| Ammonia (μmol/L)              | 145                 | 56.3 ± 46.5                | 41.0 (28.0-75.5)            |         |
| PT (second)                   | 231                 | 22.4 ± 9.7                 | 19.0 (15.5-26.8)            |         |
| APTT (second)                 | 231                 | 57.4 ± 23.3                | 52.3 (41.0-70.8)            |         |
| INR                           | 231                 | 1.9 ± 0.9                  | 1.6 (1.3-2.3)               |         |
| Ascites (no/mild/moderate-severe) | 231     | 50/109/72                   | 10/29/34                    | 0.015*  |
| Child-Pugh score              | 231                 | 10.6 ± 1.9                 | 11.0 (9.0-12.0)             |         |
| Child-Pugh class (A/B/C)      | 231                 | 5/59/167                   | 0/5/68                      | <0.001* |
| ALBI score                    | 231                 | -1.2 ± 0.5                 | -1.1 (-1.5- (-0.7))         | 0.338   |
| ALBI grade (1/2/3)            | 231                 | 1/82/148                   | 0/17/56                     | 0.044*  |
| MELD score                    | 231                 | 21.2 ± 8.4                 | 19.0 (14.0-27.0)            | 0.043*  |
| MELD-Na score                 | 231                 | 22.7 ± 8.5                 | 22.0 (16.0-29.0)            | 0.069   |
| NLR                           | 231                 | 6.0 ± 7.9                  | 3.9 (2.4-7.0)               | 0.015*  |
| In-hospital mortality         | 231                 | 32 (13.9)                  | 32 (43.8)                   | <0.001* |

Abbreviations: AIH: autoimmune hepatitis; ALBI: albumin to bilirubin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; DBIL: direct bilirubin; DILI: drug-induced liver injury; GGT: gamma-glutamyl transpeptidase; HBV: hepatitis B virus; HCV: hepatitis C virus; HE: hepatic encephalopathy; IBIL: indirect bilirubin; IQR: interquartile range; INR: international normalized ratio; MELD: model for end-stage liver diseases; MELD-Na: model for end-stage liver diseases-sodium; NLR: neutrophil to lymphocyte ratio; PBC: primary biliary cholangitis; PT: prothrombin time; RBC: red blood count; SD: standard deviation; TBIL: total bilirubin; WBC: white blood count. Note: *p value < 0.05.
| Variable                        | Patients with ACLF (n = 133) | Patients without ACLF (n = 171) | p value |
|--------------------------------|-----------------------------|--------------------------------|---------|
|                                | No. of patients (n) | Mean ± SD or no. (%) | Median (IQR) | No. of patients (n) | Mean ± SD or no. (%) | Median (IQR) |         |
| Gender (male, %)               | 133                         | 112 (84.2)                       |        | 171                        | 130 (76.0)                       |        | 0.953   |
| Age (years)                    | 133                         | 49.8 ± 11.5 (41.0-56.0)          | 50.0     | 171                        | 54.0 ± 11.9 (45.0-62.0)          | 53.0     | 0.002*  |
| Vital signs                    |                             |                                |         |                            |                                |         |         |
| Systolic blood pressure (mmHg) | 133                         | 117.5 ± 15.5 (105.5-127.0)      | 116.0    | 171                        | 117.7 ± 17.5 (105.0-129.0)      | 115.0    | 0.954   |
| Diastolic blood pressure (mmHg)| 133                         | 70.6 ± 11.1 (63.0-79.0)         | 68.0     | 171                        | 69.2 ± 11.5 (61.0-75.0)         | 68.0     | 0.296   |
| Heart rate (b.p.m.)            | 133                         | 87.1 ± 12.8 (78.0-92.5)         | 86.0     | 171                        | 87.0 ± 15.4 (77.0-96.0)         | 86.0     | 0.621   |
| Etiologies of liver diseases, n (%) | 133                       |                                |         |                            |                                |         | 0.061   |
| HBV                            | 116 (87.2)                   |                                |        | 83 (48.5)                   |                                |        |         |
| HCV                            | 0 (0)                        |                                |        | 5 (2.9)                     |                                |        |         |
| Alcohol                        | 5 (3.8)                      |                                |        | 39 (22.8)                   |                                |        |         |
| HBV+HCV                        | 0 (0)                        |                                |        | 1 (0.6)                     |                                |        |         |
| HBV+alcohol                    | 6 (4.5)                      |                                |        | 5 (2.9)                     |                                |        |         |
| HCV+alcohol                    | 0 (0)                        |                                |        | 3 (1.8)                     |                                |        |         |
| DILI                            | 0 (0)                        |                                |        | 1 (0.6)                     |                                |        |         |
| AIH                            | 2 (1.5)                      |                                |        | 3 (1.8)                     |                                |        |         |
| PBC+AIH                        | 1 (0.8)                      |                                |        | 2 (1.2)                     |                                |        |         |
| HBV+AIH                        | 1 (0.8)                      |                                |        | 0 (0)                       |                                |        |         |
| HBV+DILI                       | 0 (0)                        |                                |        | 2 (1.2)                     |                                |        |         |
| Unknown                        | 2 (1.5)                      |                                |        | 27 (15.8)                   |                                |        |         |
| Laboratory tests               |                             |                                |         |                            |                                |         |         |
| WBC (10^12/L)                  | 133                         | 8.5 ± 5.6 (5.2-10.1)            | 7.5      | 171                        | 6.7 ± 4.5 (3.6-8.6)            | 5.3      | <0.001* |
| RBC (10^12/L)                  | 133                         | 3.4 ± 1.0 (2.7-4.1)             | 3.2      | 171                        | 3.0 ± 0.8 (2.4-3.4)            | 2.8      | <0.001* |
| Hemoglobin (g/L)               | 133                         | 110.2 ± 27.0 (92.0-133.0)       | 108.0    | 170                        | 93.3 ± 26.0 (75.0-109.0)       | 90.0     | <0.001* |
| Platelet (10^9/L)              | 133                         | 81.5 ± 49.0 (46.5-113.5)        | 66.0     | 170                        | 82.2 ± 57.7 (44.8-105.0)       | 66.0     | 0.747   |
| Neutrophil (10^12/L)           | 133                         | 6.4 ± 5.1 (3.3-8.1)             | 5.4      | 171                        | 4.8 ± 3.7 (2.2-6.3)            | 3.4      | <0.001* |
| Lymphocyte (10^12/L)           | 133                         | 1.3 ± 1.1 (0.8-1.6)             | 1.0      | 171                        | 1.1 ± 1.1 (0.5-1.4)            | 0.8      | 0.001*  |
| TBIL (μmol/L)                  | 133                         | 360.3 ± 187.6 (222.8-507.8)     | 360.6    | 171                        | 121.8 ± 148.0 (58.5-126.8)     | 58.5     | <0.001* |
| DBIL (μmol/L)                  | 133                         | 251.1 ± 116.6 (124.0-300.3)     | 216.1    | 170                        | 64.8 ± 90.6 (12.5-70.5)        | 24.8     | <0.001* |
| IBIL (μmol/L)                  | 133                         | 140.1 ± 88.3 (75.6-197.4)       | 121.8    | 170                        | 57.3 ± 65.8 (33.1-198.8)       | 33.1     | <0.001* |
| Albumin (g/L)                  | 133                         | 30.4 ± 4.9 (27.2-33.5)          | 30.1     | 171                        | 29.3 ± 5.1 (25.8-32.6)         | 29.6     | 0.075   |
| ALT (U/L)                      | 133                         | 320.1 ± 515.4 (49.6-330.7)      | 95.0     | 171                        | 122.1 ± 348.3 (30.1-222.6)     | 30.1     | <0.001* |
| AST (U/L)                      | 124                         | 332.4 ± 517.1 (75.7-347.7)      | 136.4    | 161                        | 153.4 ± 344.2 (50.0-360.9)     | 50.0     | <0.001* |
| ALP (U/L)                      | 133                         | 144.4 ± 70.2 (101.0-166.0)      | 123.0    | 171                        | 140.7 ± 85.0 (87.0-176.0)      | 121.0    | 0.279   |
| Variable                  | Patients with ACLF (n = 133) | Patients without ACLF (n = 171) | p value |
|---------------------------|------------------------------|--------------------------------|---------|
|                           | No. of patients (n) | Mean ± SD or no. (%) | Median (IQR) | No. of patients (n) | Mean ± SD or no. (%) | Median (IQR) |
| GGT (U/L)                 | 133 | 91.5 ± 85.7 | 67.0 (40.5-107.9) | 171 | 90.4 ± 127.6 | 49.0 (23.0-102.0) | 0.001* |
| Blood urea nitrogen (mmol/L) | 133 | 7.9 ± 5.7 | 6.1 (4.0-9.7) | 171 | 9.5 ± 7.4 | 7.0 (4.8-11.9) | 0.011* |
| Creatinine (μmol/L)       | 133 | 91.4 ± 64.0 | 68.8 (54.0-97.2) | 171 | 100.2 ± 95.6 | 71.3 (58.1-102.0) | 0.302 |
| Potassium (mmol/L)        | 133 | 4.0 ± 0.7 | 4.0 (3.5-4.4) | 170 | 4.0 ± 0.7 | 3.9 (3.4-4.4) | 0.960 |
| Sodium (mmol/L)           | 133 | 134.9 ± 6.8 | 136.0 (130.4-139.9) | 171 | 136.6 ± 6.9 | 137.0 (132.5-141.0) | 0.028* |
| Calcium (mmol/L)          | 128 | 2.2 ± 0.3 | 2.2 (2.1-2.4) | 166 | 2.2 ± 0.3 | 2.1 (2.0-2.3) | 0.158 |
| Ammonia (μmol/L)          | 79 | 69.8 ± 65.7 | 46.0 (28.0-92.0) | 119 | 61.4 ± 50.8 | 46.0 (28.0-81.0) | 0.799 |
| PT (second)               | 133 | 28.6 ± 10.4 | 26.4 (21.5-34.8) | 171 | 18.7 ± 7.4 | 16.6 (14.7-19.5) | <0.001* |
| APTT (second)             | 133 | 68.6 ± 21.1 | 64.0 (52.3-82.7) | 171 | 49.2 ± 20.2 | 45.4 (34.1-56.7) | <0.001* |
| INR                       | 133 | 2.5 ± 0.9 | 2.2 (1.8-3.0) | 171 | 1.6 ± 0.6 | 1.4 (1.3-1.7) | <0.001* |
| Ascites (no/mild/moderate-severe) | 133 | 15/70/48 | 171 | 45/68/58 | 0.569 |
| Hepatic encephalopathy    | 133 | 98/35 | 171 | 133/38 | 0.635 |
| (grades I-II/grades III-IV) | 133 | 11.9 ± 1.6 | 12.0 (11.0-13.0) | 171 | 10.3 ± 1.9 | 10.0 (9.0-12.0) | <0.001* |
| Child-Pugh score          | 133 | 1/111/121 | 171 | 4/53/114 | 0.209 |
| Child-Pugh class (A/B/C)  | 133 | -1.0 ± 0.5 | -0.9 (-1.2-(-0.7)) | 171 | -1.3 ± 0.5 | -1.3 (-1.7-(-0.9)) | <0.001* |
| ALBI score                | 133 | 1/21/111 | 171 | 0/78/93 | 0.694 |
| ALBI grade (1/2/3)        | 133 | 26.9 ± 6.7 | 27.0 (23.0-31.0) | 171 | 17.7 ± 7.3 | 16.0 (13.0-21.0) | <0.001* |
| MELD score                | 133 | 28.2 ± 6.7 | 29.0 (24.0-33.0) | 171 | 19.3 ± 7.7 | 18.0 (14.0-23.0) | <0.001* |
| MELD-Na score             | 133 | 6.6 ± 8.9 | 4.7 (2.5-8.0) | 171 | 6.2 ± 7.2 | 3.7 (2.4-7.9) | 0.182 |
| NLR                       | 133 | 38 (28.6) | 171 | 26 (15.2) | 0.878 |

Abbreviations: ACLF: acute-on-chronic liver failure; AIH: autoimmune hepatitis; ALBI: albumin to bilirubin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AST: aspartate aminotransferase; DBIL: direct bilirubin; DILI: drug-induced liver injury; GGT: gamma-glutamyl transpeptidase; HBV: hepatitis B virus; HCV: hepatitis C virus; IBIL: indirect bilirubin; IQR: interquartile range; INR: international normalized ratio; MELD: model for end-stage liver diseases; MELD-Na: model for end-stage liver diseases-sodium; NLR: neutrophil to lymphocyte ratio; PBC: primary biliary cholangitis; PT: prothrombin time; RBC: red blood count; SD: standard deviation; TBIL: total bilirubin; WBC: white blood count. Note: *p value < 0.05.
Table 3). Statistical differences were observed in the Child-Pugh class/score \((p < 0.001)\), ALBI grade \((p = 0.044)\), MELD score \((p = 0.043)\), and NLR scores \((p = 0.015)\) between the two groups. In the multivariate logistic regression models, only ALT and BUN were significantly associated with HE severity (Table S2).

3.5. Variables Associated with ACLF Incidence. The characteristics of patients with and without ACLF were shown in Table 4. A total of 133 patients suffered from ACLF, and 171 patients were exempted from ACLF. The mortality was 28.9% and 15.2%, respectively. Higher levels of WBC, RBC, hemoglobin, neutrophil, and lymphocyte were observed in patients with ACLF in comparison to those without. The ACLF group also exhibited more severe liver dysfunction (higher levels of liver serological indexes and prognostic scores). Multivariate regression analysis revealed that hemoglobin, TBIL, BUN, and INR were independent variables concerning ACLF occurrence (Table S3).

3.6. Diagnostic Accuracies of Five Scores in the ACLF Subgroup. The AUCs of Child-Pugh, ALBI, MELD, MELD-Na, and NLR to predict in-hospital death in the ACLF group were 0.621 (95% CI: 0.533-0.703, \(p = 0.0165\)), 0.578 (95% CI: 0.489-0.663, \(p = 0.1487\)), 0.531 (95% CI: 0.443-0.618, \(p = 0.5870\)), 0.500 (95% CI: 0.412-0.588, \(p = 0.9963\)), and 0.701 (95% CI: 0.616-0.778, \(p = 0.0003\)), respectively (Table 2, Figure 2). NLR performed superior discriminative ability to the other four scores in the ACLF subgroup. When compared among these five scores, statistical difference was found between NLR and MELD-Na \((p = 0.0309)\). No significant differences were observed among other comparisons.

4. Discussion

This retrospective study is aimed at detecting the associated risk factors and selecting suitable prognostic assessment tools of cirrhotic patients presenting with HE. Several findings in our present research need to be addressed.

Firstly, of the whole population, the Child-Pugh score had superior discriminative ability to other scores in assessing in-hospital mortality. It is well known that the Child-Pugh score is widely used as the criterion for the evaluation of liver function in patients with underlying liver diseases in clinical settings. HE grade is one of the indicators that is composed of Child-Pugh calculation, which may contribute to the superiority. This finding is consistent with previous relevant researches. The study conducted by Bhanji et al.
revealed that the Child-Pugh class of patients with HE was higher than that of those without [16]. In a prospective study, Duah et al. found that Child-Pugh score elevation was independently associated with the incidence of HE in hospitalized cirrhotic patients [17]. Tag et al. investigated the predictive performances of noninvasive models in cirrhotic patients with HE who were admitted to ICU, followed by chronic liver failure-sequential organ failure assessment (CLIF-SOFA), APACHE II, and Child-Pugh score, which showed a better discriminative value of prognosis than MELD [18]. Patients admitted to ICU were under severe conditions, mostly complicated with organ failures or comorbidities, which might account for the advantages of models evaluating organ failures or serious conditions. Liu et al. led a retrospective study that analyzed cirrhotic patients who suffered from transjugular intrahepatic porto-systemic shunt (TIPS). Child-Pugh was identified as an independent risk indicator of the incidence of OHE after TIPS. In this study, a newly established scale incorporating Child-Pugh and spleen volume was proposed as a reliable predictor [19].

Secondly, in our ACLF subgroup, NLR exhibited better predictive accuracy than other scores in predicting hospital death. ACLF is an acute and fatal syndrome that mainly affects patients with preexisting chronic liver diseases. Inflammation is considered one of the precipitating factors and participates in the progression of ACLF, and immune dysfunction is also observed in ACLF patients, which may explain the superiority of NLR; the indicator represents inflammation and immunity. Bernsmeier et al. conducted a multicenter study enrolling cirrhotic patients who developed acute decompensation and ACLF. NLR and monocyte-lymphocyte ratio were independent indicators of in-hospital death [20]. Miao et al. performed a single-center retrospective study to propose that elevated NLR was independently correlated with HBV-related ACLF poor outcome, and its combination with the chronic liver failure-organ failure assessment (CLIF-OF) score could be applied for better prediction of the prognosis of patients [21]. Liu et al. suggested that NLR could be used as a prognostic biomarker in the prediction of 8-week mortality of HBV-related ACLF [22]. A study by Lin et al. also confirmed the effectiveness of NLR for valuing long-term mortality in ACLF populations [23].

Thirdly, serum indicators including WBC, neutrophil, TBIL, ALT, AST, and BUN were observed to be significantly different between comparisons of all groups. In multivariate analyses, neutrophil and TBIL were the independent risk factors in association with in-hospital mortality. BUN was a risk biomarker concerning HE severity and ACLF incidence. The results indicate that regardless of hepatic, renal, and coagulation deterioration, inflammation may play a vital role in the development of HE and ACLF in cirrhotic patients. Recent studies suggest that other than ammonia, inflammation also involves the pathophysiology and progression of HE. Our study strengthens this viewpoint. Moreover, BUN may be a reliable predictor of outcome in these patients.

Fourthly, although the wide application of antiviral medications increased the eradication of hepatitis B virus (HBV) and hepatitis C virus (HCV), HBV infection is still prevailing in cirrhotic patients in our study.

The occurrence and development of HE are highly associated with impairment of liver function, portal hypertension, skeletal muscle, nutrition, and gut microbiome. Therefore, sarcopenia, myosteatosis, and fried frailty index have been testified effectively in the prediction of HE [24–26]. The brief antisocial behavior scale (BABS), which consists of bilirubin, albumin, beta-blocker, and statin use, is also involved in the development of OHE [27]. CHE has a higher risk for the progression of OHE; thus, early identification and diagnosis of CHE are important for reducing recurrence and mortality related to HE. Tests for CHE are mainly aimed at evaluating psychology and neurophysiology, which include the psychometric hepatic encephalopathy score (PHES), critical flicker frequency (CFF), animal naming test (ANT), Epworth sleepiness scale (ESS), continuous reaction time (CRT), inhibitory control test (ICT), and electrophrophology [28]. Combined utilization of risk factors and the above evaluation tools may prevent the progression of OHE and improve survival and quality of life for HE patients.

There are some limitations of our study. Firstly, our data are retrospectively gathered that the absence of laboratory indicators may induce bias of certain results. Secondly, ammonia is a serum biomarker prevalent in HE of cirrhosis, whereas it is not commonly detected in our study. Thirdly, none of the patients was diagnosed with nonalcoholic fatty liver diseases. This phenomenon may be due to the fact that our eligible patients are with severely decompensated cirrhosis. Thus liver biopsy, the golden standard of diagnosis, carries a high risk. Admissions of patients to the hospital at an advanced stage may be another reason. Lastly, we could not explore the predictive abilities of models in the assessment of long-term outcomes.

Noninvasive prognostic tools have been investigated by quite a few studies for the assessment of the severity and outcomes of liver diseases and the incidence of liver-related complications. Simple and accurate biomarkers focus on liver dysfunction, malnutrition, and inflammation, and neuropsychiatric indexes should be proposed by well-conducted studies, which might provide long-term information during follow-up and guide clinicians to make prompt and correct strategies for HE patients. More investigators should do some efforts to establish ideally practical prognosticators, which will better stratify the high-risk patients, therefore improving the outcome and diminishing the mortality in clinical practice.

5. Conclusions

This present study provides clinical characteristics and related risk factors of cirrhotic patients exhibiting HE with or without ACLF. WBC, neutrophil, BUN, and serum liver function tests are strongly associated with outcomes of HE patients. This study also suggests that the Child-Pugh score could be applied for HE patients in the prediction of in-hospital death. NLR may be an effective model for the assessment of outcomes in patients complicated with ACLF.
Furthermore, prospective studies are aimed at establishing new models to predict outcomes in HE patients that should consider BUN a prognostic biomarker.

**Abbreviations**

| Abbreviation | Description                             |
|--------------|-----------------------------------------|
| HE           | Hepatic encephalopathy                  |
| CHE          | Covert hepatic encephalopathy           |
| OHE          | Overt hepatic encephalopathy            |
| ACLF         | Acute-on-chronic liver failure           |
| MELD         | The model for end-stage liver disease    |
| MELD-Na      | The model for end-stage liver disease-sodium |
| ALBI         | Albumin-bilirubin                        |
| HCC          | Hepatocellular carcinoma                |
| NLR          | Neutrophil to lymphocyte ratio           |
| ICU          | Intensive care unit                      |
| APACHE II    | Acute Physiology and Chronic Health Evaluation II |
| SD           | Standard deviation                       |
| ROC          | The receiver operating characteristic    |
| AUC          | The areas under the ROC curve            |
| CI           | Confidence interval                      |
| LR           | Likelihood ratio                         |
| PV           | Predictive value                         |
| WBC          | White blood count                        |
| TBL          | Total bilirubin                          |
| DBIL         | Direct bilirubin                         |
| IBIL         | Indirect bilirubin                       |
| ALT          | Alanine aminotransferase                 |
| AST          | Aspartate aminotransferase               |
| BUN          | Blood urea nitrogen                      |
| PT           | Prothrombin time                         |
| APTT         | Activated partial thromboplastin time     |
| INR          | International normalized ratio            |
| CLIF-SOFA    | Chronic liver failure-sequential organ failure assessment |
| TIPS         | Transjugular intrahepatic portosystemic shunt |
| CLIF-OE      | The chronic liver failure-organ failure   |
| HBV          | Hepatitis B virus                        |
| HCV          | Hepatitis C virus                        |
| BABS         | Brief antisocial behavior scale           |
| PHES         | Psychometric hepatic encephalopathy score |
| CFF          | Critical flicker frequency               |
| ANT          | Animal naming test                       |
| ESS          | Epworth sleepiness scale                 |
| CRT          | Continuous reaction time                 |
| ICT          | Inhibitory control test                  |

**Data Availability**

We retrospectively collected medical records of patients admitted to our hospital. Our underlying data are not freely available for the ethical policies of our hospital.

**Conflicts of Interest**

All authors have no conflict of interest to declare.

**Authors’ Contributions**

YP designed the study, searched and selected the literature, analyzed and interpreted the data, and drafted the manuscript. QW, HZ, and HW collected the data. ZW and YL analyzed the data. JC revised the manuscript and supervised the study. All authors approved the submission. Ying Peng and Qinglin Wei contributed equally to this study.

**Acknowledgments**

This study is funded by the National Natural Science Foundation for Excellent Young Scholars of China (81922012) and Third Military Medical University Science Foundation of Outstanding Youth (XZ-2019-505-001).

**Supplementary Materials**

Supplementary 1. Table S1 Logistic regression analysis of risk factors for in-hospital death.

Supplementary 2. Table S2 Logistic regression analysis of risk factors for hepatic encephalopathy severity.

Supplementary 3. Table S3 Logistic regression analysis of risk factors for acute-on-chronic liver failure.

**References**

[1] J. S. Bajaj, J. Cordoba, K. D. Mullen et al., “Review article: the design of clinical trials in hepatic encephalopathy—an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement,” *Alimentary Pharmacology & Therapeutics*, vol. 33, no. 7, pp. 739–747, 2011.

[2] P. Ferenci, A. Lockwood, K. Mullen, R. Tarter, K. Weissborn, and A. T. Blei, “Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998,” *Hepatology*, vol. 35, no. 3, pp. 716–721, 2002.

[3] J. Cordoba, M. Ventura-Cots, M. Simón-Talero et al., “Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF),” *Journal of Hepatology*, vol. 60, no. 2, pp. 275–281, 2014.

[4] R. Jalan, R. Moreau, P. S. Kamath, and V. Arroyo, “Acute-on-chronic liver failure: a distinct clinical condition,” *Seminars in Liver Disease*, vol. 36, pp. 107–108, 2016.

[5] S. W. Biggins, W. R. Kim, N. A. Terrault et al., “Evidence-based incorporation of serum sodium concentration into MELD,” *Gastroenterology*, vol. 130, no. 6, pp. 1652–1660, 2006.

[6] K. Fujita, K. Oura, H. Yoneyama et al., “Albumin-bilirubin score indicates liver fibrosis staging and prognosis in patients with chronic hepatitis C,” *Hepatology Research*, vol. 49, no. 7, pp. 731–742, 2019.

[7] P. J. Johnson, S. Berhane, C. Kagebayashi et al., “Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade,” *Journal of Clinical Oncology*, vol. 33, no. 6, pp. 550–558, 2015.

[8] W. Zhang, C. Liu, Y. Tan et al., “Albumin-bilirubin score for predicting post-transplant complications following adult-to-
adult living donor liver transplantation,” *Annals of Transplantation*, vol. 23, pp. 639–646, 2018.

[9] T. Tada, T. Kumada, A. Hiraoka et al., “Neutrophil-to-lymphocyte ratio is associated with survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib,” *Liver International*, vol. 40, no. 4, pp. 968–976, 2020.

[10] Z. J. Xiang, T. Hu, Y. Wang, H. Wang, L. Xu, and N. Cui, “Neutrophil-lymphocyte ratio (NLR) was associated with prognosis and immunomodulatory in patients with pancreatic ductal adenocarcinoma (PDAC),” *Bioscience Reports*, vol. 40, no. 6, 2020.

[11] W. Han, Y. Wang, S. Fang et al., “Associations between the neutrophil-to-lymphocyte ratio and diabetic complications in adults with diabetes: a cross-sectional study,” *Journal of Diabetes Research*, vol. 2020, pp. 1–9, 2020.

[12] Z. Benhaddouch, K. Abidi, M. Naoufel, R. Abouqal, and A. A. Zeggwagh, “Mortality and prognostic factors of the cirrhotic patients with hepatic encephalopathy admitted to medical intensive care unit,” *Annales Françaises d’Anesthésie et de Réanimation*, vol. 26, no. 6, pp. 490–495, 2007.

[13] R. N. Pugh, I. M. Murray-Lyon, J. L. Dawson, M. C. Pietroni, and R. Williams, “Transsection of the oesophagus for bleeding oesophageal varices,” *The British Journal of Surgery*, vol. 60, no. 8, pp. 646–649, 1973.

[14] P. S. Kamath and W. R. Kim, “Advanced Liver Disease Study G. The model for end-stage liver disease (MELD),” *Hepatology*, vol. 45, pp. 797–805, 2007.

[15] R. Zahorec, “Ratio of neutrophil to lymphocyte counts–rapid and simple parameter of systemic inflammation and stress in critically ill,” *Bratislavské Lekárske Listy*, vol. 102, pp. 5–14, 2001.

[16] R. A. Bhanji, C. Moctezuma-Velazquez, A. Duarte-Rojo et al., “Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis,” *Hepatology International*, vol. 12, no. 4, pp. 377–386, 2018.

[17] A. Duah, A. Agyei-Nkansah, F. Osei-Poku, F. Duah, D. Ampofo-Boobi, and B. Peprah, “The prevalence, predictors, and in-hospital mortality of hepatic encephalopathy in patients with liver cirrhosis admitted at St. Dominic Hospital in Akwata, Ghana,” *Canadian Journal of Gastroenterology and Hepatology*, K. M. Peltckian, Ed., vol. 2020, pp. 8 pages, 2020.

[18] A. Tas, M. S. Yalcin, B. Saritas, and B. Kara, “Comparison of prognostic systems in cirrhotic patients with hepatic encephalopathy,” *Turk J Med Sci*, vol. 48, pp. 543–547, 2018.

[19] J. Liu, C. Zhou, Y. Wang et al., “The combination of Child-Pugh score and quantitative CT-based spleen volume could predict the risk of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt creation,” *Abdom Radiol (NY)*, vol. 46, no. 7, pp. 3464–3470, 2021.

[20] C. Bernsmeier, A. Cavazza, E. M. Fatourou et al., “Leucocyte ratios are biomarkers of mortality in patients with acute decompensation of cirrhosis and acute-on-chronic liver failure,” *Alimentary Pharmacology & Therapeutics*, vol. 52, no. 5, pp. 855–865, 2020.

[21] J. Miao, L. Guo, L. Wang et al., “Study on the application value of MELD-Na, CLIF-C OFs, COSSH-ACLFs and NLR scoring systems in patients with hepatitis B virus related acute-on-chronic liver failure,” *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*, vol. 32, no. 12, pp. 1496–1501, 2020.