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Nomogram prediction of individual prognosis of patients with acute-on-chronic hepatitis B liver failure

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ABSTRACT

Background: The current definitions and etiologies of acute-on-chronic liver failure (ACLF) are clearly very different between East and West.
Aims: This study aimed to develop an effective prognostic nomogram for acute-on-chronic hepatitis B liver failure (ACHBLF) as defined by the Asia Pacific Association for the Study of the Liver (APASL).
Methods: The nomogram was based on a retrospective study of 573 patients with ACHBLF, defined according to the APASL, at the Beijing Ditan Hospital. The results were validated using a bootstrapped approach to correct for bias in two external cohorts, including an APASL ACHBLF cohort (10 hospitals, N = 329) and an EASL-CLIF ACHBLF cohort (Renji Hospital, N = 300).
Results: Multivariate analysis of the derivation cohort for survival analysis helped identify the independent factors as age, total bilirubin, albumin, international normalized ratio, and hepatic encephalopathy, which were included in the nomogram. The predictive value of nomogram was the strongest compared with CLIF-C ACLF, MELD and MELD-Na and similar to COSSH-ACLF in both the derivation and prospective validation cohorts with APASL ACHBLF, but the CLIF-C ACLF was better in the EASL-CLIF ACHBLF cohort.
Conclusions: The proposed nomogram could accurately estimate individualized risk for the short-term mortality of patients with ACHBLF as defined by APASL.

1. Introduction

In recent years, acute-on-chronic liver failure (ACLF) has been increasingly recognized as a specific clinical entity in patients with acute deterioration of diagnosed or undiagnosed chronic liver disease [1]. Because no universally accepted, evidence-based diagnostic criteria for ACLF are available, the current definitions of ACLF differ greatly from each other. In the East, the Asian Pacific Association for the Study of the Liver (APASL) provided the first consensus definition on ACLF in 2009 [1,2], which was updated in 2014. In the West, the European Association for the Study of the Liver-

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Chronic Liver Failure (EASL-CLIF) Consortium recently proposed novel diagnostic criteria for ACLF based on a large prospective CLIF Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study in 2013 [3,4]. The main difference is that the EASL-CLIF emphasizes established cirrhosis and single or multiple organ failure, whereas the APASL focuses on acute deterioration of preexisting chronic liver diseases, such as chronic hepatitis and/or cirrhosis.

Currently, several known models, including the Model for End-stage Liver Disease (MELD) [5] and MELD-sodium (MELD-Na) scores [6], were used to aid in decision-making regarding patients with liver dysfunction/failure for either medical treatment or liver transplantation. Recently, the CANONIC study proposed a specific prognostic score for ACLF (CLIF-C ACLFs), which was superior to the MELD MELD-Na, and Child–Turcotte–Pugh (CTP) scores in predicting mortality [7]. However, the current prognostic models were mainly established on the basis of alcohol-abuse and/or hepatitis C virus (HCV) infection population and consequently have a controversial predictive accuracy for acute-on-chronic hepatitis B liver failure (ACHBLF) [8]. Therefore, the Chinese group on the study of severe hepatitis B (COSSH) developed the Cox regression model, COSSH-ACLF prognostic score, for patients with ACHBLF based on a new developed criteria [9].

Nomograms are graphical calculating scales of predictive statistical models to optimize predictive accuracy of individuals, and they have been demonstrated to provide more precise prediction over the traditional scoring systems for various diseases [10–13]. The current study was aimed to compare the APASL and EASL-CLIF definitions of ACHBLF with regard to patient characteristics and short-term mortality. Additionally, we developed a new prognostic nomogram model to predict individual risk of death in patients with ACHBLF, and compared it with other prognostic models.

2. Materials and methods

2.1. Derivation cohort

From January 2003 to May 2016, a total of 2532 patients with chronic hepatitis B (CHB), hospitalized for an acute deterioration of liver function, were screened, and 573 patients were diagnosed with APASL ACHBLF at admission, or within 28 days after admission at Beijing Ditan Hospital (Beijing, China), Capital Medical University. The remaining 1959 patients were excluded because of the following reasons: hepatocellular carcinoma or other liver malignancy; other organ malignancies that could affect outcomes; hepatitis A, C, D, or E-virus infection; other viral infections, including cytomegalovirus, human immunodeficiency virus co-infection; liver decompensated cirrhosis; liver transplantation; autoimmune liver disease; severe chronic extrahepatic disease; pregnancy; or failure to meet the APASL criteria for ACLF. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of Beijing Ditan Hospital. Owing to the retrospective nature of the study, written informed consent could not be obtained from all the patients. Patient records and information were anonymized and de-identified prior to analysis.

2.2. External validation cohort

To examine the generalizability of the model, a prospective cohort of 329 patients with ACHBLF, satisfying APASL criteria, were enrolled at 10 centers from September 2012 to September 2013. The study protocol was designed in accordance with the guidelines outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the 10 hospitals. Written informed consent was obtained from patients or their representatives.

Additionally, 890 hepatitis B virus (HBV) cirrhotic patients with acute decompensation were screened retrospectively in a single tertiary hospital (Renji Hospital) in Shanghai, and 300 patients with EASL-CLIF ACHBLF were enrolled between January 2005 and December 2010 for model external validation. Patients were included according to the inclusion criteria, and sufficient data to score all the variables in the established nomogram was required. This study was approved by the Ethics Committee of the Renji Hospital, Shanghai Jiaotong University School of Medicine.

2.3. Data collection

Data were collected for patient demographics, laboratory variables, precipitating events (HBV reactivation, bacterial infection, active alcoholism, gastrointestinal hemorrhage, hepatotoxic drugs, surgery), complications (hyponatremia, spontaneous bacterial peritonitis, hepatic encephalopathy [HE], hepatorenal syndrome), and organ failure (liver, kidney, brain, coagulation, circulatory, respiratory), and were obtained from patient medical records or the hospital database at the time of HBV ACLF diagnosis and during hospitalization. The reactivation of HBV was diagnosed based on an acute increase in HBV DNA and alanine aminotransferase (ALT) levels in patients on continuous treatment with nucleotide analogs (NUCs) following cessation or resistance. Moreover, reactivation could be spontaneous or triggered by hormone or immunosuppressive drugs. In addition, three scoring systems associated with clinical prognosis were calculated at baseline: the CLIF-C ACLF, MELD, MELD-Na and COSSH-ACLF. All patients were followed from their diagnosis until either their death or the end of the 90-day follow-up period. Survival rates at 28 and 90 days following enrollment were obtained from patients' medical records or by direct contact with the patients or their families.

2.4. Definitions

CHB was defined by the presence of hepatitis B surface antigen for >6 months [14].

The diagnosis of cirrhosis was based on previous liver biopsy findings or a composite of clinical signs and findings obtained using laboratory test results, endoscopy, and radiologic imaging [15].

The APASL criteria for ACLF were defined as follows [2]: acute hepatic insult manifesting as jaundice, with serum total bilirubin (TBil) $\geq$5 mg dL^{-1} (85 μmol L^{-1}), and coagulopathy, with INR $\geq$1.5 or prothrombin activity <40%, complicated within 4 weeks by clinical ascites and/or HE in a patient with previously diagnosed or undiagnosed chronic liver disease. Patients with known previous decompensation with jaundice, hepatic encephalopathy, and ascites should be excluded. If the history of decompensation cirrhosis is not clear, endoscopic or radiologic investigations should be used to diagnose.

Organ failures were defined as follows [7]: liver failure was defined by a TBil level of $\geq$12.0 mg dL^{-1}; kidney failure was defined by a serum creatinine (Cr) level of $\geq$2.0 mg dL^{-1} or the use of renal replacement therapy; cerebral failure was defined as the presence of grade III or IV HE; coagulation failure was defined by an international normalized ratio (INR) >2.5; circulatory failure was defined by the use of vasoconstrictors; respiratory failure was defined by a ratio of $PaO_2/FiO_2 \leq 200$ or SpO_2 to $FiO_2 \leq 214$.

EASL-CLIF diagnostic criteria and grades of ACLF were defined as described below [4]. No ACLF included: (1) patients with no organ failure; (2) patients with a single "non-kidney" organ failure, who had a serum creatinine level <1.5 mg dL^{-1} and no HE; or (3) patients with cerebral failure alone who had a serum creatinine level <1.5 mg dL^{-1}. ACLF grade 1 included: (1) patients with kidney failure alone; (2) patients with isolated failure of the liver, coagulation system, circulation, or respiration, who had a serum

creatinine level of 1.5–1.9 mg dL^{-1} and/or mild to moderate HE; or (3) patients with cerebral failure alone, who had a serum creatinine level of 1.5–1.9 mg dL^{-1}. ACLF grade 2 included patients with failure of two organ systems, and ACLF grade 3 included patients with failure of three or more organ systems.

Prognostic models, including CLIF-C ACLF, MELD, MELD-Na, and COSSH-ACLF scores, were calculated as per previously published criteria. All scores and definitions were applied at the time of enrollment in this study.

2.5. Treatment

The patients included in the study received standard medical treatment, including absolute bed rest, energy supplements and vitamins, intravenous infusions of albumin, maintenance water, electrolyte and acid-base correction, and prevention and treatment of complications. Antiviral therapy, including lamivudine, adefovir dipivoxil, entecavir, telbivudine, or tenofovir, was administered according to HBV replication levels, financial condition, and the willingness of the patient. All patients were followed from their diagnosis until either their death or the end of the 90-day follow-up period.

2.6. Statistics

Statistical analysis was performed using SPSS 20.0 statistical package (IBM, Armonk, NY, USA). Patients' characteristics were compared using the χ^2 or Fisher's exact tests for categorical variables and the *t* test or Mann–Whitney *U* test for variables with abnormal distribution. Percentages were reported to describe categorical variables, and mean ± SD were reported to describe the normally distributed continuous variables. Univariate risk factors associated with the outcome ($p < 0.05$) were entered into the multivariate Cox regression analysis for screening of independent risk factors.

Nomogram was formulated based on the results of the multivariate Cox regression analyses performed using the RMS packages [16] in R version 3.0.2 (http://www.r-project.org/). Final selection of the nomogram model was based on a backward step-down process with the Akaike information criterion [17]. The performance of the nomograms and other score models for predicting survival were evaluated by the concordance index (C-index). The maximum C-index value is 1.0, which indicates a perfect prediction model, whereas 0.5 indicates a random chance to correctly predict outcome by the model. Bootstraps with 1000 resamples were used for validation to correct the C-index and explain the variance due to over-optimism. Comparisons between nomogram models and the other four models were performed with the rcorrp.cens function in the Hmisc package [18] in R. Calibration curves were applied to assess the agreement between the predicted survival and the observed survival. When externally validating the nomogram, the total points for each patient were computed according to the established nomogram, which were then used as factors in the Cox regression model, and the C-index and calibration curves were derived based on the regression analysis. Decision curve analyses (DCA) and plots of net benefit against threshold probability, were carried out to evaluate these predictive models by examining the theoretical relation between the threshold probability of developing an event and the relative value of false-positive and false-negative results [19]. All statistical tests were two-sided with a statistical significance level set at *p* values <0.05.

3. Results

3.1. Patient characteristics and outcomes of APASL and EASL-CLIF ACHBLF

Our study included two APASL ACHBLF cohorts and one EASL-CLIF ACHBLF cohort, and their data were collected from Beijing Ditan hospital (n = 573) and multiple centers (n = 329) and Renji hospital (n = 300), respectively. As shown in Table 1, in both the APASL and EASL-CLIF ACHBLF patients, HBV reactivation, bacterial infection, and active alcoholism were the most common precipitating events. Ascites was the most frequent complication, followed by hyponatremia and HE. The most common organ failures were liver failure and coagulation failure. These data were obtained at the time of ACLF diagnosis (at admission or during hospitalization).

When comparing the clinical characteristics and outcomes of patients diagnosed with ACHBLF between APASL and EASL-CLIF cohorts, we found that ACHBLF patients in the EASL-CLIF cohort were older and had higher precipitating events of bacterial infection and gastrointestinal hemorrhage and higher complication and organ failure rates at enrollment ($p < 0.05$). Moreover, the APASL ACHBLF cohort had higher ALT, aspartate aminotransferase, γ-glutamyl transferase, platelet count, serum sodium, hepatitis B e antigen (+), and HBV DNA and lower TBil, INR, white blood cells, and serum creatinine at the time of admission or, when indicated, at the time of diagnosis of ACHBLF ($p < 0.05$).

Consequently, the EASL-CLIF ACHBLF cohort had higher 28- and 90-day mortality rates than that in the retrospective APASL cohort (44.0% vs 26.7%, $p < 0.001$ and 50.0% vs 38.2%, $p = 0.001$, respectively).

3.2. Risk factors and derivation of the prognostic nomogram in the APASL ACHBLF cohort

Univariate analysis showed that age, HBV reactivation (oral hormones or immunosuppressive drugs within the past three months), bacterial infection, complications (hyponatremia, ascites, spontaneous bacterial peritonitis, HE, hepatorenal syndrome), organ failure (liver failure, kidney failure, brain failure, coagulation failure, circulatory failure), oral NUCs, TBil, albumin (ALB), γ-glutamyltransferase, cholinesterase, prothrombin activity, INR, white blood cell count, neutrophil count, serum potassium, serum sodium, serum creatinine, and hepatitis B e antigen (+) were significantly associated with short-term mortality in the derivation cohort ($p < 0.05$, Table 2).

The above variables were entered into multivariate Cox proportional hazard regression analyses. As Table 2 shows, only age (hazard ratio [HR] = 1.032, 95% confidence interval [CI]: 1.018–1.046, $p < 0.001$), HE I–II (HR = 2.125, 95% CI: 1.462–3.088, $p < 0.001$) and III–IV (HR = 5.058, 95% CI: 3.011–8.497, $p < 0.001$), TBil (HR = 1.004, 95% CI: 1.003–1.005, $p < 0.001$), ALB (HR = 0.956, 95% CI: 0.923–0.990, $p = 0.012$), and INR (HR = 1.961, 95% CI: 1.672–2.299, $p < 0.001$) remained independent risk factors for death of patients with ACHBLF.

The coefficients obtained from the Cox regression model were used to construct the nomogram (Fig. 1). Each subtype within the variables was assigned a score. By adding up the total score from all the variables and locating it to the total point scale we could determine probabilities of the outcomes by drawing a vertical line to the total score. The nomogram included age, TBil, ALB, INR, and HE.

3.3. Validation of the prognostic nomogram in the external APASL and EASL-CLIF ACHBLF cohorts

Table 3 shows the ability of the nomogram to predict 90-day mortality risk in patients with ACHBLF using the C-index. The C-

Table 1
Differences of clinical characteristics and outcomes between patients with ACHBLF diagnosed based on the APASL and EASL-CLIF criteria.

Patient's characteristics	Derivation cohort with APASL ACHBLF (Ditan, N = 573)	Validation cohort with APASL ACHBLF (10 centers, N = 329)	Validation cohort with EASL-CLIF ACHBLF (Renji, N = 300)
Age (yr)	43.5 ± 11.5	43.0 ± 11.1	46.5 ± 11.3[a]
Male sex	478 (83.4)	269 (81.8)	233 (77.7)[a]
Underlying disease			
Chronic hepatitis B	464 (81.0)	253(76.9)	0 (0.0)
Compensated cirrhosis	109 (19.0)	76 (23.1)	56 (18.7)
Decompensated cirrhosis	0 (0.0)	0 (0.0)	144 (81.3)[a]
Precipitating events			
HBV reactivation	424 (74.0)	273 (83.0)[a]	162 (54.0)[a]
NUC resistance	22 (3.8)	–	16 (5.3)
NUC cessation	99 (17.3)	–	11 (3.7)[a]
Spontaneous activation	288 (50.3)	–	135 (45.0)
Hormone or immunosuppressive drugs	15 (2.6)	–	–
Bacterial infection	69 (12.0)	47 (14.3)	59 (19.7)[a]
Active alcoholism	63 (11.0)	4 (1.2)[a]	30 (10.0)
Gastrointestinal haemorrhage	10 (1.7)	4 (1.2)	23 (7.7)[a]
Hepatotoxic drugs	22 (3.8)	0 (0.0)	7 (2.3)
Surgery	5 (0.9)	1 (0.3)	2 (0.7)
Complications			
Hyponatremia	219 (38.2)	102 (31.0)[a]	205 (68.3)[a]
Ascites	374 (65.3)	169 (51.4)[a]	229 (76.6)[a]
Spontaneous bacterial peritonitis	38 (6.6)	–	–
Hepatic encephalopathy I–II	88 (15.4)	21 (6.4)[a]	47 (15.7)
Hepatic encephalopathy III–IV	29 (5.1)	7 (2.1)[a]	90 (30.0)[a]
Hepatorenal syndrome	43 (7.5)	12 (3.6)[a]	112 (37.3)[a]
Organ failures			
Liver	435 (75.9)	270 (82.1)[a]	233 (77.7)
Kidney	21 (3.7)	7 (2.1)	85 (28.3)[a]
Brain	29 (5.1)	7 (2.1)[a]	71 (23.7)[a]
Coagulation	149 (26.0)	83 (25.2)	203 (67.7)[a]
Circulatory	5 (0.9)	2 (0.6)	57 (19.0)[a]
Respiratory	2 (0.3)	0 (0.0)	43 (14.3)[a]
Treatment with NUCs	487 (85.0)	288 (87.5)	–
Lamivudine alone	167/487 (34.3)	78/288 (27.1)[a]	–
Entecavir alone	258/487 (53.0)	173/288 (60.1)	–
Adefovir alone	20/487 (4.1)	13/288 (4.5)	–
Telbivudine alone	3/487 (0.6)	4/288 (1.4)	–
Tenofovir alone	1/487 (0.2)	0/288 (0.0)	–
≥2 NUCs	38/487 (7.8)	20/288 (6.9)	–
Laboratory data			
Alanine aminotransferase ($U \cdot L^{-1}$)	450.1 (174.8, 949.5)	218.5 (90.0, 599.5)[a]	92.2 (46.3, 327.0)[a]
Aspartate aminotransferase ($U \cdot L^{-1}$)	352.8 (159.8, 735.5)	193.5 (101.8, 389.8)[a]	125.5 (67.0, 252.0)[a]
Total bilirubin ($\mu mol \cdot L^{-1}$)	313.0 ± 144.7	337.9 ± 140.5[a]	451.5 ± 276.6[a]
Albumin ($g \cdot L^{-1}$)	31.3 ± 4.7	30.8 ± 4.8	32.3 ± 9.8
γ-Glutamyltransferase ($U \cdot L^{-1}$)	86.9 (52.9, 136.9)	86.0 (52.0, 136.0)	42.1 (27.7, 73.0)[a]
Cholinesterase ($U \cdot L^{-1}$)	3325.0 ± 1509.4	2784.0 ± 1989.9[a]	–
Prothrombin activity (%)	29.3 (21.7, 36.2)	33.6 (27.0, 39.0)[a]	–
International normalized ratio	2.3 ± 0.8	2.2 ± 0.6	3.2 ± 2.1[a]
White blood cell ($\times 10^9 \cdot L^{-1}$)	6.8 (5.1, 9.1)	6.3 (4.7, 8.1)[a]	9.1 (5.6, 12.8)[a]
Neutrophil count ($\times 10^9 \cdot L^{-1}$)	4.5 (3.2, 6.9)	4.0 (2.8, 5.6)[a]	–
Lymphocyte count ($\times 10^9 \cdot L^{-1}$)	1.3 (0.9, 1.8)	–	–
Platelet count ($\times 10^9 \cdot L^{-1}$)	113.4 ± 52.5	99.8 ± 49.4	85.3 ± 63.5[a]
Serum potassium ($mmol \cdot L^{-1}$)	4.0 ± 0.6	4.0 ± 0.6	–
Serum sodium ($mmol \cdot L^{-1}$)	135.7 ± 5.0	135.8 ± 4.6	129.9 ± 7.5[a]
Serum creatinine ($mg \cdot dL^{-1}$)	68.5 (58.0, 84.5)	70.1 (59.8, 83.7)	88.4 (61.9, 168.0)[a]
Hepatitis B e antigen (+)	381 (66.5)	157 (47.7)[a]	99 (35.2)[a]
HBV-DNA level (Log_{10} copies$\cdot mL^{-1}$)	5.8 ± 1.5	5.1 ± 1.8[a]	4.1 ± 1.5[a]
Mortality			
28 days	153 (26.7)	44 (13.4)[a]	132 (44.0)[a]
90 days	219 (38.2)	87 (26.4)[a]	150 (50.0)[a]

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).
Abbreviations: ACLF, acute-o chronic liver failure; HBV, hepatitis B virus; APASL, the Asia-Pacific Association for the Study of the Liver; EASL-CLIF, the European Association for the Study of the Liver-Chronic Liver Failure; NUCs, nucleotide analogs.
[a] $P < 0.05$.

index was 0.81 (95% CI: 0.78–0.83) in the derivation set. To validate more efficaciously the utility of established nomogram we used another external cohort for model validation. When the multi-center APASL ACHBLF cohort was subjected to the nomogram, the C-index was 0.70 (95% CI: 0.58–0.82). Meanwhile, the calibration plots showed fair agreements between the nomogram predictions and actual observations for the 28- and 90-day survival probability in the primary (Fig. 2A,D) and validation APASL cohorts (Fig. 2B,E) suggesting that the new model was useful in patients with ACHBLF, as defined by APASL.

Table 2
Univariate and multivariate Cox regression analysis of 90-day mortality in patients with APASL ACHBLF (derivation cohort, N = 573).

Patient's characteristics	Univariate analysis			Multivariate analysis		
	β	HR (95% CI)	P	β	HR (95% CI)	P
Age (yr)	0.038	1.039(1.027–1.051)	<0.001	0.031	1.032(1.018–1.046)	<0.001
Male sex	−0.075	0.928(0.654–1.316)	0.674			
Cirrhosis	0.598	1.818(1.349–2.451)	<0.001			
Precipitating events						
HBV reactivation	−0.348	0.706(0.530–0.940)	0.017			
NUC resistance	0.370	1.448(0.826–2.536)	0.196			
NUC cessation	−0.297	0.743(0.508–1.086)	0.125			
Spontaneous activation	−0.251	0.778(0.596–1.016)	0.066			
Hormone or immunosuppressive drugs	0.912	2.489(1.319–4.697)	0.005			
Bacterial infection	0.607	1.834(1.293–2.603)	0.001			
Active alcoholism	−0.090	0.914(0.588–1.420)	0.688			
Gastrointestinal haemorrhage	0.770	2.161(0.960–4.865)	0.063			
Hepatotoxic drugs	0.043	1.044(0.536–2.034)	0.900			
Surgery	−3.010	0.049(0.000–79.393)	0.422			
Complications						
Hyponatremia	0.678	1.970(1.511–2.569)	<0.001			
Ascites	0.525	1.691(1.253–2.284)	0.001			
Spontaneous bacterial peritonitis	0.680	1.974(1.258–3.096)	0.003			
Hepatic encephalopathy I–II	1.148	3.153(2.342–4.245)	<0.001	0.754	2.125(1.462–3.088)	<0.001
Hepatic encephalopathy III–IV	2.001	7.396(4.879–11.211)	<0.001	1.621	5.058(3.011–8.497)	<0.001
Hepatorenal syndrome	1.280	3597(2.480–5.217)	<0.001			
Organ failures						
Liver	1.102	3.011(1.985–4.568)	<0.001			
Kidney	1.442	4.230(2.606–6.867)	<0.001			
Brain	2.001	7.396(4.879–11.211)	<0.001			
Coagulation	1.166	3.209(2.453–4.199)	<0.001			
Circulatory	2.569	13.057(5.325–32.014)	<0.001			
Respiratory	3.159	23.554(5.675–97.755)	<0.001			
Treatment with NUCs	−0.605	0.546(0.392–0.760)	<0.001			
Lamivudine alone	−0.270	0.763(0.564–1.034)	0.082			
Entecavir alone	−0.056	0.945(0.724–1.235)	0.681			
Adefovir alone	−0.329	0.720(0.320–1.620)	0.427			
Telbivudine alone	−0.272	0.762(0.107–5.431)	0.786			
Tenofovir alone	1.151	3.162(0.443–22.588)	0.251			
≥2 NUCs	−0.048	0.954(0.564–1.611)	0.859			
Laboratory data						
Alanine aminotransferase ($U{\cdot}L^{-1}$)	0.000	1.000(1.000–1.000)	0.696			
Aspartate aminotransferase ($U{\cdot}L^{-1}$)	0.000	1.000(1.000–1.000)	0.743			
Total bilirubin ($\mu mol{\cdot}L^{-1}$)	0.004	1.004(1.003–1.004)	<0.001	0.004	1.004(1.003–1.005)	<0.001
Albumin ($g{\cdot}L^{-1}$)	−0.064	0.938(0.912–0.965)	<0.001	−0.045	0.956(0.923–0.990)	0.012
γ-Glutamyltransferase ($U{\cdot}L^{-1}$)	−0.002	0.998(0.996–1.000)	0.017			
Cholinesterase ($U{\cdot}L^{-1}$)	0.000	1.000(1.000–1.000)	0.003			
Prothrombin activity (%)	−0.082	0.922(0.908–0.935)	<0.001			
International normalized ratio	0.708	2.030(1.825–2.258)	<0.001	0.673	1.961(1.672–2.299)	<0.001
White blood cell ($\times 10^9{\cdot}L^{-1}$)	0.098	1.103(1.076–1.129)	<0.001			
Neutrophil count ($\times 10^9{\cdot}L^{-1}$)	0.103	1.109(1.080–1.137)	<0.001			
Lymphocyte count ($\times 10^9{\cdot}L^{-1}$)	−0.148	0.862(0.706–1.053)	0.146			
Platelet count ($\times 10^9{\cdot}L^{-1}$)	−0.001	0.999(0.996–1.001)	0.284			
Serum potassium ($mmol{\cdot}L^{-1}$)	0.334	1.396(1.150–1.695)	0.001			
Serum sodium ($mmol{\cdot}L^{-1}$)	−0.073	0.930(0.907–0.953)	<0.001			
Serum creatinine ($mg{\cdot}dL^{-1}$)	0.005	1.005(1.003–1.006)	<0.001			
Hepatitis B e antigen (+)	−0.449	0.638(0.483–0.843)	0.002			
HBV-DNA level (Log_{10} copies$\cdot mL^{-1}$)	0.005	1.005(0.923–1.095)	0.908			

Abbreviation: HBV, hepatitis B virus; NUCs, nucleotide analogs; HR, hazard ratio; CI, confidence interval.

However, in EASL-CLIF ACHBLF cohort, the C-index was 0.58 (95% CI: 0.48–0.68), and agreements between the nomogram predictions and actual observations were not satisfactory (Fig. 2C,F).

3.4. The performance of the nomogram compared with other score models

To compare the predictive abilities of the constructed nomogram with CLIF-C ACLF, MELD, and MELD-Na scores we compared the C-indexes of these models. As shown in Table 3, the nomogram had a bootstrap corrected C-index of 0.81, which was significantly better than that of the CLIF-C ACLF (0.78), MELD (0.74), and MELD-Na (0.72) scores in the derivation cohort ($p < 0.001$ for all). Meanwhile, the nomogram also had the highest area under the C-index for 90-day mortality in the prospective validation cohort with APASL ACHBLF (0.70) and with statistical significance in comparison to CLIF-C ACLF (0.64), MELD (0.63), and MELD-Na (0.66) scores ($p < 0.05$). No statistical difference was found between the nomogram and COSSH-ACLF in the derivation and prospective validation cohort. During decision curve analysis, compared to CLIF-C ACLF, MELD, and MELD-Na scores, both our nomogram and COSSH-ACLF showed better net benefit with a wider range of threshold probability and improved performance for predicting 28- and 90-day survival probability in the derivation (Fig. 3A,D) and validation APASL cohorts (Fig. 3B,E).

However, in the EASL-CLIF cohort, the CLIF-C ACLFs (0.68) had higher C-index and better net benefit than that of the nomogram (0.58), MELD (0.55), MELD-Na (0.54), and COSSH-ACLF (0.61) scores suggesting that CLIF-C ACLFs might be a much better choice for patients with EASL-CLIF ACHBLF (Table 3, Fig. 3C,F).

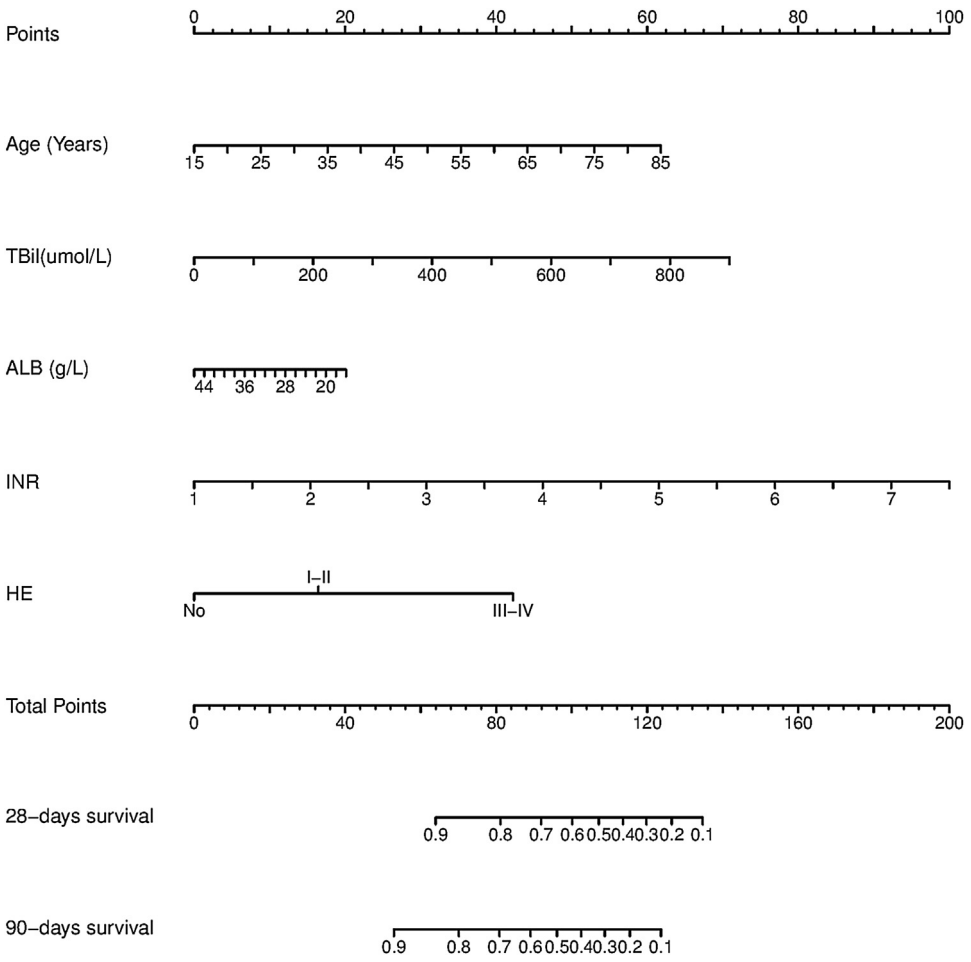

Fig. 1. A survival nomogram for APASL ACHBLF is depicted.
To use the nomogram, the value of an individual patient is located on each variable axis, and a line is drawn upward to determine the number of points received for the value of each variable. The sum of these numbers is located on the total point axis, and a line is drawn downward to the survival axes to determine the likelihood of 28- and 90-day survivals. APASL, Asia Pacific Association for the Study of the Liver; ACHBLF, acute-on-chronic hepatitis B liver failure.

Table 3
The predictive discrimination ability at 90 days of the nomogram compared to the CLIF-C ACLF, MELD and MELD-Na scoring systems in the derivation and validation cohorts.

	C-index	95% CI for C-index		Goodness of fit		Comparison of models			
		Lower	Upper	LR	R^2	Dxy	SD	Z	*p* value
Derivation cohort with APASL ACHBLF (Ditan, n = 573)									
Nomogram	0.81	0.78	0.83	288.43	0.40	–	–	–	–
COSSH-ACLF	0.81	0.79	084	281.18	0.39	0.07	0.04	1.75	0.081
CLIF-C ACLFs	0.78	0.75	0.81	219.42	0.32	0.17	0.04	3.92	<0.001
MELDs	0.74	0.71	0.77	150.25	0.23	0.42	0.04	11.67	<0.001
MELD-Nas	0.72	0.68	0.75	95.34	0.17	0.48	0.04	13.15	<0.001
Validation cohort with APASL ACHBLF (10 centers, n = 329)									
Nomogram	0.70	0.58	0.82	38.59	0.12	–	–	–	–
COSSH-ACLF	0.69	0.63	0.75	36.92	0.12	0.06	0.07	0.86	0.391
CLIF-C ACLFs	0.64	0.58	0.71	17.89	0.06	0.27	0.06	4.17	<0.001
MELDs	0.63	0.56	0.69	19.57	0.07	0.22	0.07	3.24	0.001
MELD-Nas	0.66	0.60	0.72	21.90	0.07	0.19	0.07	2.61	0.009
Validation cohort with EASL-CLIF ACHBLF(Renji, n = 300)									
Nomogram	0.58	0.48	0.68	6.47	0.03	–	–	–	–
COSSH-ACLF	0.61	0.56	0.66	7.19	0.02	0.31	0.05	−6.24	<0.001
CLIF-C ACLFs	0.68	0.64	0.72	56.12	0.18	0.32	0.05	−6.16	<0.001
MELDs	0.55	0.50	0.61	3.39	0.01	0.11	0.05	2.03	0.043
MELD-Nas	0.54	0.49	0.60	3.40	0.01	0.10	0.05	1.86	0.063

Although the bootstrap corrected C-index could be more appropriate than the AUROC in the multivariate Cox proportional hazard regression analysis, we also reported the area under the ROC curves (AUROC) for 90-day mortality of the scores (Fig. 4A–C). The results were similar to that of the C-indexes. As shown in Fig. 4A,B, in the APASL ACHBLF cohorts, the nomogram showed the highest AUROC compared with CLIF-C ACLF, MELD and MELD-Na scores, but no statistical difference was found between the nomogram and

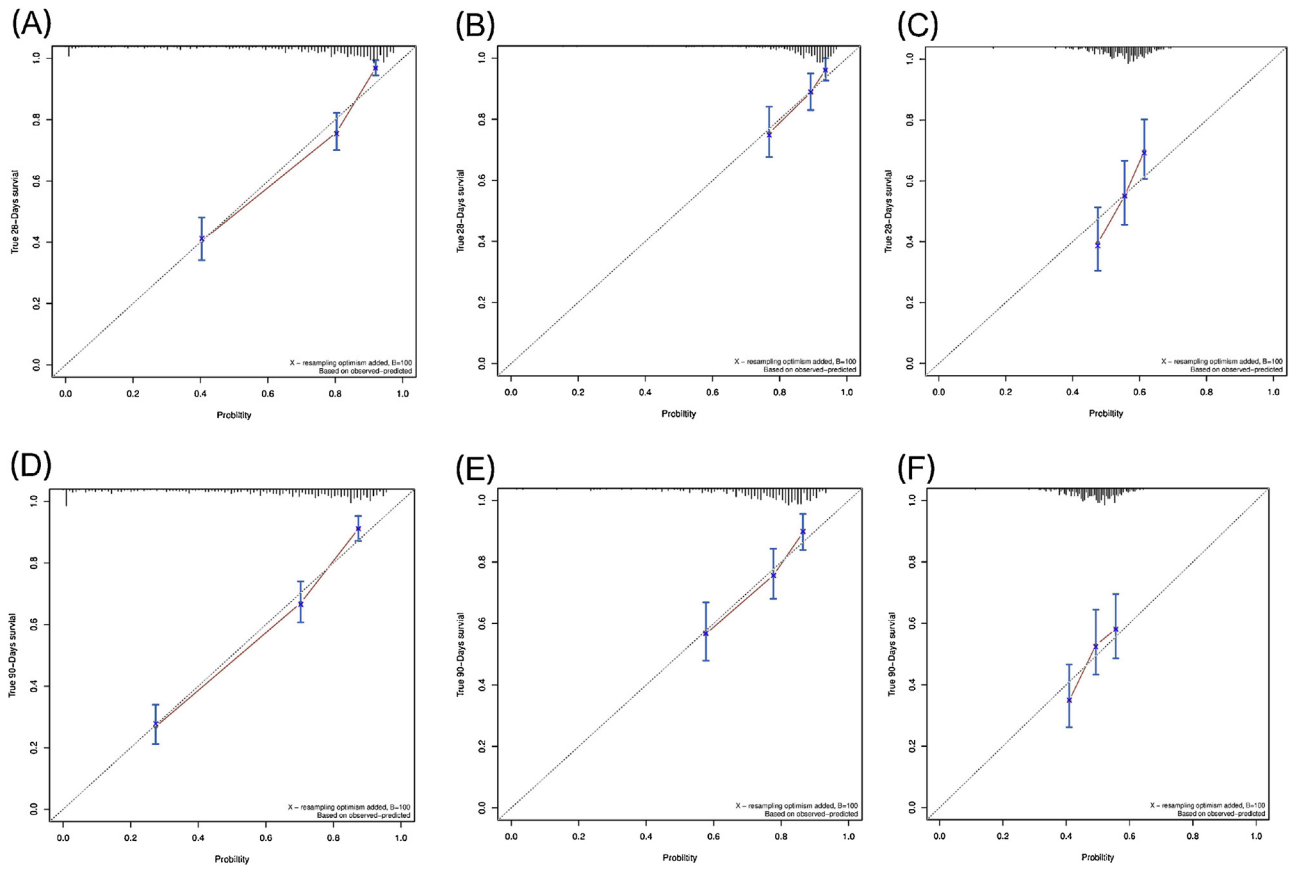

Fig. 2. The calibration curve of overall survival at 28 and 90 days in the APASL (the derivation cohort: A,D, validation cohort: B,E) and EASL-CLIF ACHBLF cohorts (C,F). Nomogram-predicted probability of survival is plotted on the x-axis, and the actual survival is plotted on the y-axis. Dashed lines along the 45-degree line through the point of origin represent perfect calibration models, in which the predicted probabilities are identical to the actual probabilities. APASL, Asia Pacific Association for the Study of the Liver; ACHBLF, acute-on-chronic hepatitis B liver failure; EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure.

COSSH-ACLF. In the EASL-CLIF cohort, the CLIF-C ACLF score was better (Fig. 4C).

4. Discussion

ACLF is one of the most challenging health problems worldwide and is characterized by acute onset, rapid progression, and dramatically high short-term mortality [2,20]. Recently, the CANONIC study developed a specific prognostic score for ACLF (CLIF-C ACLFs), which has only been validated in the alcoholism and hepatitis C population. The patient populations studied had extremely low prevalence of HBV infection [8]. Reactivation of HBV constitutes the most common cause of ACLF in the Asian-Pacific region, and the pathophysiological features of ACHBLF are very different from other causes of liver failure [21–23].

To address this issue Li et al. proposed a prognostic model specifically developed for patients with ACHBLF. It was defined by EASL-CLIF Consortium, but was not applied to patients who met APASL criteria [24]. Besides, Wu et al., Yan et al., and Shi et al. have successively established the Logistic regression model, Cox regression model, classification and regression trees, and nomogram prognostic model for APASL ACHBLF [25–28]. However, these models were established in retrospective single-center studies, which have not been compared with the CLIF-C ACLFs, and validated in patients who met EASL-CLIF criteria. Therefore, in this study, we compared the APASL and EASL-CLIF definitions of ACHBLF with regards to patient characteristics and short-term mortality and found that the EASL-CLIF ACHBLF cohort was more severely ill with higher complication and organ failure rates and 28- and 90-day mortality rates than that in the APASL cohort. In addition, we developed a new prognostic nomogram model to predict individual risk of death in patients with APASL ACHBLF and validated it in EASL-CLIF ACHBLF.

Among the prognostic nomogram, five independent factors were found to be associated with 28- and 90-day mortality among patients with APASL ACHBLF. These included age, TBil, ALB, INR, and HE. Previous studies reported that HE in hospitalized patients, particularly when associated with ACLF, is associated with a high mortality rate independent of another organ failure [5,29,30]. An important new concept that has emerged is that HE in patients with ACLF is distinct clinically, prognostically, and pathophysiologically from conventional forms represented by types A–C HE [31]. To date, the way the liver is affected by increasing age has not been fully elucidated [32]; however, age as an independent risk factor in ACLF was not surprising, since older patients usually have a higher incidence of comorbidities, a longer duration of underlying disease, and poor hepatic regeneration in response to acute insults [33]. Recently, the CANONIC study developed two prognostic scores for ACLF (CLIF-C ACLFs) and AD (CLIF-C ADs), in which old age was considered as a strong predictor of poor outcomes [8,34]. INR, TBil, and ALB are important markers of liver protein synthesis function and the extent of hepatocellular necrosis, as reported in many official criteria and studies on the diagnosis and prognosis of ACLF [2,3,13,35,36].

In current study, many patients received the lamivudine alone which is suboptimal treatment for chronic hepatitis B. One of the

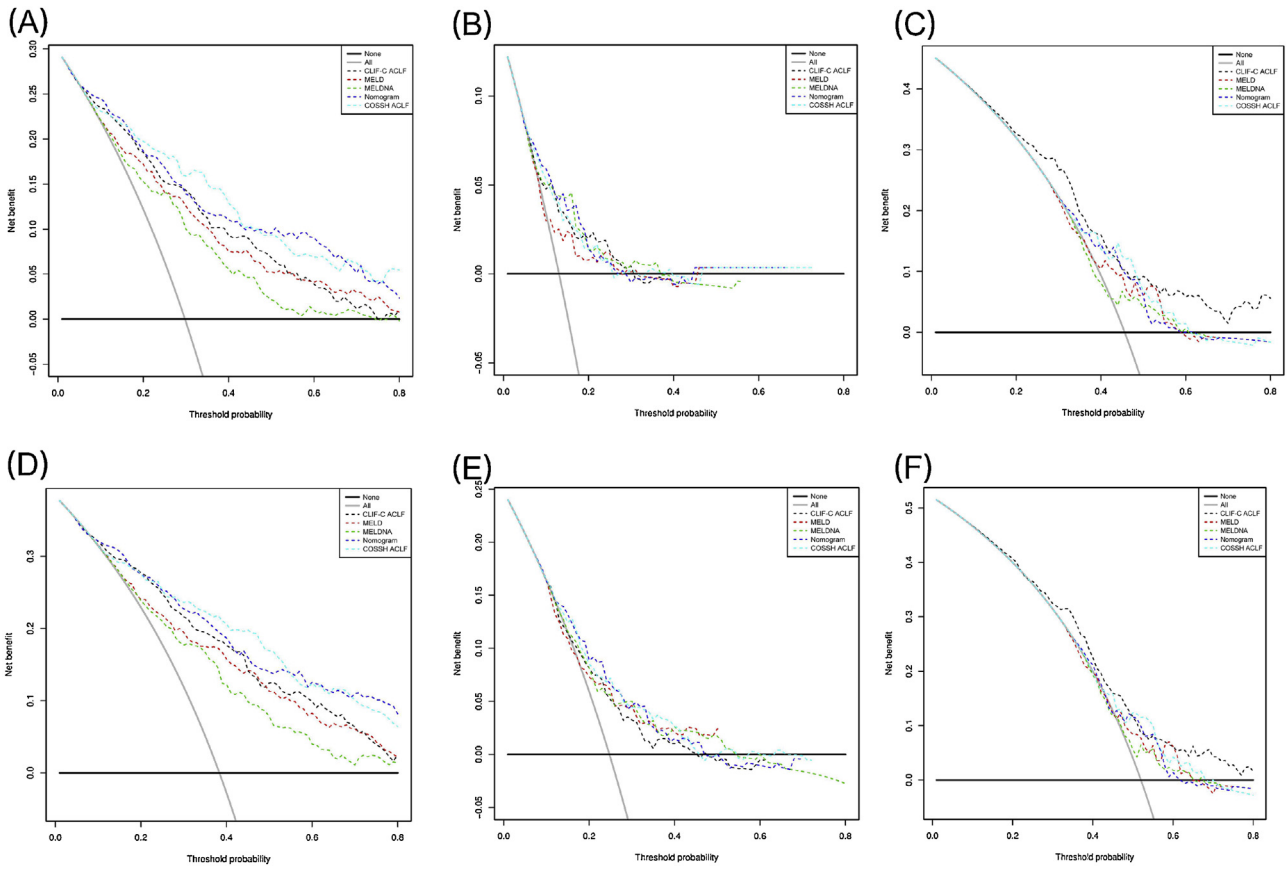

Fig. 3. Decision curve analysis at 28 and 90 days of the APASL (the derivation cohort: A,D, validation cohort: B,E) and EASL-CLIF ACHBLF cohorts (C,F).
Decision curve analyses depict the clinical net benefit in pairwise comparisons across the different models. The horizontal solid black line represents the assumption that no patients will experience the event, and the solid gray line represents the assumption that all patients will relapse. APASL, Asia Pacific Association for the Study of the Liver; ACHBLF, acute-on-chronic hepatitis B liver failure; EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure.

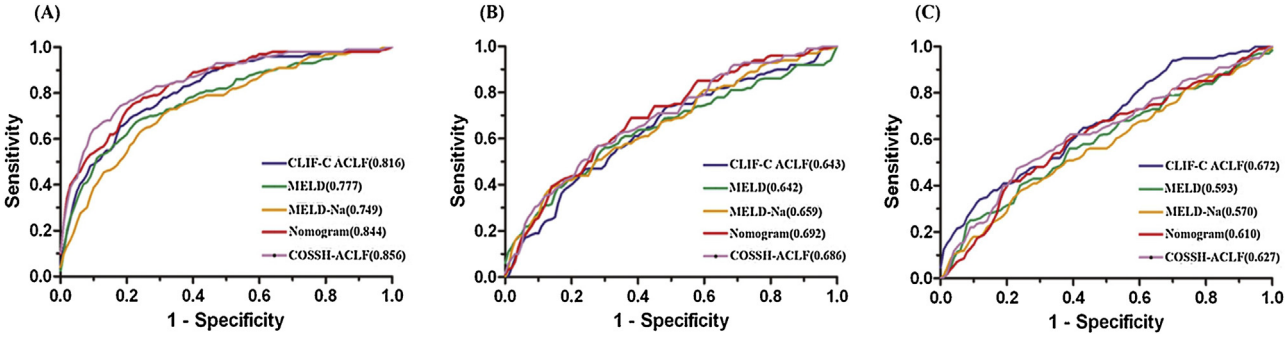

Fig. 4. Receiver operating characteristic curves of different models in predicting 90-day prognosis in the APASL (the derivation cohort: A, validation cohort: B) and EASL-CLIF ACHBLF cohorts (C).
APASL, Asia Pacific Association for the Study of the Liver; ACHBLF, acute-on-chronic hepatitis B liver failure; EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure.

reasons is that the time to market of adefovir dipivoxil, entecavir and telbivudine in China are September 2005, November 2005 and April 2007, respectively, and the lamivudine is the only option before 2005. Another is that some patients tend to choose the lamivudine considering their bad financial condition. This reflects the clinical treatment situation objectively in China.

In both the derivation and prospective validation cohorts with APASL ACHBLF, the nomogram showed superior discrimination ability and clinical usefulness compared with CLIF-C ACLF, MELD and MELD-Na scores and was similar to COSSH-ACLF in predicting 28- and 90-day mortality. However, the nomogram could be easier to use than COSSH-ACLF score, which required the assessment of HBV-SOFA. The nomogram could provide graphical and individual prediction. Moreover, we also assessed whether the nomogram could be useful if applied to the EASL-CLIF ACHBLF population. The data showed that performance of CLIF-C ACLFs was higher than that of nomogram, MELD, MELD-Na, and COSSH-ACLF scores for the patients who met EASL-CLIF criterion.

There are, however, some limitations of this study. First, the three cohorts are heterogeneous. Because of the difference of enrollment period, the ACHBLF patients in the validation cohort (2012.9–2013.9) could receive more timely treatment with the higher medical level, and more widespread use of antiviral drugs than that in the derivation cohort (2003.1–2016.5). Thus, the vali-

dation cohort with APASL ACHBLF had milder pathogenic condition and lower 28- and 90-day mortality rates. Besides, the heterogeneity of the APASL and EASL-CLIF ACHBLF is inevitable on account of different diagnostic criterias. It is the one of the objectives of our study to compare the clinical characteristics and outcomes of patients diagnosed with ACHBLF between APASL and EASL-CLIF cohorts. Second, the follow-up period was only three months (90 days), despite the objectivity of a retrospective study and stable sample size. Nevertheless, ACLF is characterized by a rapidly progressive course with high short-term and relatively stable long-term mortality.

In conclusion, although there have been many previous studies on the prognosis of ACLF, this is the first one to compare the APASL and EASL-CLIF definitions in Asian-Chinese patients with ACHBLF regarding patient characteristics and short-term mortality. In addition, we developed a prognostic nomogram, which resulted in more accurate individualized risk estimates for short-term mortality for patients with APASL ACHBLF. However, for patients with EASL-CLIF ACHBLF, the CLIF-C ACLFs might be a much better choice.

Conflict of interest

None declared.

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