Clinical Prediction Models for Hepatitis B Virus-related Acute-on-chronic Liver Failure: A Technical Report

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Abstract

Background and Aims: It is critical but challenging to predict the prognosis of hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF). This study systematically summarized and evaluated the quality and performance of available clinical prediction models (CPMs). Methods: A keyword search of articles on HBV-ACLF CPMs published in PubMed from January 1995 to April 2020 was performed. Results: Fifty-two CPMs were identified, of which 31 were HBV-ACLF specific. The modeling data were mostly derived from retrospective (83.87%) and single-center (96.77%) cohorts, with sample sizes ranging from 46 to 1,202. Three-month mortality was the most common end-point. The Asian Pacific Association for the Study of the Liver consensus (51.92%) and Chinese Medical Association liver failure guidelines (40.38%) were commonly used for HBV-ACLF diagnosis. Serum bilirubin (67.74%), the international normalized ratio (54.84%), and hepatic encephalopathy (51.61%) were the most frequent variables used in models. Model discrimination was commonly evaluated (88.46%), but model calibration was seldom performed. The model for end-stage liver disease score was the most widely used (84.62%); however, varying performance was reported among the studies. Conclusions: Substantial limitations lie in the quality of HBV-ACLF-specific CPMs. Disease severity of study populations may impact model performance. The clinical utility of CPMs in predicting short-term prognosis of HBV-ACLF remains to be undefined.

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Introduction

Acute-on-chronic liver failure (ACLF) is a critically ill illness characterized by acute exacerbations of underlying chronic liver diseases with short-term high mortality.1,2 The etiology of underlying chronic liver diseases and precipitating events are distinct between Eastern and Western ACLF, which contributes to the heterogeneity of this syndrome.3 In Eastern ACLF, especially in China, hepatitis B virus related acute-on-chronic liver failure (HBV-ACLF) is the most common type.4 There are a variety of emerging therapies for HBV-ACLF, such as extracorporeal liver support device,5,6 glucocorticoid,7,8 granulocyte colony-stimulating factor (G-CSF),9 and cell therapies,10,11 but their efficacy requires further validation.

Liver transplantation (LT) remains the only definite treatment to reduce the mortality of advanced HBV-ACLF. Therefore, it is critical to develop reliable early risk-stratification tools for LT.

Both the quality and performance of the CPMs were assessed. Results: Fifty-two CPMs were identified, of which 31 were HBV-ACLF specific. The modeling data were mostly derived from retrospective (83.87%) and single-center (96.77%) cohorts, with sample sizes ranging from 46 to 1,202. Three-month mortality was the most common end-point. The Asian Pacific Association for the Study of the Liver consensus (51.92%) and Chinese Medical Association liver failure guidelines (40.38%) were commonly used for HBV-ACLF diagnosis. Serum bilirubin (67.74%), the international normalized ratio (54.84%), and hepatic encephalopathy (51.61%) were the most frequent variables used in models. Model discrimination was commonly evaluated (88.46%), but model calibration was seldom performed. The model for end-stage liver disease score was the most widely used (84.62%); however, varying performance was reported among the studies. Conclusions: Substantial limitations lie in the quality of HBV-ACLF-specific CPMs. Disease severity of study populations may impact model performance. The clinical utility of CPMs in predicting short-term prognosis of HBV-ACLF remains to be undefined.
but is limited by a lack of organ donors, huge financial cost of the procedure, and high mortality on the waiting list. In the European Association for the Study of the Liver–Chronic Liver Failure (EASL-CLIF) Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study, ACLF patients had a 28-day mortality of 33.9%, and only 7.6% received LT.13 As a result, it is critical to precisely predict the short-term outcome of HBV-ACLF at the early stage of disease to make an accurate and prompt clinical decision of LT.

A number of clinical prediction models (CPMs) have been used to predict the short-term prognosis of HBV-ACLF utilizing laboratory and clinical variables that can be easily obtained in clinical practice. Some were specifically developed for HBV-ACLF, while others were originally developed for end-stage liver diseases [for instance, the model for end-stage liver disease (MELD) score,14 MELD-sodium (MELD-Na) score15 and Child-Turcotte-Pugh (CTP) score16], acute liver failure [King’s College Criteria (KCC)17], and other critical illness with organ failures [sequential organ failure assessment (SOFA)18]. Despite the number of available CPMs, there is no consensus on the use of optimal models to predict HBV-ACLF outcome. In addition, there are major concerns about the heterogeneity of study populations as well as model quality. Therefore, in the study, we systematically assessed both the performance and quality of available HBV-ACLF CPMs. We also analyzed the factors associated with heterogeneity and their predictive performance among different studies.

Methods

Study search and selection

A keyword search was carried out on articles related to HBV-ACLF published in PubMed from January 1995 to April 2020. The search strategy was developed as follows: (HBV OR hepatitis B) AND (severe flares of chronic hepatitis B OR chronic severe hepatitis B OR severe flare-up, chronic hepatitis B OR hepatic failure OR severe hepatitis B OR severe acute chronic hepatitis B (CHB) exacerbation OR hepatic decompensation OR severe acute exacerbation OR liver failure OR acute-on-chronic liver failure OR ACLF OR acute liver failure) AND (mortality OR prognosis OR outcome). Two reviewers (YX and LY) independently screened the searched articles based on the title, abstract, and full text sequentially. Disputes were resolved by negotiation between the two reviewers.

We included articles reporting the development of an HBV-ACLF-specific CPM or those assessing the predictive performance of previously established CPMs in non-HBV-ACLF-specific patients.

In addition, the included studies had clearly defined endpoints and reported the statistical modeling approaches if an HBV-ACLF-specific CPM was developed. For inclusion, the CPM had to contain at least two independent variables.

The exclusion criteria were as follows: (1) other types of publications, such as letters and reviews; (2) samples including patients younger than 18 years of age or pregnant women; (3) reports of biomarker-based prediction models; (4) reports of cost-benefit models; (5) experimental studies; or (6) decision-analysis studies.

Data extraction

We extracted the following information for each of the included articles: (1) year of publication; (2) study design; (3) study registration if reported; (4) diagnostic criteria for HBV-ACLF; (5) baseline characteristics of the study population; (6) sample size; (7) number of deaths or LT if reported; (8) variables included in the new CPMs; (9) statistical approaches for model development; and (10) model validation.

All information was independently extracted by the two reviewers, and disputes were resolved by negotiation between them.

Model assessment

Quality of HBV-ACLF-specific models: As shown in Supplementary Table 1, a scoring system was established by weighting study design, number of patients recruiting centers, sample size, adjustment of confounding factors, reporting of LT, and model validation. Studies with scores of 5–6 were considered high quality, 3–4 medium quality, and 1–2 low quality.

Performance of the CPMs: The performance of the CPMs was evaluated by discrimination and calibration.19 Discrimination referred to how well the model distinguished individuals at high risk of an event from those at low risk of an event.19 Calibration referred to the accuracy of absolute risk estimation.19 To measure model discrimination, we extracted the area under the receiver operating characteristic curve (AUROC) from each study. Quantitative pooled analysis of the discrimination performance of a specific model reported in several studies was performed by summary receiver operating characteristic (SROC) curves using Review Manager 5.3. To measure calibration, information on the Hosmer-Lemeshow test was extracted.

Ethics approval and consent to participate

The ethics committee of the First Affiliated Hospital of Zhejiang University reviewed and approved this study. Written consent from patients or their authorized representatives was waived.

Results

Characteristics of all CPMs

A total of 4,261 related studies were retrieved from PubMed based on the keyword search. According to the inclusion and exclusion criteria, 52 studies were selected after being screened by the title, abstract, and full text (Fig. 1). A total of 52 articles were extracted, of which 31 developed HBV-ACLF-specific CPMs and the other 21 assessed previously established CPMs. As shown in Figure 2, the number of publications is rapidly increasing each year. The studies were published in a number of academic journals (n=30), the most frequent being Chinese Journal of Hepatology [5 (9.62%)], followed by Medicine (Baltimore) [n=4 (7.69%)].

The diagnosis of HBV-ACLF in these studies was made mainly based on the Asian Pacific Association for the Study of the Liver (APASL) consensus for ACLF (51.92%) or the Chinese Medical Association (CMA) liver failure guidelines (40.38%). Among all studies, the sample size ranged from 46 to 1,202 patients. Significant heterogeneity was observed in patient characteristics among the different studies, as shown by the sex proportion (male/female) (ranging from 2.96 to 12.19), incidence of cirrhosis (24–100%), incidence of hepatic encephalopathy (10–51%), incidence of ascites (36–91%), and mean MELD score (20.97–29.00). The type of precipitating event was reported in seven studies (13.8%), with flare-up of hepatitis B being the major event in each study. Mortality varied among the different studies, with 3-month mortality ranging from 26% to 87%.
Regarding reporting of LT, 18 studies did not mention LT (34.62%), 21 excluded patients receiving LT (40.38%), and 5 defined LT and death as a composite endpoint (9.62%). LT was regarded as the censored event in six studies (11.54%). Patients with LT were defined as survivors in one study (1.92%). In one study, patients who received LT within 3 months were considered dead and more than 3 months as surviving.

In 8 studies (15.4%), dynamic parameters were used for modeling. ΔMELD or ΔMELD-Na calculated as the difference between MELD or MELD-Na at two time points was most frequent. One parameter was constructed based on the daily levels of predictive variables for 7 days after diagnosis combined with baseline risk factors. In the other studies, only baseline parameters were used.

**Characteristics of HBV-ACLF-specific CPMs**

Thirty-one CPMs were established specifically for HBV-ACLF (Table 1).

The diagnosis of HBV-ACLF in these studies was made...
Table 1. Patient characteristics of HBV-ACLF-specific CPMs

| References† | Model | ACLF diagnostic criteria | Sample | Death events | Endpoint time | Age in years | Sex, male/female | Cirrhosis, n/total | Ascites, n/total | HE, n/total | TB in mmol/L | INR | MELD score |
|-------------|-------|--------------------------|--------|--------------|--------------|--------------|-----------------|-------------------|-----------------|--------------|-------------|--------|-----------|
| [1] Ke’s model | CMA | 205 | 104 | NA | 46.8±13.2 | 170/34 | NA | NA | NA | NA | 86/204 | 318.6±175.8 | NA | 26.0±9.0 |
| [2] Li’s model | CMA | 409 | 215 | NA | 42±12 | 378/31 | NA | NA | NA | NA | NA | NA | NA | NA |
| [3] Sun’s model | CMA | 204 | 118 | 90-day | 46.8±13.2 | 170/34 | 110/204 | NA | 86/204 | 318.6±175.8 | NA | 26.0±9.0 |
| [4] LRM | APASL | 452 | 175 | 90-day | 45.6±11.5 | 361/91 | 138/452 | 334/452 | 119/452 | NA | NA | NA | NA |
| [5] He’s model | CMA | 172 | 75 | 90-day | 45.16±11.21 | 144/28 | 96/172 | NA | 297.8±109.3 | 2.4±0.7 | 26.4±4.2 |
| [6] TPPM | APASL | 248 | 133 | 90-day | 42.27±11.98 | 225/23 | 68/248 | 152/248 | 95/248 | 270.9±140.3 | 2.0±0.5 | 20.97±5.83 |
| [7] Zheng’s model | APASL | 726 | 371 | 90-day | 43.5±11.6 | 635/91 | NA | 530/726 | 251/726 | NA | NA | NA |
| [8] ALPH-Q | APASL | 214 | 81 | 90-day | NA | 160/54 | 99/214 | 123/214 | 45/214 | NA | NA | NA |
| [9] Yan’s model | APASL | 432 | 209 | 90-day | 46.9±13.3 | 329/103 | 239/432 | 346/432 | 115/432 | 351 (210) | 2.8 (1.6) | 27.8 (8.3) |
| [10] Yi’s model | APASL | 392 | 218 | 90-day | NA | 323/69 | NA | NA | 165/392 | NA | NA | NA |
| [11] Li’s model | CMA | 338 | 129 | 90-day | 44.7±10.1 | 268/70 | 222/338 | 220/338 | 54/338 | NA | NA | NA |
| [12] HBV-ACLFs | EASL-ACLF | 300 | 150 | 28-day | 46.5±11.3 | 233/67 | 300/300 | 229/300 | 71/300 | 453.2±278.7 | 3.2±2.1 | NA |
| [13] HAM | APASL | 530 | 190 | 90-day | 41 (median) | 489/41 | 246/530 | 264/530 | 95/530 | NA | NA | NA |
| [14] Chen’s model | APASL | 551 | 241 | 90-day | NA | 465/86 | 217/551 | NA | NA | NA | NA | NA |
| [15] MELD-LAC | AASL | 236 | 106 | 90-day | NA | 197/39 | 131 / 236 | NA | NA | NA | NA | NA |
| [16] HINAT ACLF | APASL | 573 | 153 (28-day), 219 (90-day) | 43.5±11.5 | 478/98 | NA | 374/573 | 117/573 | 313.0±144.7 | 2.3±0.8 | NA |
| [17] Lei’s model | CMA | 138 | NA | NA | 45.80±11.01 | 111/27 | 51/138 | 96/138 | NA | NA | NA | NA |
| [18] Lin’s model | APASL | 456 | 176 | 90-day | NA | 383/73 | 228/456 | 46/456 | NA | NA | NA | NA |

(continued)
Table 1. (continued)

| References | Model          | ACLF diagnostic criteria | Sample | Death events | Endpoint time | Age in years | Sex, male/female | Cirrhosis, n/total | Ascites, n/total | HE, n/total | TB in mmol/L | INR | MELD score |
|------------|----------------|--------------------------|--------|--------------|---------------|--------------|-----------------|--------------------|-----------------|-------------|--------------|-----|------------|
| [19]       | Shi’s model    | APASL                     | 384    | 75 (30-day), 106 (60-day), 125 (90-day), 127 (180-day) | 30-day, 60-day, 90-day, 180-day | NA           | 303/81          | 177/384           | 236/384         | 93/384     | NA           | NA  | NA         |
| [20]       | Xue’s model    | APASL                     | 305    | 87           | 30-day        | NA           | 257/48          | 89/305            | 212/305         | 92/305     | NA           | NA  | NA         |
| [21]       | Gong’s model   | CMA                       | 184    | 75           | 90-day        | NA           | 157/27          | NA                | 122/184         | NA          | NA           | NA  | NA         |
| [22]       | Lin’s model    | APASL                     | 370    | 110          | 90-day        | NA           | 314/56          | 88/370            | 248/370         | 103/370    | NA           | NA  | NA         |
| [23]       | HINT           | APASL                     | 635    | 204          | 30-day        | 46.3±11.87   | 538/97          | 455/635           | 239/635         | 108/635    | 319.1 (220.9, 421.0) | 2.02 (1.71, 2.55) | 23.07±5.95  |
| [24]       | COSSH-ACLF     | EASL-ACLF                 | 657    | 233 (28-day), 313 (90-day) | 28-day, 90-day | NA           | 586/71          | 466/657           | 366/657         | 130/657    | NA           | NA  | NA         |
| [25]       | CTP-ABIC       | CMA                       | 222    | 80           | 90-day        | NA           | 197/25          | 168/222           | 151/222         | 44/222     | NA           | NA  | NA         |
| [26]       | Gao’s model    | APASL                     | 1,202  | 329 (28-day), 456 (90-day) | 28-day, 90-day | NA           | 980/222         | 382/1,202         | 772/1,202       | 282/1,202  | NA           | NA  | NA         |
| [27]       | APM            | APASL                     | 405    | NA           | 28-day        | NA           | 358/47          | 176/405           | 144/405         | 52/405     | NA           | NA  | NA         |
| [28]       | ANN            | APASL                     | 402    | 160          | 90-day        | 47.2±13.3    | 316/86          | NA                | NA             | NA         | 297.5±169.3 | 2.9±1.7 | 28.2±6.2   |
| [29]       | ANN            | APASL                     | 684    | 175 (28-day), 251 (90-day) | 28-day, 90-day | 43.9±11.6    | 582/102         | NA                | 405/684         | 122/684    | 323.5±148.4 | 2.3±0.8 | 22.9 (20.0, 26.5) |
| [30]       | CART           | NA                        | 777    | 316          | 90-day        | NA           | 610/167         | 371/777           | NA             | NA         | NA           | NA  | NA         |
| [31]       | CART           | EASL-CLIF                 | 489    | 191 (28-day) | 28-day        | NA           | 424/65          | 234/489           | 234/489         | 63/489     | NA           | NA  | NA         |

†See Supplementary File 1. LRM, logistic regression model; HBV-ACLF, hepatitis B virus related acute-on-chronic liver failure; MELD, model for end-stage liver disease; TPMM, Tongji prognostic predictor model; HAM, HBV-ACLF MELD; MELD-lac, MELD-lactate; HINAT ACLF, HE-INR-NLR-age-TB ACLF; COSSH, Chinese Group on the Study of Severe Hepatitis B; CTP, Child-Turcotte-Pugh; ABIC, age-bilirubin-INR-creatinine; APM, artificial liver support system prognosis model; APLH-Q, age-prothrombin time-liver cirrhosis-hepatic encephalopathy-QTc; ANN, artificial neural network; CART, classification and regression tree; APASL, Asian Pacific Association for the Study of the Liver; CMA, Chinese Medical Association; AASL, American Association for the Study of Liver Failure; EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure.
mainly based on the APASL consensus \( n=18 (58.06\%) \) or the CMA liver failure guidelines \( n=8 (25.81\%) \). EASL-ACLF criteria were used in four studies \( n=2 (6.45\%) \) and Chinese Group on the Study of Severe Hepatitis B-acute-on-chronic liver failure (COSHH-ACLF) in one study \( n=1 (3.23\%) \). One study \( n=1 (3.23\%) \) adopted the diagnostic criteria of acute liver failure proposed by the American Association for the Study of Liver Disease (AASLD). One study did not mention specific diagnostic criteria \( n=1 (3.23\%) \).

As shown in Supplementary Table 1, 17 studies had a quality score of 0–2 (low quality), 12 had a score of 3–5 (medium quality), and only 2 had a score of 6–8 (high quality). Most were retrospective \( n=26 (83.87\%) \) and single-center \( n=30 (96.77\%) \), and only one was pre-registered. In terms of variable screening, most studies used regression approaches \( n=26 (83.87\%) \). The logistic regression model \( n=14 (45.16\%) \) and the Cox hazard proportional model \( n=12 (38.71\%) \) were the two methods most frequently used to identify risk variables. Two studies \( (6.45\%) \) did not mention a clear variable screening method. Among the clinical variables consisting of CPMs, serum bilirubin \( (67.74\%) \), international normalized ratio (INR) \( (54.84\%) \), and hepatic encephalopathy \( (51.61\%) \) were most frequent (Table 2). In terms of model formula, most CPMs were calculated as the results of multivariate logistic regression or Cox proportional hazard model as follows: (regression coefficients \( \beta1 \)×(variable 1)+(regression coefficients \( \beta2 \)×(variable 2)+(regression coefficients \( \beta3 \)×(variable 3)+⋯+constant (if logistic regression) \( n=19 (61.29\%) \). Three \( (9.68\%) \) were calculated based on the sum of a series of categorical variables, the values of which were equally assigned (such as the Child-Turcotte-Pugh (CTP) score); moreover, 5 \( (16.13\%) \) were represented in the form of a nomogram, 2 \( (0.66\%) \) were represented as an artificial neural network, and 2 \( (0.66\%) \) were represented as a classification and regression tree.

A total of 19 CPMs \( (61.25\%) \) were validated, including 1 model that was validated by two cohorts. Single-center and multicenter validation cohorts were used in 14 and 6 studies, respectively (a single-center cohort and a multicenter cohort were used for the CPM with two validation cohorts).

Eight of fourteen single-center validation cohorts were derived from the same center as the modeling cohorts, and Chinese Group on the Study of Severe Hepatitis B-acute-on-chronic liver failure (COSHH-ACLF) in one study \( n=1 (3.23\%) \). One study \( n=1 (3.23\%) \) adopted the diagnostic criteria of acute liver failure proposed by the American Association for the Study of Liver Disease (AASLD). One study did not mention specific diagnostic criteria \( n=1 (3.23\%) \).

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Eight of fourteen single-center validation cohorts were derived from the same center as the modeling cohorts, and the other six cohorts were derived from external centers. The validation cohort was prospective in five studies \( (26.32\%) \) and retrospective in fourteen studies \( (73.68\%) \). The patients in the model cohort and validation cohort were recruited during the same period in two studies but not in the other sixteen studies; one study did not mention the timing of recruitment. The sample size of the validation cohort was generally smaller than the derivation cohort and ranged from 88 to 300 patients.

### Characteristics of non-HBV-ACLF-specific CPMs

A total of 21 studies evaluated the performance of CPMs that were non-specific for HBV-ACLF. Eighteen were single-center studies \( (85.7\%) \) and three were multicenter studies \( (14.3\%) \). Ten models developed for other diseases were evaluated, including KCC for acute liver failure, age-bilirubin-increatinine-creatinine-creatinine (ABIC) score for alcohol liver diseases, albumin-bilirubin (ALBI) score for liver cancer, CTP, modified Child-Turcotte-Pugh (mCTP) score, MELD, MELD-Na, updated MELD (UpMELD), and MELD excluding the international normalized ratio (MELD-XI) score for end-stage liver diseases.

### Model performance

Among the 52 selected studies, 50 evaluated model predictive performance. Forty-six studies reported the AUROC, four studies reported the C-Index, and only five studies reported the Hosmer-Lemeshow test to assess model calibration.

Table 3 presents the discriminative performance of each CPM. The AUROC of all CPMs varied between 0.521 and 0.970, the sensitivity between 34% and 100%, and the specificity between 2.60% and 93.31%. The AUROC of 31 CPMs specific for HBV-ACLF ranged from 0.63 to 0.97, the sensitivity from 44.44% to 92.6%, and the specificity from 42.3% to 95.31%. As shown in Table 2, the MELD score was the most widely used CPM \( (44 \text{ studies}) \), followed by the MELD-Na score \( (21 \text{ studies}) \) and the CTP score \( (19 \text{ studies}) \).

The capacity of discrimination of MELD varied widely among different studies, as indicated by the AUROC \( (0.58 \text{ and 0.94}) \), sensitivity \( (43.70\% \text{ and } 100\%) \), specificity \( (63.8\% \text{ and } 90.2\%) \), and optimal cut-off point \( (21 \text{ and } 32 \text{ points}) \). Likewise, a large variation in predictive performance was seen in the MELD-Na score \( (0.53 \text{ and 0.922}) \), sensitivity \( (41.90\% \text{ and } 86.4\%) \), specificity \( (61.9\% \text{ and } 86.7\%) \), and optimal cut-off point \( (22.35 \text{ and } 34.28) \) and the CTP score \( (0.553 \text{ and 0.878}) \), sensitivity \( (34\% \text{ and } 99.35\%) \), specificity \( (39.71\% \text{ and } 84\%) \), and optimal cut-off point \( (9 \text{ and } 12.5 \text{ points}) \).

In addition, we performed a pooled analysis of diagnostic accuracy of several common CPMs. As shown by the summary receiver operating characteristic (SROC) curves in Figure 3, the overall discriminative performance of the MELD score and chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score seemed to be higher than those of the CTP score and MELD-Na score.

### Impact of ACLF severity and diagnostic criteria on model performance

To further analyze the factors contributing to the large variation in the predictive performance of a specific model among different studies, we compared the accuracy of MELD in HBV-ACLF defined by different diagnostic criteria. In APASL-defined ACLF patients, the AUROC of the MELD score was between 0.580 and 0.940, the sensitivity was between 43.7% and 88.9%, the specificity was between 67.2% and 90.2%, and the best cut-off point was between 21.57 and 29.6 points. In CMA-defined ACLF patients, the AUROC was between 0.612 and 0.906, the sensitivity was between 51% and 100%, the specificity was between 70.2% and 91.4%, and the best cut-off point was between 21 and 32 points.

Next, we assessed the relationship between the mean MELD value of patients at admission and the AUROC value of the MELD score. As shown in Figure 4, we found that the lower the mean MELD value of HBV-ACLF patients at admission, the greater the AUROC value. This suggested a negative correlation between disease severity at admission and the discriminative capacity of the MELD score.

### Discussion

In this study, we systematically summarized the available clinical prediction models for HBV-ACLF and performed an extensive review of each study with regard to modeling data, modeling approach and model performance. Although the number of HBV-ACLF-specific CPMs has increased rapidly in the past 10 years, there are major concerns about the quality and reproducibility of most of them. Our analysis showed that the development of most HBV-ACLF-specific
| New CPMs | Variables | Methods |
|----------|-----------|---------|
| Ke’s model | TB; PTA; WBC; serum creatinine; maximum depth of ascites; HE score; singultus score; digestive tract hemorrhage score | Not mentioned |
| Li’s model | HE; serum creatinine; PTA; TB; infection; liver size; ascites fluid level | Clinical experience |
| Sun’s model | HR; LC; hepatitis B e antigen; ALB; PTA | Logistic regression |
| LRM | HE; HR; LC; hepatitis B e antigen; PTA; Age | Logistic regression |
| He’s model | HE; serum creatinine; INR; TB at the end of 2 weeks of treatment; cholinesterase | Logistic regression |
| TPPM | TB; INR; complications; HBV DNA | Logistic regression |
| Zheng’s model | TB; serum creatinine; PTA; HE; the maximum depth of ascites; WBC | Not mentioned |
| ALPH-Q | age; LC; PT; HE; QTc | COX regression |
| Yan’s model | age; HE score; MELD | COX regression |
| Yi’s model | HE; lnPTA2; lnINR2; lnTB2 (PTA2, INR2 and TB2 corresponded to those parameters at two weeks of treatment). | Logistic regression |
| Li’s model | age; Family history of HBV; HE; HR; WBC; PLT; INR; TB; TBA; CHE; serum creatinine; serum sodium; HBV DNA; hepatitis B e antigen | Logistic regression |
| HBV-ACLFs | age; serum creatinine; WBC | COX regression |
| HAM | MELD; HE; AFP; WBC; age | Logistic regression |
| Chen’s model | MELD, age, sodium | Logistic regression |
| MELD-LAC | LAC, MELD | Logistic regression |
| HINAT ACLF | HE, INR, NLR | COX regression |
| Lei’s model | NLR; serum levels of gamma-glutamyltransferase; ALB; sodium; artificial liver support therapy | Logistic regression |
| Lin’s model | age; LAAR; MELD | COX regression |
| Shi’s model | age; TB; serum sodium; PTA | COX regression |
| Xue’s model | TB; ALB; INR; Blood neutrophils percentage count; HE; Suspicion of infection | Logistic regression |
| Gong’s model | NLR; age; TB | COX regression |
| Lin’s model | TB; evolution of bilirubin; PTA; PLT; anti-HBe | Logistic regression |
| HINT | HE; INR; neutrophil count; TSH | COX regression |
| COSSH-ACLF | INR; HBV-SOFA; Age; TB | COX regression |
| CTP-ABIC | CTP; ABIC | COX regression |
| Gao’s model | age; TB; ALB; INR; HE | COX regression |
| APM | AFP; HE score; serum sodium; INR | COX regression |
| ANN | serum sodium; TB; age; PTA; Hb; hepatitis B e antigen | Univariate analysis and Artificial neural network |
| ANN | TB, PTA, serum sodium, HE, hepatitis B e antigen, GGT, ALP, age | Univariate analysis and Artificial neural network |
| CART | TB, age, serum sodium, INR | Univariate Logistic regression and Classification and regression tree |
| CART | HE, PT, TB | Logistic regression and Classification and regression tree |

HE, hepatic encephalopathy; HB, hemoglobin; HR, hepatorenal syndrome; LC, liver cirrhosis; ALB, albumin; PTA, prothrombin activity; TB, total bilirubin; WBC, white blood cells; INR, international normalized ratio; PT, prothrombin time; QTc, the QT interval which is corrected for the heart rate; PLT, platelet; TBA, total bile acid; CHE, cholinesterase; AFP, alpha-fetoprotein; LAC, lactic acid; NLR, neutrophil–lymphocyte ratio; MELD, model for end-stage liver disease; LAAR, liver to abdominal area ratio; TSH, thyroid-stimulating hormone; GGT, γ-glutamyltransferase; ALP, alkaline phosphatase; LRM, logistic regression model; TPPM, Tongji prognostic predictor model; ANN, artificial neural network; HAM, HBV-ACLF MELD; MELD-LAC, model for end-stage liver disease-lactate; HINAT ACLF, HE-INR-Neutrophil count-thyroid stimulating hormone; COSSH, Chinese Group on the Study of Severe Hepatitis B; CTP, Child-Turcotte-Pugh; ABIC, age-bilirubin-INR-creatinine; CART, classification and regression tree; APM, artificial liver support system prognosis model; APLH-Q, age-prothrombin time-liver cirrhosis-hepatic encephalopathy-QTc; ANN, artificial neural network; CART, classification and regression tree.
Yu X. et al: Clinical prediction models for HBV-ACLF

Table 3. Discriminative performance of CPMs

| Model                | AUROC/C-Index | Sensitivity       | Specificity       | Cut-off   | References†                  |
|----------------------|---------------|-------------------|-------------------|-----------|-------------------------------|
| MELD                 | 0.58–0.94     | 43.70–100%        | 63.8–90.2%        | 21–32     | [3–6, 8–10, 12, 13, 15–46, 51], |
| Ke's model           | NA            | NA                | NA                | NA        | [1]                           |
| KCC                  | 0.642–0.783   | 41–59%            | 2.6–87.7%         | 0–0.5     | [32, 36]                      |
| CTP                  | 0.553–0.878   | 34–99.35%         | 39.71–84%         | 9–12.5    | [4, 8–10, 16–18, 20, 23, 24, 29, 32, 36, 42, 45–48], |
| MELD-Na              | 0.563–0.922   | 41.9–86.4%        | 61.9–86.7%        | 22.35–34.28 | [5, 13, 14, 16–18, 20, 22, 24–29, 34, 37, 39, 46, 47, 49, 52] |
| Li's model           | 0.953         | 97%               | 82%               | 9.5       | [2]                           |
| Sun's model          | 0.647–0.891   | 68.6–72.3%        | 52.1–52.5%        | −2.554    | [3, 4, 13]                    |
| Zhang's model       | 0.68–0.914    | 64–92.6%          | 42.3–95.1%        | −0.3264–0.5176 | [3, 4, 8, 13, 30, 36, 41] |
| MELD-Na              | 0.521–0.886   | 41.9–78.21%       | 50.5–90.16%       | 25.6–32   | [10, 12, 13, 14, 28, 36, 42, 49, 50] |
| He's model           | 0.85±0.03     | NA                | NA                | NA        | [5]                           |
| iMELD                | 0.540–0.864   | 54.7–89.58%       | 56.16–85%         | 34.705–52 | [5, 10, 13, 14, 17, 28, 3, 1, 36, 37, 39, 42] |
| MESO                 | 0.571–0.905   | 38.7–80.77%       | 75.25–91.80%      | 1.986–21.61 | [5, 10, 13, 28, 42] |
| TPPM                 | 0.786–0.970   | 84.09–89.6%       | 61.54–94.7%       | 0.22      | [6, 25, 38]                  |
| Zheng's model        | 0.900–0.970   | NA                | NA                | NA        | [7]                           |
| UpMELD               | 0.687         | 44.7%             | 87.2%             | 5.5       | [39]                          |
| MELD-XI              | 0.647         | 55.3%             | 71.8%             | 20.5      | [39]                          |
| UKMELD               | 0.766         | 57.6%             | 81.6%             | 45.5      | [39]                          |
| ALPH-Q               | 0.837–0.896   | 78–78.7%          | 85.1%             | 6.778     | [8]                           |
| Yan's model          | 0.853–0.867   | 72–76%            | 84.8–89.2%        | 4.66      | [9]                           |
| SOFA                 | 0.705–0.751   | 54.2–60%          | 80.4–84.7%        | 6.5       | [9, 16]                      |
| CLIF-SOFA            | 0.711–0.876   | 54.3–80.14%       | 64.56–91.1%       | 7–8.5     | [9, 16, 23, 44, 50]          |
| Yi's model           | 0.930±0.016   | NA                | NA                | NA        | [10]                          |
| iMELD-C              | 0.776–0.862   | 69.23–89.58%      | 78.71–80.33%      | 49.306–52.157 | [10] |
| LRM                  | 0.93          | NA                | 87.1%             | 3.16      | [11]                          |
| HBV-ACLFs            | 0.704 (C-Index)| NA               | NA                | NA        | [12]                          |
| CLIF-C ACLFs         | 0.632–0.873   | 61.86–93.65%      | 63.7–78.6%        | 36.78–43.76 | [12, 16, 23–27, 29, 31, 44, 46] |
| HAM                  | 0.868–0.894   | 84.9–91.5%        | 70.9–75%          | −1.191    | [13]                          |
| mCTP                 | 0.74          | 91%               | 48.8%             | 14        | [42]                          |
| ALBI                 | 0.583–0.784   | 62.6–65.9%        | 67.2–81.4%        | −1.119–0.95 | [17, 43, 45] |
| ALBI+MELD            | 0.912         | 76.7%             | 90.9%             | NA        | [43]                          |
| Chen's model         | 0.867         | NA                | NA                | NA        | [14]                          |
| MELD-LAC             | 0.859         | 91.5%             | 80.1%             | −0.4741   | [15]                          |
| HINAT ACLF           | 0.839–0.855   | 82%               | 74.5%             | 4.6       | [16]                          |
| CLIF-C OF            | 0.656–0.906   | 53.9–92.6%        | 72.9–78.8%        | 8.5–10.5  | [16, 24, 25, 44, 45, 46, 50] |
| Le's model           | 0.656         | 62.2%             | 64.1%             | NA        | [17]                          |
| Lin's model          | 0.854–0.890   | NA                | NA                | NA        | [18]                          |
| Shi's model          | 0.790–0.799   | NA                | NA                | NA        | [19]                          |
| Xue's model          | 0.813–0.848   | 44.44%            | 93.63%            | NA        | [20]                          |

(continued)
Table 3. (continued)

| Model               | AUROC/C-Index | Sensitivity   | Specificity | Cut-off     | References† |
|---------------------|---------------|---------------|-------------|-------------|-------------|
| ABIC                | 0.695–0.829   | 54.4–73.8%    | 81.7%       | 9.16–9.44   | [45,48]     |
| Gong's model        | 0.63–0.742    | NA            | NA          | NA          | [21]        |
| Lin's model         | 0.79–0.86     | 67.3%         | 91%         | −0.73       | [22]        |
| HINT                | 0.889–0.917   | 74.60–79.43%  | 84.56–95.31%| −0.77       | [23]        |
| COSSH-ACLF          | 0.718–0.898   | 54.9–89.04%   | 55.56–91.78%| 3.7–6.4     | [23–27,31,50]|
| CLIF AD             | 0.775         | NA            | NA          | NA          | [46]        |
| CTP-ABIC            | 0.927         | 90%           | 80.3%       | 9.08        | [48]        |
| AARC-ACLFs          | 0.790         | NA            | NA          | NA          | [25]        |
| Gao's model         | 0.58–0.80     | (C-Index)     | NA          | NA          | [26]        |
| APM                 | 0.747–0.790   | 73.2%         | 71.5%       | 2.56        | [27]        |
| ANN                 | 0.765–0.869   | NA            | NA          | NA          | [28]        |
| CART                | 0.896–0.905   | 69.7–85.2%    | 80.1–93.5%  | NA          | [30]        |
| CART                | 0.820–0.824   | 88.2–88.6%    | 62.7–68.5%  | NA          | [31]        |

†See Supplementary File 1. CTP, Child–Turcotte–Pugh; KCC, King's College Criteria; MELD, model for end-stage liver disease; SOFA, sequential organ failure assessment; LRM, logistic regression model; TPPM, Tongji prognostic predictor model; MESO, model for end-stage liver disease score to serum sodium ratio index; iMELD, integrated MELD model; UpMELD, updated MELD; MELD-Na, model for end-stage liver disease-sodium; MELD-Na, model for end-stage liver disease sodium; MELD-XI, MELD excluding the international normalized ratio; UKMELD, United Kingdom MELD; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; iMELD-C, iMELD plus complications; HBV-ACLFs, hepatitis B virus related acute-on-chronic liver failure score; CLIF-C ACLFs, chronic liver failure-consortium acute-on chronic liver failure score; HAM, HBV-ACLF MELD; mCTP, modified Child-Turcotte-Pugh; ALBI, Albumin-bilirubin; MELD-LAC, model for end-stage liver disease-lactate; HINAT ACLF, HE-INR-NLR-age-TB ACLF; CLIF-C OF, chronic liver failure-consortium organ failure; ABIC, age-bilirubin-INR-creatinine; HINT, HE-INR-neutrophil count-thyroid stimulating hormone; COSSH-ACLF, Chinese Group on the Study of Severe Hepatitis B-ACLF; CLIF AD, chronic liver failure-consortium acute decompensation; AARC-ACLFs, APASL ACLF research consortium-ACLF; LRM-Z, 2 logistic regression model; APM, artificial liver support system-prognosis model; APLH-Q, age-prothrombin time-liver cirrhosis-hepatic encephalopathy-QTc; ANN, artificial neural network; CART, classification and regression tree.

Fig. 3. Relationship between MELD score on admission and AUROC values. MELD, model for end-stage liver disease; AUROC, area under the receiver operating characteristic curve. AUROC, area under the receiver operating characteristic curve; MELD, model for end-stage liver disease.
Yu X. et al: Clinical prediction models for HBV-ACLF

Fig. 4. SROC for MELD score, CTP score, MELD-Na score, iMELD score, LRM score and CLIF-SOFA score. SROC, summary receiver operating characteristic curve; MELD, model for end-stage liver disease; CTP, Child-Turcotte-Pugh; MELD-Na, MELD-sodium; iMELD, integrated MELD; LRM, logistic regression model; CLIF-SOFA, chronic liver failure-sequential organ failure assessment.

Table 4. Similarities and differences of ACLF diagnostic criteria

|                | CMA                      | APASL                   | EASL-CLIF               | NACSLED                | COSSH                   |
|----------------|--------------------------|-------------------------|-------------------------|------------------------|-------------------------|
| Definition     | Severe liver damage caused by various insults on the basis of chronic liver disease, representing a clinical syndromes mainly manifesting as coagulopathy, jaundice, hepatic encephalopathy, ascites, etc. | Acute hepatic insult manifesting as Jaundice and coagulopathy. Complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease associated with high mortality. | An acute deterioration of pre-existing chronic liver disease usually related to a precipitating event and associated with increased mortality at 3 months due to multisystem organ failure. | A syndrome characterized by acute deterioration in a patient of cirrhosis due to infection presenting with two or more extrahepatic organ failure. | A complicated syndrome with a high short-term mortality rate that develops in patients with HBV-related chronic liver disease regardless of the presence of cirrhosis and is characterized by acute deterioration of liver function and hepatic and/or extrahepatic organ failure. |
| Proposing time | 2006 (updated on 2014)   | 2009 (updated on 2019)  | 2013                    | 2014                   | 2017                    |
| Chronic liver disease | compensated chronic liver disease | Non-cirrhotic chronic liver disease and previously compensated cirrhosis | Decompensated cirrhosis | Decompensated cirrhosis | Non-cirrhotic chronic liver disease and cirrhosis |
| Acute precipitating events | Acute hepatic insults | Acute hepatic insults | Any and frequently without identifiable events | Infection | Any and frequently without identifiable events |
| Etiology       | All                      | All                     | All                     | All                    | HBV                     |
| Definition of liver failure | PTA ≤40% and serum bilirubin ≥10 mg/dL or daily rise ≥1 mg/dL | INR ≥1.5 and serum bilirubin ≥5 mg/dL | Serum bilirubin ≥12 mg/dL | None                  | Serum bilirubin ≥12 mg/dL |

CMA, Chinese Medical Association; APASL, Asian Pacific Association for the study of the liver; EASL-CLIF, European Association for the Study of the Liver-Chronic Liver Failure consortium; NACSLED, North American Consortium for the Study of End-Stage Liver Disease; COSSH, Chinese Group on the Study of Severe Hepatitis B.
The present study identified common variables used in CPMs, in addition to the components of MELD. The presence of hepatic encephalopathy (HE) was frequently reported to be an independent variable associated with poor outcome.27 In addition, indicators of systemic inflammation, such as white blood cell (WBC) count, neutrophil percentage, and neutrophil-to-lymphocyte ratio (NLR), are common risk factors for short-term death.28 Other common variables included age, presence of ascites, serum sodium and hepatitis B e antigen presence. On the other hand, one of the MELD parameters, serum creatinine, was less frequently reported as an independent risk factor in HBV-ACLF. As a result, the overall predictive performance of MELD in HBV-ACLF is not satisfactory, and consistent with this finding, recent studies have shown limited capacity of MELD-Na in identifying ACLF patients at high risk of death on LT waiting lists.29-31 By contrast, a MELD-based scoring system that integrates HE and age outperforms the MELD score in predicting 90-day mortality of HBV-ACLF.32 In addition to the variables constituting the CPMs, model performance is determined by the weighting of specific variables. For example, although MELD does not include important criteria such as HE and ascites, the CTP with these parameters performed less well overall than the MELD score in which each variable is equally weighted.

In conclusion, a growing number of HBV-specific CPMs have been developed in recent years, but most are flawed in either the quality of the modeling data, the integrity of the modeling approach, or external validation. The MELD score is the most commonly used CPM, although it is non-HBV-specific. However, there is significant heterogeneity in the predictive performance of the MELD score among different studies due to the confounding effect of disease severity. Therefore, the clinical utility of CPMs in predicting the short-term prognosis of HBV-ACLF remains to be undefined. There is redundancy in the current HBV-ACLF CPMs, and there is an urgent need to establish high-quality prognostic models to better guide clinical practice. The development of future HBV-ACLF-specific CPMs should include the following elements to ensure the reliability of the model: (1) unified HBV-ACLF diagnostic criteria with a defined endpoint; (2) high-quality and unbiased modeling and validation data from prospective, large-sample, multicenter cohorts, as well as real-world validation; (3) selection of a couple of non-redundant and easily accessible variables for inclusion in the model via a well-adjusted process; (4) appropriate handling of events competing with death; (5) assessment of model discrimination and calibration; and (6) appropriate presentation of clinical utility.

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Conflict of interest
The authors have no conflict of interests related to this publication.

Author contributions
Conceptualization of the idea and design of the study (JS, YS), drafting of the manuscript (XY, YL), revision of the manuscript (YS, JS), and search and selection, data extraction, analysis, and interpretation (XY, YL, HT, XX, KG, JY). All authors read and approved the final manuscript.

Data sharing statement
No additional data are available.
Yu X. et al: Clinical prediction models for HBV-ACLF

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