eGastroenterology

Evidence-based incorporation of key parameters into MELD score for acute-on-chronic liver failure

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To cite: Yu X, Zhou R, Tan W, *et al*. Evidence-based incorporation of key parameters into MELD score for acute-on-chronic liver failure. *eGastroenterology* 2024;**0**. doi:10.1136/egastro-2024-100101

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/egastro-2024-100101).

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Received 31 May 2024
Accepted 25 July 2024

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ABSTRACT

Background The model for end-stage liver disease (MELD) score is widely used for the prognostication in end-stage liver disease but has limited performance in acute-on-chronic liver failure (ACLF). In this study, we identified additional predictive parameters and reformed the MELD score to predict ACLF more accurately.

Methods A meta-analysis was performed on relevant studies to identify the predictive factors of 28-day/90-day outcomes of ACLF, which were validated in two large prospective cohorts. A prognostic score was developed by incorporating predictive parameters into the MELD score. The model was evaluated with a focus on discrimination and calibration.

Results The meta-analysis incorporated 32 cohort studies with a total of 13 939 patients, of which 13 risk factors were identified, and 3 risk factors (age, neutrophil count and hepatic encephalopathy (HE) grade) besides MELD score were validated in 751 patients with ACLF derived from two prospective cohorts. A new model (Chinese Acute-on-Chronic Liver Failure Consortium (CATCH-LIFE)-MELD score) was developed as follows: 0.028×age+0.3×HE grade+0.039×neutrophil count+0.079×MELD score. CATCH-LIFE-MELD score achieved a concordance index of 0.791/0.788 for 28-day/90-day outcomes, which is superior to other traditional scores. Other discrimination indices, including net reclassification improvement, integrated discrimination improvement and probability density function, and calibration including Nagelkerke's R^2 and Brier scores confirmed its superiority. Moreover, the accuracy of CATCH-LIFE-MELD score remained stable. It was highest in patients with or without hepatitis B virus infection, cirrhosis, liver failure or under the Chinese Group on the Study of Severe Hepatitis B (COSSH) criteria or European Association for the Study of the Liver (EASL) criteria. All results were substantiated by an evaluation using an external cohort.

Conclusions CATCH-LIFE-MELD score, a modified MELD score exhibited improved accuracy in predicting the short-term prognosis of ACLF than other traditional scores.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with acute-on-chronic liver failure (ACLF) are at high-risk mortality, and accurate prediction of short-term outcomes is crucial for managing patients with ACLF.

⇒ The model for end-stage liver disease (MELD) score is extensively used for the prognostic evaluation of ACLF, yet its efficacy is constrained.

WHAT THIS STUDY ADDS

⇒ Meta-analysis approach was used to identify predictive factors for adverse outcomes in patients with ACLF, and these factors were incorporated into the MELD score to develop a new predictive model (Chinese Acute-on-Chronic Liver Failure Consortium (CATCH-LIFE)-MELD score), which was validated in cohorts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ CATCH-LIFE-MELD score can be used for predicting and stratifying the risk of death in patients with ACLF, providing direction for future research on new therapeutic approaches.

INTRODUCTION

Acute-on-chronic liver failure (ACLF) is a critical syndrome defined by the acute exacerbation of the existing chronic liver disease, leading to multiple organ failure and high short-term mortality.[1] Although there are therapies for ACLF, the 90-day mortality rate remains high and increases as the ACLF grade increases. Liver transplantation (LT) improves survival in patients with ACLF.[2] However, it is constrained by the organ allocation policy, shortage of organ donors and high mortality among those awaiting liver

transplants.[3] Therefore, it is of critical clinical relevance to accurately and early predict ACLF outcomes to tailor current therapeutic options and provide a rational basis for testing novel therapies.

The model for end-stage liver disease (MELD) score and the model for end-stage liver disease with sodium (MELD-Na) score are widely used for prognostication in ACLF and for organ prioritisation in LT.[4 5] However, MELD score and MELD-Na score have not been developed specifically for ACLF assessment and have limited performance.[6] Additional parameters should be identified and incorporated to improve MELD score. However, some prior attempts were limited by the sample size, lack of external validation or weakness of the statistical approach.[7] Besides, a selection bias may exist when screening the parameters in any specific cohort.

To overcome these weaknesses, we used a meta-analysis approach to identify the predictive factors for adverse outcomes in patients with ACLF. The selected factors were validated in two large-scale, multicentre, prospective and observational cohorts. Based on these factors, we developed and validated a prognostic score in an external cohort.

METHODS

Meta-analysis of ACLF studies to identify predictive factors

An electronic literature search in PubMed, Web of Science and EMBASE was conducted from inception until March 2023, using text or Medical Subject Headings terms as follows: “acute-on-chronic liver failure”, “mortality” and “cohort study” (online supplemental table 1). The inclusion criteria were cohort studies (either prospective or retrospective) that used the Asian-Pacific Association for the Study of the Liver (APASL) definition for ACLF and offered a follow-up period of no less than 28 or 90 days to calculate the mortality rates.

To determine the quality of design and content, the Newcastle-Ottawa Scale (NOS) was adopted for every study, and those with a score >7 were considered methodologically high-quality. The selection methodology is illustrated in the flow chart (figure 1). Detailed information about the search strategy, data analysis and quality evaluation is provided in the online supplemental data. The definition of the APASL-ACLF criteria is detailed in the online supplemental data.

Risk factors for ACLF mortality were quantified by extracting HRs with a 95% CIs. The Cochrane Q test was conducted to evaluate heterogeneity, with I^2 values >50% or p values <0.10 considered indicative of high heterogeneity. Due to the heterogeneity, a random effects model was employed to synthesise the effects of risk factors. Publication bias was assessed using Egger’s linear regression test, with a p value <0.10 considered significant.

Development and validation of a prognostic score for ACLF

The derivation cohorts were the two multicentre observational cohorts of the Chinese Acute-on-Chronic Liver Failure Consortium (CATCH-LIFE) study (January 2015 to December 2016 (NCT02457637) and September 2018 to March 2019 (NCT03641872)) as previously reported.[8 9] An external cohort of patients with ACLF from January 2015 to December 2019 was used to validate the new score. Data collection and follow-up schedules are detailed in the online supplemental material.

The predictive factors identified by the meta-analysis were validated in the derivation cohorts using a Fine-Gray competing risk model, setting LT as the competing event for death. Variables were removed if the correlation coefficient was >0.6 by a collinearity test or based on clinical relevance. A new prognostic score was developed using a Cox proportional hazard model (linear combinations of

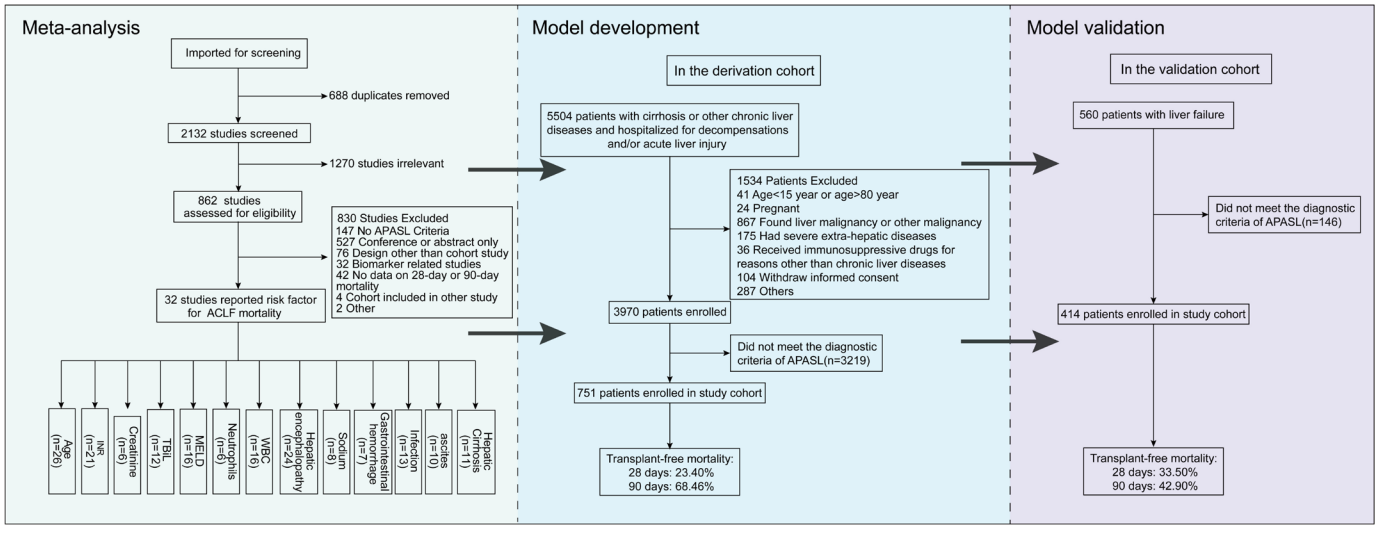

Figure 1 Flow chart of study selection. ACLF, acute-on-chronic liver failure; APASL, Asian-Pacific Association for the Study of the Liver; INR, international normalised ratio; MELD, model for end-stage liver disease; TBiL, total bilirubin; WBC, white blood cell count.

selected risk factors multiplied by their regression coefficients from Cox regression).

The predictive performance of the new score was compared with five generic scores, including Chinese Group on the Study of Severe Hepatitis B-ACLF score (COSSH-ACLFs); COSSH-ACLF II score (COSSH-ACLF IIs); Chronic Liver Failure Consortium ACLF score (CLIF-C ACLFs), MELD score and MELD-Na score. The model discrimination was further evaluated using the area under the receiver operating characteristic curve (AUROC), concordance index (C-index), probability density function (PDF), integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) metric. The discriminative performance of the model was considered good if the C-index or AUROC exceeded 0.75. An NRI or IDI >0 indicated enhanced discrimination in the new model compared with the reference model. For PDF, the overlapping coefficient was used to assess the similarity of probability distributions between survival and non-survival, with a smaller overlapping coefficient implying better discrimination of the model. The model calibration was evaluated using the Hosmer-Lemeshow (H-L) test, Nagelkerke's R^2, calibration plot and Brier score. In the H-L test, a lower χ^2 value coupled with a higher correlation p value signifies a more appropriate model fit. An H-L p value ≥0.05 is indicative of suitable calibration. Furthermore, a superior calibration is suggested by a higher R^2 and a smaller Brier score. Finally, decision curve analysis (DCA) was adopted to evaluate the clinical utility of the scoring models.

Statistical analysis

Continuous variables are expressed as the mean (SD) or median (IQR) and compared using Student's t-test or Mann-Whitney U test. Binary or nominal variables are presented as numbers (%) and compared using the χ^2 test. Competing risk regression (Fine-Gray) was performed to identify risk factors for ACLF death. The results are expressed as subdistribution HRs and 95% CIs. Statistical analysis was conducted using the SPSS software (V.26; Chicago, Illinois, USA) or R software (V.4.0.5). A p value <0.05 was considered to be statistically significant.

RESULTS

Meta-analysis of the ACLF studies

For the meta-analysis, 32 cohort studies were included, with a total of 13 939 patients with ACLF, of whom 6277 (45.03%) died during the follow-up period. The study characteristics are listed in online supplemental table 2. NOS scores are indicated in online supplemental table 3, and all included studies depicted a quality score >7.

Besides MELD score, 12 predictive factors were related to ACLF outcome from meta-analysis, as listed below: age, international normalised ratio (INR), infection, serum sodium, white blood cell count (WBC), serum creatinine, neutrophils, total bilirubin (TBiL), gastrointestinal haemorrhage, ascites, hepatic encephalopathy (HE) and liver cirrhosis. All 13 factors (online supplemental figure 3) were associated with the 90-day outcomes. The pooled effects of risk factors were as follows (HR with 95% CI): age (1.03 (1.02 to 1.03)), INR (1.67 (1.41 to 1.97)), creatinine (2.18 (1.04 to 4.00)), TBiL (1.03 (1.02 to 1.04)), MELD score (1.12 (1.08 to 1.16)), WBC (1.05 (1.02 to 1.07)), neutrophils (1.07 (1.03 to 1.12)), HE (2.09 (1.78 to 2.47)), infection (1.90 (1.42 to 2.53)), sodium (0.96 (0.92 to 0.99)), gastrointestinal haemorrhage (1.73 (1.30 to 2.29)), ascites (1.82 (1.38 to 2.42)) and hepatic cirrhosis (1.46 (1.23 to 1.73)). Ten of the 13 factors (online supplemental figure 2) were significantly associated with 28-day outcome: age (1.04 (1.02 to 1.05)), INR (1.75 (1.48 to 2.07)), TBiL (1.04 (1.02 to 1.05)), MELD score (1.07 (1.05 to 1.09)), WBC (1.13, (1.06 to 1.20)), neutrophils (1.06 (1.02 to 1.11)), infection (2.03 (1.36 to 3.04)), HE (2.69 (2.27 to 3.17)), sodium (0.96 (0.93 to 0.99)) and gastrointestinal haemorrhage (1.84 (1.25 to 2.72)). The pooled HR with 95% CI is illustrated in the forest plot (online supplemental figure 1), and the detailed results of data synthesis are presented in online supplemental figure 4–5.

Patient characteristics of the studied cohorts

Among the 751 patients with ACLF enrolled from the CATCH-LIFE cohort, 649 (86.4%) had hepatitis B virus (HBV) infection, 51 (6.8%) had alcohol abuse and 51 (6.8%) had other aetiologies. The mean age of the patients was 48±12 years, and most were males (n=662, 82.8%) (figure 1 and online supplemental table 4). Ascites were the most frequently observed complication, affecting 78.7% of patients. This was followed by infection (38.2%), HE (17.3%), hepatorenal syndrome (9.2%) and gastrointestinal haemorrhage (4.3%). Liver failure (73.4%) was the most frequent type of organ failure, followed by coagulation failure (32.1%), renal failure (5.7%) and brain failure (4.7%). The measurements of the disease severity were as follows: 6.7 (1.4) for COSSH-ACLF IIs, 7.0 (1.9) for COSSH-ACLFs, 40.1 (9.6) for CLIF-C ACLFs, 26.3 (6.5) for MELD score and 28.0 (9.5) for MELD-Na score. The LT-free mortality rates were 23.40% on 28 days and 68.46% on 90 days.

Development of a new CATCH-LIFE-MELD score

The candidate variables were subjected to the Fine-Gray competing risk regression analysis in the derivation cohort. To exclude variables with significant collinearity, age (28 days: HR 1.029 (95% CI 1.016 to 1.041), p<0.001; 90 days: 1.025 (1.016 to 1.035), p<0.001), HE grade (28 days: 1.350 (1.176 to 1.550), p<0.001; 90 days: 1.302 (1.156 to 1.465), p<0.001), neutrophil count (28 days: 1.040 (1.011 to 1.069), p=0.006; 90 days: 1.030 (1.006 to 1.055), p=0.013) were identified as additional parameters for a new prognostic model of ACLF outcome, alongside the MELD score (28 days: 1.082 (1.064 to 1.101), p<0.001, 90 days: 1.084 (1.068 to 1.101), p<0.001) (online supplemental figure 6). The CATCH-LIFE-MELD score was developed as follows: R=0.028×age+0.3×HE grade+0.039×neutrophil count+0.079×MELD score.

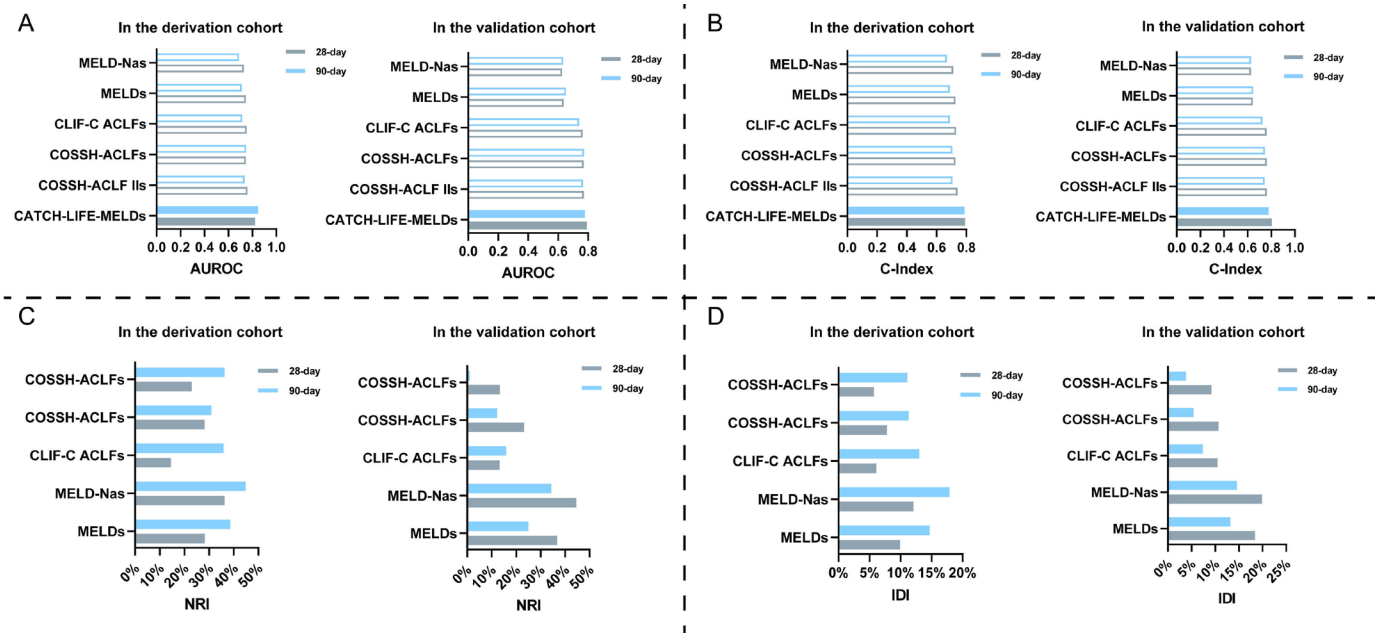

Figure 2 Discrimination of the prognostic scores for prediction of 28-day/90-day mortality. (A) Area under the receiver operating characteristic curve (AUROC) analysis and (B) concordance index (C-index) of prognostic scores for predicting 28-day/90-day mortality. (C) Net reclassification improvement (NRI) and (D) integrated discrimination improvement (IDI) of the Chinese Acute-on-Chronic Liver Failure Consortium-model for end-stage liver disease score (CATCH-LIFE-MELDs) compared with those of five other scores (MELD score (MELDs), MELD with sodium score (MELD-Nas), Chronic Liver Failure Consortium acute-on-chronic liver failure score (CLIF-C ACLFs), Chinese Group on the Study of Severe Hepatitis B-ACLF score (COSSH-ACLFs) and COSSH-ACLF II score (COSSH-ACLF IIs)).

Model performance

Model discrimination was assessed using AUROC, C-index, PDF analysis, NRI and IDI. As demonstrated in figure 2 and online supplemental table 5, the CATCH-LIFE-MELD model yielded AUROC of 0.823 and 0.848 in predicting the 28-day and 90-day outcomes of ACLF, respectively. The AUROC exhibited enhancements of 8.4%, 10.47%, 9.30%, 10.3% and 12.9%, respectively, compared with those of COSSH-ACLF IIs (0.759, p<0.001), COSSH-ACLFs (0.745, p<0.001), CLIF-C ACLFs (0.753, p<0.001), MELD score (0.746, p<0.001) and MELD-Na score (0.729, p<0.001). The C-index of CATCH-LIFE-MELD score for ACLF outcome (0.791 for 28 days and 0.788 for 90 days) was higher than that of COSSH-ACLF IIs (0.741 and 0.707), COSSH-ACLFs (0.729 and 0.706), CLIF-C ACLFs (0.731 and 0.690), MELD score (0.727 and 0.689) and MELD-Na score (0.712 and 0.669), with p<0.001 for each comparison (figure 2 and online supplemental table 6). We also compared the NRI and IDI of different models. As illustrated in online supplemental tables 7 and 8 and figure 2, CATCH-LIFE-MELD score represented significant improvements in NRI and IDI compared with the five other scores. PDF analysis (figure 3) displayed significantly lower overlapping coefficients of CATCH-LIFE-MELD score (52.78%/47.91% for 28-day and 90-day outcomes) than those of the COSSH-ACLF IIs (62.07%/66.43%), COSSH-ACLFs (66.01%/66.41%), CLIF-C ACLFs (62.83%/69.36%), MELD score (60.59%/67.42%) and MELD-Na score (62.86%/71.25%), exhibiting that it had more remarkable discrimination. The calibration plots indicated good agreement between the observed mortality and the predicted probability of death at 28 and 90 days (online supplemental figure 7). Moreover, the H-L test demonstrated a similar result (28 days: χ^2=5.779, p=0.672; 90 days: χ^2=5.786, p=0.661) (figure 4 and online supplemental table 9). As depicted in figure 4 and online supplemental table 10, CATCH-LIFE-MELD score had the largest Nagelkerke's R^2 (28 days: 0.318; 90 days: 0.411) and the lowest Brier score (28 days: 0.135; 90 days: 0.157) in predicting the 28-day/90-day outcomes of ACLF, indicating a better calibration. Finally, as illustrated by DCA (figure 5), the new model outperformed the other five models in predicting the 28-day/90-day outcomes.

Model validation

The performance of the CATCH-LIFE-MELD score model was confirmed in an independent cohort of 414 patients with ACLF. A comparison of clinical features between the training and validation patient groups can be found in online supplemental table 4.

Consistently, the C-index of the new score (0.805/0.778 for 28-day and 90-day, respectively) was superior to those of the MELD score (0.644/0.647, p<0.001/p<0.001), MELD-Na score (0.628/0.629, p<0.001/p<0.001), CLIF-C ACLFs (0.761/0.726, p<0.001/p<0.001), COSSH-ACLFs (0.762/0.747, p=0.014/p=0.034) and COSSH-ACLF IIs (0.763/0.744, p=0.009/p=0.014) (online supplemental table 11 and figure 2). In the validation cohort, the AUROCs of the model were similar to those in the

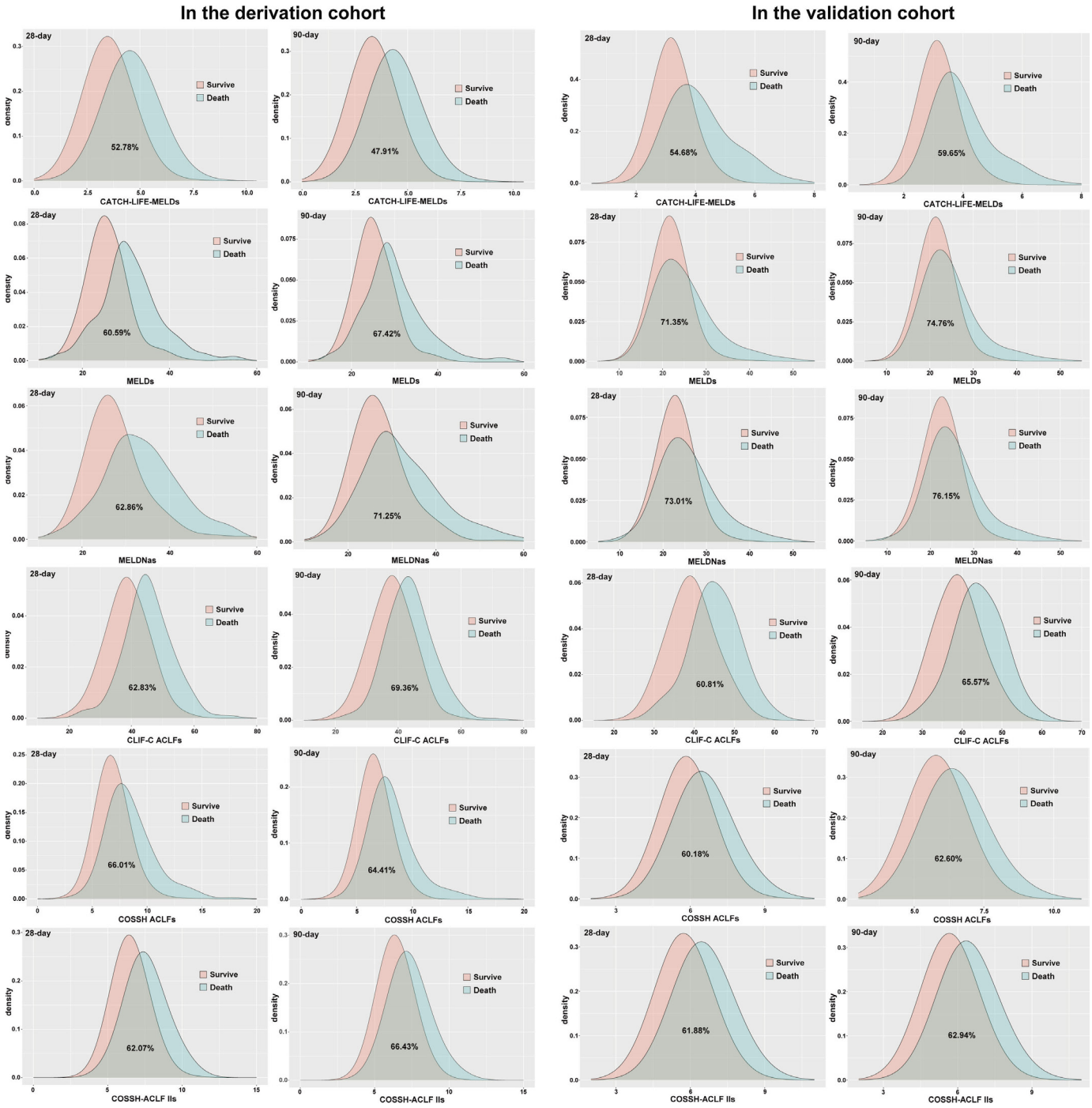

Figure 3 Probability density function of the prognostic scores for the 28-day/90-day prognosis of surviving and non-surviving patients in the derivation and validation groups. ACLF, acute-on-chronic liver failure; CATCH-LIFE-MELDs, Chinese Acute-on-Chronic Liver Failure Consortium-MELD score; CLIF-C ACLFs, Chronic Liver Failure Consortium ACLF score; COSSH ACLFs, Chinese Group on the Study of Severe Hepatitis B ACLF score; COSSH-ACLF IIs, COSSH-ACLF II score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD with sodium score.

derivation cohort (online supplemental table 12 and figure 2). Furthermore, the overlapping coefficient of CATCH-LIFE-MELD score between survivors and non-survivors in the validation cohort was reduced in the PDF analysis (CATCH-LIFE-MELD score: 54.68%/59.65%; COSSH-ACLF IIs: 61.88%/62.94%; COSSH-ACLFs: 60.18%/62.10%; CLIF-C ACLFs: 60.81%/65.57%; MELD score: 71.35%/74.76% and MELD-Na score: 73.01%/76.15%, figure 3). CATCH-LIFE-MELD score displayed a slight improvement compared with COSSH-ACLF IIs (NRI: 13.3%/1.1%; IDI: 9.2%/3.8%), COSSH-ACLFs (NRI: 23.3%/12.3%; IDI: 10.7%/5.4%) and CLIF-C ACLFs (NRI: 13.2%/15.9%; IDI: 10.5%/7.4%). A significant improvement in NRI and IDI for 28-day/90-day mortality was observed in comparison with MELD score (NRI: 36.7%/25.0%; IDI: 18.4%/13.2%) and MELD-Na

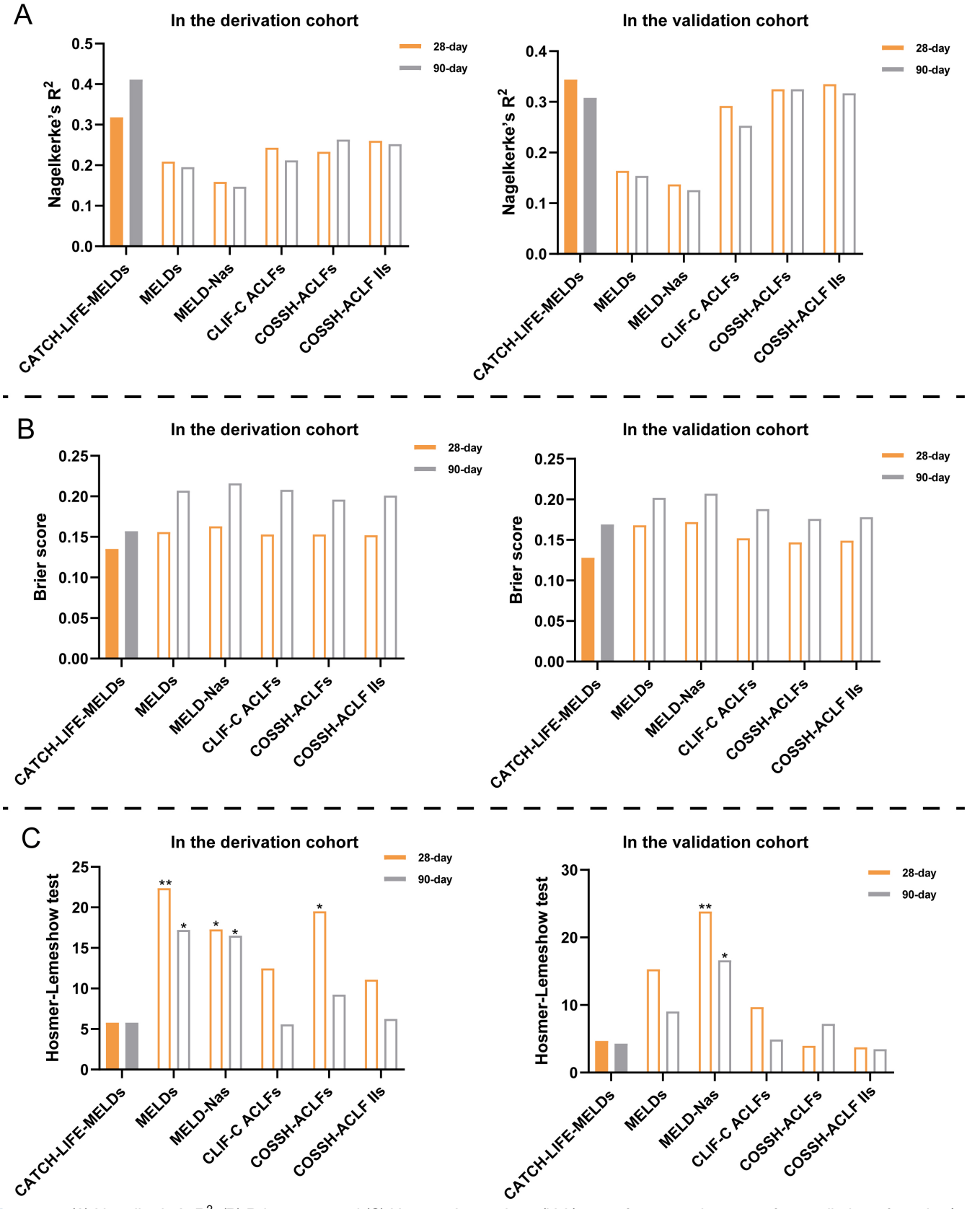

Figure 4 (A) Nagelkerke's R^2, (B) Brier score and (C) Hosmer-Lemeshow (H-L) test of prognostic scores for prediction of 28-day/90-day mortality. For H-L test, the smaller X^2, the greater the correlation p value, and the better the goodness of fit. Suitable calibration is indicated by H-L p value ≥ 0.05. The ordinate represents X^2. *: 0.01 ≤ p value < 0.05; **: 0.001 ≤ p value < 0.01. ACLF, acute-on-chronic liver failure; CATCH-LIFE-MELDs, Chinese Acute-on-Chronic Liver Failure Consortium-MELD score; CLIF-C ACLFs, Chronic Liver Failure Consortium ACLF score; COSSH ACLFs, Chinese Group on the Study of Severe Hepatitis B ACLF score; COSSH-ACLF IIs, COSSH-ACLF II score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD with sodium score.

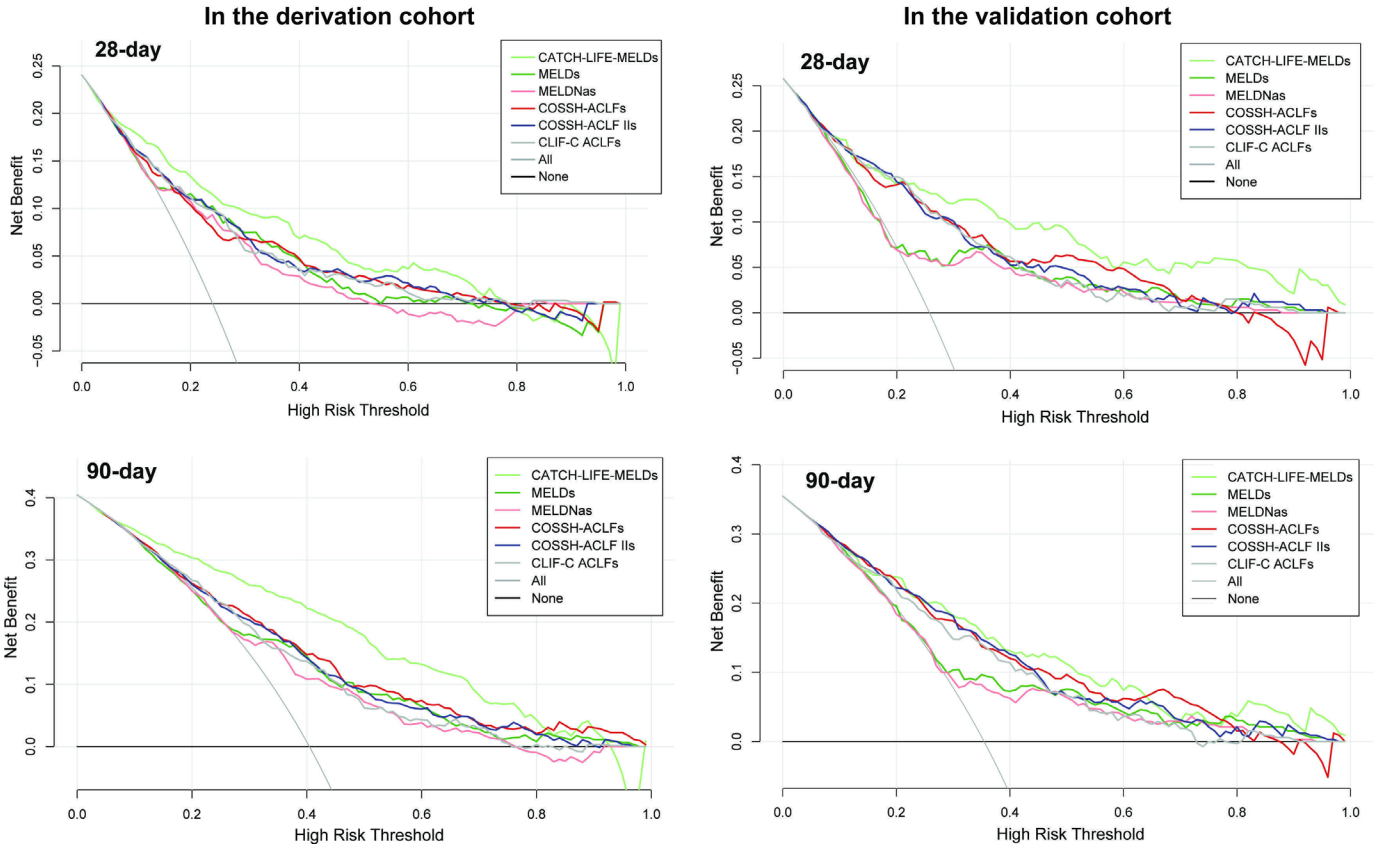

Figure 5 Decision curve analysis for predicting the 28-day/90-day prognosis of patients with acute-on-chronic liver failure (ACLF). CATCH-LIFE-MELDs, Chinese Acute-on-Chronic Liver Failure Consortium-MELD score; CLIF-C ACLFs, Chronic Liver Failure Consortium ACLF score; COSSH ACLFs, Chinese Group on the Study of Severe Hepatitis B ACLF score; COSSH-ACLF IIs, COSSH-ACLF II score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD with sodium score.

score (NRI: 44.6%/34.4%; IDI: 19.9%/14.6%) (online supplemental tables 13 and 14 and figure 2).

The calibration analysis of CATCH-LIFE-MELD score depicted a good fit (28 days: χ^2=4.682, p=0.666; 90 days: χ^2=4.299, p=0.797, online supplemental table 9, online supplemental figures 3 and 7) in the validation cohort. Similar to the derivation cohort, CATCH-LIFE-MELD score had the largest Nagelkerke's R^2 (28 days: 0.344; 90 days: 0.308) and the lowest Brier score (28 days: 0.128; 90 days: 0.169) in predicting outcomes at both 28 and 90 days (online supplemental table 10 and figure 4).

Finally, DCA was evaluated in the validation cohort. As indicated in figure 5, the new model was better than the other five models in predicting 28-day or 90-day mortality, indicating that the new model had a good clinical benefit.

Risk stratification by CATCH-LIFE-MELD score

An X-tile plot was used for the risk stratification of CATCH-LIFE-MELD score. Patients with ACLF were categorised into three risk strata of death determined by two optimal cut-off points (3.09 and 5.04): low risk (<3.09), intermediate risk (3.09–5.04) and high risk (>5.04). The 28-day or 90-day mortality significantly varied among the groups (figure 6). The HRs for 28-day or 90-day deaths were 5.23/4.61 (p<0.001) in the intermediate-risk group and 11.84/7.61 (p<0.001) in the high-risk group compared with the low-risk group. Moreover, the above risk stratification in the validation cohort still indicated a similar separation efficiency (28/90 days, intermediate-risk groups: 4.30/2.88, p<0.001; high-risk groups: 7.79/4.38, p<0.001) to the derivation cohort. These results indicated that CATCH-LIFE-MELD score are a better tool for risk stratification in patients with ACLF than other prognostic scores.

Performance of CATCH-LIFE-MELD score in specific subgroups of ACLF

As illustrated in figure 7 and online supplemental tables 15–18, the prediction efficiency of CATCH-LIFE-MELD score in HBV-ACLF and non-HBV-ACLF was >0.75, significantly better than other traditional models. Moreover, the predictive efficiency of all models was undermined by the presence of liver cirrhosis. Nevertheless, the new model had a C-index >0.750 in patients with liver cirrhosis, which still significantly surpassed other models. Moreover, the performance of CATCH-LIFE-MELD score was only mildly affected by liver failure. In contrast, the prediction performance of other traditional models was significantly worse in patients with ACLF without liver failure. We further divided patients with cirrhosis into liver failure and non-liver failure subgroups. We found that the C-index of the new model in the cirrhosis-liver

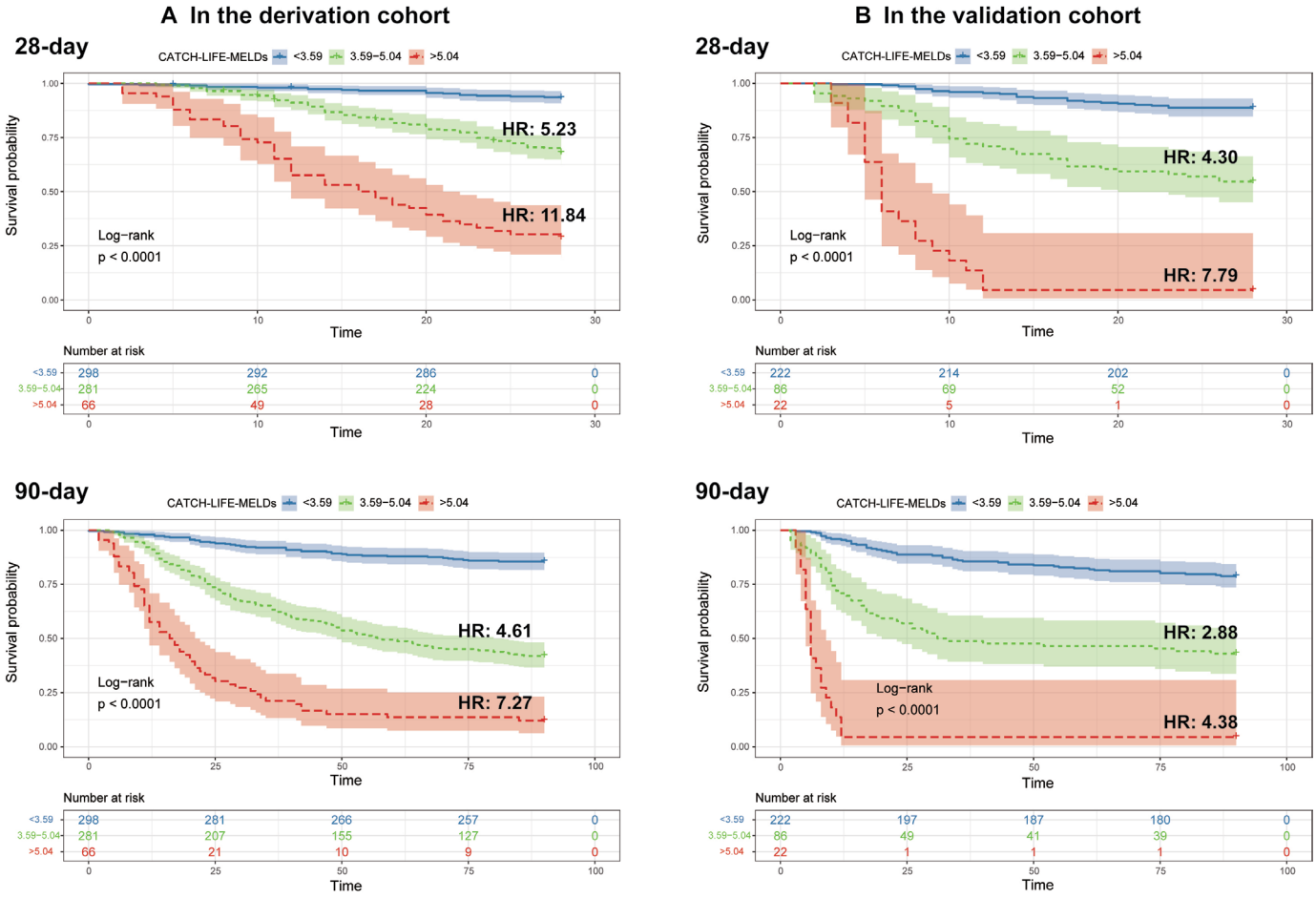

Figure 6 Risk stratification of patients with acute-on-chronic liver failure (ACLF) by the Chinese Acute-on-Chronic Liver Failure Consortium-model for end-stage liver disease score (CATCH-LIFE-MELDs). (A) Derivation cohort. (B) Validation cohort. The cumulative incidence of death at 28/90 days was stratified according to the CATCH-LIFE-MELDs classification rule (low risk/intermediate risk/high risk: CATCH-LIFE-MELDs <3.09/3.09–5.04/>5.04). P<0.001 (log-rank test) for comparisons of survival probability among the three risk strata.

failure subgroup decreased by only 2.05% (28 days) and 2.46% (90 days) compared with the cirrhosis-non-liver failure subgroup. However, there was a significant downward trend in the other traditional models (COSSH-ACLF IIs: 14.13%/12.09%; COSSH-ACLFs: 19.28%/11.76%; CLIF-C ACLFs: 14.83%/10.66%; MELD score: 23.59%/20.87%; MELD-Na score: 17.47%/15.24%). In conclusion, the CATCH-LIFE-MELD score was more stable and accurate in predicting short-term outcomes in different subgroups of patients with ACLF.

Validation of the CATCH-LIFE-MELD score under COSSH criteria and EASL criteria

We further validated the performance of the CATCH-LIFE-MELD score under COSSH criteria and European Association for the Study of the Liver (EASL) criteria. As illustrated in online supplemental tables 19–22 and figure 8, the C-index of CATCH-LIFE-MELD score for 28-day or 90-day outcomes (in the derivation cohort: COSSH criteria, 0.805/0.801; EASL criteria, 0.718/0.712; in the validation cohort: COSSH criteria, 0.793/0.775; EASL criteria, 0.758/0.737) were significantly higher than other score systems whether under COSSH or EASL criteria.

DISCUSSION

Accurate prediction of short-term outcomes is vital for managing patients with ACLF because of the high risk of death. MELD score was initially established to predict the outcome of patients with cirrhosis who underwent trans jugular intrahepatic portosystemic shunt.[4] It has been widely used to assess the severity of end-stage liver disease and organ prioritisation of LT.[10] MELD-Na score is a modified prediction model based on MELD score that incorporates serum sodium levels and provides more prognostic information than MELD alone.[5] Both MELD score and MELD-Na score have limited performance in predicting ACLF outcomes,[6] suggesting that key prognostic elements that reflect the pathophysiological mechanisms of ACLF are lacking. Our study identified additional predictive factors for ACLF outcomes and incorporated them into MELD score. The new CATCH-LIFE-MELD score was better at predicting ACLF outcomes than MELD score, MELD-Na score and other classical prognostic scores for ACLF.

In this study, three additional predictive variables (age, neutrophil count and HE score) for ACLF outcomes

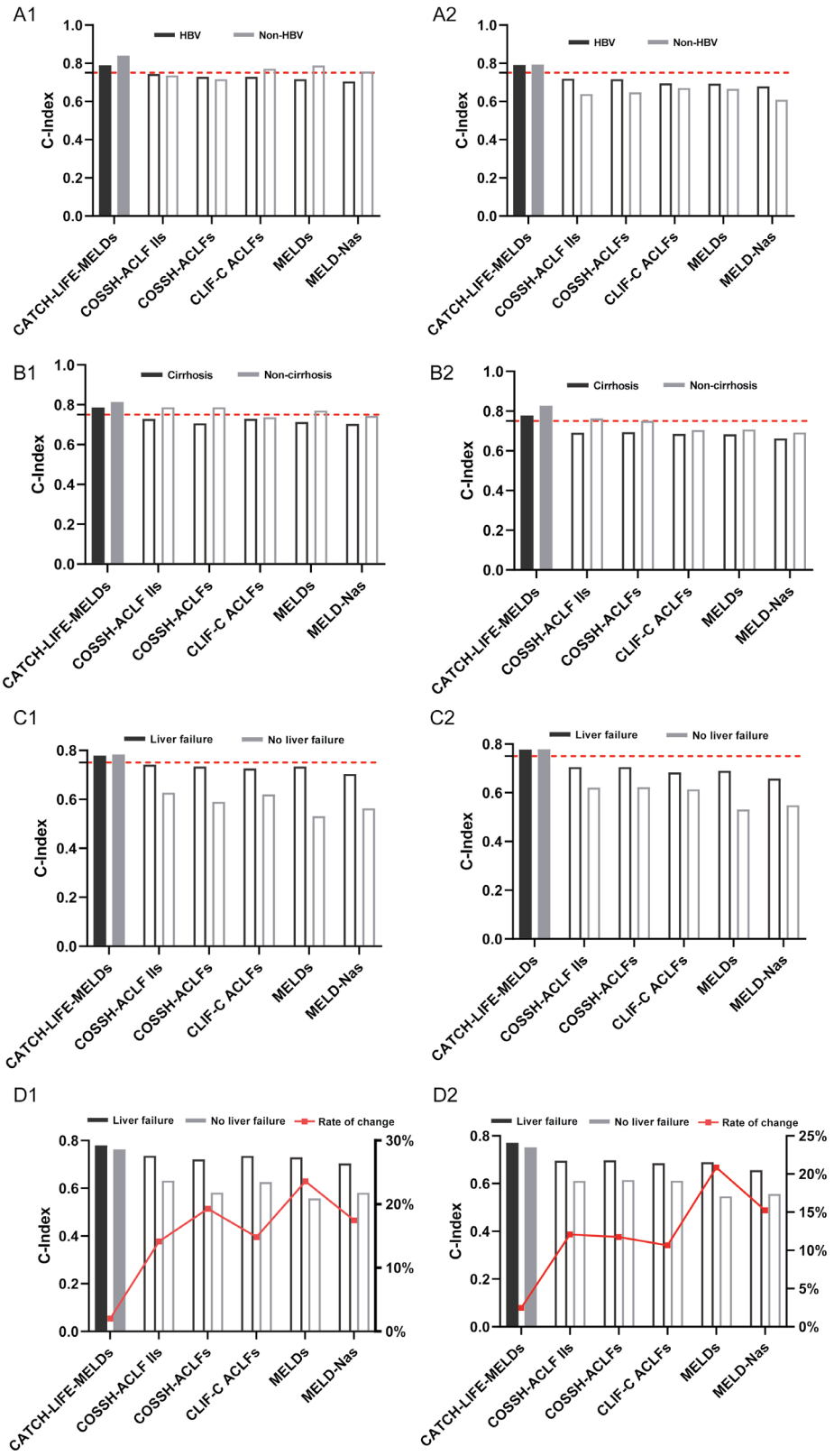

Figure 7 Concordance index (C-index) of prognostic scores for predicting 28-day/90-day mortality in patients with acute-on-chronic liver failure (ACLF) with or without hepatitis B virus (HBV) infection (A1 and A2), with cirrhosis or without cirrhosis (B1 and B2), with liver failure or without liver failure (C1 and C2) and cirrhosis subgroup with liver failure or without liver failure (D1 and D2). Cut-off line y=0.75. The broken line represents the rate of change of the C-index between the cirrhosis-liver failure subgroup and the cirrhosis-non-liver failure group. CATCH-LIFE-MELDs, Chinese Acute-on-Chronic Liver Failure Consortium-MELD score; CLIF-C ACLFs, Chronic Liver Failure Consortium ACLF score; COSSH ACLFs, Chinese Group on the Study of Severe Hepatitis B ACLF score; COSSH-ACLF IIs, COSSH-ACLF II score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD with sodium score.

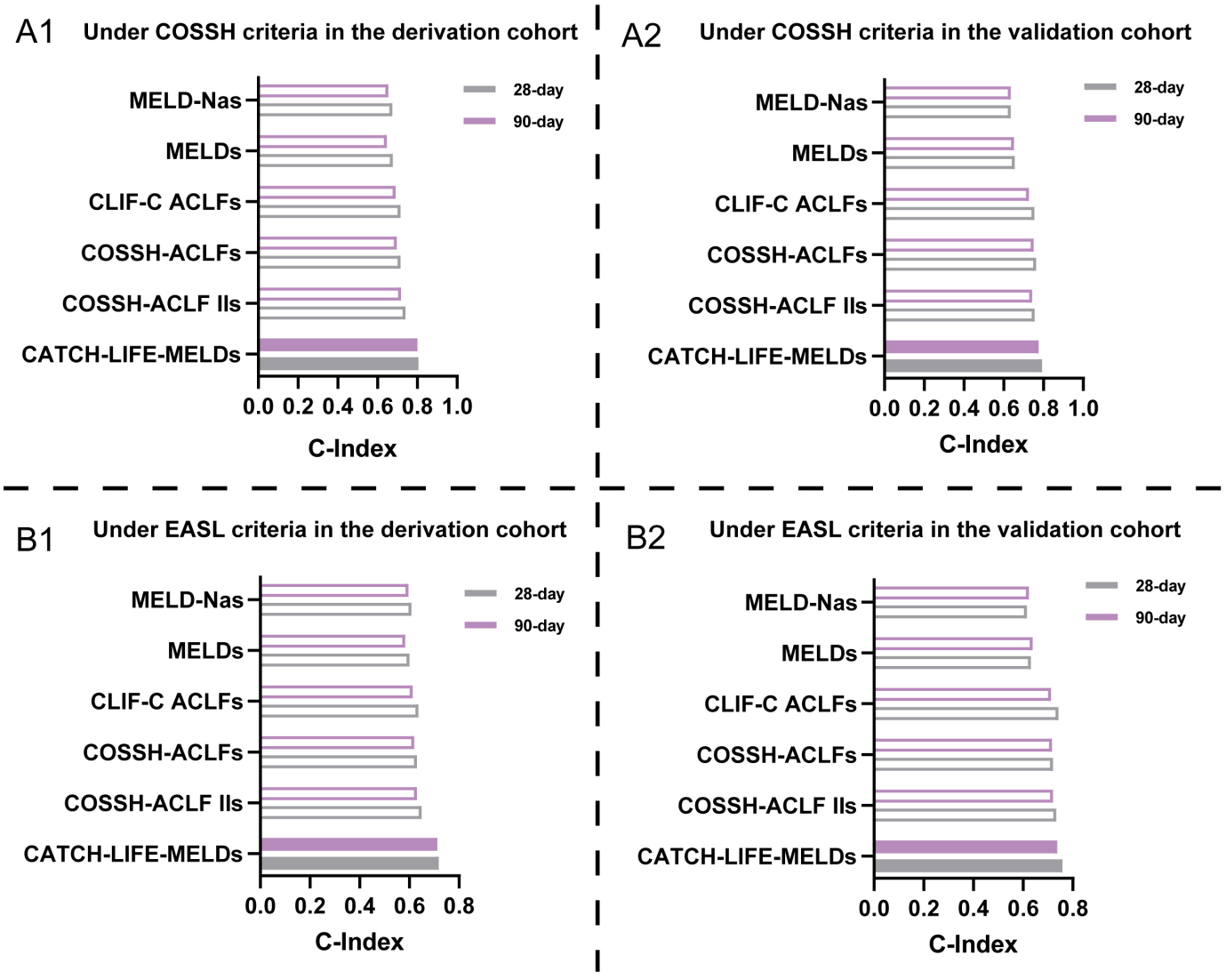

Figure 8 Concordance index (C-index) of prognostic scores for predicting 28-day/90-day mortality under (A) Chinese Group on the Study of Severe Hepatitis B (COSSH) diagnostic criteria and (B) European Association for the Study of the Liver (EASL) diagnostic criteria. ACLF, acute-on-chronic liver failure; CATCH-LIFE-MELDs, Chinese Acute-on-Chronic Liver Failure Consortium-MELD score; CLIF-C ACLFs, Chronic Liver Failure Consortium ACLF score; COSSH ACLFs, COSSH-ACLF score; COSSH-ACLF IIs, COSSH-ACLF II score; MELDs, model for end-stage liver disease score; MELD-Nas, MELD with sodium score.

were identified. Age is widely recognised as a significant risk factor associated with ACLF mortality, as older age is typically associated with a higher frequency of comorbidities, a longer duration of underlying disease, a decline of organ tolerance to acute injury and a poorer liver regeneration to liver damage.[11] The neutrophil count is a surrogate for systemic inflammation, which is believed to be the driving mechanism of ACLF initiation and progression.[12 13] Our findings illustrated that HE serves as a key prognostic indicator of ACLF. It was displayed that patients with high MELD scores who do not develop HE tend to have lower mortality (data not illustrated). The effect of HE on ACLF outcomes is independent of failure in other organs.[14] Therefore, incorporating these additional parameters strengthens the model's performance.

Furthermore, in this study, we performed a risk stratification of the patients' CATCH-LIFE-MELD score using the X-tile software (low risk: <3.59; medium risk: 3.59–5.04; high risk: >5.04). As revealed in online supplemental table 23, we compared the number of organ failures, types of organ failures, number of liver transplant recipients, common risk scores and mortality rates without transplantation among patients with ACLF at different risk levels following the model's risk stratification. It can be observed that as the model's risk stratification level increases, the number of organ failures in patients significantly rises. Moreover, at the low-risk stratification level, patients mainly exhibit intrahepatic organ failure with a lower mortality rate. However, when patients reach the high-risk stratification level, the proportion of extrahepatic organ failure noticeably increases, the severity of disease scores also significantly increases and the prognosis of patients markedly worsens. In this study, we plotted survival curves and compared the high-risk stratification group with

the low-risk and medium-risk stratification groups. The HR for the high-risk stratification group is significantly elevated (p<0.001). The above findings confirmed that the risk stratification of the CATCH-LIFE MELD score has good discriminative power. Through this stratification, we aimed to identify high-risk groups of patients with ACLF more accurately and quickly, thereby guiding clinicians to make the correct decisions.

Besides the higher performance of discrimination and calibration compared with other classical prognostic scores, the new model has different strengths. First, the new model was developed using a three-step methodology, including a high-evidence-based meta-analysis and two large-scale, prospective cohorts of high data quality. This approach was designed to minimise the selection bias of candidate variables and ensure the validity of the model. Second, the new model performance was stable in COSSH-ACLF and EASL-ACLF and less affected by cirrhosis or liver failure than other classical prognostic scores for ACLF. Finally, the new model consists of easily acquired and updated variables in clinical practice and can be available in low- and middle-income countries or areas.

Nevertheless, our study still have some limiations. Firstly, the new score was developed and validated in the Asian ACLF population which were mainly of HBV etiology, and therefore should be further tested in the Western ACLF cohort with mainly non-viral etiologies, for instance, alcohol liver disease-related ACLF. Second, although the new model had better discrimination ability than other models, the C-index for 28-day and 90-day mortality rates did not reach 0.80 or even 0.90, which is required for a highly accurate prognostic model. Third, since ACLF is a dynamic syndrome, the sequential use of the new model should be tested in future studies for informing the updated status of patients.

In conclusion, our study developed a new prognostic score by incorporating additional parameters into MELD score. The new CATCH-LIFE-MELD score performed better than other traditional scores for ACLF. CATCH-LIFE-MELD score can be used to predict and stratify the risk of death in patients with ACLF, thereby informing the clinical decisions regarding transplantation and guiding future studies on new therapies. However, the clinical utility of this model should be further validated in Western ACLF cohorts.

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Funding This work was supported by the National Key Research and Development Programme of China (No. 2022YFC2304501, No. 2021YFC2301800), Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (No. 2022RC141), the Fundamental Research Funds for the Central Universities (No. 226-2023-00127, No. 2021FZZX001-41), Medical and Health, Science and Technology Planning Project of Zhejiang Province, China (No. 2021436801), the National Natural Science Foundation of China (81870425, 81930061, 81900579, 81473641, 81271884, 81700561, 81470038, 82070650 and 81660333), the Shanghai Hospital Development Commission (SHDC2020CR1037B), the Chongqing Natural Science Foundation (CSTC2019jcyj-zdxmX0004) and Shandong Province Natural Science Foundation (ZR2019PH052).

Competing interests The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Patient consent for publication Not required.

Ethics approval The study was approved by the Ethics Committee of Renji Hospital (approval no. (2014) 148 k and (2016) 142 k) and the First Affiliated Hospital of Zhejiang University (2021-670). The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all study participants or their legal representatives.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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