Research Square

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Development and Internal Validation of a Nomogram for Identifying Documented Infection During Hospitalisation in Patients with HBV-ACLF

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Research Article

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Abstract

Background

Infection is frequently documented during hospitalisation in patients with HBV-related acute-on-chronic liver failure (HBV-ACLF) and is associated with adverse outcomes. We aimed to develop and internally validate a nomogram for identifying infection status documented during hospitalisation in this population.

Methods

This single-centre retrospective cohort study included 632 patients with HBV-ACLF admitted between January 2023 and December 2025. Infection status was retrospectively ascertained primarily from infection diagnoses recorded at discharge. Laboratory measurements were anchored to the assessment used to confirm eligibility; CRP was the measurement closest in time to that assessment, before or after, without selection according to its value. Thirty-four prespecified candidate variables were evaluated using multiple imputation, LASSO regression with 5-fold cross-validation, and multivariable logistic regression. Discrimination, calibration, bootstrap internal validation (B = 200), and decision curve analysis were assessed.

Results

Infection was documented in 372 of 632 patients (58.9%). The final model retained eight predictors: respiratory failure, renal failure, artificial liver support, ascites, neutrophil count, platelet count, C-reactive protein, and Child-Pugh score. Apparent AUC was 0.7414 (95% CI 0.7031–0.7797), and bootstrap-corrected AUC was 0.7021. The Hosmer-Lemeshow test was non-significant (P = 0.3005), and the apparent Brier score was 0.2007. The model showed higher apparent discrimination than MELD, MELD-Na, Child-Pugh, NLR, and CRP alone (all DeLong P < 0.001).

Conclusions

The eight-predictor nomogram showed moderate discrimination and acceptable calibration for identifying infection documented during hospitalisation in patients with HBV-ACLF. It may support structured assessment of documented infection as an adjunct to clinical evaluation.

1. Background

With an estimated 254 million individuals chronically infected with hepatitis B virus (HBV) worldwide—70 million of whom reside in China—HBV persists as a predominant cause of chronic liver disease globally[1]. Acute-on-chronic liver failure (ACLF) constitutes a distinct and severe syndrome,

characterized by acute hepatic decompensation in the setting of pre-existing chronic liver disease, frequently culminating in multiorgan failure and substantial short-term mortality[2]. Short-term mortality in ACLF remains high, with reported 28-day mortality ranging from 40% to 80%, and the global disease burden continues to grow. In China, HBV represents the primary etiology of ACLF, positioning HBV-ACLF as a central focus of both clinical management and translational investigation[3].

Infection is among the most frequent triggers and complications of ACLF, affecting 50%–70% of hospitalised patients and substantially worsening prognosis[4, 5]. The heightened susceptibility to infection in this population reflects multiple pathological processes, including cirrhosis-associated immune dysfunction (CAID), gut dysbiosis, and impaired intestinal barrier function, which may promote bacterial translocation and systemic infection[6, 7]. Pathogen-associated molecular patterns trigger systemic inflammatory responses that in turn exacerbate organ dysfunction, establishing a self-perpetuating cycle between infection and progressive liver failure[8]. Bacterial and fungal infections in ACLF have been associated with substantially higher short-term mortality than in uninfected patients, and the role of multidrug-resistant organisms is increasingly recognized[9].

The MELD, MELD-Na, and Child-Pugh scores are widely used for prognostic assessment in advanced liver disease[10, 11]. Their constituent variables largely reflect hepatorenal dysfunction rather than the combined inflammatory and organ-failure profile associated with infection[12]. Inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) are associated with infection and adverse outcomes in cirrhosis[13–15], but an interpretable composite model for identifying infection documented during hospitalisation in HBV-ACLF remains clinically relevant.

In this context, we developed and internally validated a nomogram to identify documented infection during hospitalisation in patients with HBV-ACLF. LASSO regression was used to reduce the prespecified candidate set, followed by multivariable logistic regression and nomogram construction[16, 17].

2. Materials and Methods

2.1 Study Design and Ethics

This single-centre retrospective cohort study was reported in accordance with the TRIPOD reporting guidelines[18]. The study protocol was approved by the Institutional Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine (Approval No. : 2024 − 0144), and informed consent was waived owing to the retrospective design.

2.2 Participants

We screened all patients with HBV-ACLF admitted to the Department of Infectious Diseases at our centre between January 2023 and December 2025.

Inclusion criteria were: (1) chronic HBV infection (HBsAg-positive for > 6 months); (2) ACLF diagnosed according to the Chinese Society of Infectious Diseases Guidelines for Diagnosis and Treatment of Liver Failure (2024 edition) using the COSSH-ACLF criteria, including an INR of ≥ 1.5; (3) age 18–70 years; (4) hospital stay > 48 hours[19–21].

Patients were excluded if they had: (1) pregnancy; (2) missing key laboratory values (total bilirubin and/or INR) precluding confirmation of ACLF diagnosis.

2.3 Definition of Infection Documented During Hospitalisation

Infection status was retrospectively ascertained primarily from infection diagnoses recorded in the discharge diagnoses for the index hospitalisation. Patients with an infection diagnosis recorded at discharge were classified as having documented infection; those without a recorded infection diagnosis were classified as having no documented infection. Infection categories included spontaneous bacterial peritonitis, pulmonary infection, urinary tract infection, bloodstream infection, biliary tract infection, skin and soft-tissue infection, and infection of unknown source[22]. CRP concentration was not used as a criterion for classifying infection status. Because the available records did not provide a reliable onset time for every episode, the outcome represents infection documented during hospitalisation and was not classified as incident nosocomial infection.

2.4 Data Collection

The index assessment was the laboratory time point used to confirm that the liver biochemistry and coagulation results fulfilled the HBV-ACLF eligibility criteria. Laboratory measurements were collected at the index assessment or at the time point closest to it. For CRP, the measurement with the smallest absolute time difference from the index assessment was selected, whether obtained before or after that assessment, without regard to the CRP value. Extracted variables included demographics; albumin, total bilirubin, INR, WBC, neutrophil count, platelet count, NLR, CRP, and creatinine; MELD, MELD-Na, and Child-Pugh scores; complications documented during hospitalisation, including ascites, hepatic encephalopathy, respiratory failure, and renal failure; and receipt of artificial liver support. The CRP measurement date was used only to identify the selected laboratory result and was not treated as the onset or diagnosis date of infection. Hospital-course variables were included as model features.

2.5 Statistical Analysis

Continuous variables are presented as mean +/- standard deviation or median (interquartile range), as appropriate, and were compared using Student's t-test or the Mann-Whitney U test. Categorical variables are reported as frequencies (percentages) and compared using the chi-square test. Crude 28-day mortality proportions were compared descriptively between infection-status groups.

Thirty-four candidate predictors were prespecified based on prior literature and clinical availability. Procalcitonin was excluded from modelling because 46.8% of values were missing. Univariable logistic

regression was descriptive and was not used as a preselection filter. In each of the 20 imputed datasets, all 34 candidates entered LASSO regression with 5-fold cross-validation using the lambda.1se penalty; predictors selected in at least 10 of 20 datasets were retained for multivariable modelling[17].

Variables retained by majority vote were entered into multivariable logistic regression in each imputed dataset, and estimates were pooled using Rubin's rules. The pooled model was visualised as a nomogram[12]. Predictors were retained according to the prespecified LASSO procedure rather than post-selection P values.

Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow test, bootstrap calibration curve, and Brier score. Internal validation used 200 bootstrap samples; each iteration repeated single imputation, LASSO selection, and logistic regression, and optimism was estimated from bootstrap-sample and original-sample performance. DeLong tests were used to compare the apparent AUC of the nomogram with those of MELD, MELD-Na, Child-Pugh, NLR, and CRP[23]. Decision curve analysis quantified net benefit across clinically relevant threshold probabilities.

Missing data among the 34 candidate predictors were handled using multiple imputation by chained equations (m = 20), with model estimates pooled according to Rubin's rules. CRP was missing in 18 cases (2.8%); other candidate variables had less than 1% missingness. A complete-case sensitivity analysis across all 34 candidates included 606 patients. Analyses used R version 4.5.1; two-sided $P < 0.05$ was considered statistically significant.

3. Results

3.1 Patient Characteristics and Infection Distribution

A total of 632 patients met the eligibility criteria. Infection was documented during hospitalisation in 372 patients (58.9%), whereas no infection was documented in 260 (41.1%). Patient characteristics and hospital-course features by documented infection status are summarised in Table 1.

Table 1
Patient characteristics and hospital-course features by documented infection status

Variable	Documented infection (n = 372)	No documented infection (n = 260)	P value
Age (years)	54 (45–61)	55 (45–62)	0.813
Male sex, n (%)	329 (88.4%)	224 (86.2%)	0.463
ALB (g/L)	31.1 (28.5–33.5)	31.4 (28.9–33.4)	0.244
TBil (μmol/L)	342.4 (288.5–436.4)	344.4 (291.4–428.2)	0.994
INR	2.1 (1.8–2.7)	2.0 (1.7–2.6)	0.019
WBC (×10⁹/L)	8.8 (5.7–12.4)	6.6 (4.9–9.2)	< 0.001
Neutrophil count (×10⁹/L)	6.8 (4.1–10.2)	4.6 (3.2–7.0)	< 0.001
PLT (×10⁹/L)	79.5 (50.8–115.0)	92.0 (55.8–133.0)	0.017
NLR	7.2 (4.0–14.4)	4.6 (2.7–7.9)	< 0.001
CRP (mg/L)	13.8 (8.3–31.4)	12.1 (7.1–18.1)	0.002
MELD	27.0 (24.5–34.0)	26.0 (24.0–30.0)	< 0.001
MELD-Na	32.0 (30.5–36.0)	31.0 (30.0–34.0)	< 0.001
Child-Pugh score	11.0 (10.0–12.0)	10.0 (9.0–11.0)	< 0.001
Ascites, n (%)	276 (74.2%)	168 (64.6%)	0.012
Hepatic encephalopathy, n (%)	239 (64.2%)	134 (51.5%)	0.002
Respiratory failure, n (%)	94 (25.3%)	13 (5.0%)	< 0.001
Renal failure, n (%)	119 (32.0%)	30 (11.5%)	< 0.001
Artificial liver support, n (%)	199 (53.5%)	127 (48.8%)	0.285

Data are median (IQR) unless otherwise stated. ALB, albumin; TBil, total bilirubin; INR, international normalised ratio; WBC, white blood cell count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; MELD, Model for End-Stage Liver Disease.

Levels of WBC, neutrophil count, NLR, CRP, MELD, MELD-Na, and Child-Pugh score were all significantly higher in the documented infection group (all $P < 0.05$). The documented infection group also had higher rates of ascites, hepatic encephalopathy, respiratory failure, and renal failure. Pulmonary infection and SBP were the most frequent infection subtypes.

3.2 Infection Status and Crude 28-Day Mortality

Twenty-eight-day outcome data were available for 578 patients. Crude 28-day mortality was 34.0% (115/338) among patients with documented infection and 18.8% (45/240) among those without documented infection ($P < 0.001$). This comparison was descriptive because infection status and several clinical variables were documented across the hospital course (Fig. 1C).

3.3 Feature Association and Selection

3.3.1 Univariable Analysis

Univariable logistic regression results for all 34 candidate predictors are shown in Fig. 2A. These analyses were descriptive and were not used to determine entry into LASSO regression.

3.3.2 LASSO Variable Selection

All 34 prespecified candidate predictors entered LASSO regression with 5-fold cross-validation in each of the 20 imputed datasets. Using the lambda.1se penalty and a majority-vote threshold of at least 10 of 20 datasets, eight predictors were retained: respiratory failure, renal failure, artificial liver support, ascites, neutrophil count, platelet count, CRP, and Child-Pugh score.

3.3.3 Multivariable Logistic Regression

All eight LASSO-selected predictors entered the pooled multivariable model. Respiratory failure, renal failure, artificial liver support, ascites, neutrophil count, platelet count, and CRP were statistically significant; Child-Pugh score was retained by the prespecified selection procedure. Results are shown in Table 2 and Fig. 2C.

Table 2
Multivariable logistic regression results

Variable	OR	95% CI	P value
Respiratory failure	4.138	2.081–8.231	< 0.001
Renal failure	2.014	1.194–3.399	0.0089
Artificial liver support	2.094	1.440–3.047	< 0.001
Ascites	1.606	1.061–2.431	0.0253
Neutrophil count (per 10^9/L)	1.080	1.030–1.132	0.0016
Platelet count (per 10^9/L)	0.997	0.994–1.000	0.0307
CRP (per mg/L)	1.013	1.005–1.021	0.0020
Child–Pugh score	1.090	0.938–1.267	0.2598

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.

3.4 Nomogram Development and Validation

3.4.1 Nomogram Construction

We constructed an eight-predictor nomogram from the pooled multivariable model (Fig. 3A). The total point score corresponds to the estimated probability of documented infection during hospitalisation.

3.4.2 Discrimination

The apparent AUC was 0.7414 (95% CI 0.7031–0.7797). Bootstrap internal validation yielded an optimism estimate of 0.0393 and a bootstrap-corrected AUC of 0.7021, indicating moderate discrimination after optimism correction (Fig. 3B).

3.4.3 Comparison with Existing Scores

The nomogram showed higher apparent discrimination than MELD (AUC 0.5807), MELD-Na (0.5878), Child-Pugh (0.5906), NLR (0.6474), and CRP (0.5804); all pairwise DeLong P values were < 0.001 (Fig. 3C)[23].

3.4.4 Calibration

The Hosmer-Lemeshow test was non-significant (P = 0.3005). The apparent Brier score was 0.2007, and the bootstrap calibration curve showed close agreement across most of the observed probability range (Fig. 3D).

3.4.5 Decision Curve Analysis

In the apparent decision curve analysis, the model showed positive net benefit over the treat-none strategy across a broad threshold range and incremental net benefit over the treat-all strategy at intermediate and higher thresholds (Fig. 3E).

3.4.6 Optimal Cutoff

The Youden-optimal probability threshold was 0.599, with sensitivity of 58.9% and specificity of 77.7%.

3.4.7 Sensitivity Analyses

Complete-case analysis (n = 606) yielded an AUC of 0.7538, compared with 0.7414 in the primary multiple-imputation analysis, suggesting limited sensitivity to the handling of missing data.

3.4.8 Subgroup Analysis

Subgroup AUCs were apparent values. Apparent discrimination differed by age (≥ 60 years: AUC 0.6809; <60 years: AUC 0.7712; interaction P = 0.024). No statistically significant interaction was detected by COSSH grade (P = 0.606), MELD-Na stratum (P = 0.599), or sex (P = 0.981) (Table 3).

Table 3
Subgroup analysis results

Subgroup	n	AUC (95% CI, apparent)	Interaction P
COSSH Grade 1	430	0.6868 (0.6372–0.7365)	0.606
COSSH Grade 2–3	202	0.7217 (0.6371–0.8063)	
MELD-Na > 30	445	0.7386 (0.6918–0.7855)	0.599
MELD-Na ≤ 30	185	0.7153 (0.6417–0.7889)	
Age ≥ 60 years	206	0.6809 (0.6069–0.7549)	0.024
Age < 60 years	426	0.7712 (0.7273–0.8152)	
Male	553	0.7430 (0.7020–0.7840)	0.981
Female	79	0.7371 (0.6271–0.8470)	

AUC values are apparent (not Bootstrap-corrected).

4. Discussion

In this retrospective cohort of 632 patients with HBV-ACLF, an eight-variable nomogram discriminated documented infection during hospitalisation with an apparent AUC of 0.7414 and a bootstrap-corrected AUC of 0.7021. Its apparent discrimination exceeded that of commonly used liver-severity scores and single inflammatory markers. The model was developed to identify documented infection during hospitalisation rather than to predict the onset of infection at a specific time point.

Infection was documented in 58.9% of the cohort, consistent with the high burden reported in hospitalised patients with cirrhosis and ACLF[24, 25]. Crude 28-day mortality was higher among patients with documented infection, highlighting the clinical relevance of infection assessment, while the retrospective timing of infection status precludes causal interpretation of this comparison.

Respiratory failure showed the largest association with documented infection status (OR 4.138), followed by artificial liver support and renal failure[26, 27]. These variables reflect disease severity and interventions occurring during hospitalisation and may be associated with documented infection through several clinical pathways[28, 29].

eutrophil count and CRP remained informative in the pooled model, while lower platelet count also contributed after PCT was excluded from modelling. Together with organ dysfunction and Child-Pugh score, these variables capture complementary inflammatory, haematological, and disease-severity information relevant to documented infection status[29, 30].

The model is specific to HBV-ACLF, uses multiple imputation with repeated LASSO selection across imputed datasets, and remains directly interpretable. Its corrected AUC indicates moderate discrimination, supporting its use as an adjunct to clinical assessment rather than as a stand-alone diagnostic tool.

Several limitations should be noted. First, this was a retrospective single-centre study without external validation. Second, infection status was based primarily on diagnoses recorded at discharge rather than independent endpoint adjudication, and reliable onset times were unavailable. The model therefore identifies infection documented during hospitalisation and does not establish temporal or causal relationships. Third, CRP was selected by temporal proximity to the eligibility assessment, but clinical testing was not performed at uniform intervals. Fourth, organ-failure and treatment variables could occur before or after infection recognition, resulting in potential temporal ambiguity. Fifth, PCT was excluded because 46.8% of values were missing, and microbiological confirmation was incomplete. Sixth, subgroup analyses were exploratory, and the observed age interaction requires independent confirmation. Finally, internal validation used single imputation within each bootstrap iteration and does not represent full propagation of multiple-imputation variance.

5. Conclusion

We developed an eight-predictor nomogram for identifying documented infection during hospitalisation in patients with HBV-ACLF. The model demonstrated moderate discrimination after bootstrap correction and acceptable calibration and may support assessment of documented infection as an adjunct to clinical evaluation. External validation is required before clinical deployment.

Abbreviations

ACLF, acute-on-chronic liver failure

ALB, albumin

AUC, area under the receiver operating characteristic curve

CAID, cirrhosis-associated immune dysfunction

CI, confidence interval

COSSH-ACLF, Chinese Group on the Study of Severe Hepatitis B-associated acute-on-chronic liver failure

CRP, C-reactive protein

HBV, hepatitis B virus

HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure

INR, international normalized ratio

IQR, interquartile range

LASSO, least absolute shrinkage and selection operator

MELD, Model for End-Stage Liver Disease

MELD-Na, Model for End-Stage Liver Disease-Sodium

NLR, neutrophil-to-lymphocyte ratio

OR, odds ratio

PLT, platelet count

ROC, receiver operating characteristic

SBP, spontaneous bacterial peritonitis

TBil, total bilirubin

TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis

WBC, white blood cell count

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by the Institutional Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine (Approval No.: 2024-0144). Informed consent was waived by the Institutional Review Board owing to the retrospective study design.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the First Affiliated Hospital, Zhejiang University School of Medicine, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the First Affiliated Hospital, Zhejiang University School of Medicine.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: JJC, SJ

Methodology: SJ

Formal analysis and investigation: SJ

Data curation: SJ, CZ, CYH, WXL

Writing – original draft preparation: SJ

Writing – review and editing: JJC, SJ, CZ, CYH, WXL

Funding acquisition: JJC

Supervision: JJC

All authors read and approved the final manuscript.

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Figures

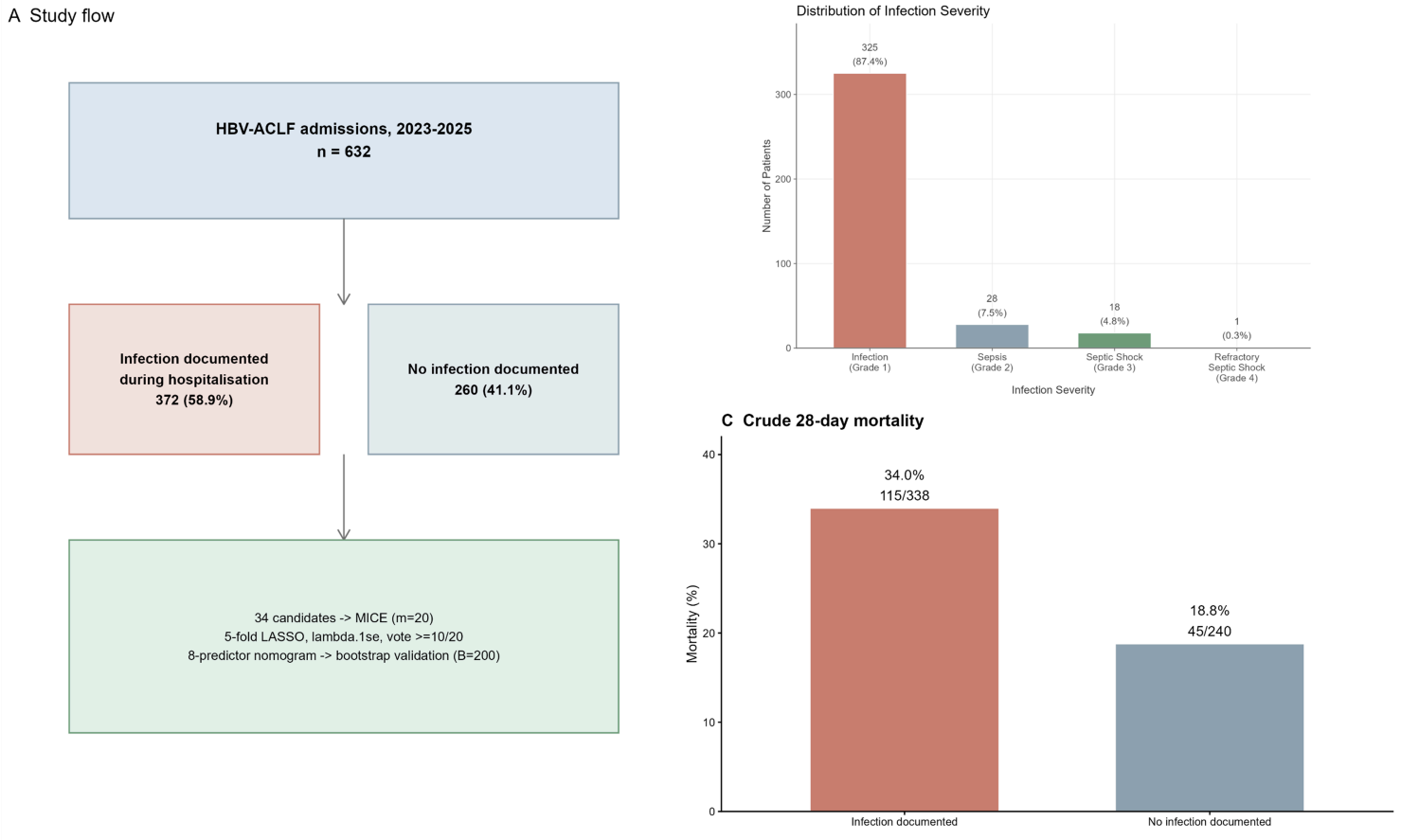


Figure 1

Study population and descriptive outcomes. A, Study flow and modelling pipeline. B, Distribution of infection severity among 372 patients with documented infection. C, Crude 28-day mortality proportions by documented infection status.

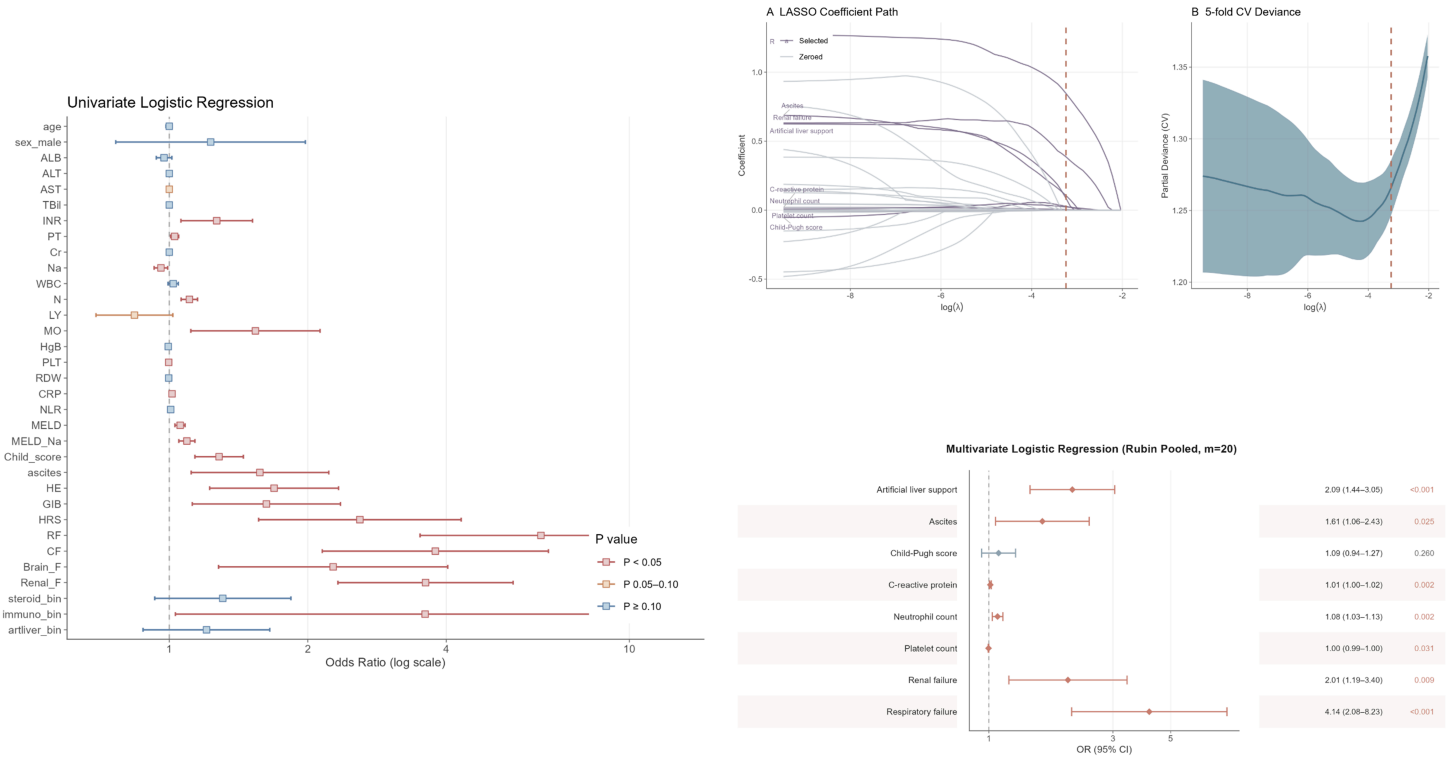


Figure 2

Feature association, selection, and multivariable modelling. A, Descriptive univariable logistic regression for 34 candidates. B, Representative LASSO coefficient path and 5-fold cross-validation curve from the first imputed dataset; the dashed line marks lambda.1se. C, Multivariable logistic regression with Rubin-pooled estimates.

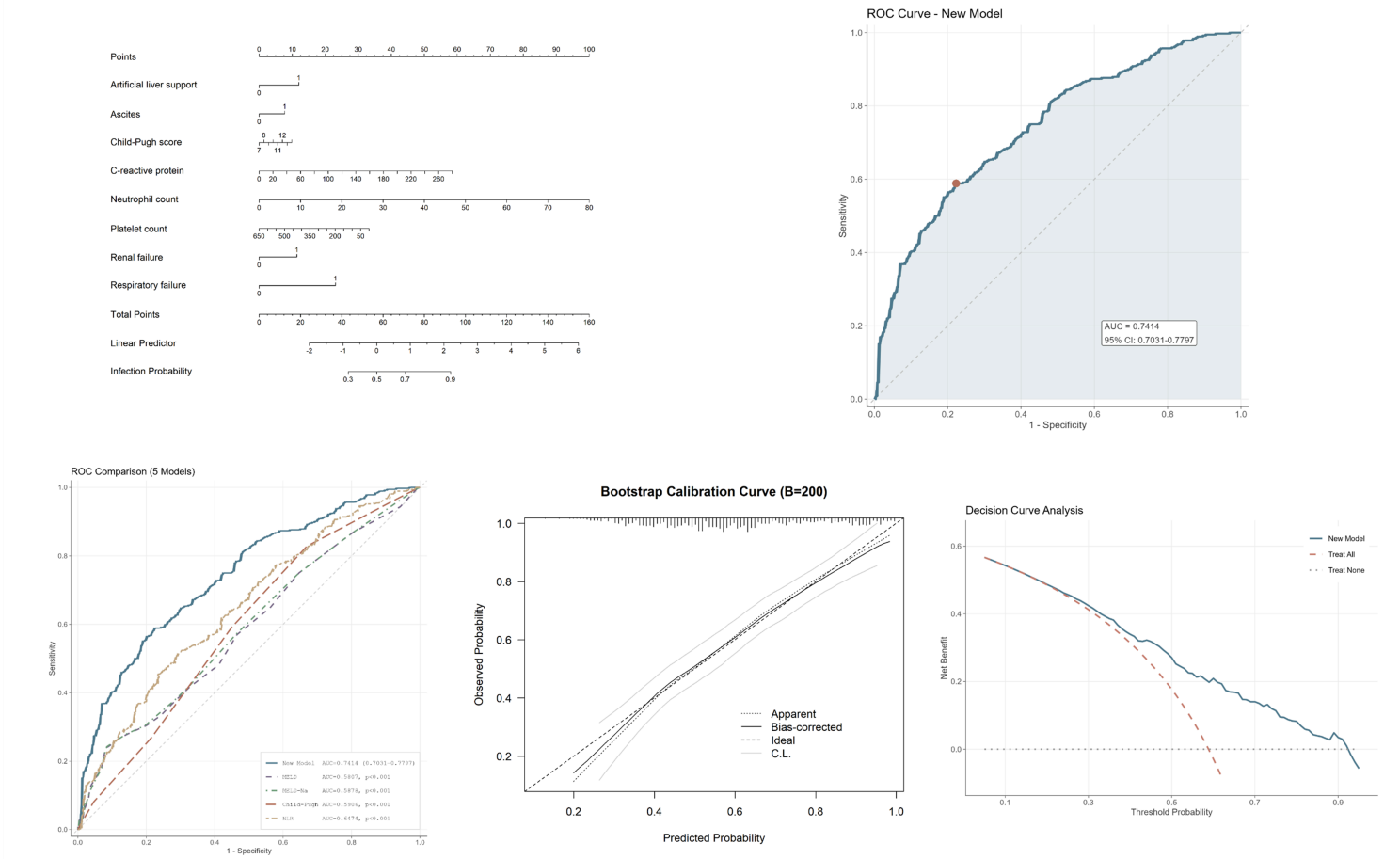


Figure 3

Nomogram and model performance. A, Eight-predictor nomogram constructed using Rubin-pooled coefficients for documented infection during hospitalisation. B, ROC curve (AUC 0.7414, 95% CI 0.7031-0.7797). C, Apparent ROC comparison with selected comparators (MELD, MELD-Na, Child-Pugh, and NLR); the CRP comparison is reported in the text. D, Bootstrap calibration curve (B = 200). E, Apparent decision curve analysis.