Prognostic factors for mortality in patients with acute-on-chronic liver failure

Huijie Jiang, Zhihao Zhao, Shiyu Cui, Xianggen Kong and Xuemei Jiang

Objective The aim is to explore significant prognostic factors for 90-day mortality in patients with acute-on-chronic liver failure (ACLF) and assist clinicians in the early identification of critically ill ACLF patients.
Methods A retrospective analysis was conducted on 288 ACLF patients, who were classified into survivors (n = 187) and nonsurvivors (n = 101) based on 90-day outcomes. Multivariate stepwise logistic regression analyses were employed to identify significant prognostic factors and construct a novel prognostic model, the AHUCTPI. The model's performance was assessed and the internal validation was performed. Additionally, the influence of dynamic changes in laboratory markers on 90-day mortality was examined.
Results Independent risk factors for 90-day mortality included age ≥45 years, presence of hepatic encephalopathy (HE), and upper gastrointestinal bleeding (UGB) during hospitalization, imaging-confirmed cirrhosis at admission, elevated baseline total bilirubin (TBIL), reduced baseline platelet-to-neutrophil ratio (PNR), and elevated baseline international normalized ratio (INR) ($P < 0.05$ for all). The AHUCTPI model's formula is as follows: Logit (p) = −10.019 + 1.808 × age (1 if ≥45 years, 0 if <45 years) + 1.048 × HE (1 if present, 0 if absent) + 1.721 × UGB (1 if present, 0 if absent) + 1.362 × cirrhosis (1 if present, 0 if absent) + 0.008 × TBIL (μmol/L) − 0.039 × PNR + 1.963 × INR. The AUHCTPI model demonstrated superior predictive accuracy compared with the MELD (Model for End-Stage Liver Disease) score, with the area under the receiver operating characteristic curve values of 0.914 and 0.739, respectively, and calibration curves closely approximating the ideal curve.
Conclusion ACLF is a complex, dynamic syndrome. Age, HE, and UGB during hospitalization, imaging-diagnosed cirrhosis at admission, baseline TBIL, PNR, and INR were significant predictors for 90-day mortality in ACLF patients, and the AHUCTPI model provides excellent calibration and discrimination. Dynamic monitoring of laboratory trends enhances prognostic accuracy and supports timely clinical decision-making. Eur J Gastroenterol Hepatol 37: 833–843

Introduction

Acute-on-chronic liver failure (ACLF) is a complex and dynamic clinical syndrome characterized by rapid hepatic decompensation, resulting in high short-term mortality. The condition has garnered increasing global attention due to its prevalence and severity. A systematic review and meta-analysis reported that the global prevalence of ACLF among patients with decompensated cirrhosis is approximately 35%, with a 90-day mortality rate of 58% [1]. Variability in definitions and diagnostic criteria across regions, largely due to differences in etiologies and precipitating factors, complicates the clinical approach to ACLF [2]. Key definitions have been proposed by the Asia-Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL)-Chronic Liver Failure (CLIF) Consortium, the North American Consortium for the Study of End-Stage Liver Disease (NACSELD), and the Chinese Medical Association (CMA). While these definitions are widely accepted, the lack of consensus hinders progress in advancing treatment strategies [3].

ACLF presents a significant clinical challenge due to its poor response to available treatments. Current therapeutic management largely focuses on symptomatic relief, as there are no definitive treatments. Experimental approaches, including artificial liver support systems (ALSS), immunotherapies, and stem cell therapies, are under investigation, yet liver transplantation remains the most effective intervention. Liver transplantation, however, faces significant barriers, including limited donor availability, long wait times, high surgical risk, and substantial financial cost. These limitations make accurate short-term prognosis predictions critical for optimizing clinical management, especially regarding decisions on early intensive care, organ support, and the potential need for liver transplantation [4].

Despite the existence of various prognostic models and scoring systems, including the Child-Turcotte-Pugh score [5], Model for End-Stage Liver Disease (MELD) score

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Keywords: acute-on-chronic liver failure, dynamic trends, influencing factors, prediction model, prognosis

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[6], APASL ACLF Research Consortium (AARC) score [7], CLIF-CACLF score [8], NACSELD Infection-Related ACLF score [9], and the Chinese Group on the Study of Severe Hepatitis ACLF score [10], predicting outcomes in ACLF remains a significant challenge [11].

Recent studies have emphasized the importance of dynamic assessment over static evaluation in forecasting disease progression. For example, Gustot *et al*. [4] demonstrated that the ACLF grade between days 3 and 7 after diagnosis better predicts short-term mortality than the initial grade, as patients' final ACLF stage is often established within this timeframe. Similarly, the APASL recommends using the AARC-ACLF score at admission with subsequent assessments on days 4 and 7 to track disease progression [7].

This study aims to identify prognostic factors for 90-day mortality in ACLF patients and develop a logistic regression model to aid in the early detection of critically ill patients, ultimately improving clinical decision-making and reducing mortality in ACLF populations.

Patients and methods

Study population

This study enrolled 288 patients diagnosed with ACLF who were hospitalized at the Liver Disease Center of Shandong Public Health Clinical Center between January 2021 and May 2024. Patients were categorized into two groups based on their 90-day outcomes: the survival group (n = 187) and the death group (n = 101) (Fig. 1).

Inclusion criteria: (1) age ≥16 years and (2) meeting the diagnostic criteria for ACLF as defined by the CMA in its Guideline for Diagnosis and Treatment of Liver Failure: 'ACLF is characterized by acute hepatic insult, manifesting as jaundice [serum total bilirubin (TBIL) ≥10 times the upper limit of normal or a daily increase ≥17.1 μmol/L] and coagulopathy (INR ≥ 1.5 or prothrombin activity <40%) complicated within 4 weeks by ascites, encephalopathy, or other related complications in a patient with underlying chronic liver disease or cirrhosis' [12].

All patients received comprehensive internal medical care, including etiological treatment (e.g. antiviral therapy, cessation of hepatotoxic drugs, and alcohol abstinence), supportive care (e.g. nutritional supplementation and albumin therapy), symptomatic treatment (e.g. liver-protective drugs, bilirubin-lowering agents, enzyme inhibitors, and correction of electrolyte disturbances), and complication-specific therapies (e.g. antibiotics, acid suppression, diuretics, and ammonia-lowering treatments).

Exclusion criteria: (1) presence of malignant tumors in intrahepatic or extrahepatic organs, (2) severe cardiac or other life-threatening comorbidities, (3) HIV infection, (4) pregnancy, (5) hospitalization duration <7 days, and (6) severely incomplete clinical data.

Data collection

We collected comprehensive data on demographic characteristics, treatment, complications, imaging findings, and laboratory parameters at admission. Demographic characteristics: age, gender, and etiology. Treatment during hospitalization: with/without ALSS treatment.

Complications during hospitalization: bacterial infections (BI), hepatic encephalopathy (HE), hepatorenal syndrome (HRS), and upper gastrointestinal bleeding (UGB). Imaging findings: ascites and cirrhosis. Laboratory parameters: alanine transaminase (ALT), aspartate transaminase (AST), albumin (ALB), TBIL, glucose (Glu), total

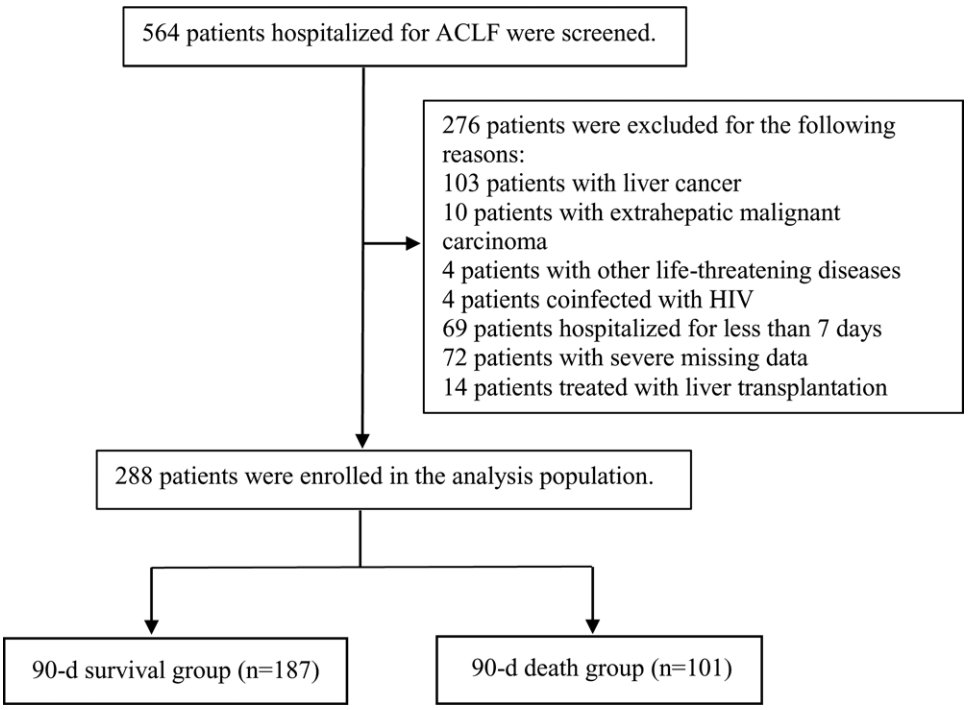

Fig. 1. Screening, enrolment, and classification of patients with ACLF. ACLF, acute-on-chronic liver failure.

Table 1. Comparison of different etiologies in the survival and death group of patients with acute-on-chronic liver failure

	Analysis group (*n* = 288)	Survival group (*n* = 187)	Death group (*n* = 101)	χ^2	*P* value
Etiologies				4.076	0.396
HBV	169 (58.7%)	109 (64.5%)	60 (35.5%))		
ALD	52 (18.1%)	34 (65.4%)	18 (34.6%)		
HBV + ALD	24 (8.3%)	18 (75%)	6 (25%)		
Other single etiology	24 (8.3%)	12 (50%)	12 (50%)		
Other dual etiologies	19 (6.6%)	14 (73.7%)	5 (26.3%)		

Other single etiology, including drug-induced liver disease, autoimmune liver disease, hepatitis E virus infection, and unknown etiology liver disease. Other dual etiologies, any combination of the above two etiologies, except for hepatitis B virus infection combined with alcoholic liver disease. *P* value was calculated with χ^2 test.
ALD, alcoholic liver disease; HBV, hepatitis B virus infection; HBV + ALD, hepatitis B virus infection combined with alcoholic liver disease.

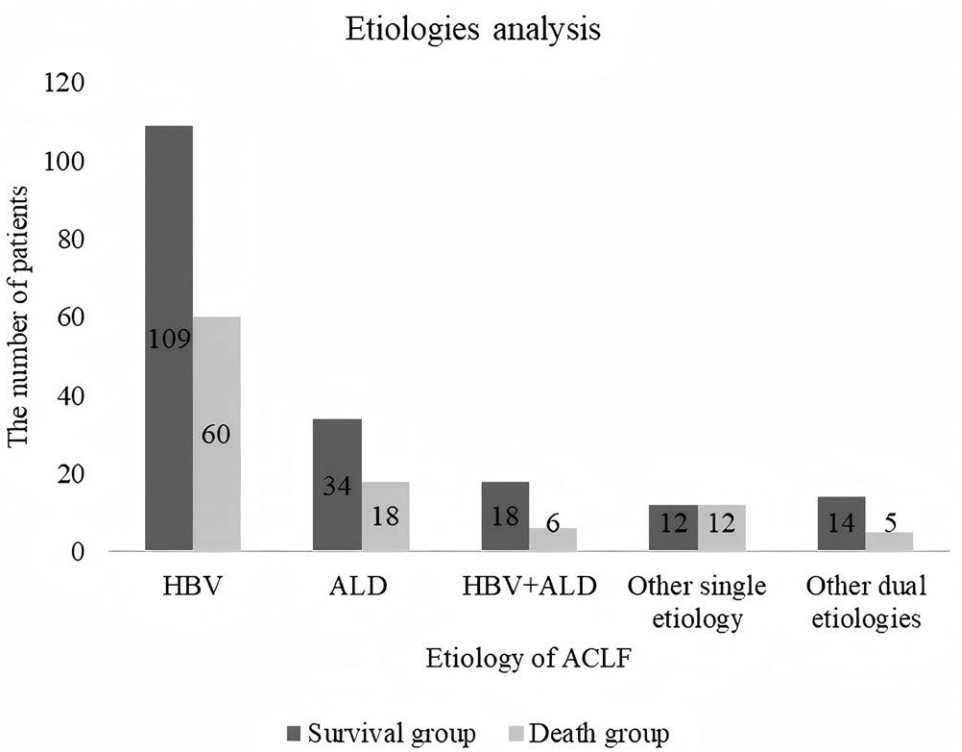

Fig. 2. Etiologies analysis in the survival and death group of patients with ACLF. ACLF, acute-on-chronic liver failure; ALD, alcoholic liver disease; HBV, hepatitis B virus infection; HBV + ALD, hepatitis B virus infection combined with alcoholic liver disease. Other single etiology, including drug-induced liver disease, autoimmune liver disease, hepatitis E virus infection, and unknown etiology liver disease. Other dual etiologies, any combination of the above two etiologies, except for hepatitis B virus infection combined with alcoholic liver disease.

cholesterol (TCh), creatinine (Cr), serum sodium (Na), white blood cell count (WBC), percentage of neutrophils (NE%), neutrophil-to-lymphocyte ratio (NLR), hemoglobin (HB), platelet count (PLT), platelet-to-neutrophil ratio (PNR), international normalized ratio (INR), blood ammonia, alpha-fetoprotein (AFP), serum procalcitonin (PCT), interleukin-6 (IL-6).

We also collected the laboratory indicators on day 7 during hospitalization to assess the dynamic trends of laboratory indicators (e.g. ΔALT = ALT on day 7 of hospitalization/ALT at admission). A prognostic MELD score was calculated. The equation is as follows: MELD = 3. 78 × ln [TBIL (mg/dl)] + 11. 2 × ln (INR) + 9. 57 × ln [Cr (mg/dl)] + 6. 43 × etiology (0 for cholestatic or alcoholic, 1 for others) [6]. All laboratory indicators were completed in the testing center of Shandong Province Public Health Clinical Center.

Research contents

The collected data were retrospectively analyzed to identify independent predictors of 90-day mortality in ACLF patients. Logistic regression equations were constructed, and the performance of the predictive model was assessed. Additionally, the impact of dynamic changes in laboratory parameters on 90-day mortality was explored.

Statistical analyses

Statistical analyses were conducted using SPSS version 25 (IBM Corporation, Armonk, New York, USA) and R software version 4.1 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± SD for normally distributed data and as medians with interquartile ranges for non-normally distributed data. Categorical variables were

Table 2. Univariate analysis of clinical characteristics for 90-day mortality of acute-on-chronic liver failure patients

Variables	Survival group (*n* = 187)	Death group (*n* = 101)	Univariate analysis	
			P value	OR (95% CI)
Age ≥ 45 years	118 (63.10%)	87 (86.14%)	<0.001	3.634 (1.920~6.876)
Sex (female)	32 (17.11%)	24 (23.76%)	0.175	1.510 (0.832~2.739)
ALSS	73 (39.04%)	66 (65.35%)	<0.001	2.945 (1.779~4.876)
Complication				
BI	143 (76.47%)	95 (94.06%)	<0.001	4.872 (1.998~11.882)
HE	39 (20.86%)	55 (54.46%)	<0.001	4.537 (2.679~7.686)
HRS	6 (3.21%)	18 (17.82%)	<0.001	6.542 (2.506~17.082)
UGB	4 (2.14%)	14 (13.86%)	0.001	7.362 (2.354~23.023)
Imaging				
Ascites	166 (88.77%)	92 (91.09%)	0.540	1.293 (0.569~2.940)
Cirrhosis	97 (51.87%)	89 (88.12%)	<0.001	6.881 (3.530~13.415)
Laboratory				
ALT (U/L)	168.00 (64.00–490.00)	165.00 (57.50–298.00)	0.926	1.000 (0.999~1.000)
AST (U/L)	177.00 (96.00–361.00)	170.00 (98.50–304.50)	0.504	1.000 (0.999~1.001)
ALB (g/L)	30.90 (28.10–34.60)	32.20 (28.55–35.55)	0.926	0.998 (0.949~1.049)
TBIL (μmol/L)	324.00 (232.00–395.60)	392.30 (335.37–510.99)	<0.001	1.006 (1.004~1.008)
Glu (mmol/L)	4.90 (4.28–6.39)	5.23 (3.92–7.48)	0.060	1.067 (0.997~1.141)
TCh (mmol/L)	2.33 (1.74–2.96)	2.09 (1.46–2.62)	0.092	0.800 (0.616~1.038)
Cr (μmol/L)	59.00 (50.00–76.10)	62.00 (51.40–88.15)	0.011	1.007 (1.001~1.012)
Na (mmol/L)	137.00 (134.00–139.00)	135.00 (131.50–137.50)	0.044	0.952 (0.908~0.999)
WBC (×109/L)	6.21 (4.57–8.60)	7.56 (5.78–10.58)	0.010	1.067 (1.015~1.121)
NE%	70.50% (60.40–79.50%)	79.30% (69.10–86.30%)	<0.001	1.058 (1.034~1.082)
NLR	3.78 (2.38–7.72)	7.43 (4.15–14.00)	0.332	1.007 (0.993~1.022)
HB (g/L)	116.89 ± 24.00	116.38 ± 23.97	0.862	0.999 (0.989~1.009)
PLT (×109/L)	93.00 (66.00–129.00)	86.00 (59.00–118.00)	0.168	0.997 (0.992~1.001)
PNR	23.00 (16.25–31.81)	15.13 (8.91–21.53)	<0.001	0.942 (0.919~0.965)
INR	1.92 (1.61–2.27)	2.46 (2.00–2.89)	<0.001	5.161 (3.092~8.615)
BA (μmol/L)	59.20 (42.00–84.20)	65.90 (46.55–95.45)	0.040	1.007 (1.000~1.013)
AFP (ng/ml)	44.13 (6.09–225.82)	26.67 (4.34–56.52)	0.032	0.999 (0.998~1.000)
PCT (ng/ml)	0.303 (0.092–0.605)	0.419 (0.602–1.017)	0.633	0.990 (0.948~1.033)
IL-6 (pg/ml)	17.80 (8.60–37.15)	28.87 (18.42–50.25)	0.098	1.001 (1.000~1.003)

P values were calculated by the log-rank test.
AFP, alpha-fetoprotein; ALB, albumin; ALSS, artificial liver support systems; ALT, alanine transaminase; AST, aspartate transaminase; BA, blood ammonia; BI, bacterial infections; CI, confidence interval; Cr, creatinine; Glu, glucose; HB, hemoglobin; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; IL-6, interleukin-6; INR, international normalized ratio; Na, serum sodium; NE%, percentage of neutrophils; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratios; PCT, serum procalcitonin; PLT, platelet count; PNR, platelet-to-neutrophil ratio; TBIL, total bilirubin; TCh, total cholesterol; UGB, upper gastrointestinal bleeding; WBC, white blood cell count.

Table 3. Multivariate analysis of influencing factors for 90-day mortality of acute-on-chronic liver failure patients

Variables	*B*	Multivariate analysis	
		P value	OR (95% CI)
Age ≥ 45 years	1.808	<0.001	6.101 (2.325~16.010)
HE	1.048	0.006	2.853 (1.358~1.358)
UGB	1.721	0.026	5.588 (1.229~25.420)
Cirrhosis	1.362	0.001	3.905 (1.688~9.036)
TBIL (μmol/L)	0.008	<0.001	1.008 (1.005~1.011)
PNR	–0.039	0.014	0.962 (0.932~0.992)
INR	1.963	<0.001	7.118 (3.462~14.637)

P values were calculated by the log-rank test.
B, regression coefficient; CI, confidence interval; Cirrhosis, imaging-confirmed cirrhosis; HE, hepatic encephalopathy; INR, international normalized ratio; OR, odds ratios; PNR, platelet-to-neutrophil ratio; TBIL, total bilirubin; UGB, upper gastrointestinal bleeding.

expressed as frequencies (percentages). Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Univariate and multivariate stepwise logistic regression analyses were employed to identify independent predictors of 90-day mortality and construct the logistic regression model. The discrimination and calibration of the new prediction model were evaluated using the area under the receiver operating characteristic (ROC) curve (AUC) and calibration curves, respectively. Internal validation was performed using the Bootstrap resampling method. The association between dynamic trends in laboratory parameters and 90-day mortality was also analyzed using univariate and multivariate stepwise logistic regression. Statistical significance was set at $P < 0.05$.

Ethical consideration

The study protocol was approved by the Ethics Committee of Clinical Center of Public Health Affiliated to Shandong University. Written informed consent was waived due to the retrospective nature of the study.

Results

Clinical characteristics of acute-on-chronic liver failure patients

A total of 288 ACLF patients were included in the study, with 187 survivors (64.93%) and 101 nonsurvivors (35.07%) at the 90-day follow-up. There was no statistically significant difference between the survival and death groups in terms of the underlying etiology ($P = 0.396$) (Table 1 and Fig. 2).

Of these patients, 232 (80.56%) were male and 56 (19.44%) were female, with an average age of 50.53 ± 11.46 years. No significant difference was observed in the distribution of sex between the survival and death groups. The prevalence of individuals aged 45 years or older, however,

Table 4. Receiver operating characteristic curve analysis of the independent prognostic factors for 90-day mortality of acute-on-chronic liver failure patients

Variables	AUC (95% CI)	Sensitivity	Specificity	Cutoff
Age ≥ 45 years	0.615 (0.550~0.681)	0.861	0.369	0.5
HE	0.668 (0.600~0.736)	0.545	0.791	0.5
UGB	0.559 (0.487~0.630)	0.139	0.977	0.5
Cirrhosis	0.651 (0.587~0.715)	0.842	0.460	0.5
TBIL (μmol/L)	0.717 (0.658~0.776)	0.762	0.588	334.37
PNR	0.693 (0.630~0.756)	0.624	0.711	0.39
INR	0.753 (0.695~0.810)	0.584	0.780	2.33

AUC, the area under the receiver operating characteristic curve; CI, confidence interval; Cirrhosis, imaging-confirmed cirrhosis; HE, hepatic encephalopathy; INR, international normalized ratio; PNR, platelet-to-neutrophil ratio; TBIL, total bilirubin; UGB, upper gastrointestinal bleeding.

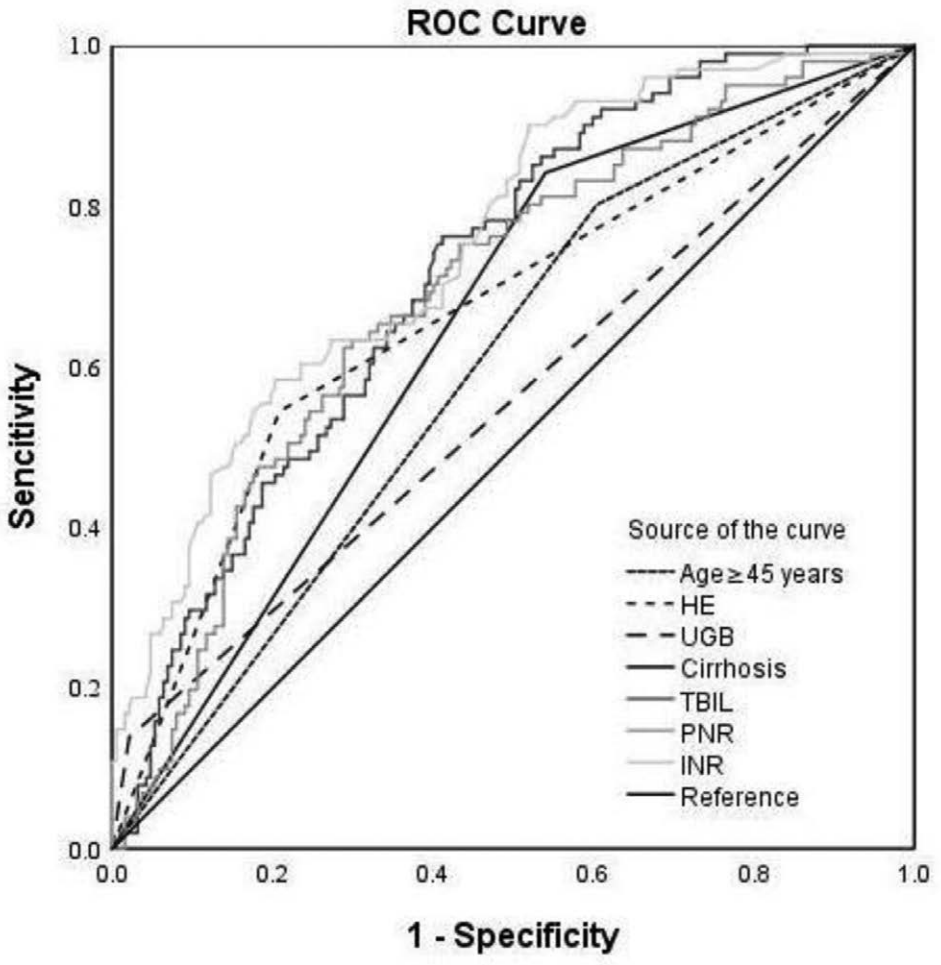

Fig. 3. ROC curve of the independent prognostic factors for 90-day mortality of ACLF patients. ACLF, acute-on-chronic liver failure; Cirrhosis, imaging-confirmed cirrhosis; HE, hepatic encephalopathy; INR, international normalized ratio; PNR, platelet-to-neutrophil ratio; ROC, receiver operating characteristic; TBIL, total bilirubin; UGB, upper gastrointestinal bleeding.

was significantly higher in the death group compared with the survival group (86.14 vs. 63.10%, $P < 0.001$). Of the 139 patients who underwent at least one ALSS treatment, a significantly higher proportion was found in the death group compared with the survival group (65.35 vs. 39.04%, $P < 0.001$). During hospitalization, major complications included BI (94.06 vs. 76.47%), HE (54.46 vs. 20.86%), HRS (17.82 vs. 3.21%), and UGB (13.86 vs. 2.14%). These complications were significantly more common in the death group compared with the survival group ($P < 0.001$).

Regarding imaging findings at admission, the prevalence of ascites (91.09 vs. 88.77%) showed no statistically significant differences between the death and survival groups. The prevalence of cirrhosis, however, was significantly higher in the death group compared with the survival group (88.2 vs. 51.87%, $P < 0.001$). Baseline laboratory results indicated that TBIL, Cr, WBC, NE%, and INR were significantly higher in the death group, while Na, PNR, AM, and AFP were lower, with statistically significant differences ($P < 0.05$). No significant differences were found between the survival and death groups for

Table 5. Receiver operating characteristic curve analysis of Model for End-Stage Liver Disease and AHUCTPI model for 90-day mortality of acute-on-chronic liver failure patients

Model	AUC (95% CI)	Sensitivity	Specificity	Cutoff
MELD	0.739 (0.679~0.799)	0.743	0.626	21.84
7dMELD	0.793 (0.740~0.847)	0.752	0.706	22.63
AHUCTPI	0.914 (0.882~0.946)	0.950	0.749	−1.256
7dAHUCTPI	0.932 (0.905~0.960)	0.851	0.872	−0.249

7dAHUCTPI, the AHUCTPI score at day 7 during hospitalization; 7dMELD, MELD at day 7 during hospitalization; AUC, area under the receiver operating characteristic curve; AHUCTPI, the prognostic model score incorporating age, hepatic encephalopathy, upper gastrointestinal bleeding, cirrhosis, total bilirubin, platelet-to-neutrophil ratio, and international normalized ratio; CI, confidence interval; MELD, Model for End-Stage Liver Disease.

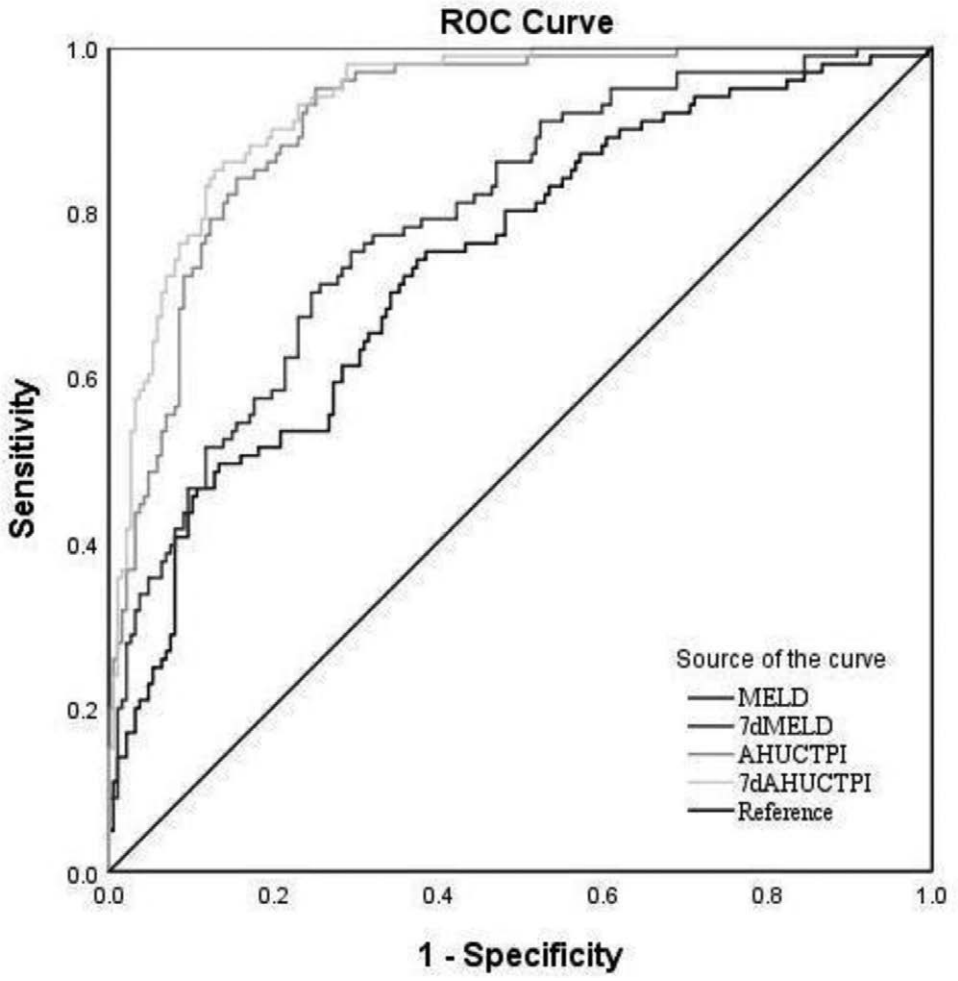

Fig. 4. ROC curve of MELD and AHUCTPI model for 90-day mortality of ACLF patients. 7dAHUCTPI, the AHUCTPI score at day 7 during hospitalization; 7dMELD, MELD at day 7 during hospitalization; AHUCTPI, the prognostic model score incorporating age, hepatic encephalopathy, upper gastrointestinal bleeding, cirrhosis, total bilirubin, platelet-to-neutrophil ratio, and international normalized ratio; MELD, Model for End-Stage Liver Disease; ROC, receiver operating characteristic.

ALT, AST, GGT, ALB, Glu, TCh, NLR, HB, PLT, PCT, and IL-6 ($P \geq 0.05$) (Table 2).

Independent risk factors for 90-day mortality in acute-on-chronic liver failure patients

Univariate analysis identified several variables with P values <0.05, which were subsequently included in multivariate logistic regression analysis using the forward stepwise method. Independent risk factors for 90-day mortality included age ≥45 years ($P < 0.001$, OR = 6.101, 95% CI = 2.325~16.010), HE during hospitalization ($P = 0.006$, OR = 2.853, 95% CI = 1.358~1.358), UGB during hospitalization ($P = 0.026$, OR = 5.588, 95% CI = 1.229~25.420), imaging-diagnosed cirrhosis at admission ($P = 0.001$, OR = 3.905, 95% CI = 1.688~9.036), high baseline TBIL ($P < 0.001$, OR = 1.008, 95% CI = 1.005~1.011), low baseline PNR ($P = 0.014$, OR = 0.962, 95% CI = 0.932~0.992), and high baseline INR ($P < 0.001$, OR = 7.118, 95% CI = 3.462~14.637) (Table 3).

The ROC curve analysis of individual prognostic factors can be seen in Table 4 and Fig. 3, and the cutoff values for TBIL, PNR, and INR were determined to be 334.34 μmol/L, 0.39, and 2.33, respectively.

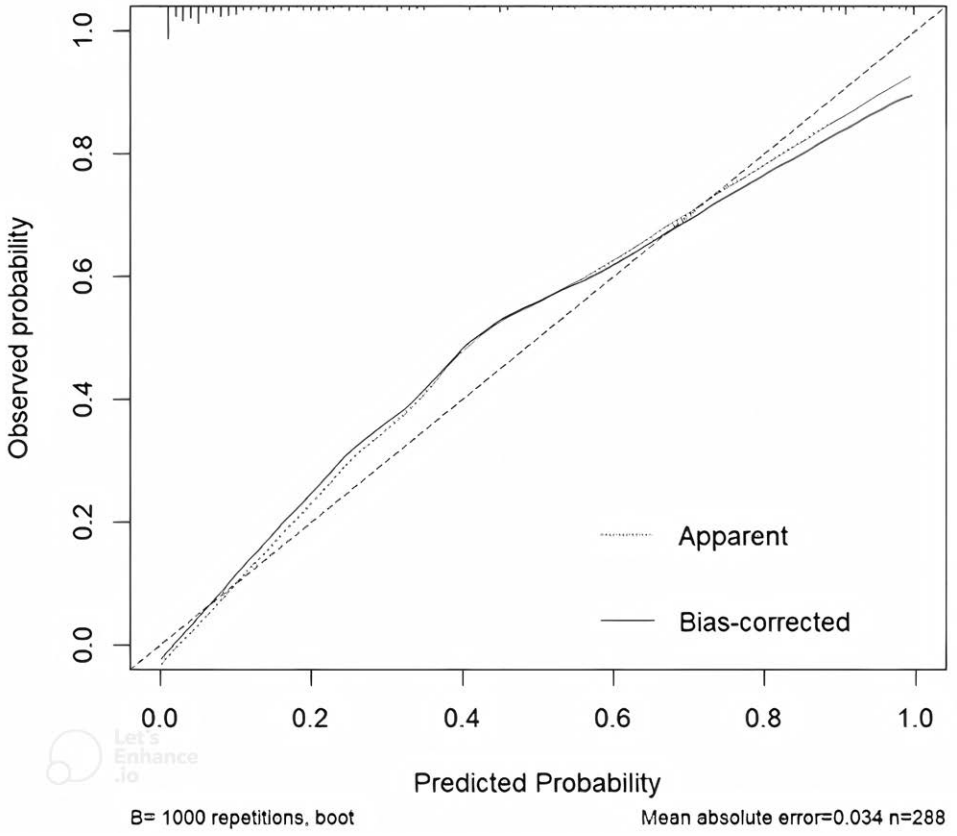

Fig. 5. Calibration curve of the AHUCTPI model for the 90-day mortality of ACLF patients. ACLF, acute-on-chronic liver failure; AHUCTPI, the prognostic model score incorporating age, hepatic encephalopathy, upper gastrointestinal bleeding, cirrhosis, total bilirubin, platelet-to-neutrophil ratio, and international normalized ratio.

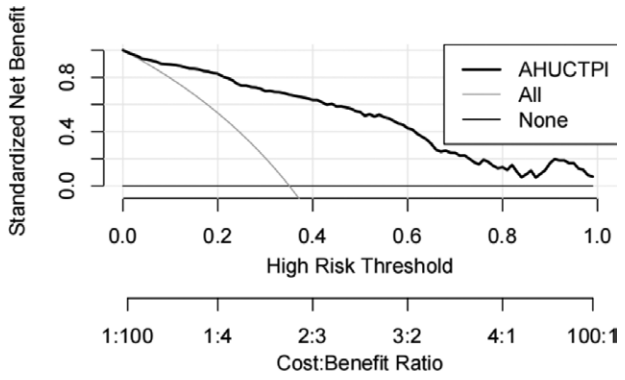

Fig. 6. DCA curve of the AHUCTPI model for the 90-day mortality of ACLF patients. ACLF, acute-on-chronic liver failure; AHUCTPI, the prognostic model score incorporating age, hepatic encephalopathy, upper gastrointestinal bleeding, cirrhosis, total bilirubin, platelet-to-neutrophil ratio, and international normalized ratio; DCA, decision curve analysis.

Evaluation and validation of the new model for 90-day mortality in acute-on-chronic liver failure patients

Based on the independent prognostic factors, the AHUCTPI model was developed, and the designation was derived from the initials of the seven built-in indicators. The model formula is: Logit (p) = −10.019 + 1.808 × age (1 if ≥45 years, 0 if <45 years) + 1.048 × HE (1 if present, 0 if absent) + 1.721 × UGB (1 if present, 0 if absent) + 1.362 × cirrhosis (1 if present, 0 if absent) + 0.008 × TBIL (μmol/L) − 0.039 × PNR + 1.963 × INR. The AHUCTPI model showed strong predictive performance for 90-day mortality with an AUC of 0.913, outperforming the MELD score (AUC = 0.739). The AHUCTPI score at 7 days had an AUC of 0.932, also surpassing the 7-day MELD score (AUC = 0.793). Additionally, the specific cutoffs for clinical decision-making, such as identifying patients with a poor prognosis who may benefit from intensive care or liver transplantation, were determined to be −1.256 for the AHUCTPI score and 21.84 for the MELD score, respectively (Table 5 and Fig. 4). Calibration curves demonstrated good consistency between the AHUCTPI model and 90-day mortality predictions, with a Brier score of 0.115 (Fig. 5). The decision curve analysis indicates that within a threshold probability range of 0.05–0.99, utilizing the AHUCTPI model for predicting the 90-day mortality risk in patients can yield significant clinical benefits and guide effective treatment interventions (Fig. 6).

Internal validation using the Bootstrap resampling method showed a C-index of 0.914 and a corrected C-index of 0.902, indicating robust internal stability of the model. External validation was conducted in 72 patients diagnosed with ACLF and hospitalized at the Liver Disease Center of Shandong Public Health Clinical Center between June 2024 and December 2024, with a training set to validation set ratio of 8 : 2. There were no significant statistical differences in any of the indices between the validation group and the training group ($P > 0.05$)

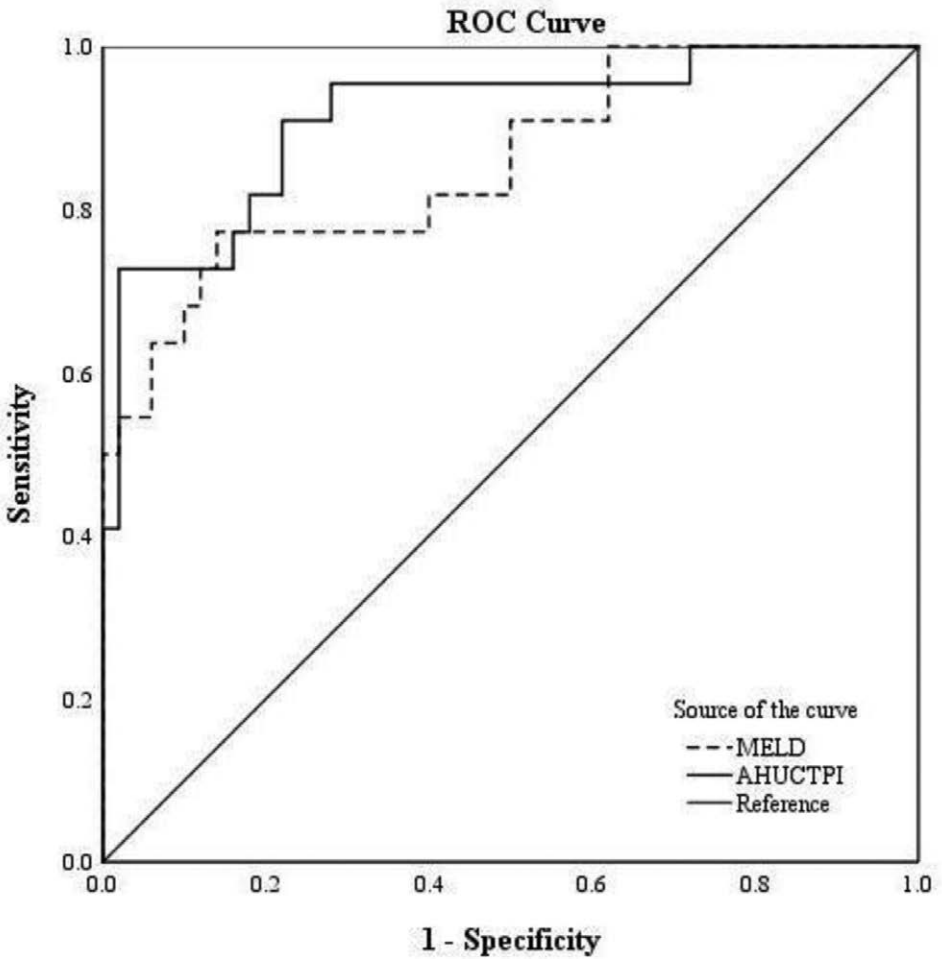

Fig. 7. ROC curve of MELD and AHUCTPI model for 90-day mortality of ACLF patients in the validation group. ACLF, acute-on-chronic liver failure; AHUCTPI, the prognostic model score incorporating age, hepatic encephalopathy, upper gastrointestinal bleeding, cirrhosis, total bilirubin, platelet-to-neutrophil ratio, and international normalized ratio; MELD, Model for End-Stage Liver Disease; ROC, receiver operating characteristic.

(Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/B145*). In the validation group, the AHUCTPI model also demonstrated robust predictive performance for 90-day mortality, achieving an AUC of 0.914, which significantly outperformed the MELD score (AUC = 0.857) (Fig. 7).

Dynamic analysis of laboratory parameters for 90-day mortality in acute-on-chronic liver failure patients

Multivariate analysis of dynamic trends in laboratory indicators revealed that patients with increasing ALT ($P = 0.003$, OR = 3.446, 95% CI = 1.543~7.699), increasing TBIL ($P < 0.001$, OR = 3.603, 95% CI = 5.373~34.442), decreasing HB ($P = 0.001$, OR = 0.012, 95% CI = 0.001~0.170), and decreasing PLT ($P = 0.046$, OR = 0.442, 95% CI = 0.181~0.985) were associated with significantly higher 90-day mortality (Table 6).

Discussion

China bears one of the highest global burdens of hepatitis B virus infection [13], and ACLF in China predominantly arises from chronic hepatitis B, as reflected in our study cohort. This differs from Europe and the USA, where alcoholic liver disease is a more common etiology for ACLF. Despite these regional differences, our study found no significant effect of different etiologies on 90-day mortality, aligning with some previous studies [14]. The higher proportion of ALSS therapy in the death group, though not an independent factor for mortality, likely reflects the severity of the patient's conditions requiring such intervention.

Our study identified age ≥45 years as an independent risk factor for 90-day mortality in ACLF patients. This finding is consistent with studies by Jalan *et al.* [15] and Li *et al.* [16], which also linked advanced age with poorer outcomes in ACLF patients. Aging is associated with reduced immunity, decreased organ reserve, and diminished stress response, contributing to a poorer prognosis.

Cirrhosis, a consequence of long-term liver damage, was significantly associated with 90-day mortality in our study. This relationship may stem from reduced resistance to acute hepatic insults and decreased liver regenerative potential. The role of cirrhosis in short-term prognosis, however, remains debated. While Wu *et al.* [17] supported our findings, studies by Li *et al.* [18] and Thanapirom *et al.* [19] presented conflicting results, with the latter suggesting

Table 6. Univariate and multivariate analyses of dynamic trends of laboratory indicators in patients with acute-on-chronic liver failure

Variables	Survival group (*n* = 187)	Death group (*n* = 101)	Univariate analysis			Multivariate analysis	
			P value	OR (95% CI)	*B*	*P* value	OR (95% CI)
ΔALT	0.47 (0.28–0.75)	0.57 (0.37–0.87)	0.009	2.137 (1.205~3.790)	1.237	0.003	3.446 (1.543~7.699)
ΔAST	0.58 (0.33–0.82)	0.69 (0.45–0.98)	0.342	1.209 (1.817~1.790)			
ΔALB	1.09 (0.99–1.24)	1.11 (1.00–1.23)	0.251	2.121 (1.588~7.652)			
ΔTBIL	0.91 (0.69–1.11)	1.18 (0.97–1.31)	<0.001	9.882 (1.263~22.904)	2.61	<0.001	13.603 (5.373~34.442)
ΔGlu	1.00 (0.84–1.21)	0.98 (0.75–1.30)	0.905	0.986 (1.780~1.246)			
ΔTCh	0.97 (0.82–1.17)	0.88 (0.73–1.10)	0.072	0.531 (1.266~1.059)			
ΔCr	1.02 (0.86–1.17)	1.00 (0.84–1.30)	0.132	1.512 (1.882~2.592)			
ΔNa	1.00 (0.98–1.01)	0.99 (0.97–1.03)	0.882	0.667 (0.003–141.404)			
ΔWBC	0.90 (0.66–1.14)	0.89 (0.70–1.30)	0.699	0.982 (1.896~1.077)			
ΔNE%	0.94 (0.84–1.04)	0.98 (0.91–1.07)	0.235	2.187 (1.602~7.942)			
ΔNLR	0.81 (0.54–1.24)	0.92 (0.61–1.43)	0.369	1.108 (1.886~1.385)	−4.407	0.001	0.012 (0.001~0.170)
ΔHB	0.92 (0.85–0.98)	0.87 (0.82–0.93)	0.004	0.037 (1.004~0.342)	−0.862	0.046	0.442 (0.181~0.985)
ΔPLT	0.88 (0.68–1.11)	0.75 (0.55–1.01)	0.021	0.430 (1.210~0.881)			
ΔPNR	0.96 (0.71–1.55)	0.89 (0.54–1.22)	0.011	0.609 (1.416~0.891)			
ΔINR	0.98 (0.88–1.09)	1.03 (0.89–1.21)	0.001	6.087 (1.137~17.336)			
ΔBA	1.00 (0.77–1.36)	0.98 (0.64–1.25)	0.056	0.616 (1.375~1.013)			
ΔAFP	0.77 (0.57–1.12)	0.64 (0.45–0.81)	0.134	0.854 (1.694~1.050)			
ΔPCT	0.85 (0.59–1.19)	0.97 (0.71–1.50)	0.602	0.991 (0.960~1.024)			
ΔIL-6	0.73 (0.39–1.29)	1.03 (0.54–2.66)	0.414	1.010 (1.986~1.035)			

P values were calculated by the log-rank test.

ΔAFP, alpha-fetoprotein on day 7 of hospitalization/at admission; ΔALB, albumin on day 7 of hospitalization/at admission; ΔALT, alanine transaminase on day 7 of hospitalization/at admission; ΔAST, aspartate transaminase on day 7 of hospitalization/at admission; ΔBA, blood ammonia on day 7 of hospitalization/at admission; ΔCr, creatinine on day 7 of hospitalization/at admission; ΔGlu, glucose on day 7 of hospitalization/at admission; ΔHB, hemoglobin on day 7 of hospitalization/at admission; ΔIL-6, interleukin-6 on day 7 of hospitalization/at admission; ΔINR, international normalized ratio on day 7 of hospitalization/at admission; ΔNa, serum sodium on day 7 of hospitalization/at admission; ΔNE%, percentage of neutrophils on day 7 of hospitalization/at admission; ΔNLR, neutrophil-to-lymphocyte ratio on day 7 of hospitalization/at admission; ΔPCT, serum procalcitonin on day 7 of hospitalization/at admission ; ΔPLT, platelet count on day 7 of hospitalization/at admission; ΔPNR, platelet-to-neutrophil ratio on day 7 of hospitalization/at admission; ΔTBIL, total bilirubin on day 7 of hospitalization/at admission; ΔTCh, total cholesterol on day 7 of hospitalization/at admission; ΔWBC, white blood cell count on day 7 of hospitalization/at admission; *B*, regression coefficient; CI, confidence interval; OR, odds ratios.

that ACLF patients without cirrhosis had higher 90-day mortality.

Complications such as HE and UGB were strong predictors of mortality in our study. HE, a common decompensation in ACLF, is associated with systemic inflammation, multiorgan failure, and poor liver function, thereby predicting mortality [20]. UGB remains a life-threatening complication despite advances in treatment modalities, contributing to high mortality rates [21].

Additionally, our study also highlighted high baseline TBIL and high baseline INR as independent risk factors for 90-day mortality. The liver's roles in bilirubin metabolism and coagulation factor synthesis mean that elevated TBIL and INR reflect severe liver damage and can accurately predict prognosis in liver failure [22]. Notably, a lower baseline PNR was associated with increased mortality. As an easily obtainable hematological marker reflecting systemic inflammation, PNR has been validated as a prognostic marker in other conditions [23,24], whereas its role in the prognosis of ACLF warrants further investigation. This observation aligns with the systemic inflammation hypothesis [25] of ACLF progression, in which sustained inflammatory responses may drive multiorgan failure through cytokine storm and immune dysregulation. Substantiating this mechanism, accumulating evidence [26–28] highlights the prognostic value of inflammatory biomarkers including NLR, PCT, and IL-6 in ACLF. As our understanding of the role of systemic inflammatory in the pathophysiology of ACLF continues to deepen [29], emerging therapeutic strategies targeting inflammatory pathways have demonstrated promising results in preclinical models. For instance, the use of Toll-like receptor-4 antagonist and TNF-α inhibitors has shown potential in modulating the inflammatory cascade in ACLF [30,31]. Translating these findings into clinical practice, however, necessitates careful consideration of the delicate balance between immune modulation and infection risk in this vulnerable patient population.

The AHUCTPI model, developed from multivariate logistic regression analysis, showed superior predictive accuracy for 90-day mortality compared with the MELD score, a widely used tool to predict the outcome of end-stage liver disease or organ allocation in liver transplantation. Extra incorporating age, complications, cirrhosis, and systemic inflammatory response, the AHUCTPI model provided a more comprehensive assessment of patient prognosis.

ACLF is a dynamic condition and relying solely on baseline indicators has limitations. Our study's analysis of dynamic trends in laboratory indicators over 7 days provided additional prognostic insights, highlighting the importance of monitoring changes in ALT, TBIL, HB, and PLT. The decreasing trend in ALT and TBIL in survivors and the significant downward trends in HB and PLT in nonsurvivors suggest that these markers could inform treatment decisions. Of note, PLT has been considered as a regulator of pathophysiological processes including inflammation, immunity, and even liver regeneration [32], and the dynamic trend of PLT count can serve as a novel and valuable predictive indicator for a 90-day survival rate of ACLF [33]. A recent study supports the potential of PLT as a therapeutic target for liver diseases [34].

Conclusions

Our study identified several significant predictors of 90-day mortality in ACLF patients, including age, complications, cirrhosis, TBIL, INR, and PNR. The AHUCTPI model, incorporating the above several significant predictors,

demonstrated excellent performance and outperformed the MELD score. Dynamic monitoring of laboratory indicators further enhances prognostic evaluation and aids in clinical decision-making.

This study has several limitations and future prospects. It is a single-center, retrospective study conducted in China and primarily utilizes the CMA's ACLF criteria, which may affect the generalizability of the findings. Additionally, the retrospective nature of the study may introduce selection bias and incomplete data. Future research should focus on the prospective validation of the AHUCTPI model across diverse patient populations and healthcare settings, including regions using EASL or APASL definitions. While internal validation using Bootstrap resampling and preliminary external validation was performed, a more comprehensive external validation in a larger, multicenter cohort is necessary to confirm the robustness and applicability of the AHUCTPI model. Furthermore, the AHUCTPI model incorporates arithmetic operations including addition, subtraction, multiplication, and division of seven indicators, which may pose challenges for its practicality and user-friendliness in routine clinical application. There is considerable potential for developing automated tools, including web-based calculators, mobile applications, and systems integrated with electronic medical records, to calculate the AHUCTPI score. Further studies should explore the integration of additional biomarkers and advanced imaging techniques to enhance prognostic accuracy. Investigating the impact of specific therapeutic interventions on dynamic prognostic indicators could provide valuable insights into ACLF management.

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Conflicts of interest

There are no conflicts of interest.

References

1 Mezzano G, Juanola A, Cardenas A, Mezey E, Hamilton JP, Pose E, *et al*. Global burden of disease: acute-on-chronic liver failure, a systematic review and meta-analysis. *Gut* 2022; 71:148–155.
2 Luo J, Li J, Li P, Liang X, Hassan HM, Moreau R, Li J. Acute-on-chronic liver failure: far to go-a review. *Crit Care* 2023; 27:259.
3 Kulkarni AV, Sarin SK. Acute-on-chronic liver failure - steps towards harmonization of the definition! *J Hepatol* 2024; 81:360–366.
4 Gustot T, Fernandez J, Garcia E, Morando F, Caraceni P, Alessandria C, *et al*; CANONIC Study Investigators of the EASL-CLIF Consortium. Clinical course of acute-on-chronic liver failure syndrome and effects on prognosis. *Hepatology* 2015; 62:243–252.
5 Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; 60:646–649.
6 Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, *et al*. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33:464–470.
7 Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, *et al*; APASL ACLF Research Consortium (AARC) for APASL ACLF Working Party. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL): an update. *Hepatol Int* 2019; 13:353–390.
8 Hernaez R, Solà E, Moreau R, Ginès P. Acute-on-chronic liver failure: an update. *Gut* 2017; 66:541–553.
9 Bajaj JS, O'Leary JG, Reddy KR, Wong F, Biggins SW, Patton H, *et al*; North American Consortium for the Study of End-Stage Liver Disease (NACSELD). Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. *Hepatology* 2014; 60:250–256.
10 Wu T, Li J, Shao L, Xin J, Jiang L, Zhou Q, *et al*; Chinese Group on the Study of Severe Hepatitis B (COSSH). Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *Gut* 2018; 67:2181–2191.
11 Ma L, Liu S, Xing H, Jin Z. Research progress on short-term prognosis of acute-on-chronic liver failure. *Expert Rev Gastroenterol Hepatol* 2023; 17:45–57.
12 Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Disease and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. [Guideline for diagnosis and treatment of liver failure]. *Zhonghua Gan Zang Bing Za Zhi* 2019; 27:18–26.
13 Liu J, Liang W, Jing W, Liu M. Countdown to 2030: eliminating hepatitis B disease, China. *Bull World Health Organ* 2019; 97:230–238.
14 Hafsa F, Chaudary ZI, Tariq O, Riaz Z, Shehzad A, Irfan Jamil M, Naeem I. Acute-on-chronic liver failure: causes, clinical parameters, and predictors of mortality. *Cureus* 2024; 16:e52690.
15 Jalan R, Saliba F, Pavesi M, Amoros A, Moreau R, Ginès P, *et al*; CANONIC Study Investigators of the EASL-CLIF Consortium. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *J Hepatol* 2014; 61:1038–1047.
16 Li J, Liang X, You S, Feng T, Zhou X, Zhu B, *et al*; Chinese Group on the Study of Severe Hepatitis B (COSSH). Development and validation of a new prognostic score for hepatitis B virus-related acute-on-chronic liver failure. *J Hepatol* 2021; 75:1104–1115.
17 Wu SJ, Yan HD, Zheng ZX, Shi KQ, Wu FL, Xie YY, *et al*. Establishment and validation of ALPH-Q score to predict mortality risk in patients with acute-on-chronic hepatitis B liver failure: a prospective cohort study. *Medicine (Baltim)* 2015; 94:e403.
18 Li N, Huang C, Yu KK, Lu Q, Shi GF, Zheng JM. Validation of prognostic scores to predict short-term mortality in patients with HBV-related acute-on-chronic liver failure: the CLIF-C OF is superior to MELD, CLIF SOFA, and CLIF-C ACLF. *Medicine (Baltim)* 2017; 96:e6802.
19 Thanapirom K, Teerasarntipan T, Treeprasertsuk S, Choudhury A, Sahu MK, Maiwall R, *et al*; APASL ACLF Working Party. Impact of compensated cirrhosis on survival in patients with acute-on-chronic liver failure. *Hepatol Int* 2022; 16:171–182.
20 Verma N, Dhiman RK, Choudhury A, Taneja S, Duseja A, Singh V, *et al*; APASL ACLF Research Consortium (AARC) for APASL ACLF Working Party. Dynamic assessments of hepatic encephalopathy and ammonia levels predict mortality in acute-on-chronic liver failure. *Hepatol Int* 2021; 15:970–982.
21 Zhao H, Zhao R, Hu J, Zhang X, Ma J, Shi Y, *et al*. Upper gastrointestinal hemorrhage in acute-on-chronic liver failure: prevalence, characteristics, and impact on prognosis. *Expert Rev Gastroenterol Hepatol* 2019; 13:263–269.
22 Li H, Chen LY, Zhang NN, Li ST, Zeng B, Pavesi M, *et al*. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. *Sci Rep* 2016; 6:25487.
23 Jin P, Li X, Chen J, Zhang Z, Hu W, Chen L, *et al*. Platelet-to-neutrophil ratio is a prognostic marker for 90-days outcome in acute ischemic stroke. *J Clin Neurosci* 2019; 63:110–115.
24 Wang H, Qing X, Wang H, Gu Y. Association between platelet to neutrophil ratio (PNR) and clinical outcomes in STEMI patients after successful pPCI: a secondary analysis based on a cohort study. *Cardiovasc Ther* 2022; 2022:2022657.
25 Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. *J Hepatol* 2015; 63:1272–1284.
26 Sun J, Guo H, Yu X, Zhu H, Zhang X, Yang J, *et al*. A neutrophil-to-lymphocyte ratio-based prognostic model to predict mortality in patients with HBV-related acute-on-chronic liver failure. *BMC Gastroenterol* 2021; 21:422.
27 Janka T, Tornai D, Papp M, Vitális Z. The value of neutrophil-to-lymphocyte ratio to identify bacterial infection and predict short-term mortality in patients with acutely decompensated cirrhosis. *Diagnostics (Basel)* 2023; 13:2954.
28 Murakami S, Imamura M, Uchida T, Suehiro Y, Namba M, Fujii Y, *et al*. Serum interleukin-6 level predicts the prognosis for patients

with alcohol-related acute-on-chronic liver failure. *Hepatol Int* 2023; 17:1225–1232.
29 Clària J, Arroyo V, Moreau R. Roles of systemic inflammatory and metabolic responses in the pathophysiology of acute-on-chronic liver failure. *JHEP Rep* 2023; 5:100807.
30 Engelmann C, Habtesion A, Hassan M, Kerbert AJ, Hammerich L, Novelli S, *et al*. Combination of G-CSF and a TLR4 inhibitor reduce inflammation and promote regeneration in a mouse model of ACLF. *J Hepatol* 2022; 77:1325–1338.
31 Yang F, Li X, Wang LK, Wang LW, Han XQ, Zhang H, Gong ZJ. Inhibitions of NF-κB and TNF-α result in differential effects in rats with acute on chronic liver failure induced by d-Gal and LPS. *Inflammation* 2014; 37:84857.
32 Starlinger P, Assinger A. Importance of platelet-derived growth factors in liver regeneration. *Expert Rev Gastroenterol Hepatol* 2016; 10:557–559.
33 Xu X, Hou Z, Xu Y, Gu H, Liang G, Huang Y. The dynamic of platelet count as a novel and valuable predictor for 90-day survival of hepatitis B virus-related acute-on-chronic liver failure patients. *Clin Res Hepatol Gastroenterol* 2021; 45:101482.
34 Maruyama T, Murata S, Takahashi K, Tamura T, Nozaki R, Ikeda N, *et al*. Platelet transfusion improves liver function in patients with chronic liver disease and cirrhosis. *Tohoku J Exp Med* 2013; 229:213–220.