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Lactate predicts 90-day acute-on-chronic liver failure in acute decompensated cirrhosis: A retrospective cohort study

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Research Article

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Lactate predicts 90-day acute-on-chronic liver failure in acute decompensated cirrhosis: A retrospective cohort study

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Abstract

Background & Aims

Existing prognostic models demonstrate insufficient sensitivity in predicting acute-on-chronic liver failure (ACLF) among patients with cirrhosis experiencing acute decompensation (AD). We postulated that serum lactate levels, indicative of systemic metabolic dysregulation, could enhance the stratification of ACLF risk.

Methods

This retrospective cohort study included 831 hospitalized patients with AD from The Second Hospital of Nanjing, spanning the years 2015 to 2024. Serum lactate levels were assessed upon admission. The primary outcome was the development of ACLF, as defined by the EASL-CLIF criteria, within a 90-day period. Multivariable Cox regression, receiver operating characteristic (ROC) analysis, and competing risk models were employed to evaluate the prognostic significance of lactate levels and to establish an optimal threshold. A nomogram was subsequently developed and subjected to internal validation.

Results

ACLF developed in 272/831 (32.7%) patients. ACLF patients had higher lactate (median 4.6 vs 3.5 mmol/L, p<0.001). Each 1-mmol/L lactate increase independently predicted ACLF risk (HR 1.16, 95% CI 1.10–1.22). A lactate threshold of 4.8 mmol/L stratified high-risk patients (sensitivity 47.8%, specificity 72.8%). A nomogram integrating lactate, infection, INR, bilirubin, and creatinine outperformed traditional models (AUC 0.783 vs MELD 0.701). Results remained robust in competing risk analyses (sHR 1.15, 95% CI 1.07–1.23).

Conclusions

Lactate is an independent predictor of 90-day ACLF in AD cirrhosis. A cut-off of 4.8 mmol/L enhances risk stratification, and lactate-integrated models improve prognostic accuracy. Routine lactate measurement may guide early intervention.

Key Words

acute decompensation, acute-on-chronic liver failure, lactate, Risk Prediction mo del, Prognostic biomarkers, Bacterial infection, Nomogram

Introduction

Acute decompensation (AD) of cirrhosis is characterised by the sudden onset or development of ascites, hepatic encephalopathy (HE), gastrointestinal bleeding or bacterial infections. It marks an important transition to a high-risk clinical state in patients with cirrhosis[1,2]. One such condition is acute-on-chronic liver failure (ACLF), which is defined by the European Association for the Study of Chronic Liver Failure (EASL-CLIF) consortium as acute hepatic and extrahepatic organ failure in cirrhotic patients[3]. Studies have shown that, once ACLF develops, the 90-day mortality rate in AD patients can exceed 50%[4–7]. Another large international cohort study (the PREDICT study) showed that almost 30% of hospitalised AD patients progress to ACLF within 3 months[6]. Therefore, identifying individual patients with high-risk AD at an early stage in order to intervene promptly is a key issue to improve the prognosis of patients with cirrhotic decompensation.

Unfortunately, the prognostic models commonly used in clinical practice, including the MELD, CTP and CLIF-C AD scores, have not demonstrated sufficient sensitivity in practice[8,9]. In addition to considering the influence of factors such as region and patient population, we hypothesise that this may be because these models primarily rely on liver dysfunction markers (e.g. bilirubin, INR and albumin) but ignore severe metabolic disorders, potentially resulting in some high-risk AD patients being overlooked. In fact, metabolic disorders in ACLF are closely intertwined with and mutually reinforce inflammatory storms, immune paralysis, haemodynamic abnormalities, microcirculatory disorders and multiorgan failure, forming a vicious circle[10,11]. Hyperlactatemia, in particular, is a key component of systemic metabolic disturbances in ACLF. It reflects impaired hepatic metabolism due to reduced functional hepatocyte mass in the cirrhotic state, as well as inadequate tissue perfusion and hypoxia due to microcirculatory dysfunction and/or sepsis[12].

Previous studies have clearly demonstrated that lactate is a valid prognostic marker for sepsis and shock[13]. Furthermore, previous clinical cohort studies have confirmed a higher proportion of bacterial infections in decompensated events in patients who developed ACLF within 90 days[5,6].

Based on the background above, we hypothesized that serum lactate, as a direct readout of systemic metabolic disorders, may be superior to traditional biomarkers in predicting ACLF. We therefore designed and conducted this study to clarify the value of lactate for predicting the occurrence of ACLF within 90 days in patients with AD. The study also aimed to assess whether clinically feasible lactate cut-off values can optimize risk stratification as well as to effectively improve the early identification of individual patients with high-risk AD when lactate is incorporated into a prediction model, with the aim of providing new ideas for individualized risk assessment and timely intervention for ACLF.

Material and Methods

Study Design and Participants

This single-center retrospective cohort study consecutively enrolled patients hospitalized with acute decompensated cirrhosis at The Second Hospital of Nanjing between January 2015 and October 2024. Patients were enrolled if they met all the following conditions: (1) aged 18-80 years; (2)confirmed diagnosis of cirrhosis established by:histopathological evidence, or combination of clinical signs, laboratory parameters, endoscopic evidence of portal hypertension, and/or radiological features of cirrhosis; (3) hospitalization for acute decompensation (AD) defined as first or recurrent grade 2 or 3 ascites on the basis of preexisting decompensated cirrhosis within 2 weeks, first or recurrent acute hepatic encephalopathy in a previously conscious patient, acute gastrointestinal hemorrhage, and any type of acute bacterial infection, or any combination of the above. (4) provision of written informed consent prior to enrollment. Exclusion criteria were: (1) age <18 or >80 years; (2) non-AD-related hospitalization;(3) prior liver transplantation or hepatectomy; (4) Active immunosuppression: Immunodeficiency syndromes or systemic immunosuppressive therapy (>10 mg/day prednisone equivalent for >4 weeks); (5) hepatocellular carcinoma exceeding Milan criteria; (6) extrahepatic malignancies; (7) pregnancy or lactation; (8) inability to provide informed consent.

Data Collection

Baseline demographic, clinical, and laboratory data were extracted from electronic medical records or telephone follow-up. Especially, serum lactate is venous blood lactate, and the samples were collected and stored in EDTA sodium fluoride tubes within 2 hours of admission, with laboratory testing completed within 15 minutes. AD type(Infection) is defined as a liver cirrhosis patient admitted to the hospital with bacterial infection.

The primary outcome was development of ACLF within 90 days, defined according to the EASL-CLIF Consortium criteria[3]. Secondary outcomes included 90-day all-cause mortality, liver transplantation status and readmission for further

treatment.

Statistical Analysis

The analysis used mean (SD) for normally distributed continuous variables and median (IQR) for non-normally distributed ones, with frequencies and percentages for categorical variables. Data distribution was assessed using normality tests and QQ plots. Welch's t-test or ANOVA was used for group comparisons of normally distributed continuous variables, while the Wilcoxon rank-sum or Kruskal-Wallis test was used for non-normal distributions. For categorical data, the Fisher exact test was used for expected frequencies <5, otherwise the Chi-squared test was applied. Results with a p-value of <0.05 were considered significant. In the research, all statistical analyses were performed using the R software (version 4.2.2), along with MSTATA software (www.mstata.com).

Please refer to the Supplementary Methods for the detailed *Statistical analysis.*

Results

Patient Characteristics

A total of 3,602 patients hospitalized with decompensated cirrhosis were initially screened between January 2015 and October 2024. Following the application of exclusion criteria, 1,565 patients were deemed eligible after this initial screening. Subsequently, 734 patients were excluded due to incomplete 90-day follow-up data (n=402) or missing critical laboratory or clinical variables (n=332). This resulted in 831 patients comprising the final analytic cohort. Fig. S1shows a flow chart depicting the process used to screen patients. Please refer to the Supplementary Results for the detailed Patients Exclusion. Supplementary Fig. S1shows a flow chart depicting the process used to screen patient.

Table 1 presents the baseline characteristics of 831 patients stratified by the occurrence of ACLF within 90 days (No: n=559; Yes: n=272). No significant differences were observed between groups regarding age , gender distribution , or cirrhosis etiology. However, significant disparities emerged in AD type distribution (p<0.001), with infection (23.2% vs. 12.7%) and multiple reasons (37.9% vs. 14.0%) being more prevalent in the ACLF group. Laboratory parameters showed marked differences, including higher INR (median 2.5 vs. 2.0, p<0.001), TBil (3.5 vs. 1.9 mg/dL, p<0.001), Cr (0.8 vs. 0.7 mg/dL, p<0.001), and lactate (4.6 vs. 3.5 mmol/L, p<0.001), but lower Alb (29.0 vs. 31.0 g/L, p<0.001) in ACLF patients. Severity scores were significantly worse in the ACLF group (MELD: 23.3 vs. 18.1; CLIF-C AD: 49.4 vs. 44.5; CTP: 10 vs. 9; all p<0.001). The ACLF group had substantially lower 90-day survival (54.8% vs. 85.9%, p<0.001) and shorter median survival time (54.0 vs. 90.0 days, p<0.001), while readmission rates were comparable between groups (20.6% vs. 19.1%, p=0.622).

Univariate and Multivariate Cox Regression Analyses

Univariate analyses were used to compare the indices between non-ACLF and ACLF group in Table 2. The candidate predictors were reduced to 5 potential predictors after LASSO regression and tenfold cross-validation (Supplementary Fig.

S2). Further multivariate Cox analyses revealed significant associations between 90-day ACLF occurrence and AD type(Infection), INR, TBil, Cr, and lactate (Table 2). Patients with infection exhibited a higher risk of mortality compared to those without infection (HR, 2.14; 95% CI 1.67–2.72; p<0.001). Each unit increase in INR was associated with a 2.54-fold increased risk of mortality (95% CI 2.13–3.03; p<0.001). Similarly, higher levels of TBil and Cr were associated with increased 90-day ACLF occurrence risk. Additionally, each unit increase in lactate levels was associated with a 16% increased risk of 90-day ACLF(HR, 1.16; 95% CI 1.10–1.22; p<0.001). The findings indicate that lactic acid serves as a critical predictor for the occurrence of ACLF within a 90-day period. Variance inflation factor and tolerance suggest that the collinearity of independent variables in the model is low (Supplementary Table S1). Our comparative analysis of the Multivariate model against the MELD score, CTP score, and CLIF-C AD score revealed that the inclusion of lactic acid in the multifactor model significantly enhances its predictive capability for ACLF (Fig. 1a). Furthermore, integrating lactate into these conventional models also demonstrated an improvement in their predictive efficiency to a certain extent (Fig. 1b-d).

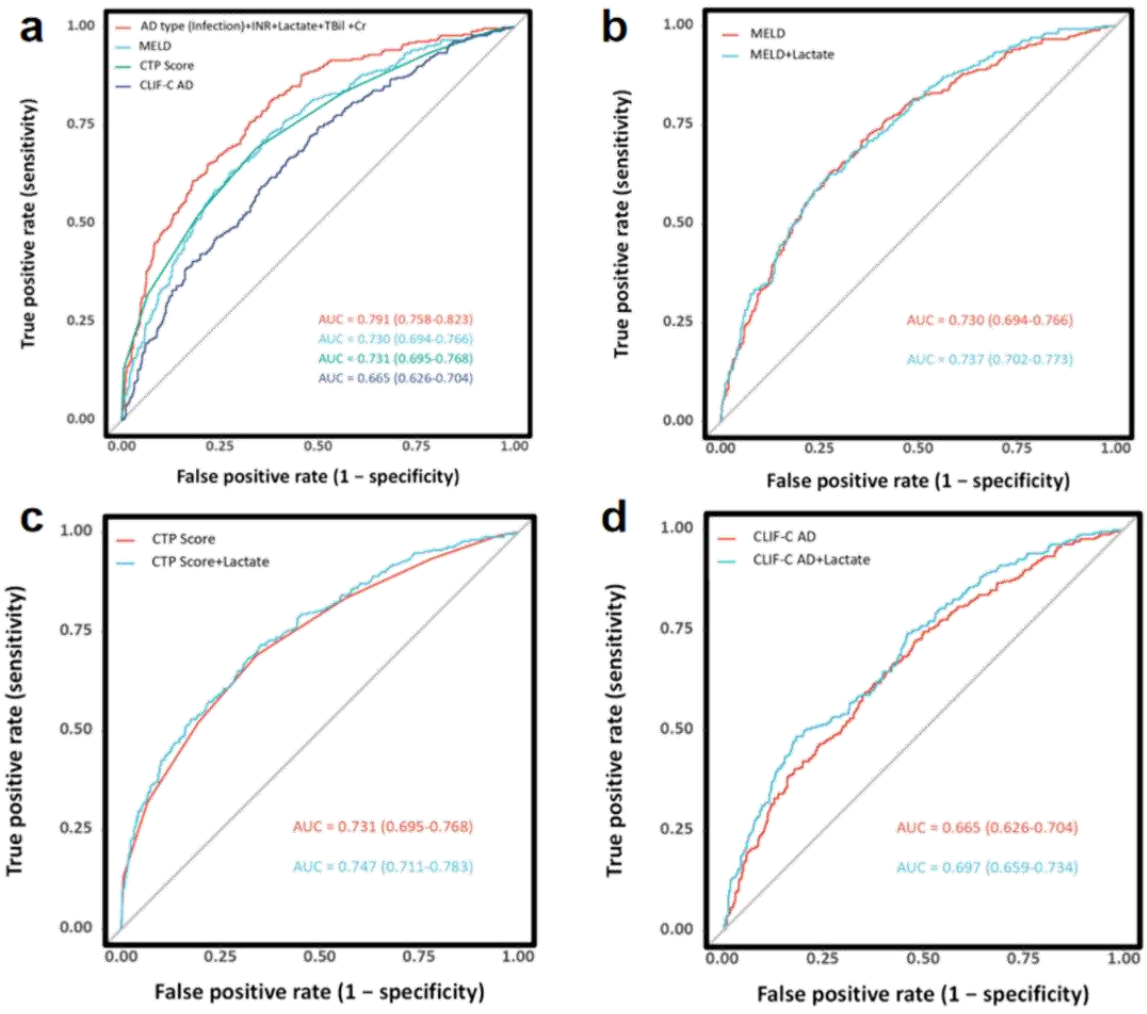


Fig. 1 Comparison of receiver operating characteristic curve between traditional

models and lactate adjusted Models. a: Multivariate Cox Regression model vs. MELD vs. CTP Score vs. CLIF-C-AD; b: MELD vs. MELD+lactate; c: CTP Score vs. CTP Score+lactate; d: CLIF-C-AD vs. CLIF-C-AD+lactate.

Competing Risk Analysis and Subgroup Analysis

We performed Fine-Gray competing risk regression to account for liver transplantation or death as competing events(Fig. 2a). We found that the association between lactate and ACLF risk remained robust (sHR=1.15, 95% CI 1.07-1.23), consistent with the Cox model (HR=1.16, 1.10-1.22; p=0.24).

Subgroup analyses observed significant interaction between lactate and AD type (p for interaction<0.001), with particularly strong associations in patients presenting with acute ascites/hepatic hydrothorax (HR 1.33, 95% CI 1.17-1.51, p<0.001) and hepatic encephalopathy (HR 1.36, 95% CI 1.05-1.76, p=0.019). AD type(Infection), cirrhosis etiology and previous ACLF status did not significantly modify the association (p for interaction=0.168), suggesting uniform prognostic value of lactate across these subgroups (Fig. 2b).

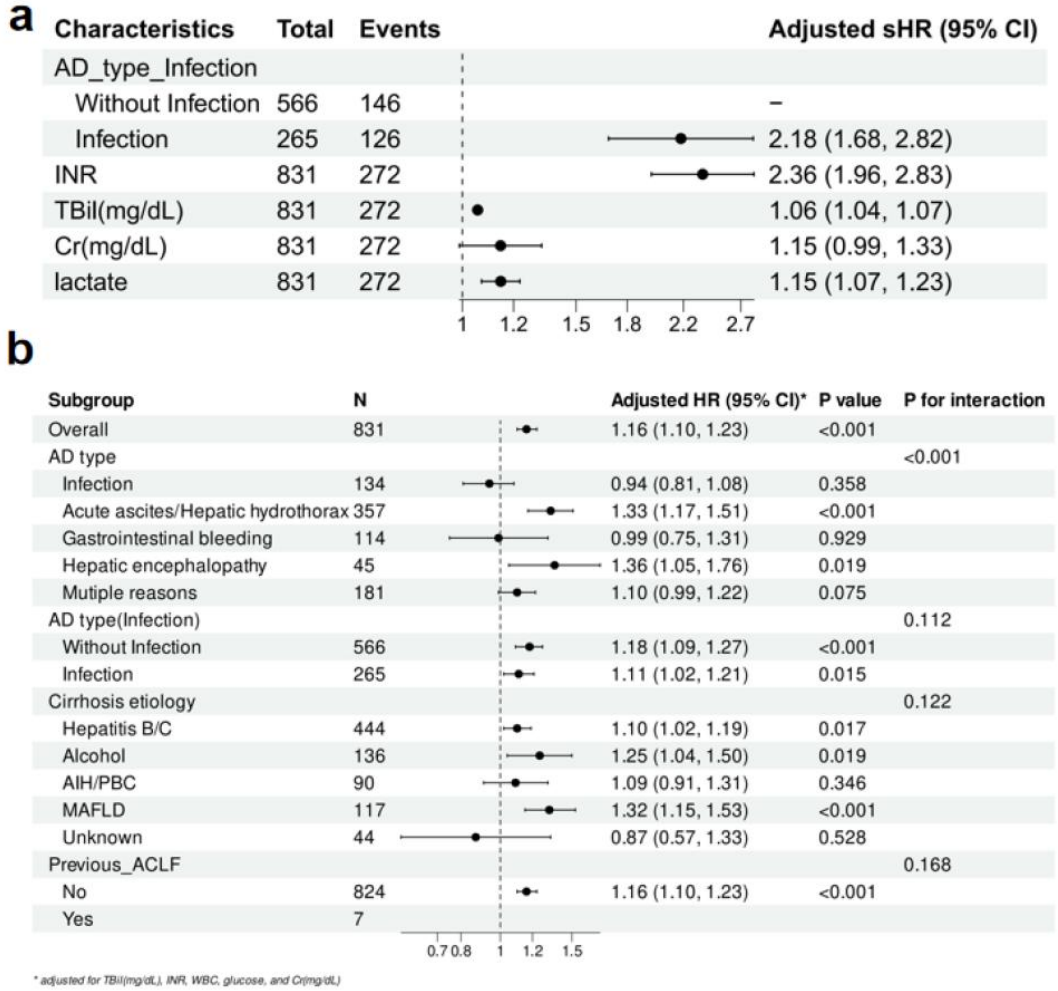


Fig. 2 Forest map of competitive risk analysis and subgroup analysis forest map. a: Fine-Gray competing risk regression to account for liver transplantation or death as competing events. b: Subgroup analyses between lactate and AD type, AD

type(Infection), cirrhosis etiology and previous ACLF status, adjusted for TBil, INR, WBC, glucose and Cr.

Restricted Cubic Spline Analysis and Identification of Lactate Thresholds

Supplementary Fig.3 restricted cubic spline shows a significant overall relationship between lactate levels and hazard ratio (P-overall <0.001), but no significant nonlinearity (P-nonlinear = 0.900), suggesting a likely linear relationship across the lactate range examined.

In the context of linearity absence, we determined an optimal prognostic threshold for lactate levels through ROC curve analysis. Utilizing the Youden index maximization method, a cut-point of 4.8 mmol/L was established (sensitivity: 47.8%, specificity: 72.8%; see Fig. 3a and Supplementary Table S2). Patients were subsequently categorized into two distinct risk groups based on this threshold. Kaplan-Meier analysis demonstrated significantly different cumulative incidences of 90-day ACLF between these groups (P<0.001, log-rank test; refer to Fig. 3b). The high-risk group, defined by lactate ≥ 4.8 mmol/L, showed a substantially increased likelihood of ACLF development compared to the low-risk group.

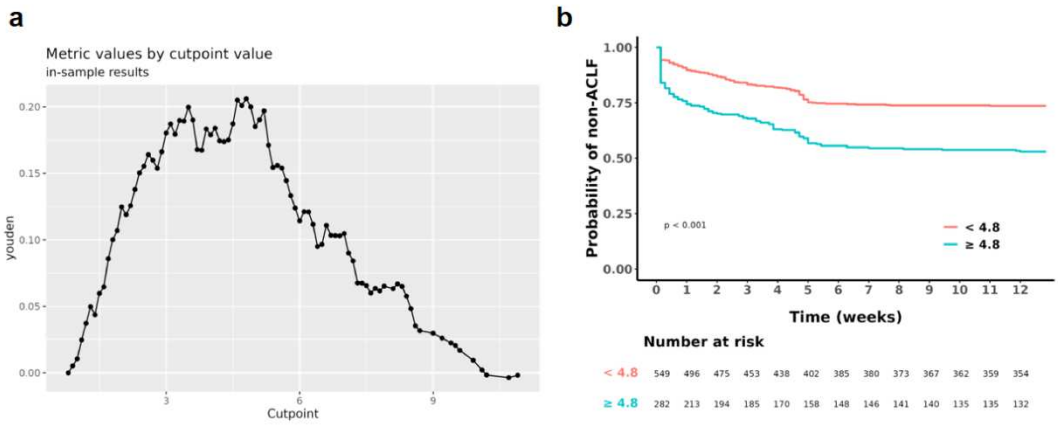
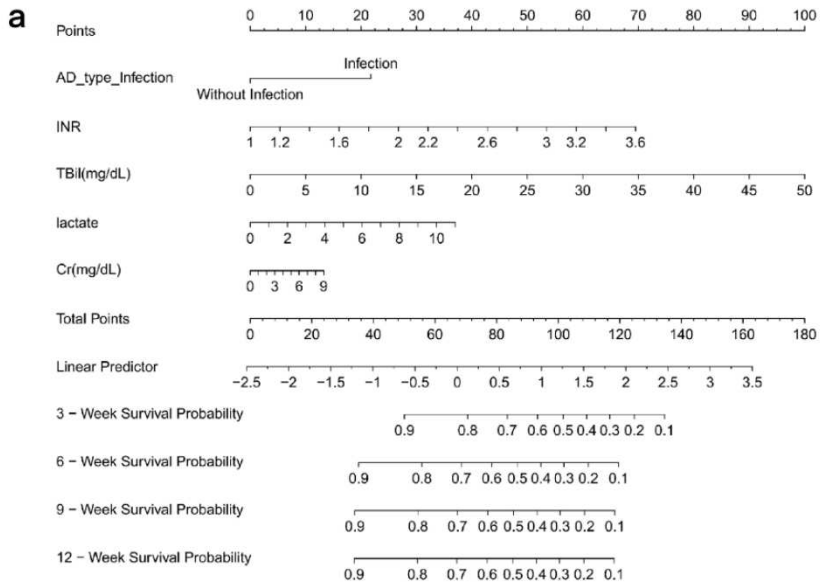


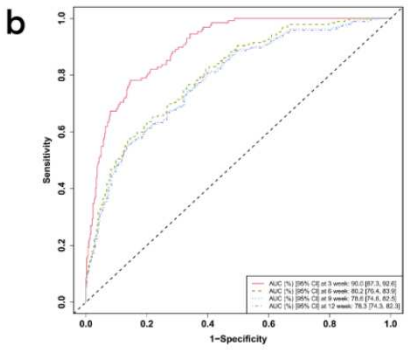
Fig. 3 Identification and validation of Lactate Thresholds. a:Y-axis represents the Youden index to present 90-day ACLF occurrence for different cut-points of lactate; b: Kaplan-Meier curve for cumulative incidences of 90-day ACLF between high-risk group(lactate ≥ 4.8 mmol/L) and low-risk group(lactate < 4.8 mmol/L), the differences were examined by log rank test.

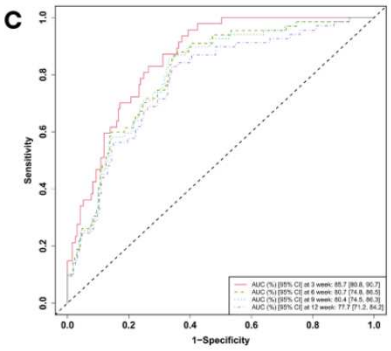
Development and Validation of the Lactate-Based Prediction Model (Nomogram)

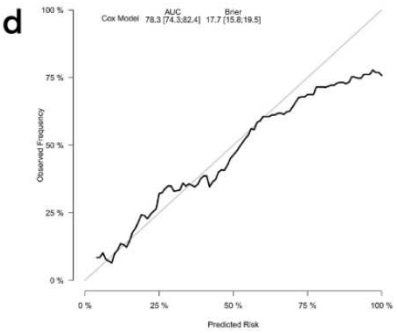
The cohort was randomly partitioned into a training cohort (n=582, 70%) and a validation cohort (n=249, 30%) to facilitate model development and internal validation. An analysis of baseline characteristics revealed that the distributions

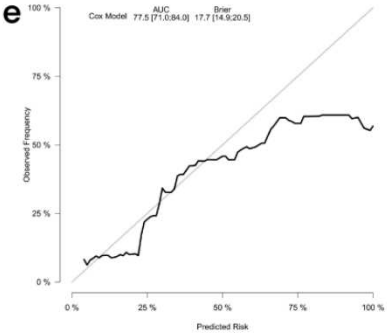
between the training and validation cohorts were generally balanced, indicating that the two groups were well-matched(as detailed in Supplementary Table S3). This balance supports the validity of the subsequent predictive analyses. Subsequently, the univariate and multivariate Cox regression analyses conducted on the training cohort yielded results that were consistent with the prior analysis of the entire cohort (refer to Supplementary Table S4). The final Cox model identified five independent predictors —AD type (Infection), INR, TBil, Cr, and lactate—and was developed into an accessible nomogram, as depicted in Fig.4a. The AUCs of the model in the different cohorts were shown in Fig.4b-c, suggest the prediction model has good efficiency in the training cohort (AUC=0.783 at 12 week, 95% CI 0.743-0.823) and stability in the validation cohort (AUC=0.777 at 12 week, 95% CI 0.712-0.842). The calibration plots show a strong match between observed and predicted risks, confirming the nomogram's validity in validation sets (Fig.4d-e). The calibration curve closely aligns with the ideal, indicating consistent predictions. The DCA curves demonstrate that the nomogram provides substantial net benefits for clinical use (Fig.4f-g). This nomogram is also available online at https://liruiqi.shinyapps.io/dynnomapp/.

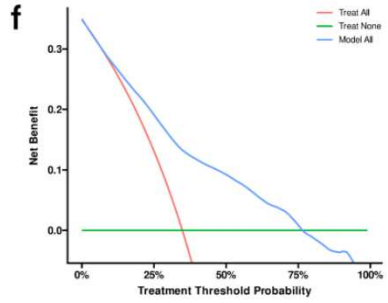

a
Points
0 10 20 30 40 50 60 70 80 90 100
AD_type_Infection
Infection
Without Infection
INR
1 1.2 1.6 2 2.2 2.6 3 3.2 3.6
TBil(mg/dL)
0 5 10 15 20 25 30 35 40 45 50
lactate
0 2 4 6 8 10
Cr(mg/dL)
0 3 6 9
Total Points
0 20 40 60 80 100 120 140 160 180
Linear Predictor
−2.5 −2 −1.5 −1 −0.5 0 0.5 1 1.5 2 2.5 3 3.5
3 − Week Survival Probability
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1
6 − Week Survival Probability
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1
9 − Week Survival Probability
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1
12 − Week Survival Probability
0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1


b
Sensitivity
1−Specificity
0.0 0.2 0.4 0.6 0.8 1.0


c
Sensitivity
1−Specificity
0.0 0.2 0.4 0.6 0.8 1.0


d
AUC
Brier
Cox Model 78.3 [74.3;82.4] 17.7 [15.8;19.5]
Observed Frequency
Predicted Risk
0 % 25 % 50 % 75 % 100 %


e
AUC
Brier
Cox Model 77.5 [71.0;84.0] 17.7 [14.9;20.5]
Observed Frequency
Predicted Risk
0 % 25 % 50 % 75 % 100 %


f
Treat All
Treat None
Model All
Net Benefit
0.0 0.1 0.2 0.3
Treatment Threshold Probability
0% 25% 50% 75% 100%

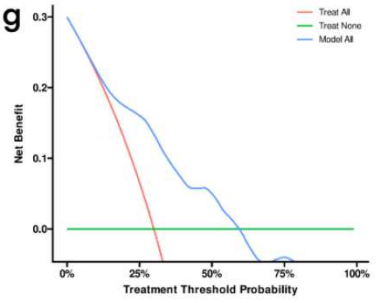

g
Treat All
Treat None
Model All
Net Benefit
0.0 0.1 0.2 0.3
Treatment Threshold Probability
0% 25% 50% 75% 100%

Fig. 4 Development and Validation of Nomogram prediction model. a: Nomogram prediction model. b: ROC curves of the nomogram prediction model in training cohort. c: ROC curves of the nomogram prediction model in internal test cohort.d: Calibration plot of the model to predict 90-day ACLF risks in training cohort. e: Calibration plot of the model to predict 90-day ACLF risks in validation cohort. f: DCA curves of the model to predict 90-day ACLF risks in training cohort. g: DCA curves of the model to predict 90-day ACLF risks in validation cohort.

Discussion

This large retrospective cohort study demonstrated that venous serum lactate is an independent predictor of 90-day ACLF occurrence in patients with acute decompensated cirrhosis. An increase of 1 mmol/L in lactate was associated with a 16% increase in the risk of ACLF (HR 1.16, 95% CI 1.10–1.22), with an optimal predictive threshold of 4.8 mmol/L. A multivariate model combining lactate levels and infection status provided a more accurate prediction than conventional scoring systems (AUC 0.783). These findings remained robust in competing risk analyses and consistent in internal validation.

The pathophysiologic role of lactate in the development of ACLF is multifaceted. In cirrhosis, hepatic lactate clearance is significantly impaired due to reduced functional hepatocyte mass, intrahepatic microcirculatory disturbances, and the presence of portal shunts, while circulatory dysfunction secondary to a hypoxic or hypoperfused state of the tissues forces anaerobic cellular fermentation for lactate production[14]. Especially at the end stage of the disease, inflammatory storms (cytokines, endotoxins) can directly inhibit mitochondrial oxygen utilization, and even if the oxygen supply is sufficient, glycolysis can be accelerated to promote lactic acid production under the effect of inflammatory hypermetabolism and stress hormones[15], and at the same time form a vicious circle superimposed on each other with multi-organ failure such as cardiac, pulmonary, and renal failure[10,16]. Furthermore, the strong correlation between infection and ACLF (HR 2.14) in our study is consistent with the concept that sepsis-induced hyperlactatemia may serve as an early marker of impending organ failure[17]. Therefore, we believe that hyperlactate levels may reflect a combination of impaired hepatic metabolic capacity, impaired tissue tissue oxygenation, uncontrolled inflammation, and multiorgan failure, reflecting the pathophysiological process of ACLF, and therefore may predict the risk of ACLF in patients with AD. The threshold of 4.8 mmol/L of venous serum lactate identified in our study may represent a critical threshold where compensatory mechanisms fail and a cascade toward multiorgan dysfunction begins.

Our findings extend the relevant biomarkers that can be used to predict the development of ACLF in AD patients, and while previous studies evaluating various markers including soluble triggering receptor-1 (sTREM-1), cytokine profiles, plasma metabolome profiles and blood ammonia have shown some predictive ability[18–22]. Lactate has distinct advantages in terms of availability, cost-effectiveness and rapid turnaround time, making it an ideal biomarker for resource-limited settings. A

previous retrospective study demonstrated that the MELD-LA score was an independent risk factor for 15-day mortality in critically ill patients with cirrhosis[23], but it performed poorly in long-term prognostic prediction, which we consider is usually associated with poor outcomes in the general intensive care population. In contrast, our model may be attributed to the inclusion of additional clinical variables, the inclusion of ACLF as a specific endpoint, and a longer follow-up period, which ultimately also achieved a more favorable predictive performance. Also, the large sample size and the use of competing risk analysis to account for liver transplantation and death further strengthened the reliability of our results.

Interestingly, subgroup analyses revealed particularly interesting insights regarding the interaction between lactate and AD type. The stronger correlation between patients with ascites/hepatic pleural fluid and hepatic encephalopathy may be due to the fact that ascites or hepatic pleural fluid mainly reflects portal hypertension-dominated decompensation[24], elevated lactate suggests gut hypoxia due to visceral stasis, and hepatic encephalopathy is usually synergized with hyperammonemia, where ammonia inhibits hepatocyte clearance of lactate, creating a vicious circle[25]. It has also been previously shown that blood ammonia-adjusted CTP scores can be used to predict the occurrence of ACLF in AD patients[21]. These findings also remind us that in patients whose decompensated events are ascites/hepatic pleural fluid and hepatic encephalopathy, it is recommended to initiate early monitoring and intervention measures promptly once lactate levels exceed the threshold. Notably, although infection was the strongest predictor, lactate maintained its independent association even after adjustment, suggesting that it captures pathophysiologic information other than infection, which may require further study in the future by dynamic lactate level monitoring.

Admittedly, our study has some shortcomings. First, the single-center retrospective design may limit generalizability, and the exclusion patients because of incomplete follow-up or missing data may introduce selection bias. Second, we only measured baseline venous lactate levels and failed to determine the level of dynamic changes in collected lactate, and the predictive value of dynamic changes in lactate (Δlactate) needs to be clarified by further studies in the future,. Third, the lack of external validation remains a significant limitation, although internal validation showed consistent performance. Fourth, we did not assess the effect of specific therapeutic interventions on lactate levels or ACLF development, which may confound the observed associations. Finally, the relatively high lactate threshold may reflect our specific patient population, and validation in a different cohort is necessary.

Future research should focus on several key areas. First, prospective multicenter studies are needed to validate our findings in different populations and different medical centers, and to test whether lactate-guided therapeutic strategies can reduce the incidence of ACLF. Second, there is a need to further evaluate the dynamics of lactate levels with machine learning algorithms thereby further improving the accuracy of real-time risk prediction. Third, exploring the integration of lactate with other emerging biomarkers may further improve risk stratification and guide

therapeutic decisions.

In summary, serum lactate is an independent predictor of 90-day ACLF occurrence in patients with acute decompensated cirrhosis. Incorporating lactate into the clinical assessment, particularly using the 4.8 mmol/L threshold, may enhance risk stratification and potentially improve prognosis through early intervention. Validated web-based nomogram (https://liruiqi.shinyapps.io/dynnomapp/) provide a practical tool for individualized risk assessment. These findings support routine measurement of lactate in all hospitalized patients with acute decompensation and highlight its potential role in the evolution of liver disease toward precision medicine.

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CRediT - Authorship contribution statement

Jun Guo: Investigation, Data curation, Visualization, Software, Investigation, Data curation, Writing-Original draft; **Shuling Chen:** Formal analysis, Methodology, Validation; **Ruiqi Li:** Investigation, Data curation; **Jiale Shen:**Formal analysis, Methodology; **Xiaoying Dong:**Formal analysis;**Hongli Liu:** Formal analysis; **Hao Ren:** Investigation; **Changhua Yi:** Resources; **Qingfang Xiong:** Resources; **Xixuan Wang:** Investigation, Data curation, Conceptualization, Visualization, Methodology, Supervision, Writing – review & editing; **Yongfeng Yang:** Funding acquisition, Project administration, Resources.

Data availability

The datasets generated during the current study are available from the corresponding author upon reasonable request. This study adheres to the STROBE guidelines for observational research.

Declarations

Conflict of interest

The authors have no relevant conflicts of interest.

Ethical approval

The research adhered to both the Declaration of Helsinki andthe Declaration of Istanbul and was approved by the Eth-ics Committee of the Second Hospital of Nanjing. All patients induded gave written informed consent.

Clinical trial number: not applicable.

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Tables

Table 1.Baseline characteristics

Characteristic	ACLF (90d)		p-value
	No N = 559[1]	Yes N = 272[1]	
Age (years)	58.0 (51.0, 64.0)	57.0 (50.0, 64.0)	0.457[2]
Gender			0.585[3]
Male	299 (53.5%)	140 (51.5%)	
Female	260 (46.5%)	132 (48.5%)	
Cirrhosis etiology			0.510[3]
Hepatitis B/C	289 (51.7%)	155 (57.0%)	
Alcohol	98 (17.5%)	38 (14.0%)	
AIH/PBC	64 (11.4%)	26 (9.6%)	
MAFLD	77 (13.8%)	40 (14.7%)	
Other	31 (5.5%)	13 (4.8%)	
AD type			<0.001[3]
Infection	71 (12.7%)	63 (23.2%)	
Acute ascites/Hepatic hydrothorax	302 (54.0%)	55 (20.2%)	
Gastrointestinal bleeding	94 (16.8%)	20 (7.4%)	
Hepatic encephalopathy	14 (2.5%)	31 (11.4%)	
Mutiple reasons	78 (14.0%)	103 (37.9%)	
AD type (Infection)			<0.001[3]
Without Infection	420 (75.1%)	146 (53.7%)	
Infection	139 (24.9%)	126 (46.3%)	
Ascites	479 (85.7%)	229 (84.2%)	0.568[3]
Hepatic encephalopathy	69 (12.3%)	30 (11.0%)	0.583[3]
Previous ACLF	5 (0.9%)	2 (0.7%)	>0.999[4]
Previous AD	224 (40.1%)	110 (40.4%)	0.919[3]
Splenectomy	61 (10.9%)	28 (10.3%)	0.787[3]

TIPS history	12 (2.1%)	8 (2.9%)	0.483[3]
Banding history	30 (5.4%)	9 (3.3%)	0.188[3]
HCC	38 (6.8%)	18 (6.6%)	0.923[3]
Charlson index	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)	0.591[2]
CRP (mg/L)	12.3 (7.3, 21.5)	12.4 (8.2, 20.2)	0.959[2]
WBC (×10^9/L)	10.8 (7.0, 14.7)	11.7 (7.4, 14.8)	0.177[2]
Neutrophil pct (%)	79.0 (72.0, 87.0)	80.0 (72.0, 87.0)	0.697[2]
Hb (g/L)	105.9 ± 20.40	105.0 ± 19.35	0.508[5]
PLT (×10^{12}/L)	86.0 (61.0, 110.0)	81.0 (58.0, 110.5)	0.300[2]
PT (s)	19.5 (15.2, 24.8)	19.7 (15.0, 24.2)	0.926[2]
INR	2.0 (1.5, 2.6)	2.5 (2.0, 3.2)	<0.001[2]
TBil (mg/dL)	1.9 (1.1, 4.7)	3.5 (1.6, 15.4)	<0.001[2]
Alb (g/L)	31.0 (28.0, 34.0)	29.0 (26.0, 32.0)	<0.001[2]
ALT (U/L)	39.0 (24.0, 64.0)	40.0 (26.0, 64.0)	0.498[2]
AST (U/L)	60.0 (36.0, 108.0)	67.5 (40.5, 99.0)	0.391[2]
GGT (U/L)	55.0 (35.0, 82.0)	55.0 (38.0, 80.5)	0.885[2]
ALP (U/L)	412.0 (193.0, 601.0)	424.5 (218.5, 613.5)	0.551[2]
Cr (mg/dL)	0.7 (0.6, 0.9)	0.8 (0.7, 1.2)	<0.001[2]
BUN (mmol/L)	5.0 (3.8, 7.1)	5.5 (4.2, 9.7)	<0.001[2]
Na (mmol/L)	135.0 (131.0, 139.0)	135.0 (131.0, 138.0)	0.340[2]
LDH (U/L)	800.0 (421.0, 1,192.0)	703.5 (397.5, 1,138.0)	0.258[2]
Lactate (mmol/L)	3.5 (2.2, 4.9)	4.6 (3.2, 6.1)	<0.001[2]
Glucose (mmol/L)	6.5 (5.1, 8.1)	6.3 (5.0, 8.1)	0.739
Uric acid (μmol/L)	308.0 ± 101.36	307.0 ± 96.46	0.890
TG (mmol/L)	4.9 (3.9, 6.5)	4.9 (3.7, 6.6)	0.455[2]
TC (mmol/L)	3.1 ± 1.01	3.2 ± 0.96	0.518[5]
HDL (mmol/L)	0.8 ± 0.31	0.8 ± 0.28	0.421[5]
LDL (mmol/L)	2.1 (1.6, 2.7)	2.1 (1.7, 2.7)	0.988[2]
ApoA Ⅰ (g/L)	0.6 (0.5, 0.8)	0.7 (0.5, 0.9)	0.500[2]
ApoB (g/L)	0.8 ± 0.19	0.8 ± 0.20	0.311[5]
Lpa (g/L)	8.0 (4.0, 13.0)	8.0 (4.0, 13.0)	0.357[2]
MELD Score	18.1 (14.1, 21.7)	23.3 (19.5, 27.9)	<0.001[2]
CLIF-C AD	44.5 (37.5, 50.5)	49.4 (44.1, 55.7)	<0.001[2]
CTP Score	9.0 (8.0, 10.0)	10.0 (9.0, 12.0)	<0.001[2]
Survival (90d)	480 (85.9%)	149 (54.8%)	<0.001[3]
Survival time (d)	82.1 ± 19.33	61.9 ± 23.96	<0.001[2]
Transplant (90d)	30 (5.4%)	9 (3.3%)	0.188[3]
Transplant time (d)	82.1 ± 19.33	71.7 ± 23.99	<0.001[2]

Readmission (90d)	107 (19.1%)	56 (20.6%)	0.622[3]
readmission (d)	74.4 ± 25.22	74.2 ± 25.57	0.949[2]

[1]Median (Q1, Q3); n (%); Mean ± SD; [2]Wilcoxon rank sum test; [3]Pearson's Chi-squared test; [4]Fisher's exact test; [5]Welch Two Sample t-test. Abbreviations: ACLF: Acute-on-Chronic Liver Failure, AD: Acute Decompensation, TIPS: Transjugular Intrahepatic Portosystemic Shunt, HCC: Hepatocellular CarcinomaAIH: Autoimmune Hepatitis, PBC: Primary Biliary Cholangitis, MAFLD: Metabolic Associated Fatty Liver Disease, CRP: C-Reactive Protein, WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelet, PT: Prothrombin Time, INR: International Normalized Ratio, TBil: Total Bilirubin, Alb: Albumin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transferase, ALP: Alkaline Phosphatase, Cr: Creatinine, BUN: Blood Urea Nitrogen, Na: Sodium, LDH: Lactate Dehydrogenase, TG: Triglyceride, TC: Total Cholesterol, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, Apo: Apolipoprotein, Lpa: Lipoprotein(a), MELD: Model for End-Stage Liver Disease, CLIF-C AD: Chronic Liver Failure Consortium Acute Decompensation, CTP: Child-Turcotte-Pugh.

Table 2.Univariate and multivariate analysis of influencing factors for ACLF in 90 days (Cox regression)

Characteristic	Univariable					Multivariable				
	N	Event N	HR	95% CI	p-value[1]	N	Event N	HR	95% CI	p-value[1]
Age (years)	831	272	0.99	0.98, 1.01	0.317					
Gender										
Male	439	140	—	—						
Female	392	132	1.09	0.86, 1.39	0.467					
AD type (Infection)										
Without Infection	566	146	—	—		566	146	—	—	
Infection	265	126	2.00	1.58, 2.54	<0.001***	265	126	2.14	1.67, 2.72	<0.001***
Cirrhosis etiology										
Hepatitis B/C	444	155	—	—						
Alcohol	136	38	0.76	0.54, 1.09	0.138					
AIH/PBC	90	26	0.79	0.52, 1.20	0.274					
MAFLD	117	40	0.96	0.68, 1.36	0.830					
Other	44	13	0.85	0.48, 1.50	0.581					
Ascites	708	229	0.90	0.65, 1.24	0.505					
Hepatic encephalopathy	99	30	0.89	0.61, 1.30	0.544					
Previous ACLF	7	2	0.77	0.19, 3.11	0.719					
Previous AD	334	110	1.03	0.81, 1.32	0.794					
Splenectomy	89	28	0.95	0.64, 1.41	0.800					
TIPS history	20	8	1.32	0.65, 2.67	0.435					

HCC	56	18	0.94	0.58, 1.52	0.808					
Charlson index	831	272	0.97	0.89, 1.06	0.492					
CRP (mg/L)	831	272	0.99	0.99, 1.00	0.249					
WBC (×10^9/L)	831	272	1.02	0.99, 1.05	0.152					
Neutrophil pct (%)	831	272	1.00	0.99, 1.02	0.654					
Hb (g/L)	831	272	1.00	0.99, 1.00	0.487					
PLT (×10^{12}/L)	831	272	1.00	0.99, 1.00	0.235					
PT (s)	831	272	1.00	0.98, 1.02	0.968					
INR	831	272	2.27	1.91, 2.69	<0.001***	831	272	2.54	2.13, 3.03	<0.001***
ALT (U/L)	831	272	1.00	1.00, 1.00	0.923					
AST (U/L)	831	272	1.00	1.00, 1.00	0.782					
TBil(mg/dL)	831	272	1.06	1.05, 1.08	<0.001***	831	272	1.07	1.05, 1.08	<0.001***
Alb (g/L)	831	272	0.95	0.93, 0.98	<0.001***					
GGT (U/L)	831	272	1.00	1.00, 1.00	0.487					
ALP (U/L)	831	272	1.00	1.00, 1.00	0.516					
Cr(mg/dL)	831	272	1.30	1.19, 1.43	<0.001***	831	272	1.16	1.04, 1.29	0.010**
BUN (mmol/L)	831	272	1.02	1.01, 1.03	<0.001***					
Na (mmol/L)	831	272	0.98	0.96, 1.01	0.186					
LDH (U/L)	831	272	1.00	1.00, 1.00	0.280					
Lactate (mmol/L)	831	272	1.20	1.14, 1.27	<0.001***	831	272	1.16	1.10, 1.22	<0.001***
Glucose (mmol/L)	831	272	1.00	0.95, 1.06	0.990					
Uric acid (μmol/L)	831	272	1.00	1.00, 1.00	0.940					
TG (mmol/L)	831	272	0.98	0.93, 1.04	0.470					
TC (mmol/L)	831	272	1.04	0.93, 1.18	0.470					
HDL (mmol/L)	831	272	1.18	0.80, 1.74	0.412					
LDL (mmol/L)	831	272	1.04	0.90, 1.21	0.608					
ApoA Ⅰ (g/L)	831	272	1.20	0.78, 1.83	0.408					
ApoB (g/L)	831	272	1.34	0.73, 2.46	0.351					
Lpa (g/L)	831	272	0.99	0.98, 1.00	0.207					

[1]*p<0.05; **p<0.01; ***p<0.001.

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio, ACLF: Acute-on-Chronic Liver Failure, AD: Acute Decompensation, TIPS: Transjugular Intrahepatic Portosystemic Shunt, HCC: Hepatocellular CarcinomaAIH: Autoimmune Hepatitis, PBC: Primary Biliary Cholangitis, MAFLD: Metabolic Associated Fatty Liver Disease, CRP: C-Reactive Protein, WBC: White Blood Cell, Hb: Hemoglobin, PLT: Platelet, PT: Prothrombin Time, INR: International Normalized Ratio, TBil: Total Bilirubin, Alb: Albumin, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transferase, ALP: Alkaline Phosphatase, Cr: Creatinine, BUN: Blood Urea Nitrogen, Na: Sodium, LDH: Lactate Dehydrogenase, TG: Triglyceride, TC: Total Cholesterol, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, Apo: Apolipoprotein, Lpa: Lipoprotein(a), MELD: Model for End-Stage Liver Disease, CLIF-C AD: Chronic Liver Failure Consortium Acute Decompensation, CTP: Child-Turcotte-Pugh.

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