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ORIGINAL RESEARCH

Lactate Dehydrogenase-to-Albumin Ratio as a Predictor of In-Hospital Mortality in Predicted Severe Acute Pancreatitis: Evidence from an 18-Year Cohort Study

Yaoyu Zou*, Maobin Kuang*, Shixuan Xiong*, Xin Xu, Xueyang Li, Ling Ding, Cong He, Nianshuang Li, Huajing Ke, Xin Huang, Yupeng Lei, Huifang Xiong, Wenhua He, Liang Xia, Nonghua Lu, Jianhua Wan, Yin Zhu

Department of Gastroenterology, Jiangxi Provincial Key Laboratory of Digestive Diseases, Jiangxi Clinical Research Center for Gastroenterology, Digestive Disease Hospital, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yin Zhu; Jianhua Wan, Email ndyfy01977@ncu.edu.cn; ndyfy07545@ncu.edu.cn

Background: Severe acute pancreatitis (SAP) carries a mortality rate of up to 30%. This study evaluated the association between the lactate dehydrogenase-to-albumin ratio (LAR) and in-hospital mortality in patients with predicted SAP.

Methods: A total of 4605 patients (APACHE II ≥8) admitted to the First Affiliated Hospital of Nanchang University from 2005 to 2023 were retrospectively analyzed. Cox regression, restricted cubic splines, Kaplan–Meier curves, and Log rank tests assessed the association between LAR and mortality. Receiver operating characteristic (ROC) and time-dependent ROC curves evaluated predictive performance. Subgroup and sensitivity analyses confirmed robustness.

Results: Elevated LAR independently predicted in-hospital mortality (adjusted HR per SD: 1.14; 95% CI: 1.09–1.19; $P < 0.001$). Kaplan–Meier curves showed significantly lower survival in high-LAR groups ($P < 0.05$). LAR outperformed LDH, albumin, SIRS, and APACHE II (AUC = 0.847; 95% CI: 0.826–0.869). A non-linear association with a threshold at LAR = 20.58 was identified. Predictive value remained stable across etiologies and both short-term (≤14 days) and long-term (30–90 days) mortality. Stronger associations were seen in younger, male, hypertriglyceridemic patients and those without persistent multiple organ failure.

Conclusion: Higher LAR was associated with greater in-hospital mortality among patients with predicted severe acute pancreatitis; LAR may serve as a simple, low-cost adjunct for early risk assessment.

Keywords: acute pancreatitis, lactate dehydrogenase-to-albumin ratio, mortality, survival analysis

Introduction

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract with escalating incidence rates, currently affecting 3.4 to 73.4 cases per 100,000 worldwide.[1] Approximately 20–30% of AP cases progress to severe acute pancreatitis (SAP), characterized by persistent organ failure (OF) lasting more than 48 hours,[2] mortality may be as high as 30%–40%.[3] Despite significant advancements have been made in the management of SAP, the high mortality and heavy financial burden on health-care system make SAP still a tremendous challenge.

Predicted SAP is defined as a special type of AP at its early stage with a score of acute physiology and chronic health evaluation (APACHE) II over or equal to 8.[4–6] It has been reported that about 70%–80% predicted SAP may progress into SAP.[5,7] Current guidelines highlight a lack of reliable tools for the early prediction of SAP upon hospital admission.[8] Although systemic inflammatory response syndrome (SIRS) exhibits high sensitivity and specificity, its positive

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predictive value (PPV) remains limited. Other scoring systems, such as BISAP, Ranson, and APACHE II, are relatively complex, underscoring the clinical need for a simpler, accurate, and broadly applicable prediction tool.[9] Previous research has evaluated several serum biomarkers for their predictive value in AP. For instance, C-reactive protein (CRP) measured around 48 hours after disease onset effectively differentiates between severe and mild AP, with the classic threshold being 150 mg/L.[10] Persistent SIRS predicts SAP with a PPV of 56%, which increases to 85% when IL-6 levels exceed 160 pg/mL.[11] Additionally, advanced age and poor nutritional status have consistently been associated with adverse outcomes.[12,13] Nonetheless, no single biomarker fully captures the multifaceted pathological features of AP.

Lactate dehydrogenase (LDH) is an important enzyme in anaerobic glycolysis. It acts as a marker of cell death and is strongly linked to pancreatic necrosis and systemic problems in AP.[14,15] Some studies have also shown that serum albumin (ALB) is a useful marker for predicting persistent organ failure and death in AP.[16,17] The combination of LDH and ALB, called the lactate dehydrogenase-to-albumin ratio (LAR), reflects both inflammation and nutrition status. It has recently been recognized as a new marker for prognosis in different conditions. Most past research on LAR has focused on cancers.[18,19] Recent studies suggest that LAR is also linked to the prognosis of patients with sepsis and lower respiratory tract infections.[20–22] In sepsis, a higher LAR was associated with a higher risk of death during hospitalization,[21] suggesting its potential utility in systemic inflammatory syndromes. Nevertheless, the prognostic value of LAR has not been investigated in AP.

Consequently, we conducted this large study on patients with predicted SAP. We aimed to assess the value of LAR in predicting mortality risk, which could help with early treatment and more precise medical strategies.

Materials and Methods

Study Design and Population

This was a retrospective cohort study with an analysis of patients with AP who were hospitalized in the Department of Gastroenterology of the First Affiliated Hospital of Nanchang University, a tertiary care referral center in China, from July 2005 to December 2023. We used data from a prospectively maintained database, which is a data repository for the clinical data of all AP patients admitted to our department, and involved human participants were reviewed with the approval of the Ethics Committee of the First Affiliated Hospital of Nanchang University (ethical approval number: 2023–234). The waiver for the need to obtain written informed consent was approved by the Ethics Committee due to the retrospective nature of the study. All patient data were confidential and handled in compliance with ethical guidelines. The current study was conducted in line with the Declaration of Helsinki and adhered to the STROBE reporting guidelines.

A total of 14650 consecutive patients with AP were initially screened for eligibility. The diagnosis of AP was re-evaluated to confirm the diagnosis by the Atlanta definitions in 2012.[2] According to the purpose of this study, we excluded the following patients: 1) age less than 18, or older than 75 years; 2) pregnancy; 3) end-stage liver or kidney disease; 4) a score of APACHE II <8; and 5) missing data on LAR or outcome data. Finally, a total of 4605 patients were included, and details of the inclusion/exclusion process were shown in Figure 1.

Data Collection and Measurement

In this study, general baseline information was gathered, which included sex, age, body mass index (BMI), the etiology of AP, smoking and drinking status, history of cardiovascular disease, history of hyperlipidemia (HTG), or diabetes, and vital signs. The laboratory parameters obtained at admission are shown in Table 1. The systemic inflammatory response syndrome (SIRS) score[23] and APACHE II score[24] were used to assess AP severity. The LAR was defined by dividing the LDH level by the ALB level.

The outcomes included the severity of AP, OF, Pancreatic local complications, infected pancreatic necrosis (IPN), length of hospital stays, length of intensive care unit (ICU) stays and mortality during the hospitalization were also assessed. The severity and types of AP was divided in line with the revised Atlanta classification.[2] The respiratory, cardiovascular and renal systems were assessed, and OF was defined as a score of 2 or more using the modified Marshall

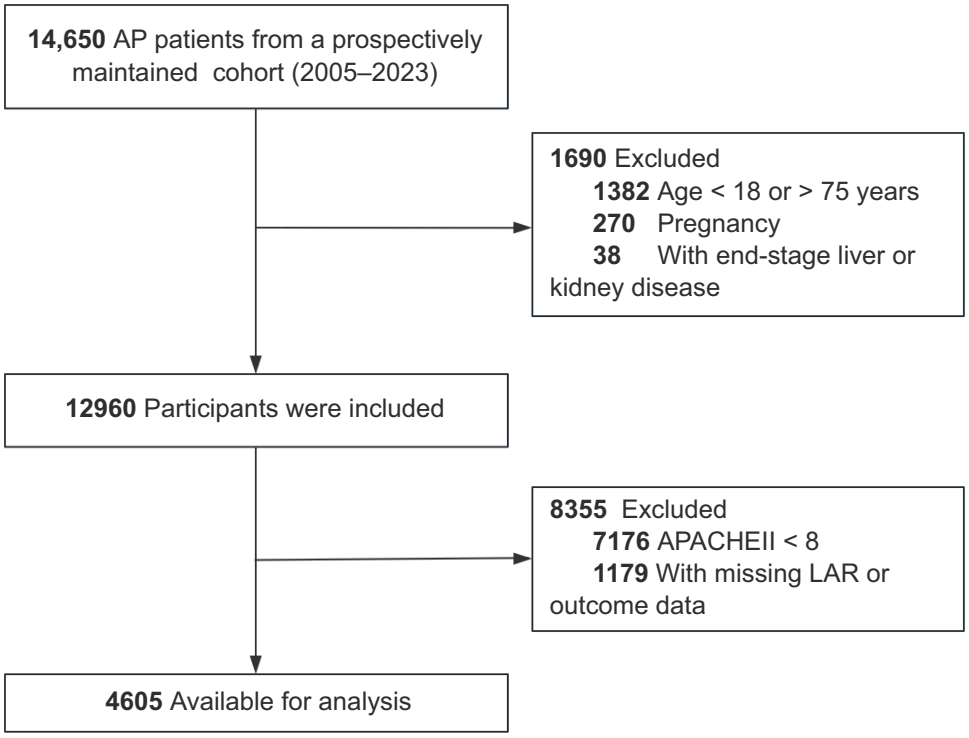

Figure 1 The flow chart of the study.
Abbreviations: AP, acute pancreatitis; LAR, lactate dehydrogenase-to-albumin ratio.

scoring system, and persistent multiple organ failure (PMOF) was defined as failure of at least two organs persistent lasting more than 48 hours.[25]

Handling of Missing Data

A fully conditional specification imputation method was used based on the amount of missing data for each variable. First, the percentage of missing values was calculated (Supplementary Table 1). Variables with higher missing rates, such as C-reactive protein (CRP, 21.1%), BMI (20.9%), and arterial oxygen partial pressure (PaO_2, 18.9%), were handled

Table 1 Basic Characteristics in Enrolled Patients Classified According to the LAR Tertile

Characteristics	Tertile 1 (n=1535) LAR: 5.7 (4.7, 6.5)	Tertile 2 (n=1535) LAR: 9.5 (8.3, 10.7)	Tertile 3 (n=1535) LAR: 19.4 (15.2, 27.5)	*P*
Male, n (%)	935 (60.9)	831 (54.1)	895 (58.3)	<0.001
Age (years)	53.0 ± 13.9	53.7 ± 13.9	51.0 ± 13.9	< 0.001
BMI, kg/m^2	23.6 ± 4.0	24.2 ± 3.7	24.7 ± 3.6	< 0.001
Etiology, n (%)				< 0.001
Biliary, n (%)	734 (47.8)	838 (54.6)	711 (46.3)	
HTG, n (%)	464 (30.2)	415 (27)	545 (35.5)	
Alcoholic, n (%)	95 (6.2)	79 (5.1)	83 (5.4)	
Others, n (%)	242 (15.8)	203 (13.2)	196 (12.8)	
Smoking, n (%)	453 (29.5)	368 (24)	441 (28.7)	< 0.001
Drinking, n (%)	439 (28.6)	413 (26.9)	468 (30.5)	0.090
Cardiovascular disease, n (%)	352 (23)	344 (22.5)	358 (23.4)	0.839
History of hyperlipidemia, n (%)	156 (10.2)	129 (8.4)	161 (10.5)	0.110
History of diabetes, n (%)	237 (15.4)	206 (13.4)	219 (14.3)	0.277

(*Continued*)

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Table 1 (Continued).

Characteristics	Tertile 1 (n=1535) LAR: 5.7 (4.7, 6.5)	Tertile 2 (n=1535) LAR: 9.5 (8.3, 10.7)	Tertile 3 (n=1535) LAR: 19.4 (15.2, 27.5)	*P*
Temperature, °C	36.8 ± 0.6	37.0 ± 0.7	37.3 ± 0.8	< 0.001
Pulse, times/min	87.8 ± 18.2	93.3 ± 19.5	106.4 ± 22.0	< 0.001
Respirations, times/min	20.2 ± 2.8	21.2 ± 3.8	25.3 ± 7.7	< 0.001
SBP, mmHg	129.4 ± 19.6	131.1 ± 20.2	130.9 ± 22.7	0.043
DBP, mmHg	83.3 ± 32.1	83.7 ± 44.8	82.7 ± 24.5	0.721
WBC, 10^9/L	10.1 ± 4.9	13.3 ± 5.5	14.9 ± 6.2	< 0.001
NEU, 10^9/L	8.2 ± 4.6	11.4 ± 5.3	13.1 ± 5.8	< 0.001
Hb, g/L	130.2 ± 25.3	131.7 ± 27.4	135.1 ± 32.7	< 0.001
HbA1c, %	6.8 ± 2.5	6.9 ± 2.1	7.1 ± 2.3	0.188
HCT, %	38.2 ± 8.2	38.8 ± 8.1	39.8 ± 9.3	< 0.001
LYM, 10^9/L	1.2 (0.9, 1.7)	1.0 (0.7, 1.4)	0.9 (0.7, 1.3)	< 0.001
PLT, $\times 10^9$/L	212.6 ± 87.4	212.5 ± 95.7	195.1 ± 90.7	< 0.001
ALT, U/L	27.0 (15.0, 61.0)	33.0 (17.1, 111.0)	29.5 (17.0, 77.0)	< 0.001
AST, U/L	25.0 (19.0, 45.0)	33.3 (22.5, 80.0)	45.1 (28.2, 86.8)	< 0.001
TBIL, μmol/L	15.1 (9.9, 24.3)	18.7 (12.1, 32.1)	21.5 (13.5, 35.8)	< 0.001
DBIL, μmol/L	4.0 (2.4, 8.1)	6.0 (3.4, 13.0)	7.4 (4.2, 16.7)	< 0.001
ALB, g/L	39.9 ± 5.7	36.3 ± 5.6	32.7 ± 5.7	< 0.001
LDH, U/L	219.0 (187.0, 252.0)	341.0 (299.0, 389.9)	641.0 (505.0, 884.1)	< 0.001
CK, U/L	60.0 (38.0, 90.0)	61.0 (36.9, 103.0)	124.8 (61.0, 289.2)	< 0.001
TG, mmol/L	1.6 (1.0, 3.9)	1.5 (0.9, 3.7)	2.1 (1.2, 6.6)	< 0.001
TC, mmol/L	5.4 ± 3.2	5.3 ± 3.3	5.4 ± 4.0	0.675
GLU, mmol/L	8.2 ± 4.3	9.0 ± 4.8	11.0 ± 6.4	< 0.001
LIP, U/L	116.0 (53.6, 298.6)	125.5 (58.0, 339.1)	149.7 (69.4, 436.3)	< 0.001
AMY, U/L	143.0 (64.0, 439.0)	220.5 (76.2, 591.0)	307.2 (87.0, 787.0)	< 0.001
BUN, mmol/L	4.6 (3.5, 6.0)	4.8 (3.5, 6.4)	6.8 (4.4, 11.1)	< 0.001
Cr, μmol/L	63.8 (51.0, 78.3)	61.7 (48.4, 77.0)	76.6 (54.4, 147.5)	< 0.001
CRP, mg/L	38.5 (8.5, 109.0)	129.0 (57.9, 205.0)	213.0 (139.0, 302.8)	< 0.001
PaO_2, mmHg	84.4 ± 23.2	81.2 ± 26.8	81.4 ± 27.1	0.003
$PaCO_2$, mmHg	36.0 ± 6.8	34.3 ± 6.9	31.7 ± 7.3	< 0.001
LAR	5.7 (4.7, 6.5)	9.5 (8.3, 10.7)	19.4 (15.2, 27.5)	< 0.001
SIRS Score	1.1 ± 1.0	1.6 ± 1.1	2.3 ± 1.0	< 0.001
APACHE II Score	10.5 ± 2.5	11.1 ± 2.8	12.7 ± 4.0	< 0.001

Notes: P-values were calculated using a weighted linear regression model for continuous variables. For categorical variables, proportions are presented, and P-values were determined using a weighted chi-square test. A *P*-value of less than 0.05 was considered statistically significant.
Abbreviations: LAR, Lactate Dehydrogenase-to-Albumin Ratio; BMI, Body Mass Index; HTG, Hypertriglyceridemia; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell; NEU, Neutrophil; Hb, Hemoglobin; HbA1c, Glycated Hemoglobin; HCT, Hematocrit; LYM, Lymphocyte; PLT, Platelet; ALT, Alanine Transaminase; AST, Aspartate Transaminase; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; LDH, Lactate Dehydrogenase; CK, Creatine Kinase; TG, Triglyceride; TC, Total Cholesterol; GLU, Glucose; LIP, Lipase; AMY, Amylase; BUN, Blood Urea Nitrogen; Cr, Creatinine; CRP, C-reactive Protein; PaO_2, Partial Pressure of Arterial Oxygen; $PaCO_2$, Partial Pressure of Arterial Carbon Dioxide; SIRS, Systemic Inflammatory Response Syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II.

using multiple imputation. For variables with very few missing values, mean imputation was used.[26,27] The main analyses were done using the original dataset, even though some values were missing. The imputed dataset was later used for sensitivity analyses to check the reliability of the main findings.

Statistical Analysis

The study population was first stratified into tertiles based on admission LAR, Continuous variables were expressed as mean ± standard deviation or median (interquartile ranges), while categorical variables were presented as frequencies (percentages). For intergroup comparisons, one-way ANOVA was employed for normally distributed continuous

variables, whereas the Kruskal–Wallis H-test was applied to non-normally distributed data. Categorical variables were analyzed using chi-square tests or Fisher's exact test or chi-square tests.

Subsequently, Kaplan-Meier survival curves were plotted for each LAR tertile to illustrate survival status during follow-up. The Log rank test was used to assess differences in survival probabilities among the groups. Before constructing the regression models, the proportional hazards assumption was tested using Schoenfeld residual analysis. Potential collinearity among covariates was evaluated using multiple linear regression, with variance inflation factor (VIF) values greater than 5 considered indicative of collinearity. Variables identified as collinear were excluded from subsequent model adjustments.[28] Multivariate Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for in-hospital mortality risk associated with the LAR index and its constituent parameters, and confounders adjusted in the model were selected according to the characteristic of AP. To standardize the HR corresponding to the LAR index and its constituent parameters, we performed a Z-transformation on each of these parameters and expressed the final results uniformly as the HR associated with Per SD. First, an Unadjusted Model I was established, and then Model II adjusted for sex, age, smoking history, drinking history, history of HTG, history of diabetes, temperature, pulse, and respiration; Model III built upon Model II and further adjusted for systolic blood pressure, diastolic blood pressure, mean arterial pressure, neutrophil, hemoglobin, hematocrit, total bilirubin, creatine kinase, blood urea nitrogen, partial pressure of arterial oxygen, CRP.

We also used restricted cubic splines (RCS) in the Cox regression model to analyze the relationship between LAR and in-hospital mortality. If a non-linear pattern was found, possible turning points were identified using a recursive algorithm. Then, segmented Cox regression was applied to assess HRs before and after these points.

To further assess and compare the predictive value of baseline LAR and its components for in-hospital mortality over different time periods, we created time-dependent receiver operating characteristic (ROC) curves for all these parameters. We then calculated the AUCs and predictive thresholds for each parameter at different time points.

Based on the fully adjusted model, stratified analyses were conducted to explore potential effect modifications across different subgroups, including age (≤ 65 years vs > 65 years), sex (male vs female), history of diabetes, history of HTG, HTG-associated AP (HTG-AP), and PMOF status.

Several sensitivity analyses were conducted to check the reliability of the findings: (1) To handle missing data, we used mean imputation or multiple imputation methods and repeated the main analyses with the imputed dataset. (2) To reduce bias from very short disease courses, we excluded patients who stayed in the hospital for ≤ 24 hours and re-examined the link between LAR and in-hospital mortality.

All statistical analyses were performed using R software (version 4.3.1) and Free Statistics (version 2.1). A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics of Study Participants

This study included 14,650 patients diagnosed with AP between 2005 and 2023. After applying inclusion and exclusion criteria, 4605 patients remained for analysis. Patients were divided into three groups based on LAR levels: Tertile 1 (median: 5.7), Tertile 2 (median: 9.3), and Tertile 3 (median: 19.4). Baseline details are shown in Table 1. The average age was 52.6 ± 13.9 years, and 57.8% were male. Patients in Tertile 3 were usually younger, had a higher BMI, and more commonly had HTG-AP. Higher LAR was connected with higher inflammatory markers (WBC, NEU, and CRP levels), kidney dysfunction (BUN, Cr), and higher liver enzymes (ALT, AST, and TBIL). Also, Tertile 3 patients had higher APACHE II and SIRS scores, indicating more severe disease. LAR values showed greater differences between survivors and non-survivors compared to LDH or albumin alone (Figure 2A).

Relationship Between LAR and Clinical Outcomes

Clinical outcomes varied significantly across LAR tertiles (Supplementary Table 2). Patients in the highest LAR tertile (Tertile 3) exhibited the highest incidence of organ failure (75.0%), including respiratory failure (71.3%), renal failure (29.9%), and circulatory failure (17.2%). PMOF (25.1%) and SAP (61.0%) were also markedly more common in this

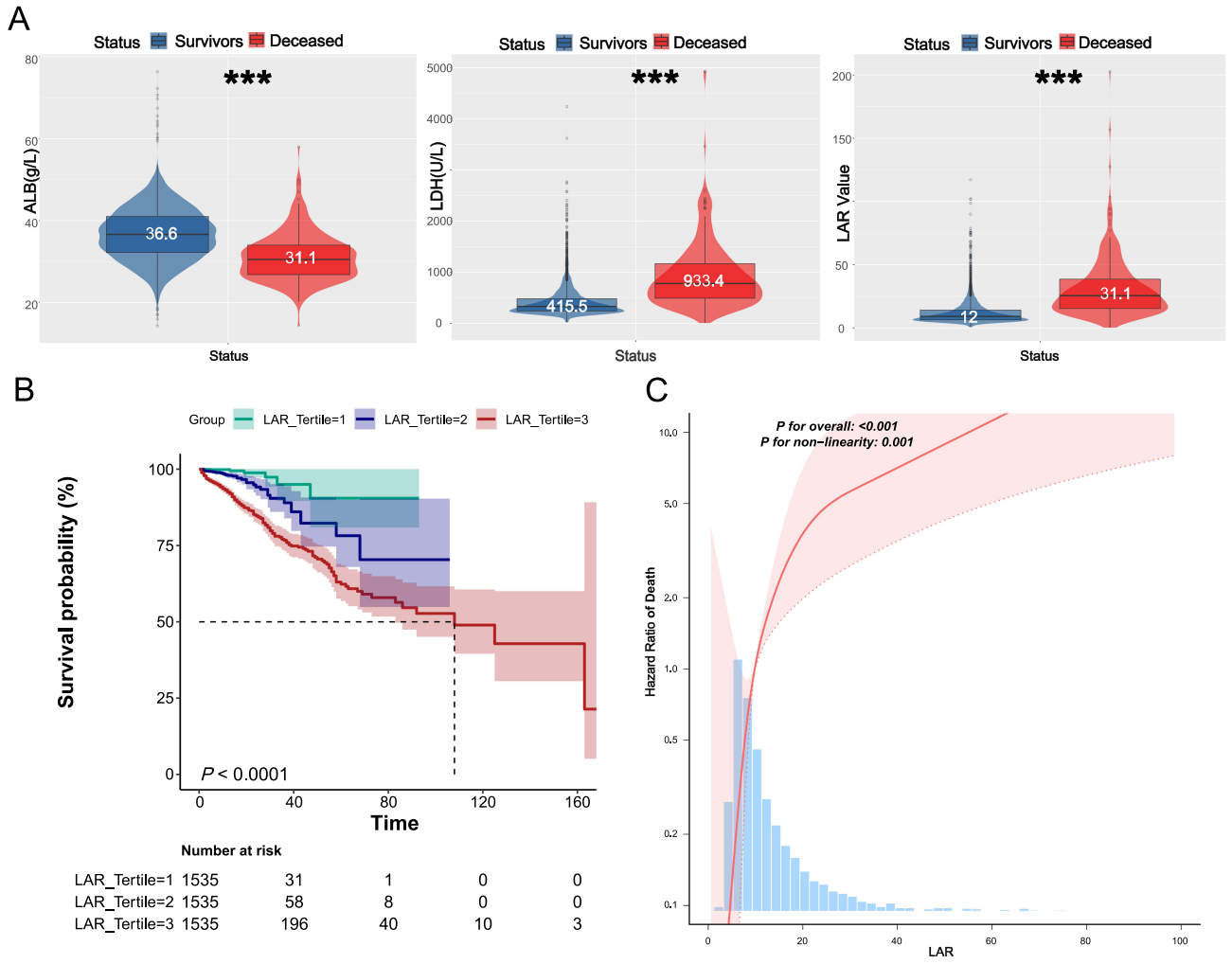

Figure 2 Prognostic value of LAR in the study cohort. (**A**) Baseline comparison of LDH, ALB, and LAR between the mortality and survival groups. (**B**) The Kaplan-Meier survival curves of subjects in the cohort grouped by LAR tertiles. (**C**) Visualizing the relationship between LAR and the in-hospital mortality risk of subjects using a 4-knots RCS. ***: *P* <0.001.

Abbreviations: LAR, lactate dehydrogenase-to-albumin ratio; LDH, lactate dehydrogenase; ALB, albumin; RCS, restricted cubic spline.

group. Furthermore, patients in Tertile 3 had significantly prolonged hospital (median, 15 days) and ICU stays (median, 3 days). Notably, the highest in-hospital mortality rate was observed in Tertile 3 (14.9%), compared with 2.7% in Tertile 2 and 0.5% in Tertile 1 ($P < 0.001$).

Survival Analysis

Kaplan-Meier (KM) survival analysis showed clear differences in survival rates among patients stratified by LAR tertiles (Log rank test, $P < 0.0001$). Patients in Tertile 3 had the lowest survival rate compared to other groups. Patients in Tertile 2 also had lower survival rates than those in Tertile 1 (Figure 2B).

Association Between LAR and In-Hospital Mortality Risk in Patients with Predicted SAP

The results of collinearity tests showed no issues (Supplementary Table 3). Schoenfeld residual tests confirmed that LAR met proportional hazards requirements ($P > 0.05$) (Supplementary Figure 1). In the crude unadjusted model (Model I), LAR was significantly associated with increased in-hospital mortality (HR per SD increase: 1.19; 95% CI: 1.16–1.22; $P < 0.001$), with its hazard ratio (HR) consistently exceeding those of its individual components, LDH and ALB. After

adjusting for demographic factors (sex and age), clinical history variables (smoking, drinking, HTG, diabetes), and vital signs including temperature, pulse, and respiration rate (Model II), the relationship remained robust (HR: 1.16; 95% CI: 1.12–1.20; $P < 0.001$). Further adjustment for inflammation and organ function indicators (SBP, DBP, MAP, NEU, Hb, HCT, TBIL, CK, BUN, PaO_2, and CRP) did not substantially weaken this association (Model III; HR: 1.14; 95% CI: 1.09–1.19; $P < 0.001$). When stratified into tertiles, patients in the highest LAR tertile exhibited significantly higher mortality risk compared to the lowest tertile (Model III; HR: 7.75; 95% CI: 2.31–26.05; $P < 0.001$) (Table 2). Based on the fully adjusted model (Model III), the RCS curve further visualized the relationship between LAR and the risk of mortality in the cohort. Additionally, a non-linear relationship was observed between LAR and mortality (P for non-linearity < 0.001) (Figure 2C). A two-piecewise Cox regression analysis identified an inflection point at an LAR value of 20.58. Below this threshold, each unit increase in LAR was significantly associated with increased mortality risk (HR 1.19; 95% CI 1.12–1.26; $P < 0.0001$), whereas above this point, the association was attenuated but remained statistically significant (HR: 1.01; 95% CI: 1.00–1.01; $P = 0.0043$) (Table 3).

Table 2 Association Between Admission LAR and Its Constituent Parameters with in-Hospital Mortality in Patients Hospitalized with Predicted SAP

Exposure	HR (95% CI), *P* value		
	Model I	**Model II**	**Model III**
LAR PerSD	1.19 (1.16~1.22), <0.001	1.16 (1.12~1.19), <0.001	1.14 (1.09~1.19), <0.001
LDH PerSD	1.17 (1.15~1.20), <0.001	1.14 (1.11~1.18), <0.001	1.13 (1.08~1.18), <0.001
ALB PerSD	0.56 (0.49~0.64), <0.001	0.63 (0.53~0.75), <0.001	0.68 (0.53~0.88), 0.004
LAR tertile			
Tertile 1	Ref	Ref	Ref
Tertile 2	4.62 (2.07~10.31), <0.001	3.30 (1.25~8.69), 0.016	1.79 (0.48~6.6), 0.385
Tertile 3	14.03 (6.58~29.93), <0.001	9.15 (3.67~22.8), <0.001	7.75 (2.31~26.05), <0.001

Notes: Model adjustments: Model I: No adjustments. Model II: Adjusted for sex, age, smoking history, drinking history, history of hyperlipidemia, history of diabetes, temperature, pulse, and respiration. Model III: Adjusted for the same variables as Model 2, plus SBP, DBP, MAP, NEU, Hb, HCT, TBIL, CK, BUN, PaO_2, and CRP.

Abbreviations: HR, Hazard Ratio; LAR, Lactate Dehydrogenase-to-Albumin Ratio; MAP, Mean Arterial Pressure; SD, Standard Deviation; BMI, Body Mass Index; HTG, Hypertriglyceridemia; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell; NEU, Neutrophil; Hb, Hemoglobin; HbA1c, Glycated Hemoglobin; HCT, Hematocrit; LYM, Lymphocyte; PLT, Platelet; ALT, Alanine Transaminase; AST, Aspartate Transaminase; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; LDH, Lactate Dehydrogenase; CK, Creatine Kinase; TG, Triglyceride; TC, Total Cholesterol; GLU, Glucose; LIP, Lipase; AMY, Amylase; BUN, Blood Urea Nitrogen; Cr, Creatinine; CRP, C-reactive Protein; PaO_2, Partial Pressure of Arterial Oxygen; $PaCO_2$, Partial Pressure of Arterial Carbon Dioxide; SIRS, Systemic Inflammatory Response Syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 3 The Result of the Two-Piecewise Cox Regression Model

	HR (95% CI)	***P***
Fitting model by two-piecewise cox regression		
The inflection point of LAR	20.58	
<20.58	1.19 (1.12, 1.26)	<0.0001
>20.58	1.01 (1.00, 1.01)	0.0043
Log-likelihood ratio test		<0.001

Abbreviations: HR, hazard ratios; CI, confidence interval; LAR, Lactate Dehydrogenase-to-Albumin Ratio; BMI, Body Mass Index; HTG, Hypertriglyceridemia; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell; NEU, Neutrophil; Hb, Hemoglobin; HbA1c, Glycated Hemoglobin; HCT, Hematocrit; LYM, Lymphocyte; PLT, Platelet; ALT, Alanine Transaminase; AST, Aspartate Transaminase; TBIL, Total Bilirubin; DBIL, Direct Bilirubin; ALB, Albumin; LDH, Lactate Dehydrogenase; CK, Creatine Kinase; TG, Triglyceride; TC, Total Cholesterol; GLU, Glucose; LIP, Lipase; AMY, Amylase; BUN, Blood Urea Nitrogen; Cr, Creatinine; CRP, C-reactive Protein; PaO_2, Partial Pressure of Arterial Oxygen; $PaCO_2$, Partial Pressure of Arterial Carbon Dioxide; SIRS, Systemic Inflammatory Response Syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Predictive Value of LAR for In-Hospital Mortality in Patients with Predicted SAP

ROC analysis showed LAR predicted hospital death better than traditional scoring systems and single markers (Figure 3A). The calculated AUC values, sensitivity, specificity and optimal threshold points were summarized in Supplementary Table 4. Specifically, the AUC for LAR (0.847, 95% CI: 0.826–0.869) was significantly higher than that of LDH (AUC: 0.818), ALB (AUC: 0.745), SIRS (AUC: 0.743), and APACHE II (AUC: 0.767; all $P < 0.05$, DeLong test). Stratified ROC analyses further confirmed LAR's consistently higher predictive performance across different etiologies, including biliary-AP (AUC: 0.849), HTG-AP (AUC: 0.875), alcoholic pancreatitis (AUC: 0.857), and other etiologies (AUC: 0.859) (Figure 3B–E), with detailed sensitivity and specificity data provided in Supplementary Table 5. Additionally, time-dependent ROC curves suggested that LAR maintained consistently high predictive accuracy at various time points (3–90 days), particularly in early phases (3–14 days) (Figure 3F and Supplementary Table 6). Although APACHE II exhibited slightly higher predictive accuracy than LAR within the first week, its performance markedly decreased after day 14. Moreover, LAR showed good discrimination for persistent organ failures (PMOF, AUC 0.873, 95% CI 0.857–0.890), moderate discrimination for necrotic/infectious complications (ANC/

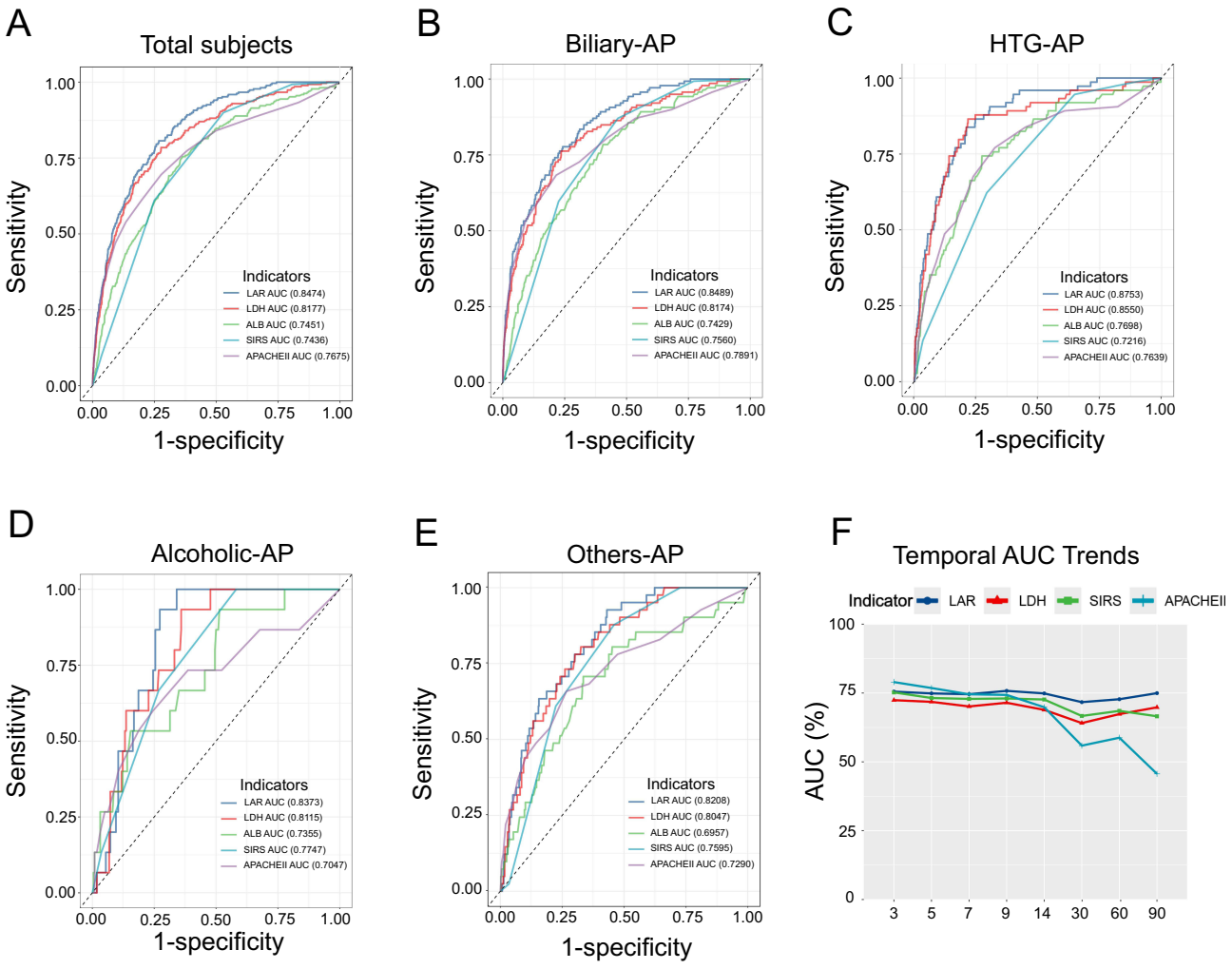

Figure 3 The ROC curves for predicting in-hospital mortality events in the cohort subjects (**A**) and different types of AP ((**B**) Biliary-AP, (**C**) HTG-AP, (**D**) Alcoholic-AP, (**E**) Others-AP) using LAR, LDH, ALB, SIRS and APACHE II. (**F**) Time-dependent ROC analysis of LAR, LDH, SIRS and APACHE II in participants.

Abbreviations: LDH, lactate dehydrogenase; ALB, albumin; LAR, lactate dehydrogenase-to-albumin ratio; SIRS, Systemic Inflammatory Response Syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; ROC, Receiver operating characteristic; ROC, Receiver operating characteristic.

IPN, AUC 0.705/0.658), but limited accuracy for early/local collections (APFC/PPC/WON, AUC 0.557–0.619) (Supplementary Figure 2).

Stratified Analyses

To further validate the stability of the association between LAR and the risk of in-hospital mortality, and to explore potential subgroups of interest, we conducted association analyses across various subgroups based on gender, age (<65, ≥65 years), sex, history of diabetes, history of HTG, HTG-AP and PMOF (Figure 4). Subgroup analyses indicated that the association between LAR and in-hospital mortality was consistent across different groups stratified by diabetes and HTG (both *P* for interaction > 0.05). However, significant interactions were noted with age (*P* for interaction < 0.001), sex (*P* for interaction < 0.001), HTG-AP (*P* for interaction = 0.002), and PMOF (*P* for interaction < 0.001). Notably, the predictive value of LAR was stronger in patients aged<65 years, male, those presenting with HTG-AP, and patients without PMOF.

Sensitivity Analysis

To evaluate the robustness of our findings, sensitivity analyses were conducted by excluding patients with a hospital stay of ≤ 1 day and by performing multiple imputations for missing data (Supplementary Tables 7 and 8). After excluding patients with very short hospital stays, LAR remained significantly associated with in-hospital mortality in the fully adjusted model (HR 1.15; 95% CI: 1.10–1.21; *P* < 0.001), with consistent associations observed for LDH (HR 1.14; 95% CI: 1.09–1.19) and ALB (HR 0.72; 95% CI: 0.55–0.94; both *P* < 0.001). To address potential bias from missing data, multiple imputation was performed, yielding similar results. LAR remained a strong independent predictor (HR 1.36; 95% CI: 1.28–1.45; *P* < 0.001).

Subgroup	Total, n	Event, n(%)	HR (95%CI)	*p* value	*p* for interaction
Age					**<0.001**
< 65	3465	195 (5.6)	1.67 (1.42−1.96)	<0.001	
≥ 65	1140	81 (7.1)	1.03 (0.92−1.15)	0.590	
Sex					**<0.001**
Female	1944	117 (6)	1.11 (1.06−1.17)	<0.001	
Male	2661	159 (6)	1.64 (1.39−1.94)	<0.001	
Diabetes					**0.307**
No	3943	240 (6.1)	1.14 (1.09−1.19)	<0.001	
Yes	662	36 (5.4)	1.14 (0.55−2.33)	0.730	
Hyperlipidemia					**0.137**
No	4159	248 (6)	1.16 (1.1−1.22)	<0.001	
Yes	446	28 (6.3)	2.42 (1.11−5.29)	0.030	
HTG-AP					**0.002**
No	3051	188 (6.2)	1.11 (1.03−1.2)	0.010	
Yes	1554	88 (5.7)	1.79 (1.37−2.34)	<0.001	
PMOF					**<0.001**
No	4151	24 (0.6)	2.22 (1.41−3.49)	<0.001	
Yes	454	252 (55.5)	1.1 (1.03−1.17)	0.010	

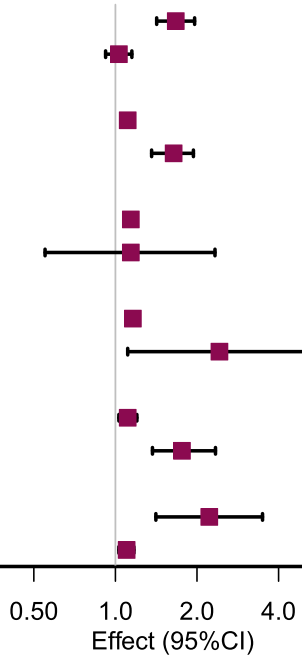

Figure 4 Forest plot showing HR for in-hospital mortality across subgroups (age, sex, history of diabetes, history of HTG, HTG-AP, and PMOF) from the fully adjusted Model III (sex, age, smoking history, drinking history, history of HTG, history of diabetes, temperature, pulse, and respiration, SBP, DBP, MAP, NEU, Hb, HCT, TBIL, CK, BUN, PaO_2, and CRP).

Abbreviations: HR, Hazard Ratio; LAR, Lactate Dehydrogenase-to-Albumin Ratio; HTG, Hypertriglyceridemia; HTG-AP, hypertriglyceridemia-associated acute pancreatitis; PMOF, Persistent Multiple Organ Failure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; NEU, Neutrophil; Hb; Hemoglobin; HCT, Hematocrit; TBIL, Total Bilirubin; CK, Creatine Kinase; BUN, Blood Urea Nitrogen; PaO_2, Partial Pressure of Arterial Oxygen; CRP, C-reactive protein.

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Discussion

This large-sample, single-center retrospective study investigated the performance of baseline LAR—a composite biomarker combining LDH and ALB—for predicting in-hospital mortality among patients with predicted SAP. An elevated admission LAR was independently associated with increased disease severity, organ failure, and mortality. RCS analysis indicated a nonlinear association, identifying an inflection point at 20.58. LAR demonstrated higher predictive performance (AUC = 0.8474) than LDH, ALB alone, and traditional scoring systems (APACHE II, SIRS), maintaining predictive accuracy across both short-term and long-term outcomes. These results suggest that LAR could serve as a useful clinical decision-making tool for patients with predicted SAP.

LDH is widely expressed in various tissues, including myocardium, skeletal muscle, and pancreas, among others and is often used as an indicator of cell death.[29,30] During the development of AP, elevated LDH levels may relate to inflammatory response, ischemic necrosis of pancreatic acinic cells and OF.[15,31] Consequently, LDH holds potential as a prognostic marker for the AP severity and mortality. ALB is mainly produced by the liver, indicates the nutritional status of the body and plays a pivotal role in systemic inflammation. The decrease of ALB levels in AP can attributed to the fasting and high catabolism state,[32] the increased vascular permeability increases the transcapillary loss of ALB,[33,34] and the increasing production of several anti-inflammatory substances during oxidative stress, which requires a significant amount of ALB.[35] Additionally, some studies have demonstrated that ALB might predict the outcomes of AP, particularly in predicting OF and death.[35,36] Although previous studies have independently evaluated these biomarkers separately, few have integrated their combined predictive value. Our study proposes LAR as a novel biomarker that incorporates tissue injury, systemic inflammation, and nutritional status, thereby providing a more comprehensive assessment of patient outcomes.

Multiple studies have demonstrated that an elevated LAR serves as an independent risk factor for poor outcomes in various diseases, including certain types of cancer and inflammatory diseases such as sepsis, pneumonia and lower respiratory tract infection, stroke, and critically ill patients.[19–21,37–39] Previously, Helliksson et al[39] confirmed that LAR was more accurate in multiple organ failure in critically ill patients at the time of admission to ICU, compared with either LDH or ALB. In septic patients, Guan et al[22] demonstrated that LAR ≥10.57 was associated with significantly higher ICU mortality and served as a robust predictor with an AUC of 0.688. Moreover, Hu et al found LAR to be a reliable prognostic factor for overall survival for patients with operable colorectal cancer, with more accurate prognostic prediction than current TNM stage.[18] However, the prognostic value of LAR for AP patients has not been previously reported.

Our study further confirmed a nonlinear relationship between LAR and in-hospital mortality risk (P for non-linearity < 0.05), with higher admission LAR significantly associated with increased mortality. LAR also showed superior predictive accuracy over LDH, ALB, SIRS, and APACHE II. Notably, this is the first study to report temporal variations in the prognostic performance of LAR. Using time-dependent ROC analysis at 3, 5, 7, 9, 14, 30, 60, and 90 days post-admission, LAR consistently outperformed LDH, SIRS, and maintained stronger long-term predictive ability than APACHE II (AUC at 90 days: LAR 74.95 vs APACHE II 45.65). However, LAR exhibited higher sensitivity but lower specificity than APACHE II in predicting in-hospital mortality, likely due to differences in their biological rationale and indicator characteristics. By integrating tissue hypoxic injury (increased LDH) with inflammation-induced capillary leakage and nutritional depletion (decreased ALB), LAR captures systemic metabolic-inflammatory disturbances earlier and more consistently, enhancing its sensitivity to mortality risk.[40–42] Nevertheless, both LDH and albumin levels are easily influenced by various confounding factors, such as concurrent infections, cardiopulmonary diseases, nutritional status, or fluid-volume changes, potentially leading to false-positive results and reduced specificity.[40] In contrast, APACHE II focuses on severe physiological derangements associated with overt organ dysfunction, utilizing stricter thresholds and thus providing higher specificity. However, its complexity limits sensitivity in detecting early inflammation-driven subclinical changes.

Subgroup analysis further indicated that the predictive effect of LAR significantly differed by age, sex, HTG, HTG-AP, and PMOF, as evidenced by significant interaction terms (all P for interaction < 0.05). Notably, the prognostic impact was stronger in younger patients (< 65 years), males, those presenting with HTG or HTG-AP, and individuals without

PMOF. The enhanced predictive value observed in younger and male patients could be attributable to stronger inflammatory responses or metabolic disturbances typically observed in these subpopulations.[43–45] Additionally, HTG is often associated with severe systemic inflammation and oxidative stress,[46,47] potentially amplifying the predictive capacity of LAR in the HTG and HTG-AP subgroups. Interestingly, we observed stronger associations in patients without PMOF, possibly reflecting a greater value of LAR for early identification of high-risk patients before PMOF emerges.

This study has following notable strengths. Firstly, the current study, for the first time, specifically explore the correlation between the LAR and in-hospital mortality among patients with predicted SAP. Secondly, a large scale of 4605 subjects were included in this study and further employment of time-dependent ROC analysis on this basis allowed us to more comprehensively compare the predictive value of the baseline LAR for the incidence of in-hospital mortality at different time points in the future. Lastly, the findings of the current study are relatively reliable as several sensitivity analyses and adequate model adjustments were performed and the HR values of the LAR associated with in-hospital mortality risk were standardized before the comparisons.

Nevertheless, several limitations warrant mention. Firstly, the retrospective data collection at a single academic center could have caused selection bias. Secondly, this study solely assessed the association between baseline LAR at admission and in-hospital mortality, without evaluating the potential relationship between longitudinal changes of LAR during hospitalization and mortality. Finally, this study was conducted in a single center, and in future research, validation in independent, prospective cohorts is required to generalize the findings.

Conclusion

In summary, admission LAR appears to be a promising biomarker for predicting in-hospital mortality in patients with predicted SAP. It demonstrates consistent predictive performance across various timeframes and etiologies of AP and provides greater accuracy than its individual components (LDH and albumin) and several traditional clinical scoring systems. Although LAR has potential clinical utility in early risk stratification and decision-making, further prospective, multicenter studies are required to validate these findings.

Abbreviations

AP, acute pancreatitis; SAP, severe acute pancreatitis; OF, organ failure; APACHE II, acute physiology and chronic health evaluation II; LDH, lactate dehydrogenase; ALB, albumin; LAR, lactate dehydrogenase-to-albumin ratio; BMI, body mass index; HTG, hyperlipidemia; SIRS, systemic inflammatory response syndrome; IPN, infected pancreatic necrosis; ICU, intensive care unit; PMOF, persistent multiple organ failure; CECT, contrast enhanced computed tomography; CRP, c - reactive protein; PaO_2, arterial oxygen partial pressure; VIF, variance inflation factor; HR, hazard ratio; CI, confidence interval; RCS, restricted cubic splines; ROC, receiver operating characteristic; HTG - AP, hyperlipidemia-associated acute pancreatitis; WBC, white blood cell; NEU, neutrophil; BUN, blood urea nitrogen; ALT, alanine transaminase; AST, aspartate transaminase; TBIL, total bilirubin; KM, Kaplan-Meier; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Hb, hemoglobin; HCT, hematocrit; CK, creatine kinase.

Data Sharing Statement

The data that support the findings of this study are available on request from Dr Yin Zhu.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or

critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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