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Clinical significance of lactate-to-albumin ratio in patients with influenza A virus-induced acute respiratory distress syndrome: a single-center retrospective study

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Abstract

Background The lactate-to-albumin ratio (LAR) is predictive of disease prognosis in some cases. However, the clinical significance of LAR in patients with influenza A virus-induced acute respiratory distress syndrome (ARDS) has yet to be explored. This study aims to investigate whether LAR can be used as a predictor of influenza A virus-induced ARDS.

Methods In this single-center retrospective study, we enrolled 105 patients with influenza A virus pneumonia into the study and divided the patients into an ARDS group (74 patients) and a non-ARDS group (31 patients) during hospitalization. Clinical characteristics and laboratory data were collected within 24 h after admission. We explored the risk factors for ARDS using logistic regression analysis. The predictive performance of potential risk factors for ARDS and ARDS-associated complications were evaluated by receiver operating characteristic (ROC) curves, and Pearson's correlation analysis was used to evaluate the correlations between risk factors and clinical and laboratory variables.

Results LAR was an independent predictor for the development of ARDS in patients with influenza A virus pneumonia and was significantly predictive for ARDS. LAR's area under the curve (AUC) was higher than that of lactate and albumin alone; its AUC was 0.878, with a sensitivity of 71.6% and a specificity of 96.8%. The optimal ROC threshold for distinguishing ARDS from non-ARDS cases was 44.81×10^{-3}. Correlation analysis indicated that LAR was positively associated with duration of invasive ventilation, and APACHE II and SOFA scores in ARDS patients but was negatively associated with PaO_2/FiO_2 ($p < 0.001$). Subsequent ROC curve analysis determined that LAR was a robust predictor for the 14-day invasive ventilation (AUC = 0.924), septic shock (AUC = 0.860), and hepatic injury (AUC = 0.905) in hospitalized ARDS patients. It also showed a promising predictive value for 28-day mortality (AUC = 0.881).

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Conclusion LAR strongly predicted ARDS development in patients with influenza A virus pneumonia. It showed a significant correlation with disease severity and provided promising predictive efficiency for extrapulmonary complications and 28-day mortality in patients with influenza A virus-induced ARDS.

Keywords Lactate-to-albumin ratio, Influenza A virus, Acute respiratory distress syndrome

Introduction

Influenza A virus, a highly infectious respiratory pathogen, continues to spread globally among humans, causing tens of thousands of deaths annually, and poses a significant threat to human health [1]. Acute respiratory distress syndrome (ARDS) is a common complication of influenza A virus infection and is characterized by hypoxemia, respiratory distress, severe noncardiogenic pulmonary edema, and high mortality. No effective pharmacotherapies for ARDS are currently available. Extrapulmonary multiorgan dysfunction is a common complication during the development of ARDS, which exacerbates the illness and can cause fatal consequences [2]. Therefore, early recognition of the risk factors associated with ARDS and ARDS-associated complications, and accurate evaluation of disease severity and prognosis may allow for timely implementation of supportive therapies and may assist in research efforts aimed at developing personalized management strategies and decreasing mortality in patients with influenza A virus infection.

Acute Physiology and Chronic Health Evaluation II (APACHE-II) and Sequential Organ Failure Assessment (SOFA) scores are independently associated with the development of ARDS or the severity of influenza A virus infection in previous studies [3–5]. However, the two scores necessitate collecting multiple indicators and can be time-consuming and cause a heavy workload; therefore, many doctors may be unwilling to perform the scoring procedures, especially in the emergency department and intensive care units. Consequently, identifying simplified, practical, and highly sensitive and specific biomarkers may prove useful for management of patients with influenza.

Traditionally, lactate is considered a byproduct of anaerobic glycolysis which reflects the extent of inadequate tissue perfusion and cellular hypoxia, and hyperlactatemia is considered as a sign of 'oxygen debt' or 'hypoperfusion' [6]. However, a study indicated that hyperlactatemia is more logically explained by increased aerobic glycolysis secondary to activation of the stress response (adrenergic stimulation) [6]. Besides the above pathophysiological factors, microcirculatory dysfunction, mitochondrial dysfunction, liver dysfunction, and specific medication could also contribute to hyperlactatemia [6–8]. Lactate is capable of predicting organ failure and mortality in critically ill patients [9, 10]. However, the level of lactate was influenced by multiple factors. Therefore, relying solely on lactate levels for predicting disease severity and prognosis may not always ensure reliable outcomes.

Albumin is another commonly used clinical index, which is known to be associated with inflammation severity, disease prognosis, and mortality in critically ill patients [11, 12]. However, because a patient's nutritional status or chronic inflammation can influence albumin levels, managing critically ill patients solely based on albumin levels also has limitations [13].

Increased focus has recently shifted to exploring the predictive value of composite metrics in disease management. Limited studies have verified the efficacy of the lactate-to-albumin ratio (LAR) in predicting mortality in patients with sepsis and sepsis-induced organ injury [14]. However, the clinical significance of LAR in patients with influenza A virus pneumonia remains unclear. Here we aim to investigate the predictive value of LAR in the development of ARDS and ARDS-related complications in patients with influenza. Furthermore, we also evaluated the 28-day mortality predictive efficiency of LAR.

Methods

Subjects and study design

This study included patients hospitalized with influenza A viral pneumonia at the First Affiliated Hospital of Soochow University between January 1, 2011, and October 31, 2023. Patient medical records were reviewed by our team, and all indicators including APACHE II and SOFA scores for risk factor prediction were collected within the first 24 h after admission. If the indicators were repeatedly measured during the first 24 h, the worst value was selected. Patients were included in the study according to the following main inclusion criteria: (a) influenza-like symptoms, (b) positive influenza A virus nucleic acid, and (c) lactate and albumin levels measured within 24 h after admission. In this retrospective study, 142 patients aged 20 to 84 were initially considered for inclusion. After screening by exclusion criteria, 105 patients were selected for the study (Fig. 1). Patients were categorized into two groups: the ARDS group (74 patients) and the non-ARDS group (31 patients). ARDS diagnosis adhered to the Berlin definition [15]. Cardiac injury was diagnosed according to the serum levels of cardiac biomarkers or new abnormalities in electrocardiography and echocardiography [16]. The novel sepsis-3 definition was used to define septic shock [17]. Acute kidney injury was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [18]. Hepatic injury was defined

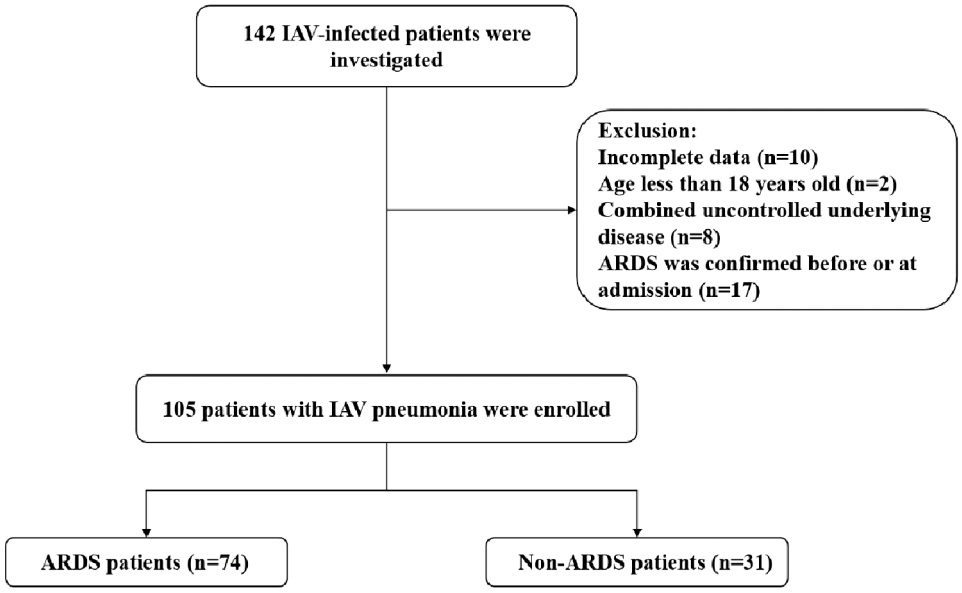

Fig. 1 Flowchart of the disposition of 142 patients who were admitted with influenza A virus (IAV) infection

according to elevation of bilirubin and aminotransferase [19]. In addition, the APACHE II and SOFA scores were calculated concerning the methods reported in previous studies [20, 21].

Statistical analysis

To verify the sample size in our study was sufficient to draw convincing conclusions, power analysis was conducted, and the result showed that efficiency value was 0.70 (significance level=0.05, power=0.9). Categorical variables, presented as numbers (percentages), were compared using the chi-square test or Fisher's exact test. Continuous variables were analyzed based on their distribution: those with a normal distribution, shown as mean±standard deviation, were assessed using Student's t-test; and those with a skewed distribution, shown as medians (interquartile ranges), were assessed using the Mann–Whitney U test. Variable correlations were assessed using the Pearson correlation coefficient. Potential risk factors were identified using univariate logistic regression analysis, with factors showing $p<0.1$ proceeding to multivariable logistic regression to determine independent risk factors for the development of ARDS. Receiver operating characteristic (ROC) analysis was used to assess the predictive ability of potential risk factors. A two-tailed test indicating $p<0.05$ was considered statistically significant. Statistical analyses were conducted with SPSS version 25.0, and results were visualized through GraphPad Prism 9.5.

Results

Comparison of demographic baseline, clinical characteristics, and laboratory results between ARDS and non-ARDS patients

According to the selection and exclusion criteria, 105 patients with influenza A virus pneumonia were included in the final analysis (Fig. 1). The demographic baseline and clinical symptoms were comparable in the ARDS and non-ARDS groups (Table 1). Compared to the non-ARDS group, patients in the ARDS group exhibited significantly higher APACHE II scores (14.00±2.04 vs. 10.35±2.18, $p<0.001$), SOFA scores (7.31±2.53 vs. 4.48±1.06, $p<0.001$), and lower PaO_2/FiO_2 ratios (160.34±30.02 vs. 188.45±22.62, $p<0.001$) (Table 1).

Additionally, laboratory indices differed between the two groups (Table 2). Compared to the non-ARDS group, patients in the ARDS group exhibited higher levels of neutrophils (NEU), lactate, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK); they also had lower albumin levels and longer activated partial prothrombin time (APTT) at admission (all $p<0.05$). D-dimer was not included in the study because this index was not universally detected within 24 h after admission. Notably, the LAR level was significantly higher in the ARDS group compared to the non-ARDS group at admission ($67.28\times10^{-3}\pm38.12\times10^{-3}$ vs. $29.33\times10^{-3}\pm9.50\times10^{-3}$, $p<0.001$).

Independent predictor for ARDS in patients with influenza A virus pneumonia

Potential predictive factors which showed significant differences ($p<0.05$) in the initial analysis (Tables 1 and 2) were included in the univariate logistic regression

Table 1 Baseline demographic and clinical features in patients with influenza A virus infection at admission

Variables	influenza A virus-non-ARDS (*n* = 31)	influenza A virus-ARDS (*n* = 74)	*P* value
Age (years)	52.61 (± 15.28)	58.26 (± 15.22)	0.086
Sex (male)	21 (67.7%)	50 (67.6%)	0.986
Active smoking habits, n (%)	3 (9.7%)	10 (13.5%)	0.751
Clinical symptoms			
Temperature ≥ 39.0℃	26 (83.9%)	64 (86.5%)	0.727
Respiratory rate (per minute)	22.94 (± 3.97)	25.15 (± 5.70)	0.051
Dry cough, n (%)	12 (38.7%)	17 (23.0%)	0.100
Expectoration, n (%)	18 (58.1%)	52 (70.3%)	0.226
Fatigue, n (%)	17 (54.8%)	46 (62.2%)	0.485
Sore throat, n (%)	16 (51.6%)	47 (63.5%)	0.256
Anorexia, n (%)	11 (35.5%)	37 (50.0%)	0.173
Myalgia, n (%)	5 (16.1%)	13 (17.6%)	0.858
Dyspnea, n (%)	13 (41.9%)	40 (54.1%)	0.257
Comorbidities, n(%)			
Hypertension	9 (29.0%)	33 (44.6%)	0.138
Diabetes mellitus	3 (9.7%)	15 (20.3%)	0.189
Cardiac disease	0 (0%)	2 (2.7%)	0.355
Chronic renal disease	0 (0%)	1 (1.4%)	0.515
Chronic lung disease	0 (0%)	6 (8.2%)	0.100
Chronic liver disease	0 (0%)	3 (4.1%)	0.255
Malignancies	0 (0%)	3 (4.1%)	0.553
APACHE II score	10.35 (± 2.18)	14.00 (± 2.04)	< 0.001
SOFA score	4.48 (± 1.06)	7.31 (± 2.53)	< 0.001
PaO_2/FiO_2 (mmHg)	188.45 (± 22.62)	160.34 (± 30.02)	< 0.001

ARDS: Acute respiratory distress syndrome; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SOFA score: Sequential Organ Failure Assessment score; PaO_2/FiO_2: the ratio of partial pressure of arterial oxygen and the concentration of inspired oxygen

Table 2 Laboratory indices of patients with influenza A virus infection between the ARDS and non-ARDS groups at admission

Variables	influenza A virus-non-ARDS (*n* = 31)	influenza A virus-ARDS (*n* = 74)	*P* value
WBC ($\times 10^9$/L)	5.66 (± 3.48)	7.86 (± 5.80)	0.052
NEU ($\times 10^9$/L)	4.54 (± 3.10)	7.07 (± 5.53)	0.019
LYM ($\times 10^9$/L)	0.65 (± 0.47)	0.52 (± 0.32)	0.097
PLT ($\times 10^9$/L)	167.26 (± 56.09)	148.45 (± 64.69)	0.161
Lactate (mmol/L)	0.97 (± 0.34)	1.90 (± 0.93)	< 0.001
hs-CRP (mg/L)	13.88 (± 1.64)	14.52 (± 1.99)	0.119
ALT (U/L)	42.19 (± 25.12)	58.87 (± 46.81)	0.064
AST (U/L)	63.35 (± 40.61)	99.59 (± 72.59)	0.01
BUN (mmol/L)	8.28 (± 5.64)	10.21 (± 7.86)	0.219
Creatinine (μmol/L)	68.94 (± 17.12)	76.14 (± 25.67)	0.155
Total cholesterol (mmol/L)	3.33 (± 0.69)	2.95 (± 1.19)	0.106
HDL-C(mmol/L)	0.90 (± 0.24)	0.81 (± 0.23)	0.067
LDL-C(mmol/L)	2.08 (± 0.59)	1.75 (± 0.87)	0.056
CK (U/L)	236.26 (± 59.89)	473.31 (± 70.40)	0.043
Albumin (g/L)	33.16 (± 3.82)	29.64 (± 4.54)	< 0.001
PT (s)	12.40(± 1.20)	13.00 (± 1.95)	0.112
APTT (s)	29.01 (± 5.89)	35.80 (± 12.41)	0.004
Fibrinogen (g/L)	3.96 (± 1.45)	3.50 (± 0.93)	0.054
Lactate /Albumin ($\times 10^{-3}$)	29.33 (± 9.50)	67.28 (± 38.12)	< 0.001

ARDS: acute respiratory distress syndrome; WBC: white blood cell; NEU: neutrophil granulocyte; LYM: lymphocyte; PLT: platelet count; hs-CRP: hypersensitive-C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; HDL-C: high-density lipoprotein; LDL-C: low-density lipoprotein; LDH: lactate dehydrogenase; CK: creatine kinase.; PT: prothrombin time; APTT: activated partial prothrombin time

analysis. ARDS and non-ARDS groups had significant differences in NEU, AST, LDH, CK, APTT, APACHE II score, SOFA score, PaO_2/FiO_2, lactate, albumin, and LAR ($p<0.1$; Fig. 2A).

Because LAR consists of lactate and albumin, our ROC curve analysis was used to determine which among these two variables and LAR were more suitable for inclusion in a multivariable logistic regression analysis. Our analysis indicated that the LAR had a better ability to predict ARDS development through the ROC curve AUC [0.878 (95% CI:0.815–0.942)] than that of lactate [0.862 (95% CI:0.793–0.932)] or albumin [0.730 (95% CI:0.633–0.827)] alone (Fig. 3; Table 3). Therefore, it was selected for multivariable logistic regression analysis. Variables in the univariate analysis with $p<0.1$ proceeded to the multivariable logistic regression analysis. Creatine kinase (CK) (OR 1.003; 95% CI 1.000–1.006; $p=0.048$), APACHE II score (OR 1.610; 95% CI 1.068–2.429; $p=0.023$) and LAR (OR 1.105; 95% CI 1.012–1.208; $p=0.027$) at admission were independently associated with the development of ARDS in patients with influenza A virus pneumonia ($p<0.05$) (Fig. 2B).

The predictive efficiency of risk factors for the development of ARDS in patients with influenza A virus pneumonia

The AUC for LAR [0.878 (95% CI: 0.815–0.942)] was stronger than that for CK [0.660 (95% CI:0.545–0.770)], and it was comparable to the APACHE II score [0.884 (95% CI:0.809–0.959)] and the SOFA score [0.851 (95% CI:0.779–0.923)] (Fig. 4; Table 3). Additionally, we identified an optimal LAR cut-off value of 44.81×10^{-3}, with a sensitivity of 71.6% and a specificity of 96.8% (Table 3).

Correlation analysis between LAR and disease severity

To further explore the clinical value of LAR, we categorized ARDS patients into a high LAR group ($LAR\geq44.81\times10^{-3}$, $n=53$) and a low LAR group

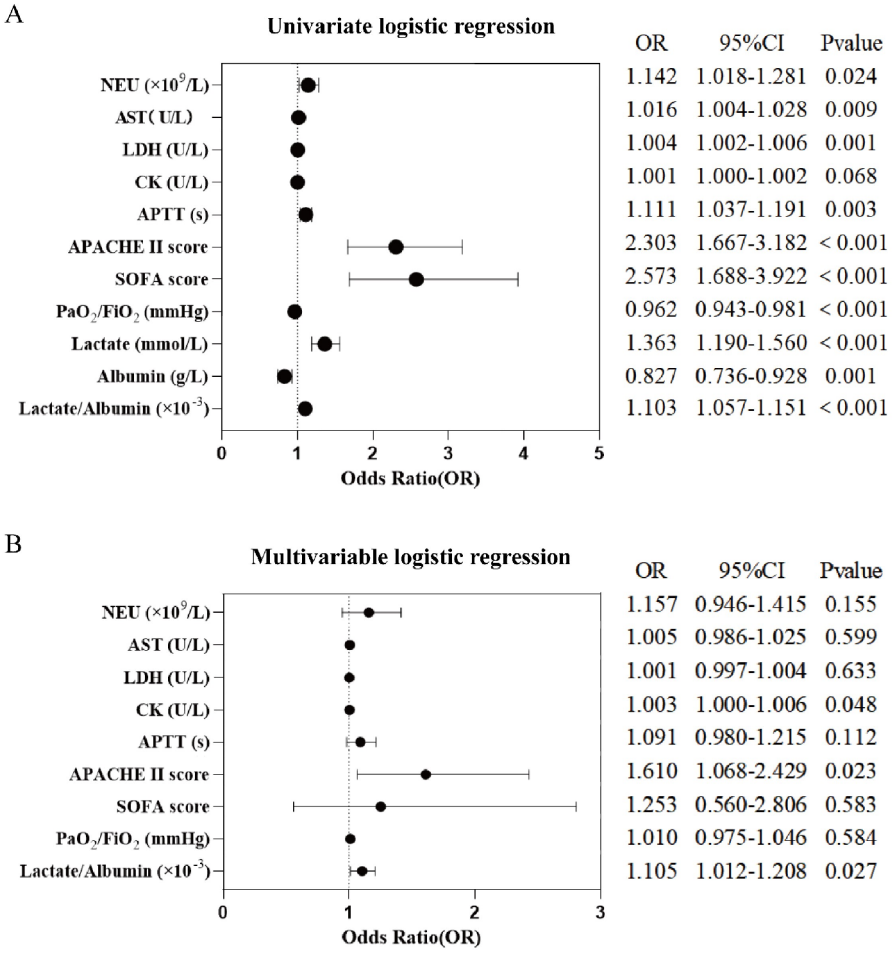

Fig. 2 Univariate and Multivariable logistic regression analysis for predicting the development of ARDS in patients with influenza A virus infection. (**A**) Univariate logistic regression analysis for predicting the development of ARDS in patients with influenza A virus infection. (**B**) Multivariable logistic regression analysis for predicting the development of ARDS in patients with influenza A virus infection

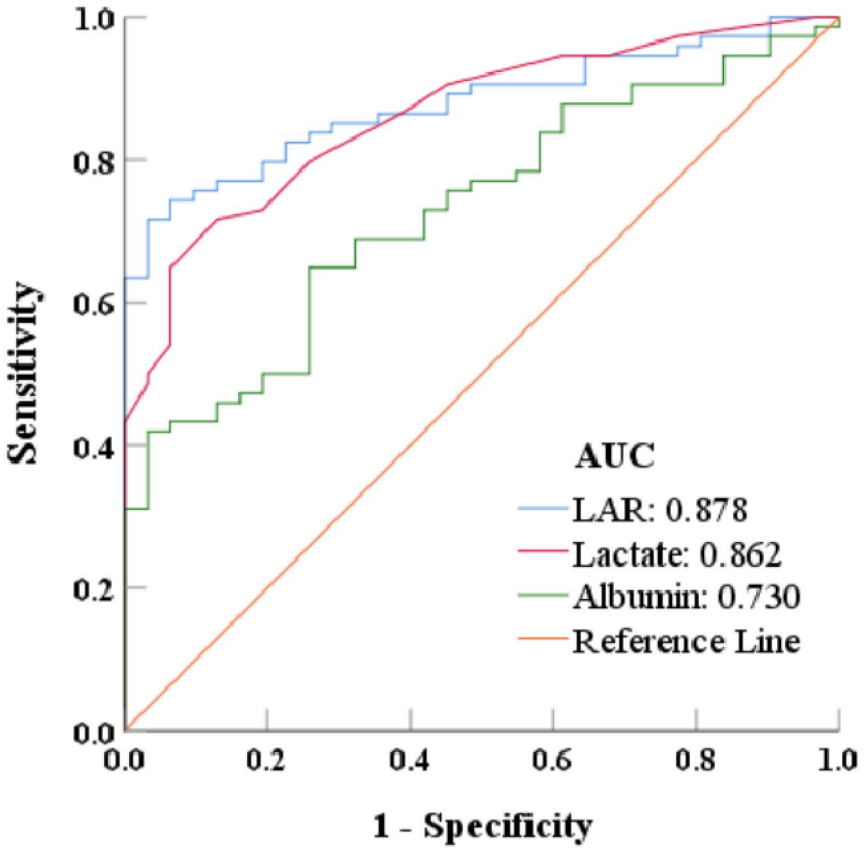

Fig. 3 ROC curves for LAR, lactate, and albumin for predicting the development of ARDS in patients with influenza A virus infection

Table 3 Indicator values in predicting ARDS in patients with influenza A virus infection

Variables	AUC	95% CI	Optimal cutoff value	Sensitivity (%)	Specificity (%)
Lactate/Albumin ($\times 10^{-3}$)	0.878	0.815–0.942	44.81	71.6	96.8
Lactate	0.862	0.793–0.932	1.35	70.1	87.1
Albumin	0.730	0.633–0.827	31.30	64.9	74.2
CK	0.660	0.545–0.770	102.90	77.0	54.8
APACHE II score	0.884	0.809–0.959	11.50	91.9	71.0
SOFA score	0.851	0.779–0.923	5.50	74.3	80.6

CK: creatine kinase; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SOFA score: Sequential Organ Failure Assessment score

(LAR$<44.81\times10^{-3}$, $n=21$) based on the optimal cut-off value. We found that the percentage of invasive ventilation, septic shock, hepatic injury, and 28-day mortality during hospitalization was significantly high in the high LAR group compared to the low LAR group ($p<0.001$) (Table 4). However, the incidence of cardiac injury and acute kidney injury was the same across the two groups (Table 4). Thereafter, we analyzed whether LAR levels correlated with patient disease severity. The level of LAR at admission was correlated positively with the duration of invasive ventilation, and the APACHE II and SOFA scores, and was negatively correlated with the PaO_2/FiO_2 ratio in patients with ARDS ($p<0.001$) (Fig. 5). Unlike the above four indicators, serum AST was correlated weakly with LAR level ($r=0.298$; $p=0.01$) (Fig. 5).

Complication and prognosis prediction efficiency of LAR in patients with influenza A virus-induced ARDS

To further validate the ability of baseline LAR to predict complications in ARDS patients, we refined the ROC curves for LAR in ARDS patients, focusing on invasive mechanical ventilation (≥14 days), septic shock, hepatic injury, and 28-day mortality. LAR demonstrated outstanding AUC values in invasive mechanical ventilation (≥14 days) [0.924 (95% CI: 0.838–1.00)], septic shock [0.860 (95% CI: 0.780–0.941)], hepatic injury [0.905 (95%

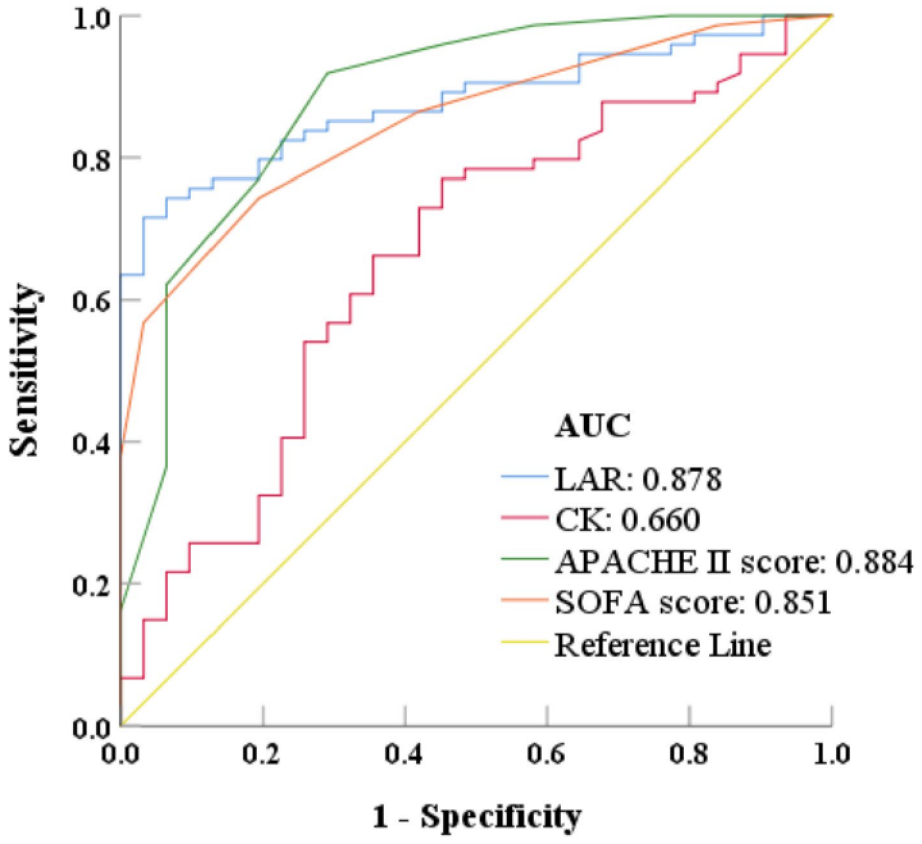

Fig. 4 ROC curves for LAR, CK, APACHE II score, and SOFA score for predicting the development of ARDS in patients with influenza A virus infection

Table 4 Complication prevalence during hospitalization of influenza A virus-infected patients with ARDS in the high LAR and Low LAR groups

Variables	High LAR: LAR ≥ 44.81×10^{-3}, $n=53$	Low LAR: LAR < 44.81×10^{-3}, $n=21$	*P* value
Invasive ventilation	52 (98.1%)	13 (61.9%)	< 0.001
Septic shock	34 (64.2%)	2 (9.5%)	< 0.001
Cardiac injury	25 (47.2%)	8 (38.1%)	0.479
Acute kidney injury	19 (35.8%)	11 (52.4%)	0.192
Hepatic injury	38 (71.7%)	2 (9.5%)	< 0.001
28-day mortality	41 (77.4%)	5 (23.8%)	< 0.001

CI: 0.839–0.971)], and 28-day mortality [0.881 (95% CI: 0.807–0.956)] (Table 5; Fig. 6). Our analysis also indicated that the AUC of LAR in predicting aforementioned complications and 28-day mortality was greater than that of lactate or albumin alone (Table 5; Fig. 6). Furthermore, the AUC of LAR was comparable to and even superior to the APACHE II and SOFA scores (Table 5; Fig. 6).

Discussion

Lactate is not only an important biomarker of tissue oxygenation, blood perfusion, and in vivo metabolism, but it also plays an important role in other aspects such as energy regulation and immune response [8, 22]. Because of these important roles, it is often used to assess disease severity and prognosis in critically ill patients [23]. Previous studies have confirmed that a dramatic increase in lactate levels was strongly associated with adverse outcomes in patients with ARDS [24]. However, the reliability of using serum lactate levels alone to predict patient prognosis is often compromised by factors such as liver disease, medications, and others [25, 26].

Previous studies have reported that hypoalbuminemia is closely associated with the development of disease and the poor prognosis of critical patients [27, 28]. However, chronic wasting disease and individual patient variation in nutritional status greatly limit the predictive value of albumin alone for patient prognosis [29].

Recent work has focused on exploring the clinical value of composite metrics in disease management. As an emerging biomarker, LAR is theoretically supposed to integrate inverse changes triggered by distinct

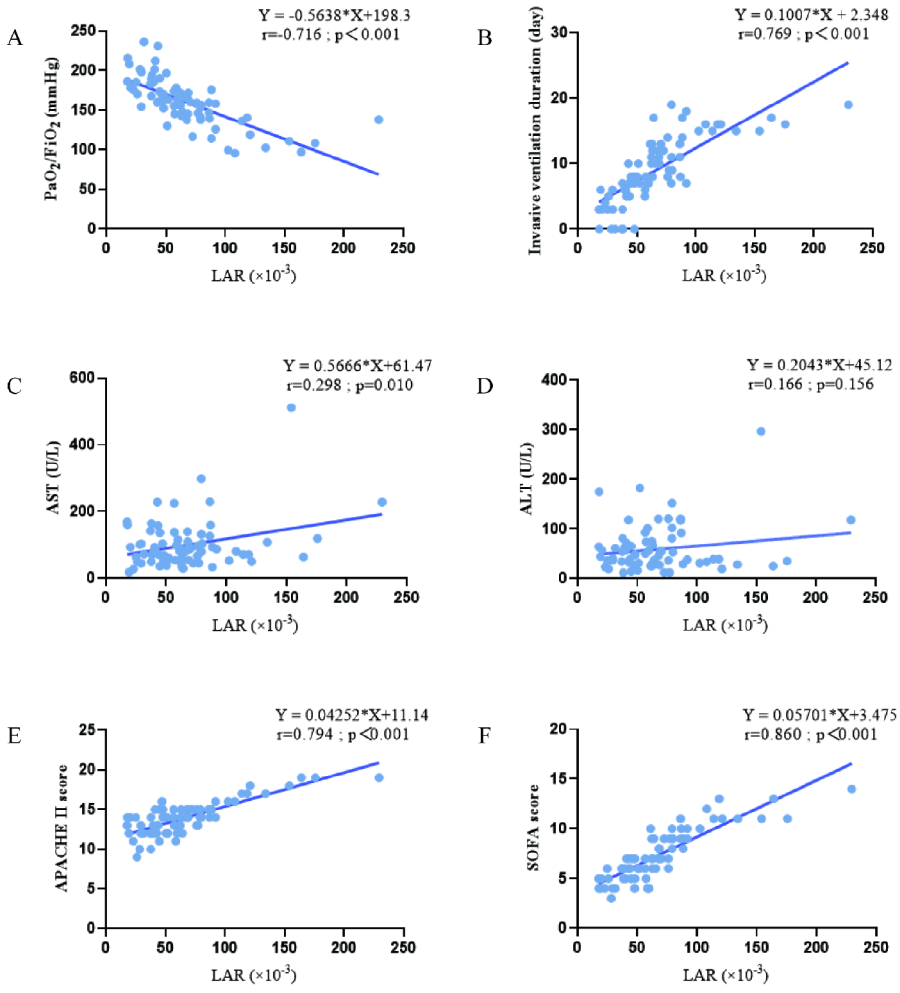

Fig. 5 Correlation analysis between LAR and markers related to complications in patients with ARDS. (**A**) Correlation analysis between LAR and PaO_2/FiO_2. (**B**) Correlation analysis between LAR and the duration of invasive ventilation. (**C**) Correlation analysis between LAR and AST. (**D**) Correlation analysis between LAR and ALT. (**E**) Correlation analysis between LAR and APACHE II score. (**F**) Correlation analysis between LAR and SOFA score

mechanisms, minimizing the impact of individual variability on regulatory processes. This approach offers a holistic view of a patient's status, encompassing nutritional and physiological alterations, thereby enabling precise stratification of critically ill individuals. Studies suggest that LAR can be used as a predictor of mortality in patients with sepsis, acute pancreatitis, and acute myocardial infarction [30–32]. However, the clinical significance of LAR in patients with influenza A virus pneumonia remains unreported. Our study provided evidence that LAR was an independent risk factor for the development of ARDS in patients with influenza A virus pneumonia. LAR also appeared closely associated with disease severity and showed powerful efficiency in predicting extrapulmonary complications and poor prognosis in influenza A virus-induced ARDS.

ARDS frequently results in intensive care unit (ICU) hospitalization and mortality among patients with influenza A virus pneumonia, which is characterized by variable and unpredictable disease progression [33]. Previous studies have shown that the mortality of influenza A virus infection complicated by ARDS is about 40–50%, and even when considered mild as categorized by severity of hypoxemia, the mortality of ARDS patients can be as high as 34.9% [34, 35]. These data suggest that early identification of contributors leading to ARDS, coupled with future research focused on ARDS prevention, may improve the prognosis of patients with influenza A virus pneumonia. Validation of simple, practical, and highly sensitive biomarkers for formulating clinical decisions may help in this regard. Additionally, early application of adequate antiviral therapy, fluid control, and individualized management in patients at high risk of ARDS may prevent the development of ARDS and ultimately improve clinical outcomes. In our study, we found that LAR has powerful ARDS predictive ability with

Table 5 Indicator values in predicting complication and prognosis in influenza A virus-infected patients with ARDS

Variables	AUC	95% CI	Optimal cutoff value	Sensitivity (%)	Specificity (%)
Invasive ventilation duration(≥ 14 days)					
Lactate /Albumin ($\times10^{-3}$)	0.924	0.838–1.000	86.73	76.5	96.5
Lactate	0.897	0.809–0.985	2.35	76.5	91.5
Albumin	0.734	0.581–0.888	27.25	70.6	78.9
APACHE II score	0.920	0.826–1.000	14.50	94.1	80.7
SOFA score	0.913	0.844–0.981	7.50	88.2	77.2
Septic shock					
Lactate /Albumin($\times10^{-3}$)	0.860	0.780–0.941	60.64	80.6	73.7
Lactate	0.779	0.672–0.886	2.20	55.6	92.1
Albumin	0.691	0.568–0.814	27.62	58.3	81.6
APACHE II score	0.859	0.775–0.943	14.50	66.7	92.1
SOFA score	0.847	0.762–0.932	6.50	83.3	68.4
Hepatic injury					
Lactate /Albumin($\times10^{-3}$)	0.905	0.839–0.971	61.80	82.5	85.3
Lactate	0.803	0.703–0.903	1.45	87.5	61.8
Albumin	0.715	0.597–0.834	26.67	47.5	88.2
APACHE II score	0.863	0.779–0.947	14.50	62.5	94.1
SOFA score	0.876	0.793–0.959	6.50	87.5	79.4
28-Day Mortality					
Lactate /Albumin($\times10^{-3}$)	0.881	0.807–0.956	62.58	73.3	89.7
Lactate	0.810	0.713–0.907	1.65	75.6	75.9
Albumin	0.638	0.509–0.766	28.57	51.1	72.4
APACHE II score	0.865	0.780–0.950	13.50	84.4	72.4
SOFA score	0.864	0.779–0.948	6.50	77.8	75.9

APACHE II score: Acute Physiology and Chronic Health Evaluation II score; SOFA score: Sequential Organ Failure Assessment score

outstanding AUC, promising sensitivity, and specificity in patients with influenza A virus pneumonia, and it was superior to lactate or albumin alone.

It is well known that ARDS can often lead to extrapulmonary multiple-organ dysfunction through mechanisms such as inflammation, stress, and hypoxia, all of which can lead to more lethal clinical outcomes [36]. Therefore, early identification and intervention of the ARDS-associated complications, as well as accurate evaluation of prognosis may help to improve the outcomes of patients with influenza A virus-induced ARDS. We found that in the high LAR ARDS patients, the percentage of invasive ventilation, septic shock, hepatic injury, and 28-day mortality were significantly higher than those in the low LAR group, and LAR level was closely correlated with disease severity and poor prognosis. We also assessed the predictive value of LAR in terms of prolonged invasive mechanical ventilation (≥14 days), septic shock, hepatic injury, and 28-day mortality. The results suggested that LAR had high predictive value in the above clinical events, presenting high sensitivity and specificity.

It has been reported that APACHE II and SOFA scores present significant association with ARDS development, and can be used to evaluate the disease severity and prognosis in critically ill patients [37, 38]. Consistent with previous findings, we confirmed that the APACHE II score was an independent risk factor for ARDS in our study. It is well known that the APACHE II score should be combined with multiple factors and this process can be time-consuming. Therefore, it is not applicable in emergencies or some departments with larger workloads. Interestingly, the LAR efficiency in our study was comparable to or even better than the APACHE II and SOFA scores in predicting ARDS in patients with influenza A virus infection. Furthermore, LAR also showed outstanding efficiency in predicting important clinical events in patients with ARDS. Thus, LAR has demonstrated superior efficacy as a simple and easily available clinical marker.

Some limitations should be mentioned in the present study. First, as with any single-center retrospective study, any findings in our study are hypothesis-generating only. Furthermore, the relatively small sample size in this study would limit the reliability and generalizability of findings. Additional prospective studies with large sample size are required to further evaluate the clinical significance of LAR in influenza. Second, the lack of an external validation cohort limits the strength of conclusions about the utility of LAR in influenza. Before any of these findings could be applied to clinical care, external validation is required. Despite these major limitations, our findings indicated a potential clinical application value of LAR in patients with influenza A virus infection.

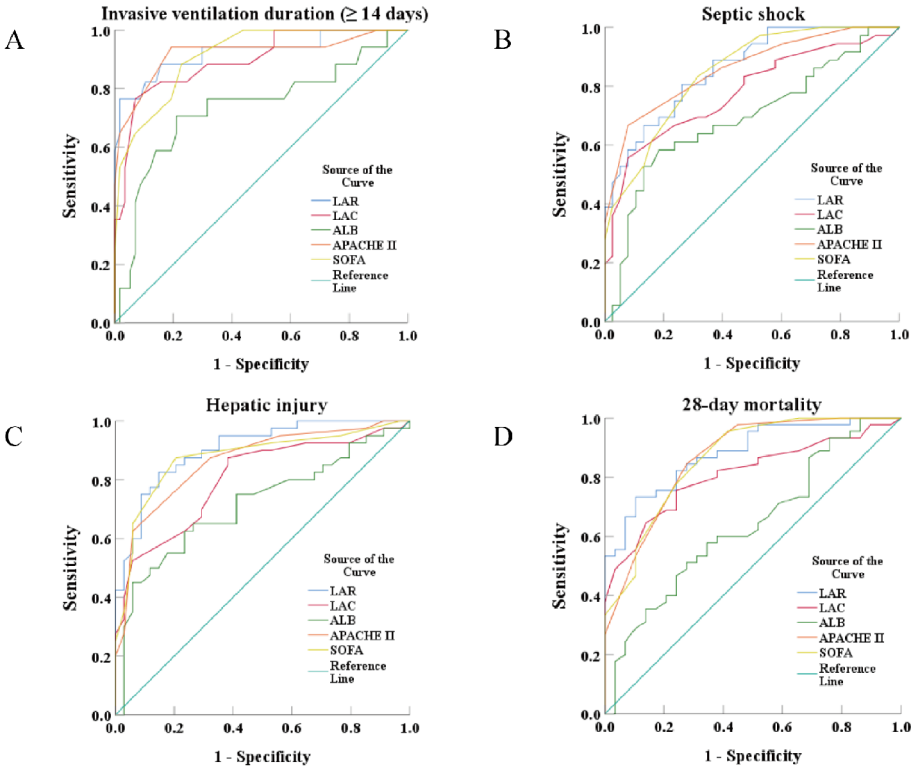

Fig. 6 LAR ROC curves are associated with predicted complications and prognosis in patients with ARDS. (**A**) ROC curves of LAR levels are associated with the prediction of invasive mechanical ventilation (14 days) in patients with ARDS. (**B**) LAR ROC curves are associated with the prediction of septic shock in patients with ARDS. (**C**) LAR ROC curves are associated with the prediction of hepatic injury in patients with ARDS. (**D**) LAR ROC curves are associated with the prediction of 28-day mortality in patients with ARDS

Conclusion

LAR was an independent risk factor for predicting the development of ARDS during hospitalization in patients with influenza A virus pneumonia and provided strong predictive efficacy in ARDS development. In addition, the level of LAR was closely associated with disease severity and poor outcomes. LAR also presented a promising predictive efficacy for invasive ventilation (≥14 days), septic shock, hepatic injury, and 28-day mortality in patients with influenza A virus-induced ARDS. With this evidence, we hope this study will provide a reference for other researchers to conduct further investigation on the value of LAR in patients with influenza A virus infection.

Abbreviations

ARDS	Acute respiratory distress syndrome
APACHE II	Acute Physiology and Chronic Health Evaluation II
SOFA	Sequential Organ Failure Assessment
LAR	Lactate-to-albumin ratio
PaO_2/FiO_2	The ratio of partial pressure of arterial oxygen and the concentration of inspired oxygen
WBC	White blood cell
NEU	Neutrophil
LYM	Lymphocyte
PLT	Platelet
Hs-CRP	Hypersensitive-C-Reactive Protein
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
HDL-C	High-density lipoprotein
LDL-C	Low-density lipoprotein
PT	Prothrombin time
APTT	Activated partial prothrombin time
LDH	Lactate dehydrogenase
CK	Creatine kinase. OR: Odds ratio
CI	Confidence interval
ROC	Receiver operating characteristics
AUC	Area under the curve

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Author contributions

All authors contributed to the content of this manuscript.Jinhui Gao, Xuanzhe Yang, Dapeng Wang, and Jiajia Wang participated in designing the framework of the dissertation, data collection, statistical analysis, and development of the graphs. In addition, Jinhui Gao, Ziyi Zhang, and Xiang Fang drafted the implementation of the dissertation research process and were responsible for dissertation revision. Finally, Jiajia Wang was responsible for formulating the manuscript ideas, guiding the writing of the article, and finalizing the document.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University, and informed consent was waived because this was a retrospective study. Further, we did not intervene in the diagnosis or treatment of patients in this retrospective study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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