

Original Article

Association of creatine kinase and arterial lactate upon admission with early ARDS exacerbation: a single-center retrospective ICU cohort study

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Abstract: Objective: To evaluate whether admission levels of creatine kinase (CK) and arterial lactate (LAC), two routinely available ICU biomarkers, are associated with early in-hospital exacerbation of acute respiratory distress syndrome (ARDS), and to assess their short-term discriminatory performance using a retrospective cohort. Methods: This single-center retrospective cohort study included 120 ARDS patients admitted to the ICU. Patients were divided into an exacerbation group and a non-exacerbation group according to whether ARDS worsened within 48 h after admission, with 60 patients in each group. CK, LAC, inflammatory markers, metabolic indices, and routine blood indices were measured at ICU admission and 24 h. Between-group comparisons, within-group dynamic comparisons, logistic regression, Spearman correlation analysis, and receiver operating characteristic curve analysis were performed. Results: CK and LAC levels were higher in the exacerbation group than in the non-exacerbation group at both 0 h and 24 h. In multivariable logistic regression, higher CK and LAC at ICU admission were independently associated with early ARDS exacerbation. The combined CK-LAC model yielded an AUC of 0.832. CK and LAC were also positively correlated with ICU length of stay and duration of mechanical ventilation. Routine inflammatory, metabolic, and blood routine indices showed limited between-group discriminative value. Conclusion: Higher admission CK and LAC levels were independently associated with early ARDS exacerbation. The combined assessment yielded a numerically higher AUC than either marker alone. However, the cut-off values were internally derived and require external validation before clinical application.

Keywords: Acute respiratory distress syndrome, creatine kinase, arterial lactate, exacerbation, intensive care unit

Introduction

Acute respiratory distress syndrome (ARDS) is frequently encountered in the intensive care unit (ICU). Its incidence among ICU inpatients has been reported to be approximately 10%-15%, and mortality rates range from 30% to 40% [1]. The clinical course may deteriorate rapidly, and marked heterogeneity is common. Early recognition of patients at risk of worsening and timely management adjustment are key priorities in ARDS care [2].

Creatine kinase (CK) is a readily available laboratory marker of systemic tissue injury, whereas arterial lactate (LAC) is routinely used to reflect tissue hypoperfusion and metabolic stress. Both are commonly measured in ICU practice and are included in routine critical

care assessment [3]. Previous studies suggest that CK and LAC may have value in ARDS monitoring [4, 5]. However, early between-group differences and short-term changes in these markers among patients with and without ARDS exacerbation have not been clearly described. Most published work has evaluated individual markers in relation to overall ARDS prognosis, whereas focused comparisons between exacerbation and non-exacerbation groups remain limited [6, 7]. In addition, routine inflammatory, metabolic, and complete routine blood indices have not been adequately compared in the setting of ARDS exacerbation [8]. As a result, routine laboratory results provide limited and inconsistent guidance for early risk stratification in clinical practice [9, 10]. Although CK and LAC have been studied in relation to critical illness severity and ARDS-related prognosis,

most available studies have focused on overall mortality, biomarker-based phenotyping, or late clinical outcomes rather than early in-hospital exacerbation [11-13]. The present study aimed to examine whether their admission values and early 24-hour changes may help identify patients with short-term ARDS worsening in routine ICU practice, rather than to redefine them as novel biomarkers. Therefore, we evaluated the CK-LAC combination as an exploratory two-marker risk-stratification approach rather than as a validated clinical prediction model or nomogram [14]. In this single-center retrospective cohort study, patients were classified into exacerbation and non-exacerbation groups according to whether ARDS worsened within 48 h after admission. CK, LAC, WBC, and other routine inflammatory, metabolic, and routine blood indices were collected at ICU admission (0 h) and 24 h. Between-group differences were examined, and associations with ICU length of stay and duration of mechanical ventilation were analyzed. Regression analysis was performed to identify factors independently associated with ARDS exacerbation, and receiver operating characteristic curve analysis was used to evaluate the exploratory discriminative performance of key indicators.

Materials and methods

Study design

This was a single-center retrospective cohort study. Clinical records, laboratory test results, and outcome follow-up data were retrospectively collected for ARDS patients admitted to the ICU of the Department of Emergency and Critical Care Medicine, the Second Affiliated Hospital of Soochow University, from January 2020 to December 2025. The study protocol was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Soochow University (Approval No.: JD-HG-2026-045), and informed consent was waived because of the retrospective design. Multivariable binary logistic regression was used to assess the associations of admission CK and LAC with early ARDS exacerbation. Residual confounding and selection bias could not be fully eliminated.

Inclusion and exclusion criteria

Inclusion criteria: (1) Adult patients aged ≥ 18 years; (2) Clinically diagnosed with ARDS ac-

cording to the Berlin definition at the time of ICU admission [15]; (3) Remained alive for more than 48 hours after ICU admission, with complete laboratory results at 0 h and 24 h after ICU admission; (4) No pre-ICU factors likely to influence CK levels, such as strenuous exercise, rhabdomyolysis, or severe skeletal muscle injury.

Exclusion criteria: (1) Pre-existing severe cardiac, hepatic, or renal dysfunctions meeting diagnostic criteria for organ failure; (2) Primary immunodeficiency, hematologic disease, malignant tumor, or other major underlying diseases; (3) Pregnant or lactating women; (4) Death within 48 hours after ICU admission, making completion of clinical assessment and data collection impossible; (5) Interrupted diagnostic and treatment records or missing outcome data due to treatment withdrawal, transfer, or other reasons; (6) Unqualified specimen collection, procedural errors during testing, or results judged to be unreliable and not suitable for statistical analysis; (7) Other severe acute or chronic diseases that could interfere with assessment of ARDS severity or evaluation of outcomes.

Study subjects

After screening, 60 patients with ARDS exacerbation (ARDS exacerbation group) were included. ARDS exacerbation was defined as progression from mild to moderate or severe, or from moderate to severe, within 48 hours after ICU admission. The non-exacerbation group included 60 ARDS patients without exacerbation. Standardized mean differences were calculated to describe baseline differences between the groups. In the non-exacerbation group, severity improved or remained stable within 48 hours after ICU admission. Group assignment was independently determined by two senior intensivists using complete data, including clinical manifestations, oxygenation indices, and imaging findings. Disagreements were resolved through departmental discussion, and the final decision was recorded.

Observation indicators

Baseline variables at ICU admission (0 h) were collected, including demographics, disease severity scores, respiratory support and comorbidities, which were used for baseline com-

parison. Creatine kinase levels were recorded at 0 h and 24 h after ICU admission. Routine inflammatory markers (WBC, CRP, and PCT), metabolic markers (LAC, ALB, and Scr), and hematological indicators (Hb, LYMPH, and PLT) were collected at 0 h and 24 h. Clinical outcomes and short-term disease-progression indicators were collected, including ICU length of stay, duration of mechanical ventilation, occurrence of multiple organ failure within 48 hours after ICU admission, and respiratory support modality during early ICU care. Multiple organ failure was defined as at least two organ systems each having a SOFA component score of ≥ 3 [16], assessed within the first 48 hours after ICU admission. The 48-hour window applied to ARDS exacerbation classification and assessment of multiple organ failure. Patients were followed from ICU admission until ICU discharge or death, whichever occurred first, to ascertain ICU length of stay and duration of mechanical ventilation. Duration of mechanical ventilation included both invasive and noninvasive ventilation; high-flow nasal oxygen therapy was not counted as mechanical ventilation. Respiratory support modality was considered as an available treatment-related covariate. Detailed data on glucocorticoid exposure and anti-infective treatment strategy were not sufficiently extractable from the structured dataset and were therefore addressed as unmeasured treatment-related confounders in the limitations. Standard binary logistic regression analysis was performed in the study cohort, with ARDS exacerbation as the dependent variable. Variables with $P < 0.10$ in univariate analyses were entered into the multivariable model as independent variables. Receiver operating characteristic (ROC) curves were constructed to evaluate the exploratory discriminative performance of individual indicators and their combinations for early ARDS exacerbation. For the combined CK-LAC assessment, predicted probabilities were generated from the multivariable logistic regression model and then entered into ROC analysis. This model was considered exploratory and internally derived; no nomogram was constructed owing to the limited sample size and lack of an external validation. ARDS etiology was not available with sufficient completeness in the extracted structured dataset. Therefore, etiology-specific subgroup models were not constructed, and this issue was addressed as a limitation.

Data collection

All data were extracted from the electronic medical record system, laboratory information system, and ICU clinical documentation. Two trained researchers independently extracted data and entered them into an Excel database according to a standardized procedure. After entry, all records were cross-checked; discrepancies were verified and corrected by reviewing original paper records, official laboratory reports, and ICU nursing documentation to ensure data accuracy and consistency.

Statistical methods

SPSS version 23.0 was used for statistical analysis. No a priori sample size calculation was performed, as this was a retrospective analysis of available eligible cases. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as mean $\pm$ standard deviation (SD) and compared between the exacerbation and non-exacerbation groups using the independent-samples t-test. Paired t-tests were used to compare 0 h and 24 h values within the same group. Categorical variables were expressed as number and percentage and compared using the chi-square test or Fisher's exact test when expected cell counts were small.

Standard binary logistic regression was performed with early ARDS exacerbation as the dependent variable (0 = non-exacerbation, 1 = exacerbation). The final multivariable model included admission CK (per 1 U/L) and LAC (per 1 mmol/L). Regression coefficients, standard errors, Wald statistics, odds ratios, and 95% confidence intervals were reported. Standardized mean differences were calculated to describe baseline differences between the groups. Absolute SMDs for continuous variables were calculated using the pooled group standard deviation. For binary variables, SMDs were calculated as the absolute difference in proportions divided by the square root of the mean of the two group-specific Bernoulli variances.

ROC curves were constructed to evaluate the discriminative performance of CK, LAC, and their combination for early ARDS exacerbation. For the combined model, predicted probabilities from the multivariable logistic regression

Table 1. Baseline characteristics of ARDS patients in the non-exacerbation group and exacerbation group

	Non-exacerbation group	Exacerbation group	t or χ^2	P	SMD
Gender, male/female	49/11	51/9	0.240	0.624	0.081
Age (years)	51.68±11.23	53.90±15.94	0.880	0.380	0.161
BMI (kg/m ²)	21.15±2.63	21.04±2.25	0.249	0.804	0.045
APACHE II	12.47±3.35	13.17±3.76	1.078	0.283	0.197
SOFA	5.55±2.22	5.72±1.79	0.453	0.651	0.083
Oxygenation index (mmHg)	231.70±53.91	241.47±72.15	0.84	0.403	0.153
Respiratory support, noninvasive ventilation/high-flow	32/28	29/31	0.300	0.584	0.100
Smoking, yes/no	22/38	25/35	0.315	0.575	0.102

Note: ARDS, acute respiratory distress syndrome; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; SMD, standardized mean difference; SD, standard deviation.

Table 2. Comparison of creatine kinase (CK) levels at 0 h and 24 h after ICU admission between the two groups

	0 h (U/L)	24 h (U/L)	t	P
Non-exacerbation group	75.05±24.26	45.69±9.66	8.712	<0.001†
Exacerbation group	93.91±15.48	65.66±11.49	11.351	<0.001†
t	5.075	10.313		
P	<0.001*	<0.001*		

Note: CK, creatine kinase; ICU, intensive care unit; h, hours; U/L, units per liter; SD, standard deviation. *Between-group comparisons using independent-sample t tests. †Within-group comparisons using paired t tests.

model were used for ROC analysis. The area under the curve (AUC) with 95% confidence interval (CI) was calculated. Optimal cut-off values were determined using the Youden index, and sensitivity, specificity, positive predictive value, and negative predictive value were calculated. As multiple comparisons were exploratory, *P* values were interpreted cautiously. A two-sided *P* value <0.05 was considered statistically significant.

Results

Comparison of baseline data between the two groups

Baseline variables at ICU admission were comparable between the two groups, with no statistically significant differences (*P*>0.05) (Table 1).

Dynamic comparison of CK levels

CK levels differed significantly between the two groups at both 0 h and 24 h after ICU admission (*P*<0.05). At 0 h, CK was 93.91±15.48 U/L in the exacerbation group and 75.05±

24.26 U/L in the non-exacerbation group. At 24 h, CK decreased to 65.66±11.49 U/L in the exacerbation group but remained higher than that in the non-exacerbation group (45.69±9.66 U/L) (Table 2).

Comparison of routine inflammatory indicators

WBC, CRP, and PCT showed no significant between-group differences at either 0 h or 24 h (*P*>0.05). However, within-group comparisons showed that WBC, CRP, and PCT decreased significantly from 0 h to 24 h in both groups (*P*<0.001). However, these trajectories did not distinguish patients with subsequent ARDS exacerbation from those without exacerbation (Figure 1).

Comparison of metabolic indicators

LAC was higher in the exacerbation group than in the non-exacerbation group at both 0 h and 24 h (both *P*<0.001). In the exacerbation group, LAC increased significantly from 0 h to 24 h (*P*<0.001), whereas the non-exacerbation group showed no significant change over time

CK and lactate as early predictors of ARDS exacerbation

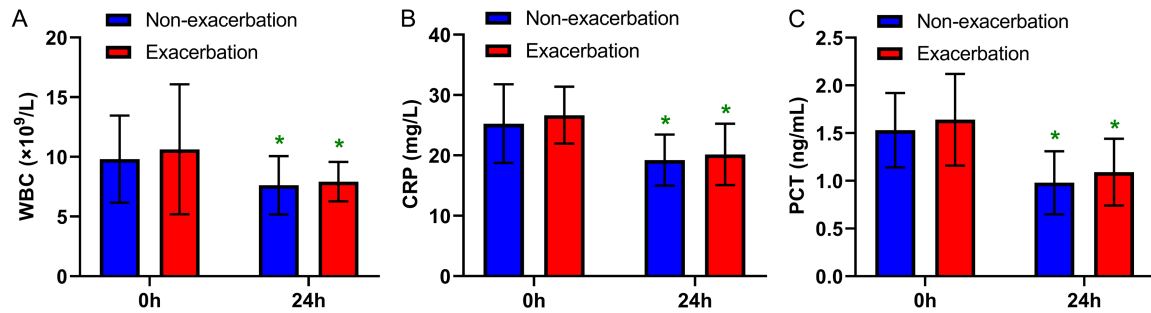


Figure 1. Routine inflammatory markers at ICU admission (0 h) and 24 h in the exacerbation and non-exacerbation groups. A. WBC. B. CRP. C. PCT. Note: ICU, intensive care unit; h, hours; WBC, white blood cell count; CRP, C-reactive protein; PCT, procalcitonin. Bars and error bars represent means and SDs, respectively (n=60 per group). *P<0.001 versus 0 h within the same group (paired t-test).

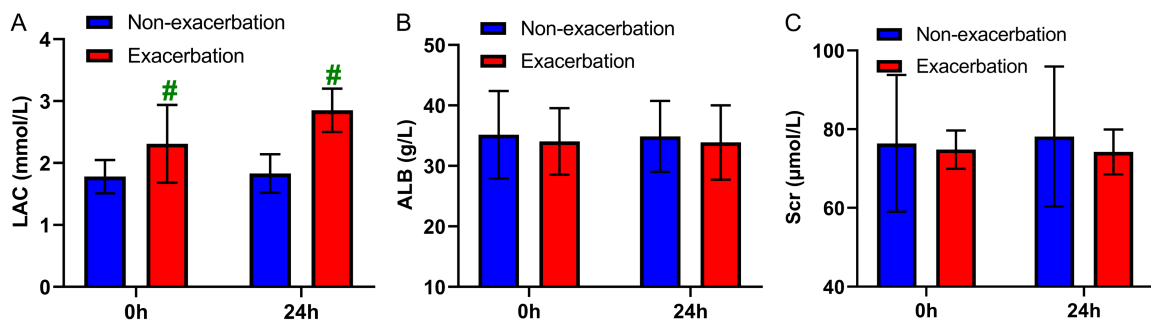


Figure 2. Metabolic indicators at ICU admission (0 h) and 24 h in the exacerbation and non-exacerbation groups. A. LAC. B. ALB. C. Scr. Note: ICU, intensive care unit; h, hours; LAC, arterial lactate; ALB, albumin; Scr, serum creatinine. Bars and error bars represent means and SDs, respectively (n=60 per group). #P<0.001 versus the non-exacerbation group at the same time point (independent-samples t-test).

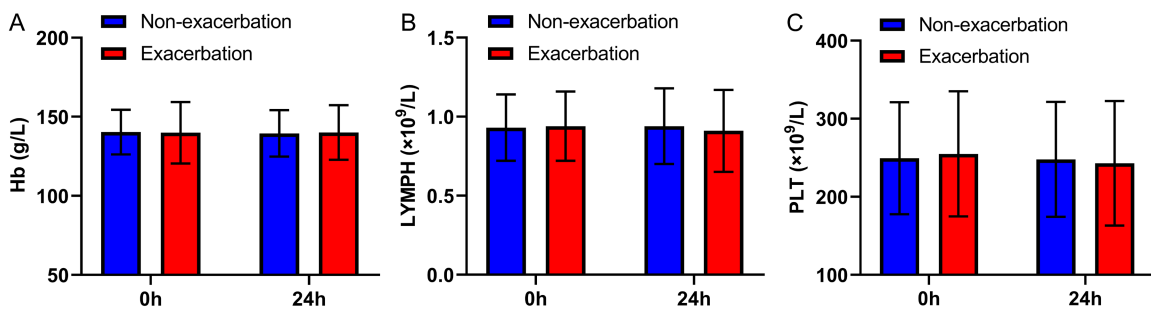


Figure 3. Routine blood indices at ICU admission (0 h) and 24 h in the exacerbation and non-exacerbation groups. A. Hb. B. LYMPH. C. PLT. Note: ICU, intensive care unit; h, hours; Hb, hemoglobin; LYMPH, lymphocyte count; PLT, platelet count. Bars and error bars represent means and SDs, respectively (n=60 per group).

(P=0.371). ALB and Scr did not differ significantly between groups at either time point and showed no significant within-group changes from 0 h to 24 h (all P>0.05) (Figure 2).

Comparison of routine blood indicators

Hb, LYMPH, and PLT did not differ between groups at 0 h or 24 h (P>0.05). No significant

within-group changes were observed from 0 h to 24 h (P>0.05) (Figure 3).

Comparison of clinical outcomes

ICU length of stay was longer in the exacerbation group than in the non-exacerbation group (15.80 ± 4.93 d vs 11.35 ± 3.19 d, P<0.001). Duration of mechanical ventilation was also

CK and lactate as early predictors of ARDS exacerbation

Table 3. Comparison of clinical outcomes between the exacerbation and non-exacerbation groups

	ICU length of stay (d)	Mechanical ventilation duration (d)	Multiple organ failure (n; %)
Non-exacerbation group	11.35±3.19	7.47±1.63	10 (16.67%)
Exacerbation group	15.80±4.93	12.37±4.19	22 (36.67%)
t or χ^2	5.875	8.434	6.136
P	<0.001	<0.001	0.013

Note: ICU, intensive care unit; d, days; SD, standard deviation.

Table 4. Multivariable logistic regression analysis of factors associated with early ARDS exacerbation in the retrospective cohort

	B	S.E.	Wald	P	OR	95% CI
CK (per 1 U/L)	0.0467	0.0131	12.607	<0.001	1.048	1.021-1.075
LAC (per 1 mmol/L)	2.277	0.555	16.853	<0.001	9.750	3.287-28.919
Constant	-8.532	1.662	26.344	<0.001	-	-

Note: ARDS, acute respiratory distress syndrome; CK, creatine kinase; LAC, arterial lactate; S.E., standard error; OR, odds ratio; CI, confidence interval; U/L, units per liter; mmol/L, millimoles per liter.

longer in the exacerbation group (12.37±4.19 d vs 7.47±1.63 d, $P<0.001$). Multiple organ failure occurred in 22 patients (36.67%) in the exacerbation group and in 10 patients (16.67%) in the non-exacerbation group, and this difference was statistically significant ($P=0.013$) (Table 3).

Associations of CK and LAC with short-term clinical progression

Spearman correlation analysis showed that admission CK was positively correlated with duration of mechanical ventilation ($r=0.293$, $P=0.001$) and ICU length of stay ($r=0.276$, $P=0.002$). Admission LAC was also positively correlated with duration of mechanical ventilation ($r=0.242$, $P=0.008$) and ICU length of stay ($r=0.239$, $P=0.009$). These results suggest that elevated CK and LAC were not only associated with early ARDS exacerbation but also related to greater short-term clinical burden.

Regression analysis of risk factors for ARDS exacerbation

ARDS exacerbation was coded as the dependent variable (0 = non-exacerbation, 1 = exacerbation). Standard binary logistic regression analysis was performed in the study cohort. Variables with clinical relevance and those with $P<0.10$ in univariate analysis were entered into the multivariable model. Higher creatine kinase at ICU admission and higher arterial lactate were independently associated with

ARDS exacerbation. For every 1 U/L increase in CK, the odds of ARDS exacerbation increased by about 4.8% (OR=1.048, 95% CI: 1.021-1.075, $P<0.001$). For every 1 mmol/L increase in LAC, the odds of ARDS exacerbation were 9.75-fold higher (OR=9.750, 95% CI: 3.287-28.919, $P<0.001$) (Table 4).

ROC curve analysis for predicting ARDS exacerbation

At 0 h, CK showed an AUC of 0.745 (95% CI: 0.656-0.835), with a cut-off value of >83.64 U/L, sensitivity 80.00%, and specificity 66.67%. LAC showed an AUC of 0.761 (95% CI: 0.670-0.852), with a cut-off value of >2.26 mmol/L, sensitivity was 55.00% and specificity was 96.67%. Combining CK and LAC using predicted probabilities from the logistic regression model increased the AUC to 0.832 (95% CI: 0.762-0.902), with a predicted-probability cut-off of >0.638, sensitivity of 61.67%, and specificity of 88.33%. Because these values were derived from the same retrospective cohort, they should be considered internally derived and require external validation (Figure 4).

Discussion

The results of this study showed that CK and LAC at ICU admission were independently associated with ARDS exacerbation, and that the combined model yielded a numerically higher AUC than either marker alone. By contrast, routine inflammatory indices, routine

CK and lactate as early predictors of ARDS exacerbation

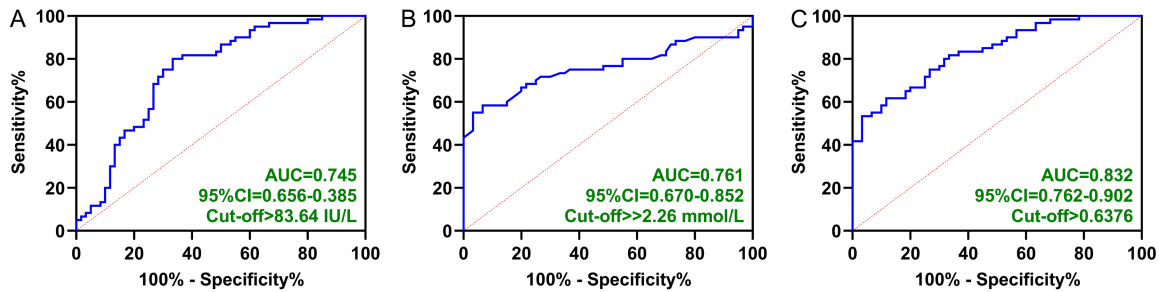


Figure 4. ROC curves for predicting ARDS exacerbation within 48 hours after ICU admission. A. CK at 0 h. B. LAC at 0 h. C. Combined CK-LAC model based on predicted probabilities from multivariable logistic regression, the cut-off in panel C refers to the predicted probability threshold rather than a biomarker concentration. Note: ROC, receiver operating characteristic; ARDS, acute respiratory distress syndrome; CK, creatine kinase; LAC, arterial lactate; AUC, area under the curve; CI, confidence interval; h, hours.

blood parameters, and metabolic indicators such as ALB and Scr did not differ between the exacerbation and non-exacerbation groups. These findings should be interpreted as evidence of short-term association and exploratory discrimination rather than as validation of a mature clinical prediction model. This cautious interpretation is consistent with previous ARDS biomarker research, which emphasizes the need for external validation, clinical-context integration, and phenotype-aware interpretation before bedside application [9, 10, 13]. The study primarily focused on early ICU admission and 24-hour biomarker patterns in patients with and without rapid ARDS worsening, rather than on long-term mortality alone.

CK is a commonly used marker of tissue injury, and higher levels are often observed in patient with greater illness severity [17, 18]. In ARDS, systemic inflammation, oxidative stress, and microcirculatory impairment may contribute to multi-organ tissue injury, including skeletal muscle damage, leading to CK release [19]. Tissue injury and breakdown products may further amplify inflammation and tissue edema, which could accelerate clinical deterioration [20]. Compared with earlier studies [21, 22], this analysis directly compared patients with and without ARDS exacerbation and evaluated CK at two early time points (0 h and 24 h), rather than relying on a single measurement.

LAC was also associated with early ARDS worsening, consistent with the established link between lactate kinetics and sepsis-related ARDS [11, 12]. LAC levels were higher in the exacerbation group at both 0 h and 24 h, and

elevated LAC at 0 h remained independently associated with exacerbation, consistent with the findings of Jose JM et al. [23]. Impaired gas exchange in ARDS leads to hypoxemia, while increased vascular permeability and reduced effective circulating volume can further impair tissue perfusion, enhance anaerobic glycolysis, and increase lactate production [24]. Lactate accumulation may contribute to endothelial injury and aggravate lung damage [25]. In this cohort, the AUC for LAC was numerically higher than that for CK (0.761 vs 0.745; absolute difference, 0.015). This may reflect the influence of concurrent factors in ICU patients, such as infection burden and renal dysfunction [26], whereas CK may more directly reflect the extent of tissue injury [27]. The combined assessment yielded a numerically higher AUC (0.832) than CK (0.745) or LAC (0.761) alone. Prior work has often examined single biomarkers or biomarker panels for ARDS prognosis, but their clinical implementation remains limited by disease heterogeneity, treatment variability, and the need for validation in independent cohorts [9, 10, 13]. These findings describe the exploratory discrimination of the combined assessment, but do not validate a clinical prediction model. The association between elevated CK/LAC and subsequent clinical course should also be interpreted in the context of treatment intensity and disease severity. In the present cohort, admission CK and LAC were positively correlated with ICU length of stay and duration of mechanical ventilation. These findings suggest that early elevations in CK and LAC may reflect a broader state of tissue injury, hypoxemia, and microcirculatory stress accompanying rapid

clinical deterioration. However, this retrospective analysis could not determine whether CK and LAC directly influenced treatment decisions or merely reflected disease severity before treatment escalation. Prospective studies with standardized treatment protocols are needed to clarify whether serial CK and LAC monitoring can guide ventilation adjustment, anti-inflammatory therapy, or other ICU interventions [11, 12].

Routine inflammatory markers (WBC, CRP, and PCT) did not differ between groups, which contrasts with some previous reports [28, 29]. The short observation window in this study (0 h and 24 h) may partly explain the finding, as inflammatory trajectories may not have diverged within this short timeframe. ARDS is heterogeneous, and inflammatory intensity varies by etiology, host response, and biological sub-phenotype, which can obscure between-group differences in routine inflammatory markers [10, 13, 30]. Standardized anti-infective and anti-inflammatory treatment after ICU admission may also have attenuated early changes in these indices.

Hb, LYMPH, and PLT also showed no between-group differences, suggesting limited value for early identification of exacerbation risk, which aligns with the findings of Harbiye A et al. [31]. These indices reflect hematopoietic status and broader immune conditions, whereas early ARDS worsening is more directly related to progression of lung injury, hypoxia, and microcirculatory disturbance. The similar LYMPH values observed in this cohort may also relate to sample size and relatively balanced baseline immune status, and should be reassessed in larger studies.

ALB and Scr were also similar between groups. This suggests that early changes in protein status and renal function did not correlate with early exacerbation in this cohort. Comparable ALB levels may reflect early nutritional support and the short time frame before severe catabolism or pronounced capillary leak becomes evident. The absence of a difference in Scr may indicate that renal dysfunction more often develops later, rather than serving as an early marker of worsening.

Several limitations of this work should be noted. First, this was a retrospective single-

center study with 120 patients, which limits statistical power and external generalizability. Selection bias and residual confounding remain possible. The primary regression model included CK and LAC, and did not adjust for all potential confounders. In particular, the study included only patients who survived for more than 48 hours after ICU admission. Exclusion of patients who died within this period may have introduced selection bias; the direction of its effect on the observed associations and discriminatory performance cannot be determined. The findings therefore apply to this selected population and should not be generalized to all patients with ARDS at ICU admission. Second, no a priori sample size calculation was performed, and multiple laboratory indicators were compared in an exploratory manner. Therefore, the risk of random errors and type I errors cannot be excluded. Third, ARDS etiology was not completely available, preventing subgroup analyses by etiology. This is important because ARDS is clinically and biologically heterogeneous, and biomarker associations may differ across sub-phenotypes [13, 30]. Fourth, treatment-related factors, including glucocorticoid exposure and anti-infective treatment strategy, may have influenced biomarker trajectories and clinical outcomes, but these variables could not be completely controlled because of the retrospective data structure. Residual treatment-related confounding may remain. Fifth, outcomes were limited to in-hospital short-term exacerbation and ICU outcomes; post-discharge pulmonary function, readmission, and long-term survival were not available, precluding assessment of long-term prognostic value of CK and LAC. Previous studies have shown that lactate trajectories and biomarker-based models may be associated with short-term or longer-term outcomes in critically ill patients and ARDS-related cohorts, which supports the need for further follow-up studies [11, 12, 32]. Finally, the combined CK-LAC model and cut-off values were internally derived and were not validated in an external cohort. Its exploratory DeLong comparisons with single biomarkers did not account adequately for same-sample fitting of nested models and cannot establish incremental predictive value. No exploratory pairwise comparison had a Holm-adjusted *P* value below 0.05. Future multicenter prospective studies should validate

model calibration, cut-off stability, and clinical usefulness before bedside application [14].

Conclusion

Admission CK and LAC were independently associated with early ARDS exacerbation in this retrospective ICU cohort. Their combined assessment yielded a numerically higher AUC than either marker alone, and both markers were positively correlated with short-term clinical outcomes, including ICU length of stay and duration of mechanical ventilation. Routine inflammatory markers, hematological parameters, and metabolic indicators such as ALB and Scr did not distinguish exacerbation risk in this cohort. Further multicenter prospective studies with independent validation cohorts are needed to verify the stability, calibration, and clinical usefulness of the CK-LAC model and its cut-off values.

Disclosure of conflict of interest

None.

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