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ORIGINAL RESEARCH

Dynamic Immune Indicator Changes as Predictors of ARDS in ICU Patients with Sepsis: A Retrospective Study

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Video abstract

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Background: Understanding the dynamic changes in immune indicators during sepsis and their predictive value for Acute respiratory distress syndrome (ARDS) is crucial for improving patient outcomes.

Methods: This single-center, observational retrospective study was conducted at Lishui Central Hospital, Zhejiang Province. Patients diagnosed with Sepsis-3 were categorized into non-ARDS and ARDS groups based on ARDS development. Data collection included demographics, clinical data, and immune parameters. Immune parameters were collected on days 1, 3, and 7 post-admission. Multivariate logistic regression analysis identified independent risk factors for ARDS, and a nomogram model was constructed. The predictive ability of the model was evaluated using ROC curves.

Results: Multivariate analysis identified key factors for the nomogram, including CD4, CD8, Treg, lymphocyte, IgG, and IgA levels on Days 3 and 7. On Day 3, CD8 ($P < 0.001$), Tregs ($P = 0.021$), IgG ($P < 0.001$), and IgA ($P < 0.001$) showed significant negative correlations with ARDS development. On Day 7, CD4 ($P < 0.001$), CD8 ($P < 0.001$), lymphocyte count ($P < 0.001$), and IgA ($P < 0.001$) similarly demonstrated significant negative correlations with ARDS risk. The nomogram model had an AUC of 0.998 (95% CI: 0.997–0.999), indicating high predictive ability.

Conclusion: Early dynamic changes in immune indicators, including CD8, CD4, Treg, IgA, IgG, and Lymphocyte, predict ARDS development in ICU sepsis patients.

Keywords: sepsis, acute respiratory distress syndrome, immune indicator dynamics, nomograph, intensive care unit

Introduction

Sepsis, a systemic inflammatory response syndrome caused by infection, is a significant challenge in critical care medicine.[1] Despite continuous advancements in medical technology, sepsis remains associated with high morbidity and mortality rates.[2] Statistics indicate that there are approximately 30 million new cases of sepsis globally each year, with up to 6 million patients ultimately succumbing to sepsis-related complications.[3] Sepsis triggers a cascade of pathophysiological events, involving both excessive inflammation and subsequent immune suppression, resulting in tissue injury and multi-organ dysfunction.[4] Within this continuum of immune dysregulation, the progression to acute respiratory distress syndrome (ARDS) represents a severe and common complication that significantly exacerbates patient outcomes.[5] ARDS is a clinically defined syndrome characterized by acute-onset hypoxemic respiratory failure and bilateral lung infiltrates in the absence of cardiogenic causes. In sepsis, ARDS develops as a direct consequence of systemic inflammation, with immune responses targeting pulmonary tissues and causing endothelial and alveolar damage.[6] The progression from systemic sepsis to localized lung injury involves both innate and adaptive immune systems, with excessive neutrophil recruitment, release of pro-inflammatory cytokines such as IL-6 and TNF-alpha, and

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activation of macrophages as key drivers of pulmonary inflammation.[7] These processes illustrate the critical link between sepsis-induced immune dysregulation and ARDS.

During early sepsis, innate immune responses dominate, with activated neutrophils and macrophages producing reactive oxygen species and releasing cytokines such as IL-1, IL-8, and IL-10. While these responses are initially aimed at pathogen clearance, dysregulation often leads to collateral tissue damage and systemic inflammation. In later stages, adaptive immunity comes into play, with T-cell exhaustion and dysregulated B-cell function contributing to immunosuppression.[8] These fluctuating immune states underline the complex, dynamic interplay of immune responses that shapes the clinical trajectory of septic patients. Recent studies indicate that sepsis is the leading extrapulmonary cause of ARDS, accounting for approximately 32% of ARDS cases. Sepsis-induced ARDS tends to be more severe than ARDS caused by other factors, resulting in a higher mortality rate of 30% to 40%.[9] The immunological mechanisms of sepsis-induced ARDS are closely related to the pathogenesis of sepsis itself, involving excessive activation of inflammatory signaling pathways and cytokines, immune cell activation, and interactions between coagulation and complement systems. Sepsis induces lung inflammation and injury by disrupting vascular endothelium, with endothelial cell activation promoting the accumulation of inflammatory cells and the secretion of inflammatory factors.[10] During sepsis, pro-inflammatory cytokines such as IL-1β and IL-6 are elevated.[11] Elevated plasma IL-6 levels in critically ill septic patients are associated with an increased risk of acute lung injury (ALI) and multiple organ dysfunction syndrome (MODS), as ALI may progress to ARDS and contribute to MODS development.[12] Compared to plasma from septic patients without ARDS and healthy controls, plasma from septic patients with ARDS shows further increases in IL-6 and sICAM-1 levels, providing proof of concept that lung endothelial microphysiological systems contribute to mechanisms of endothelial dysfunction in ARDS among sepsis patients.[13] Additionally, TNF-alpha is a critical mediator of inflammation in ARDS. Increased TNF-alpha concentrations during lung injury destabilize endothelial VE-cadherin bonds, leading to endothelial dysfunction. The alveolar epithelial barrier, the endothelial counterpart, is also affected by elevated inflammatory markers, resulting in alveolar rupture and pulmonary edema formation.[14] These findings underscore the pivotal role of immune in the progression from sepsis to ARDS, highlighting the need for dynamic monitoring of immune responses to better predict and manage ARDS risk in septic patients.

Despite extensive research on sepsis and ARDS, studies examining the continuous and dynamic changes in immune cells over time among septic patients at risk of ARDS remain scarce. Most prior studies have focused on static immune markers at single time points, overlooking the temporal patterns of immune changes that might offer greater predictive value for ARDS progression. Dynamic monitoring can capture time-dependent immune variations often missed in traditional cross-sectional studies, providing more precise insights into ARDS risk prediction. Therefore, this study aims to analyze the dynamic changes in immune cells in septic patients who develop ARDS, with an emphasis on the temporal patterns of key immune markers such as neutrophils, monocytes, and lymphocyte subsets. This research fills a gap in understanding the evolution of immune responses in sepsis and ARDS and provides a framework for integrating immune dynamics into risk prediction and therapeutic strategies.

Methods

Study Design

This study was a single-center, observational retrospective study. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Lishui Central Hospital, Zhejiang Province (approval number: 2019–177).

Study Subjects

Patients with sepsis admitted to the ICU of Lishui Central Hospital in Zhejiang Province between January 2016 and December 2023.[15] The diagnosis of ARDS was based on the Berlin definition.[16] Patients were divided into non-ARDS and ARDS groups based on whether ARDS occurred after ICU admission for sepsis. Informed consent signed by the patient's guardian or authorized representative.

Inclusion Criteria

1. Age ≥ 18 years.

2. Patients diagnosed with sepsis according to the Sepsis-3 criteria.
3. The duration of stay in ICU was expected to exceed 7 days.
4. Sequential Organ Failure Assessment (SOFA) score ≥ 2.
5. The patient's guardian or designated authorizer signed the informed consent.

Exclusion Criteria

1. Pregnant or lactating women.
2. History of immunosuppressive diseases (such as HIV infection, organ transplantation, long-term use of immunosuppressive agents, etc).
3. Severe chronic diseases (such as advanced malignant tumors, severe liver or kidney dysfunction, etc).
4. Patients allergic to or intolerant of the procedures during the study process.

Data Collection

Demographic and clinical data were collected from standardized sources, including electronic health records. A data extraction protocol was developed to ensure consistency and accuracy in data collection, which involved two independent reviewers cross-checking the extracted data to minimize errors. The collected variables included:

Demographic data: Age, gender, body mass index (BMI), duration of ICU stay, length of hospital stay, complications (pancreatitis, respiratory failure, heart failure, acute kidney injury, septic shock, secondary infection), site of infection, and medical history (hypertension, diabetes, liver disease, kidney disease, and COPD).

Clinical data: SOFA score at ICU admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, temperature, respiratory rate, heart rate, PaO_2/FiO_2 ratio, hemoglobin level, white blood cell count (WBC), C-reactive protein (CRP), and procalcitonin (PCT).

Immune parameters: Venous blood samples were collected on the first, third, and seventh days after admission. Flow cytometry was used to analyze major immune cell subsets (neutrophil, lymphocyte, treg, CD4+, CD8+). Serum protein electrophoresis was used to detect changes in immunoglobulin levels (IgG and IgA). These specific days were chosen to capture the early, middle, and later phases of the immune response during the acute phase of sepsis and potential development of ARDS. Day 1 represented the initial immune response, day 3 captured the early adaptive immune response, and day 7 reflected more prolonged immune changes and the body's ongoing response to infection and inflammation.

Data Preprocessing

Prior to analysis, data cleaning procedures were conducted to enhance the accuracy and consistency of the dataset. Specifically: (1) Handling Missing Values: Variables with more than 30% missing data were excluded from the analysis. For variables with less than 30% missing data, multiple imputation techniques were applied to preserve the integrity of the dataset. (2) Outlier Management: Outliers were identified and excluded if they exceeded three times the interquartile range.

Statistical Analysis

All statistical analyses were performed using SPSS 26.0 software. Continuous variables conforming to a normal distribution are expressed as mean ± standard deviation (Mean±SD), while those not conforming are represented by median (Q25, Q75). Categorical data are presented as frequency and percentage [n (%)]. For inter-group comparisons, parametric data conforming to a normal distribution are analyzed using Student's *t*-test or one-way analysis of variance (ANOVA), whereas non-parametric data are analyzed using the Mann–Whitney *U*-test. Categorical data are analyzed using the chi-square test or Fisher's exact test. $P < 0.05$ was considered statistically significant.

To control for confounding factors, both univariate and multivariate analyses were conducted. Variables with a $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis. This step ensured that only significant variables were considered, reducing the risk of overfitting. Multivariate analysis was performed to identify independent risk factors for the development of ARDS in sepsis patients. A logistic regression model was constructed

using these selected significant variables, and a nomogram was developed based on the model. The receiver operating characteristic (ROC) curve was plotted to evaluate the predictive ability of the model for predicting the occurrence of ARDS in sepsis patients.

Results

Baseline Characteristics of the Subjects

1836 participants were eventually included in the study. Figure 1 illustrated the recruitment process of patients. Table 1 presented the baseline characteristics of enrolled patients. Among all included patients, there were 402 cases (21.90%) of sepsis patients with ARDS and 1434 cases (78.10%) without ARDS.

Comparison of Immune-Related Indicators

Comparison of immune-related indicators between the two groups of patients showed no significant differences on the first day. However, on the third and seventh days, compared with the non-ARDS group, patients in the ARDS group exhibited significantly decreased counts of CD4, CD8, Treg, IgG, and IgA, and significantly decreased lymphocyte count on the seventh day. Conversely, neutrophil counts showed a significant increase on the third and seventh days. See Figure 2.

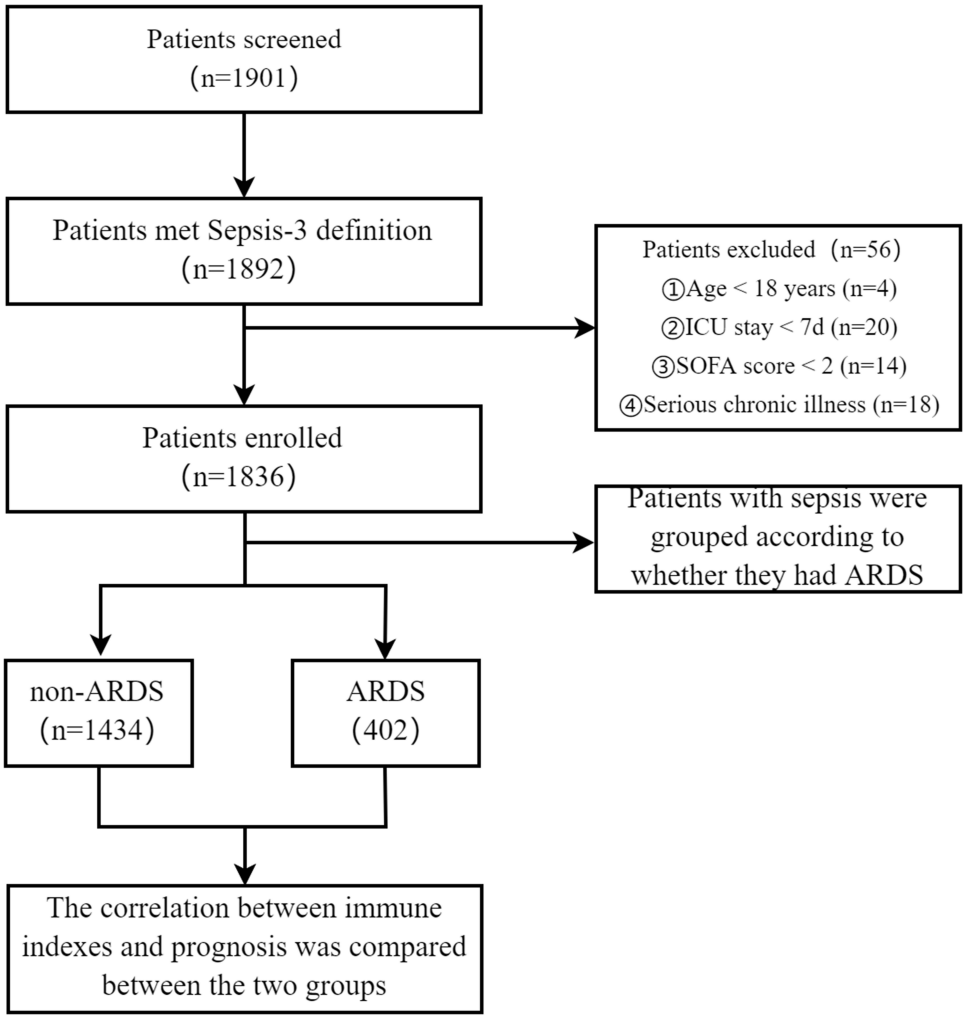

Figure 1 Study flow chart.

Table 1 Baseline Characteristics

Variables	Category	All (n=1836)	Non-ARDS (n=1434)	ARDS (n=402)	p
Demographic data					
Gender, n (%)	Female	815(44.390)	630(43.933)	185(46.020)	0.457
	Male	1021(55.610)	804(56.067)	217(53.980)	
Age, median [IQR]	-	64.000[57.000,70.000]	64.000[57.000,71.000]	63.000[55.000,70.000]	0.064
BMI,mean (±SD)	-	20.974±2.471	20.915±2.144	21.185±3.381	0.130
Clinical data					
Site of infection, n (%)	Lung	919(50.054)	689(48.047)	230(57.214)	<0.001
	Abdomen	773(42.102)	672(46.862)	101(25.124)	
	Urinary tract	124(6.754)	64(4.463)	60(14.925)	
	Other	20(1.089)	9(0.628)	11(2.736)	
APACHEII,median [IQR]	-	18.000[10.000,26.000]	16.000[9.000,24.000]	23.000[14.000,33.000]	<0.001
SOFA,median [IQR]	-	5.000[4.000,6.000]	4.000[3.000,5.000]	7.000[6.000,9.000]	<0.001
ICU stay, median [IQR]	-	11.000[9.000,14.000]	12.000[10.000,14.000]	10.000[8.000,11.000]	<0.001
Hospital stay, median [IQR]	-	20.000[17.000,23.000]	21.000[18.000,24.000]	17.000[15.000,20.000]	<0.001
Temperature, median [IQR]	-	36.390[35.840,37.040]	36.390[35.860,37.000]	36.410[35.790,37.180]	0.250
Heart rate, mean (±SD)	-	86.725±14.779	85.145±12.451	92.363±20.095	<0.001
Respiratory rate, median [IQR]	-	17.000[15.000,19.000]	16.000[14.000,17.000]	22.000[20.000,24.000]	<0.001
PaO2/FiO2,mean (±SD)	-	360.551±63.760	382.500±50.077	282.255±42.102	<0.001
Hemoglobin, median [IQR]	-	11.080[10.000,12.360]	11.160[10.070,12.390]	10.860[9.750,12.210]	0.002
WBC,median [IQR]	-	11.370[7.030,14.390]	9.660[6.420,14.320]	12.070[9.220,14.600]	<0.001
CRP,mean (±SD)	-	159.450±50.965	162.095±52.197	150.015±45.059	<0.001
PCT,median [IQR]	-	2.070[1.950,2.280]	2.100[1.960,3.000]	2.020[1.920,2.130]	<0.001
Disease history, n (%)					
Hypertension	No	886(48.257)	697(48.605)	189(47.015)	0.573
	Yes	950(51.743)	737(51.395)	213(52.985)	
Diabetes	No	1246(67.865)	996(69.456)	250(62.189)	0.006
	Yes	590(32.135)	438(30.544)	152(37.811)	
Liver disease	No	1053(57.353)	738(51.464)	315(78.358)	<0.001
	Yes	783(42.647)	696(48.536)	87(21.642)	
Kidney disease	No	1355(73.802)	1065(74.268)	290(72.139)	0.391
	Yes	481(26.198)	369(25.732)	112(27.861)	
COPD	No	1086(59.150)	901(62.831)	185(46.020)	<0.001
	Yes	750(40.850)	533(37.169)	217(53.980)	
Complication, n (%)					
Pancreatitis	No	1816(98.911)	1416(98.745)	400(99.502)	0.196
	Yes	20(1.089)	18(1.255)	2(0.498)	
Respiratory failure	No	855(46.569)	611(42.608)	244(60.697)	<0.001
	Yes	981(53.431)	823(57.392)	158(39.303)	
Heart failure	No	838(45.643)	642(44.770)	196(48.756)	0.156
	Yes	998(54.357)	792(55.230)	206(51.244)	
Acute kidney injury	No	1152(62.745)	965(67.294)	187(46.517)	<0.001
	Yes	684(37.255)	469(32.706)	215(53.483)	
Septic shock	No	1785(97.222)	1408(98.187)	377(93.781)	<0.001
	Yes	51(2.778)	26(1.813)	25(6.219)	
Secondary infection	No	1439(78.377)	1155(80.544)	284(70.647)	<0.001
	Yes	397(21.623)	279(19.456)	118(29.353)	

Note: temperature (°C), respiratory rate (bpm), heart rate (bpm), hemoglobin (g/dL), WBC ($\times 10^9$/L), PCT (μg/L), CRP (mg/L). -: indicates that the category is not classified.

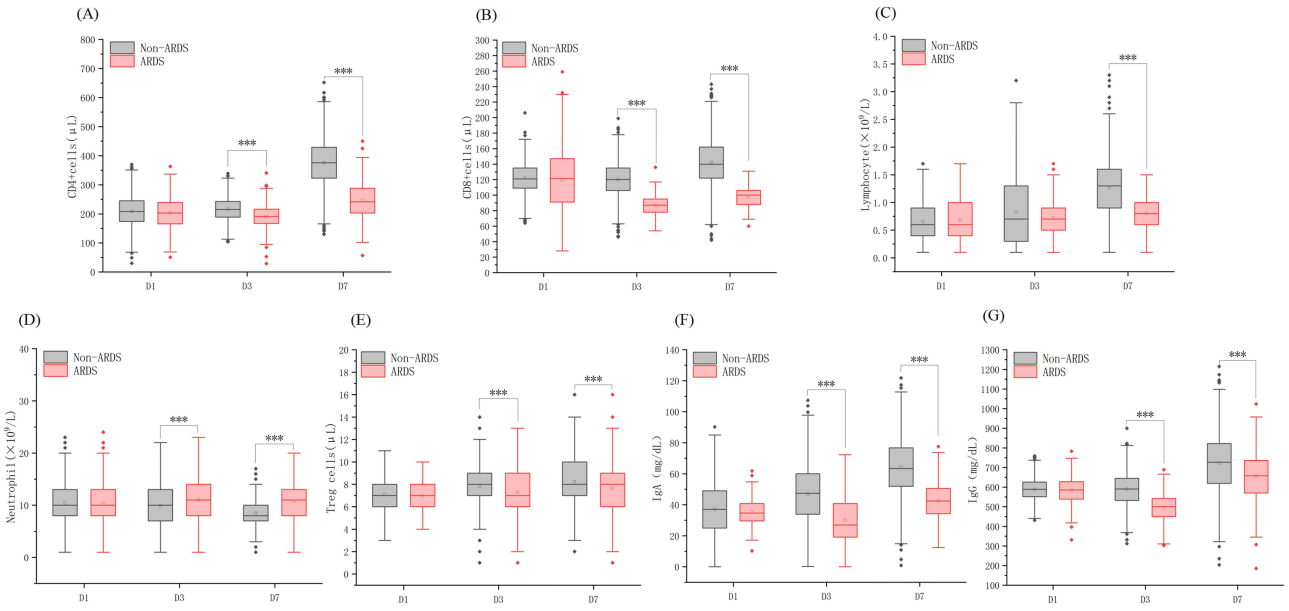

Figure 2 Box plot of immune-related indicators. (**A**) CD4+cells. (**B**) CD8+cells. (**C**) Lymphocytes. (**D**) Neutrophils. (**E**) Treg cells. (**F**) IgA. (**G**) IgG. The hollow rectangles are the averages, and the solid diamonds are the outliers. ***: $p < 0.001$.

Analysis of Risk Factors for ARDS in Patients with Sepsis

Multivariate analysis results showed that on the third and seventh days after hospital admission for sepsis, levels of CD4, CD8, Treg, lymphocyte, IgG and IgA were significantly negatively correlated with the development of ARDS (OR < 1). Specifically, on Day 3, CD8 ($P < 0.001$), Tregs ($P = 0.021$), IgG ($P < 0.001$), and IgA ($P < 0.001$) were significantly negatively correlated with ARDS development. Similarly, on Day 7, CD4 ($P < 0.001$), CD8 ($P < 0.001$), lymphocyte count ($P < 0.001$), and IgA ($P < 0.001$) also demonstrated significant negative correlations with ARDS risk. See Table 2.

Nomogram Model for Predicting ARDS in Patients with Sepsis Based on Immune Indicators

A nomogram model was constructed based on logistic regression analysis of important variables selected from the multivariate analysis (Table 3), which includes a forest plot (Figure 3A) and a nomogram (Figure 3B). The calibration curves were quite close to the standard 45-degree diagonal line, indicating perfect alignment between predicted values and actual outcomes (Figure 3C). The ROC curve of the nomogram constructed in our study was compared with those of SOFA and APACHE II (Figure 3D), yielding AUC values of 0.998 (95% CI: 0.997–0.999), 0.867 (95% CI: 0.844–0.887), and 0.651 (95% CI: 0.621–0.681). The Decision Curve Analysis (DCA) curve represented the net benefit demonstrates the good clinical validity of this column chart in predicting ARDS (Figure 3E). In summary, our model performed well in predicting ARDS in patients with sepsis by combining various evaluation parameters.

Discussion

The primary aim of this study was to explore dynamic changes in immune-related indicators and their predictive value for ARDS development in sepsis patients. This focus addresses a critical gap in existing models, which often lack longitudinal data capturing immune response trajectories. While SOFA and APACHE II scores are valuable tools, they do not account for the dynamic nature of immune responses in sepsis, which are critical in the progression to ARDS.[17] Thus, our study offers a novel perspective by incorporating immune response dynamics into a predictive model for ARDS, providing clinicians with an actionable framework for early risk assessment.

This study reveals the critical role of immune dysregulation in ARDS development among septic patients, with a dynamic progression from early innate activation to adaptive immune suppression. On Day 1, the absence of significant differences in immune-related indicators between the ARDS and non-ARDS groups reflects the shared acute-phase

Table 2 Univariate and Multivariate Analysis

Variables	Single Factor Analysis					Multi-factor Analysis				
	β	S.E	Z	*P*	OR (95% CI)	β	S.E	Z	*P*	OR (95% CI)
CD4+										
D1	−0.00	0.00	−1.78	0.074	1.00 (1.00 ~ 1.00)					
D3	−0.02	0.00	−10.80	**<0.001**	0.98 (0.98 ~ 0.99)	−0.01	0.01	−1.40	0.162	0.99 (0.98 ~ 1.00)
D7	−0.02	0.00	−19.43	**<0.001**	0.98 (0.97 ~ 0.98)	−0.02	0.00	−6.38	**<0.001**	0.98 (0.97 ~ 0.98)
CD8+										
D1	−0.00	0.00	−1.79	0.074	1.00 (0.99 ~ 1.00)					
D3	−0.10	0.01	−19.07	**<0.001**	0.90 (0.89 ~ 0.91)	−0.11	0.01	−7.24	**<0.001**	0.90 (0.87 ~ 0.93)
D7	−0.08	0.00	−18.47	**<0.001**	0.92 (0.91 ~ 0.93)	−0.08	0.01	−7.16	**<0.001**	0.92 (0.90 ~ 0.94)
Lymphocyte										
D1	0.26	0.17	1.57	0.116	1.30 (0.94 ~ 1.80)					
D3	−0.33	0.11	−3.17	**0.002**	0.72 (0.58 ~ 0.88)	−0.74	0.50	−1.47	0.141	0.48 (0.18 ~ 1.28)
D7	−2.21	0.15	−14.42	**<0.001**	0.11 (0.08 ~ 0.15)	−2.29	0.54	−4.25	**<0.001**	0.10 (0.04 ~ 0.29)
Neutrophil										
D1	−0.01	0.01	−0.73	0.465	0.99 (0.96 ~ 1.02)					
D3	0.07	0.01	5.01	**<0.001**	1.07 (1.04 ~ 1.10)	0.09	0.05	1.74	0.082	1.09 (0.99 ~ 1.20)
D7	0.26	0.02	12.56	**<0.001**	1.30 (1.25 ~ 1.35)	0.13	0.07	1.93	0.053	1.14 (1.00 ~ 1.31)
Treg										
D1	−0.08	0.04	−1.84	0.065	0.92 (0.84 ~ 1.01)					
D3	−0.16	0.03	−5.20	**<0.001**	0.86 (0.81 ~ 0.91)	−0.26	0.11	−2.31	**0.021**	0.77 (0.62 ~ 0.96)
D7	−0.12	0.03	−4.44	**<0.001**	0.89 (0.84 ~ 0.94)	−0.09	0.10	−0.91	0.364	0.91 (0.74 ~ 1.12)
IgG										
D1	−0.00	0.00	−1.94	0.052	1.00 (1.00 ~ 1.00)					
D3	−0.02	0.00	−16.82	**<0.001**	0.98 (0.98 ~ 0.99)	−0.02	0.00	−5.46	**<0.001**	0.98 (0.97 ~ 0.99)
D7	−0.01	0.00	−8.22	**<0.001**	0.99 (0.99 ~ 0.99)	−0.00	0.00	−1.79	0.073	1.00 (0.99 ~ 1.00)
IgA										
D1	−0.01	0.00	−1.95	0.051	0.99 (0.99 ~ 1.00)					
D3	−0.06	0.00	−14.76	**<0.001**	0.94 (0.94 ~ 0.95)	−0.07	0.01	−4.71	**<0.001**	0.93 (0.91 ~ 0.96)
D7	−0.08	0.00	−17.32	**<0.001**	0.92 (0.91 ~ 0.93)	−0.09	0.02	−5.13	**<0.001**	0.91 (0.88 ~ 0.94)

Note: Bold type indicates P < 0.05, which is significant.

Table 3 Logistic Regression Analysis

Predictor	Estimate	SE	Z	p	Odds Ratio	Lower	Upper
(Intercept)	48.085	4.67	10.296	0.0	7.64114347 1e+20	2.133402996e+17	2.202223407e+25
CD4 D7	−0.024	0.003	−6.851	0.0	0.977	0.969	0.983
CD8 D3	−0.109	0.014	−7.904	0.0	0.897	0.871	0.92
CD8 D7	−0.079	0.01	−7.775	0.0	0.924	0.905	0.941
Lymphocyte D7	−2.17	0.494	−4.389	0.0	0.114	0.041	0.289
Treg D3	−0.244	0.102	−2.385	0.017	0.783	0.636	0.953
IgG D3	−0.02	0.003	−5.865	0.0	0.98	0.973	0.986
IgA D3	−0.066	0.013	−4.999	0.0	0.937	0.911	0.96
IgA D7	−0.092	0.016	−5.617	0.0	0.912	0.881	0.94

responses, dominated by nonspecific mechanisms like neutrophil recruitment and cytokine release.[18] By Days 3 and 7, however, immune alterations in ARDS patients became evident, including reductions in CD4+, CD8+, and Lymphocyte cells, as well as IgG and IgA levels, coupled with increased neutrophil counts. These findings point to a transition toward immune exhaustion, characterized by impaired T-cell function, diminished humoral immunity, and unresolved inflammation.[19] Among these markers highlight their importance in pathogen clearance and immune homeostasis.

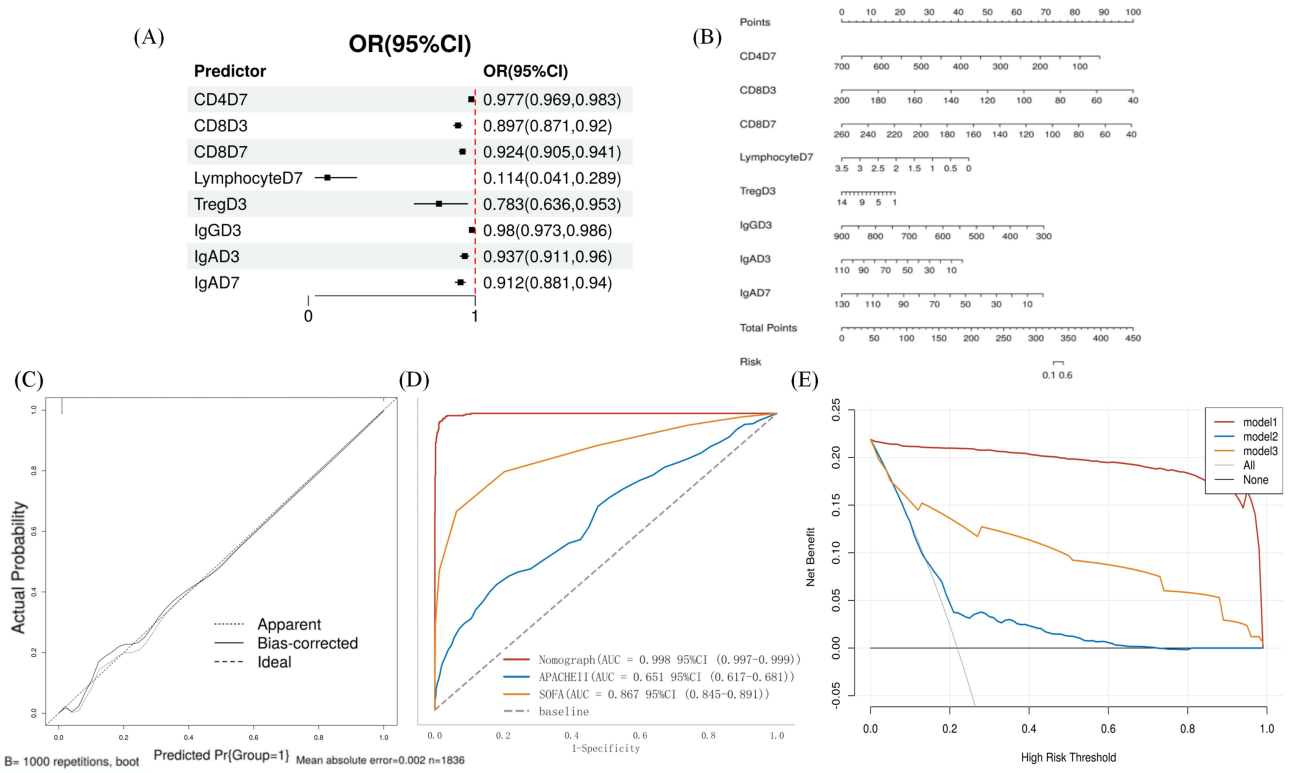

Figure 3 Nomogram comparison and evaluation. (**A**) Forest plot. The dashed line (OR=1) is an invalid line. Squares represent OR values for each feature, with horizontal lines showing 95% CI. Left of the invalid line indicates a negative relationship; Otherwise, the relationship is positive. (**B**) Nomograph. Each variable corresponds to a scale that represents its contribution to the total score. By summing the scores of each variable, the total score is obtained. (**C**) Calibration curve. The curve shows predicted vs observed probabilities. An ideal curve is close to the 45-degree line, indicating high prediction accuracy. (**D**) ROC curve of the scoring model. AUC close to 1 indicates strong discriminative ability of the model. (**E**) DCA curve. Model 1: Nomogram. Model 2: APACHEII. Model 3: SOFA. The X-axis represents the threshold predicted by the model, and the Y-axis represents the net benefit. The higher the net benefit, the better the utility performance of the prediction model.

Previous studies have explored biomarker panels, including markers like RAGE, Ang-2, and CXCL16, to predict ARDS in sepsis and improve diagnostic accuracy.[20] Another investigation identified biomarkers of inflammation and epithelial injury, such as SP-D and IL-8, achieving moderate predictive capability for severe ARDS diagnosis.[21] Compared to these studies, our research uniquely highlights the temporal patterns of immune cell dynamics, such as the depletion of CD8+ T cells and IgA over time, which may offer superior insights into disease progression and allow for tailored immune monitoring. Elevated neutrophil counts on Day 7, meanwhile, indicate persistent innate activation, contributing to lung epithelial injury and prolonged systemic inflammation.[22] These observations provide a clearer understanding of the immunological shifts driving ARDS and emphasize the potential of these biomarkers for early risk stratification and therapeutic intervention. Monitoring these immune parameters over time could guide more targeted treatment strategies for sepsis-related ARDS.

Previous studies have highlighted the role of individual immune markers in predicting outcomes in sepsis,[23] and have demonstrated the prognostic value of single-time-point measurements of cytokines and immune cells in sepsis and ARDS.[24] In addition, the study by Yao et al utilized gene expression profiles and clinical data from severe septic patients to identify six differential expressed genes linked to ARDS development. These genes, alongside clinical parameters were integrated into a nomogram. The nomogram exhibited strong predictive performance with an AUROC of 0.86.[25] Xu et al conducted a retrospective cohort study using a large dataset of sepsis patients. They identified thirteen clinical predictors, including BMI, respiratory rate, and various biochemical markers. Their nomogram demonstrated robust predictive ability with AUROC of 0.812.[26] However, these studies often lacked the longitudinal data necessary to fully understand the temporal dynamics of the immune response. Our approach addresses this gap by highlighting the importance of monitoring changes over time, thereby offering a more accurate prediction model. Furthermore, while SOFA and APACHE II are widely used to assess disease severity and predict outcomes in critical care,[27] our findings

suggest that immune function data offer greater predictive accuracy for ARDS. This comparison highlights that incorporating immune dynamics provides a more holistic view of the patient's condition, potentially leading to better-targeted interventions. For example, in patients showing a marked decrease in CD4, CD8, and Treg cells on the third and seventh days, clinicians might consider intensifying their monitoring and therapeutic interventions.

While it is true that patients diagnosed with sepsis are already receiving treatment for both sepsis and the underlying infection, the early identification of those at high risk for ARDS remains crucial for optimizing patient outcomes. By recognizing the early signs of immune dysregulation, healthcare providers can intensify monitoring, adjust therapeutic interventions, and potentially employ early immunomodulatory therapies aimed at mitigating the progression toward ARDS. Although the clinical management of ARDS remains challenging, and previous attempts to develop therapies that prevent organ dysfunction have often been disappointing, our study highlights a critical aspect that may have been overlooked: the timing and trajectory of immune response. Unlike static measurements, which provide a snapshot of the patient's condition, dynamic monitoring captures the evolving nature of the immune response, offering a more comprehensive understanding of the patient's immunological status. This real-time data can be instrumental in clinical decision-making, potentially allowing for more timely and targeted interventions.

There are some limitations to this study. First, this study was conducted in a single-center, which may limit the generalizability of the findings. However, the study collected data from patients in both the ICU and emergency departments, which may provide a broader perspective. Second, due to resource constraints, no external validation of the model was conducted. Third, while the nomogram model is a valuable tool, its clinical applicability may be limited by the need for specific laboratory tests that may not be available in all clinical environments. Finally, other time points were not considered due to management challenges to minimize patient burden.

Conclusions

This study underscores the pivotal role of dynamic immune indicator changes in predicting ARDS development among ICU sepsis patients. By incorporating immune cell and immunoglobulin dynamics into a nomogram, we introduced a novel approach that outperforms traditional scoring systems. This innovative perspective highlights the importance of continuous immune monitoring to better understand sepsis and ARDS progression. In the future, this could enable early identification of high-risk patients and support personalized therapeutic strategies to improve outcomes in critically ill sepsis patients.

Ethics Statement

The study followed the Declaration of Helsinki and was approved by the Ethics committee of Lishui Central Hospital of Zhejiang Province (approval number: 2019-177). Interventional human clinical trials were not involved in this study.

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Disclosure

The authors have no conflicts of interest in this work.

References

1. Salomão R, Ferreira B, Salomão M, et al. Sepsis: evolving concepts and challenges. *Braz J Med Biol Res*. 2019;52:e8595. doi:10.1590/1414-431X20198595
2. Watkins RR, Bonomo RA, Rello J. Managing sepsis in the era of precision medicine: challenges and opportunities. *Expert Rev Anti Infect Ther* 2022;20(6):871–880.
3. Ahmed MM, Zaki A, Alhazmi A, et al. Identification and validation of pathogenic genes in sepsis and associated diseases by integrated bioinformatics approach. *Genes*. 2022;13(2):209. doi:10.3390/genes13020209

4. Sygitowicz G, Sitkiewicz D. Organ damage in sepsis: molecular mechanisms. *Infect Sepsis Develop*. 2021:263.
5. Gong H, Chen Y, Chen M, et al. Advanced development and mechanism of sepsis-related acute respiratory distress syndrome. *Front Med*. 2022;9:1043859. doi:10.3389/fmed.2022.1043859
6. Kumar V. Pulmonary innate immune response determines the outcome of inflammation during pneumonia and sepsis-associated acute lung injury. *Front Immunol*. 2020;11:1722. doi:10.3389/fimmu.2020.01722
7. Effah CY, Drokow EK, Agboyibor C, et al. Neutrophil-dependent immunity during pulmonary infections and inflammations. *Front Immunol*. 2021;12:689866. doi:10.3389/fimmu.2021.689866
8. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. *Immunity*. 2021;54(11):2450–2464. doi:10.1016/j.immuni.2021.10.012
9. Li W, Li D, Chen Y, et al. Classic signaling pathways in alveolar injury and repair involved in sepsis-induced ALI/ARDS: new research progress and prospect. *Dis Markers*. 2022;2022:6362344. doi:10.1155/2022/6362344
10. Xu H, Sheng S, Luo W, Xu X, Zhang Z. Acute respiratory distress syndrome heterogeneity and the septic ARDS subgroup. *Front Immunol*. 2023;14:1277161. doi:10.3389/fimmu.2023.1277161
11. Leung G, Middleton EA. The role of platelets and megakaryocytes in sepsis and ARDS. *J Physiol*. 2024;602(22):6047–6063. doi:10.1113/JP284879
12. Liu Y, Chen L. Impact of interleukin 6 levels on acute lung injury risk and disease severity in critically ill sepsis patients. *World J Clin Cases*. 2024;12(23):5374–5381. doi:10.12998/wjcc.v12.i23.5374
13. Liang NW, Wilson C, Davis B, et al. Modeling lung endothelial dysfunction in sepsis-associated ARDS using a microphysiological system. *Physiol Rep*. 2024;12(13):e16134. doi:10.14814/phy2.16134
14. Rissel R, Kirchner L, Renz M, et al. Resveratrol influences pulmonary mechanics and inflammatory response in a porcine ARDS model. *Life Sci*. 2023;319:121410. doi:10.1016/j.lfs.2023.121410
15. Seymour CW, Liu VX, Iwashyna TJ. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315(8):762–774. doi:10.1001/jama.2016.0288
16. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012;38(10):1573–1582. doi:10.1007/s00134-012-2682-1
17. Senthil Kumar E. *Comparative Analysis of Apache-II Score and Sofa Score as Predictors of Mortality in Patients Admitted With Sepsis and Multi Organ Dysfunction Syndrome*. Chennai: Madras Medical College; 2016.
18. Xu Y, Xin J, Sun Y, et al. Mechanisms of sepsis-induced acute lung injury and advancements of natural small molecules in its treatment. *Pharmaceuticals*. 2024;17(4):472. doi:10.3390/ph17040472
19. Cao C, Yu M, Chai Y. Pathological alteration and therapeutic implications of sepsis-induced immune cell apoptosis. *Cell Death Dis*. 2019;10(10):782. doi:10.1038/s41419-019-2015-1
20. Villar J, Herrán-Monge R, González-Higueras E, et al. Clinical and biological markers for predicting ARDS and outcome in septic patients. *Sci Rep*. 2021;11(1):22702. doi:10.1038/s41598-021-02100-w
21. Ware LB, Koyama T, Zhao Z, et al. Biomarkers of lung epithelial injury and inflammation distinguish severe sepsis patients with acute respiratory distress syndrome. *Critical Care*. 2013;17(5):R253. doi:10.1186/cc13080
22. Potey PM, Rossi AG, Lucas CD, Dorward DA. Neutrophils in the initiation and resolution of acute pulmonary inflammation: understanding biological function and therapeutic potential. *J Pathol*. 2019;247(5):672–685. doi:10.1002/path.5221
23. Cajander S, Kox M, Scicluna BP, et al. Profiling the dysregulated immune response in sepsis: overcoming challenges to achieve the goal of precision medicine. *Lancet Respir Med*. 2023;12:305–22.
24. Angurana SK, Bansal A, Muralidharan J, Aggarwal R, Singhi S. Cytokine levels in critically ill children with severe sepsis and their relation with the severity of illness and mortality. *J Intensive Care Med*. 2021;36(5):576–583.
25. Yao R-Q, Shen Z, Ma Q-M, et al. Combination of transcriptional biomarkers and clinical parameters for early prediction of sepsis indued acute respiratory distress syndrome. *Front Immunol*. 2023;13:1084568. doi:10.3389/fimmu.2022.1084568
26. Xu C, Zheng L, Jiang Y, Jin LJBPM. A prediction model for predicting the risk of acute respiratory distress syndrome in sepsis patients: a retrospective cohort study. *BMC Pulmon Med*. 2023;23(1):78. doi:10.1186/s12890-023-02365-z
27. Lakhani JD. SOFA vs APACHE II as ICU scoring system for sepsis: a dilemma. *J integr Health Sci*. 2015;3(2):3–7.