British Journal of Hospital Medicine

Br. J. Hosp. Med. (Lond) **2026**; 87(7): 56282
https://doi.org/10.31083/BJHM56282

Article

Predictive Value of Inflammatory and Immune Markers for Acute Respiratory Failure in Patients With Community-Acquired Pneumonia

Jinping Sun[1,*], Jun Zhao[1]

[1]Department of Internal Medicine, Zhuji Sixth People's Hospital, 311801 Shaoxing, Zhejiang, China
*Correspondence: sjp780213@163.com (Jinping Sun)

Academic Editor: Emanuele Pontali
Submitted: 2 December 2025 Revised: 5 March 2026 Accepted: 3 April 2026 Published: 23 July 2026

Abstract

Aims/Background: Acute respiratory failure (ARF) may develop in some patients with community-acquired pneumonia (CAP), resulting in a significantly increased mortality rate. Early identification of high-risk patients is essential for improving prognosis. This study aimed to investigate the predictive value of inflammatory and immune markers for acute respiratory failure in patients with community-acquired pneumonia. **Methods:** This single-center retrospective cohort study included 334 patients with community-acquired pneumonia admitted at Zhuji Sixth People's Hospital, between January 2021 and December 2024. Patients were divided into a CAP-only (non-event) group and a CAP-ARF (event) group based on the development of acute respiratory failure. Inflammatory markers (white blood cell count, neutrophil count, tumor necrosis factor-α, etc.) and immune markers (complement components 3 and 4[C3andC4], immunoglobulins A and G [IgAand IgG], etc.) were collected within 24 hours of admission. Univariate and multivariate logistic regression analyses were performed to identify independent predictive factors, and the predictive performance of individual and combined indicators was evaluated using receiver operating characteristic (ROC) curves. **Results:** Multivariate analysis showed that elevated white blood cell count, neutrophil count, and tumor necrosis factor-α levels were independent risk factors for acute respiratory failure, while decreased levels of complement C3 and C4, and IgA and IgG, were independent protective factors. The combined predictive model incorporating these indicators demonstrated excellent predictive performance for acute respiratory failure, with an area under the curve (AUC) of 0.853. **Conclusion:** In patients with community-acquired pneumonia, inflammatory and immune markers exhibit significant predictive value for the development of acute respiratory failure. A combined assessment of white blood cell count, neutrophil count, tumor necrosis factor-α, complement C3 and C4, and IgA and IgG may facilitate early identification of high-risk patients and inform clinical decision-making.

Keywords: community-acquired pneumonia; acute respiratory failure; inflammatory markers; immune markers

1. Introduction

Community-acquired pneumonia (CAP), one of the most clinically challenging lower respiratory tract infections, continues to impose a substantial global disease burden [1]. CAP is generally defined as pneumonia acquired outside of a hospital setting or an acute parenchymal lung infection occurring within 48 hours of hospital admission. Typical clinical manifestations include cough, fever, purulent sputum, and radiographic evidence of pulmonary infiltrates [2]. Epidemiological studies indicate that CAP remains a leading infectious cause of mortality worldwide, with elderly individuals and those with underlying comorbidities at particularly high risk [3]. The prevalence of community-acquired pneumonia in urban areas of China is also increasing at approximately 7.13 cases per 1000 person-years, underscoring its significance as a major public health concern. Clinical outcomes among CAP patients vary considerably. While most patients respond to standard anti-infective therapy, approximately 8–20% of hospitalized patients progress to severe community-acquired pneumonia (S-CAP), with some requiring intensive care [4]. In more severe cases, patients may develop acute respiratory failure (ARF) and can rapidly progress to acute respiratory distress syndrome (ARDS) [5,6]. Once ARF develops in CAP patients, the need for mechanical ventilation and circulatory support increases significantly, and the in-hospital mortality rate may rise from 5–15% in general CAP patients to 25–40%, with critical cases exceeding 50% [7]. Therefore, early identification of patients at risk of ARF and timely implementation of targeted interventions are essential steps to improve prognosis.

The core mechanism underlying the progression of CAP to ARF involves the overactivation of the immune-inflammatory response. Following pathogen invasion, pathogen-associated molecular patterns (PAMPs) and host-derived damage-associated molecular patterns (DAMPs) are recognized by the immune system, thereby activating multiple inflammatory pathways, including those involving neutrophils, monocytes/macrophages, and the complement system [8,9,10]. When this inflammatory cascade is dysregulated, it leads to increased alveolar-capillary membrane permeability, resulting in protein leakage and diffuse lung injury. This uncontrolled systemic inflammatory response and immune dysregulation are considered cen-

tral drivers of CAP progression, highlighting the potential value of related biomarkers in predicting disease severity and complications [11]. Currently, commonly used inflammatory markers in clinical practice include white blood cell count (WBC), neutrophil percentage, C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Although these indicators correlate with CAP severity and complications, the sensitivity and specificity of commonly used markers such as CRP and PCT for predicting ARF remain suboptimal [12,13]. In recent years, immune-related markers, including lymphocyte count, lymphocyte subsets, cluster of differentiation 4/cluster of differentiation 8 (CD4/CD8) ratio, and immunoglobulin levels, have received increasing attention [14]. Lymphopenia has been shown to be significantly associated with post-infection immunosuppression, disease progression, and an increased risk of mortality. Composite indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are sensitive markers of systemic inflammation, have also been shown to be closely associated with the development of respiratory failure and severe community-acquired pneumonia [15].

Recent studies have increasingly focused on the role of the complement system in pulmonary inflammation. The complement system exerts a dual role in pathogen clearance and in amplifying the inflammatory response; its activation products, including complement component 3a (C3a), complement component 4b (C4b), and complement component 5a (C5a), can induce increased vascular permeability, excessive neutrophil aggregation, and tissue damage [16]. Immune imbalance resulting from excessive complement activation is considered a key mechanism contributing to CAP exacerbation [17]. However, the clinical value of complement components such as C3 and C4 in predicting the progression of CAP to ARF remains unclear and warrants further investigation.

Although numerous studies have demonstrated associations between inflammatory and immune indicators and CAP severity, significant gaps remain. Previous studies have largely focused on long-term outcomes, such as mortality or intensive care unit (ICU) admission, with limited emphasis on early prediction of ARF. Furthermore, numerous studies have focused on critically ill populations, with insufficient risk stratification among general CAP patients, which limits the generalizability of findings. Against this background, this study aimed to systematically evaluate the predictive value of inflammatory and immune markers for acute respiratory failure, thereby facilitating early risk stratification and optimized treatment strategies for high-risk patients. Through intergroup comparisons, multivariate logistic regression, and ROC curve analysis, this study further investigated the clinical value of inflammatory markers, such as IL-6 and WBC, as well as immune markers, including lymphocyte count, C3, and C4, in predicting acute respiratory failure. By assessing the role of inflammatory and immune responses in the progression of community-acquired pneumonia using clinical data, this study provides more robust and clinically applicable evidence to inform early diagnostic and therapeutic decision-making.

2. Methods

2.1 Criteria for Participant Inclusion

This retrospective observational cohort study was conducted using Zhuji Sixth People's Hospital electronic medical records. Patients hospitalized with community-acquired pneumonia between January 2021 and December 2024 were retrospectively identified. According to hospital administrative data, 673 patients were admitted with CAP at Zhuji Sixth People's Hospital during the study period. Among these, 353 patients had complete inflammatory and immune marker panels (including cytokines, complement components, and immunoglobulins) measured within 24 hours of admission and recorded in the electronic medical records. After applying predefined inclusion and exclusion criteria, a total of 334 patients were included in the final analysis. Patients were grouped according to whether they developed acute respiratory failure within the first 24 hours after admission. Patients who developed ARF were assigned to the CAP-ARF group (event group, n = 72), while those without ARF were assigned to the CAP-only group (non-event group, n = 262). The study protocol was reviewed and approved by the Ethics Committee of Zhuji Sixth People's Hospital (approval number: 2025-06). In accordance with national regulations governing retrospective studies, the requirement for individual informed consent was waived by the Ethics Committee of Zhuji Sixth People's Hospital given the retrospective design, use of anonymized data, and minimal risk to participants.

The diagnosis of CAP was established based on widely accepted international guidelines [18]. Eligible patients were required to have an epidemiological history consistent with community-onset CAP, present with clinical manifestations of acute lower respiratory tract infection (such as new or worsening cough, sputum production, fever, moist rales, or focal signs), and demonstrate chest imaging findings (chest X-ray or computed tomography [CT]) showing new patchy exudates, consolidation, or ground-glass opacities. Non-infectious etiologies, including tuberculosis, lung tumors, cardiogenic pulmonary edema, interstitial lung disease, and pulmonary embolism, were excluded. Acute respiratory failure was defined according to commonly used European Respiratory Society/American Thoracic Society (ERS/ATS) criteria: arterial partial pressure of oxygen (PaO_2) <60 mmHg (on room air) or arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg on admission; requirement for non-invasive or invasive mechanical ventilation; or the presence of acute hypercapnia (arterial partial pressure of carbon dioxide [$PaCO_2$] >45 mmHg) with acidosis (pH <7.35) [19]. To ensure consistency in group classifi-

cation, blood gas parameters and supportive interventions within the first 24 hours after admission were used as the reference time point.

Inclusion criteria were as follows: age ≥18 years; meeting the above-mentioned diagnostic criteria for CAP; completion of all pre-specified inflammatory and immune marker tests within 24 hours of admission; and availability of complete blood gas, imaging, and clinical outcome data from electronic medical records, laboratory systems, or imaging databases. Exclusion criteria included: a history of long-term immunosuppression (including ongoing chemotherapy, organ transplantation, or long-term hormone or immunosuppressive therapy); pre-existing chronic respiratory failure or long-term oxygen therapy; comorbid conditions such as confirmed interstitial lung disease, pulmonary embolism, severe heart failure, hematological disorders, or rheumatic immune diseases that can independently influence study indicators; and missing admission data or key laboratory tests. After the above screening procedures and exclusion of ineligible individuals, 334 eligible patients were retained for statistical analysis. Fig. 1 illustrates the patient selection process.

2.2 Measurement and Evaluation of Clinical Indicators

All clinical and laboratory data were obtained from the patient's medical records. Venous blood samples were collected within 24 hours of admission, under fasting or routine conditions, and processed according to standardized laboratory protocols. Routine hematological indicators (complete blood count and differential) were measured by the hospital's clinical laboratory using a Sysmex series automated hematology analyzer (Sysmex XE-2100, Sysmex Corporation, Kobe, Japan). C-reactive protein was quantified using immunoscattering methods. Pro-inflammatory and anti-inflammatory cytokines (IL-6, IL-8, TNF-α, etc.) were quantified using validated enzyme-linked immunosorbent assay (ELISA) kits (Human IL-6 ELISA Kit, catalog No. KHC0061; Human IL-8 ELISA Kit, catalog No. KHC0081; Human TNF alpha Uncoated ELISA Kit, catalog No. 88-7346-88; Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. Complement components 3 and 4 (C3, C4) and immunoglobulins G, M and A (IgG, IgM, IgA) were determined using immunonephelometry and immunoturbidimetry techniques. Basic demographic characteristics (including age, gender, smoking history, and body mass index [BMI]), comorbidities (hypertension, chronic obstructive pulmonary disease [COPD], diabetes mellitus, and heart disease), early treatment factors (broad-spectrum antibiotic use, guideline-concordant therapy), and in-hospital clinical outcomes were also extracted from patient medical records.. To ensure data quality, laboratory results were directly exported from the laboratory information system to minimize manual transcription errors. Demographic and clinical data were manually extracted and cross-checked against multiple sources within the medical records. All collected data were screened for out-of-range values and logical inconsistencies, and any discrepancies were verified against the original medical records prior to final statistical analysis.

2.3 Statistical Analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were initially assessed for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation (mean ± SD), and comparisons between groups were performed using independent samples *t*-tests. Non-normally distributed data are presented as median (interquartile range) [M (Q_1, Q_3)], and comparisons between groups were conducted using the Mann-Whitney *U* test. Categorical variables are expressed as frequencies (n) and percentages (%), and comparisons between groups were performed using the chi-square (χ^2) test or Fisher's exact test, as appropriate.

To identify factors independently associated with acute respiratory failure, univariate logistic regression analysis was first performed. Based on the univariate analysis results ($p < 0.05$), candidate variables were selected and entered into the multivariate logistic regression model to adjust for potential confounding effects. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs). To enhance model stability, the event-to-variable ratio principle was applied, ensuring that each independent variable in the final model corresponded to at least 10 endpoint events to control for overfitting [20]. Receiver operating characteristic (ROC) curve analysis was subsequently performed to evaluate the discriminative performance of the predicted probabilities derived from the multivariate regression model for ARF. To assess potential multicollinearity among the independent variables included in the multivariate logistic regression model, the variance inflation factor (VIF) was calculated. A VIF value greater than 10 was considered indicative of significant multicollinearity that could compromise the stability of the model estimates. All statistical tests were two-sided, with $p < 0.05$ considered statistically significant.

3. Results

3.1 Comparison of Patient Baseline Characteristics

This study ultimately included 334 patients with community-acquired pneumonia, of whom 262 (78.44%) did not develop respiratory failure, and 72 (21.56%) did. As shown in Table 1, no statistically significant differences between the two groups in baseline characteristics were observed, including age, body mass index (BMI), smoking status, gender, IL-6, IL-8, CRP, early treatment factors, comorbidities, and IgM (all $p > 0.05$), suggesting that these variables may not be significantly associated with the risk of respiratory failure in CAP patients. However, regarding

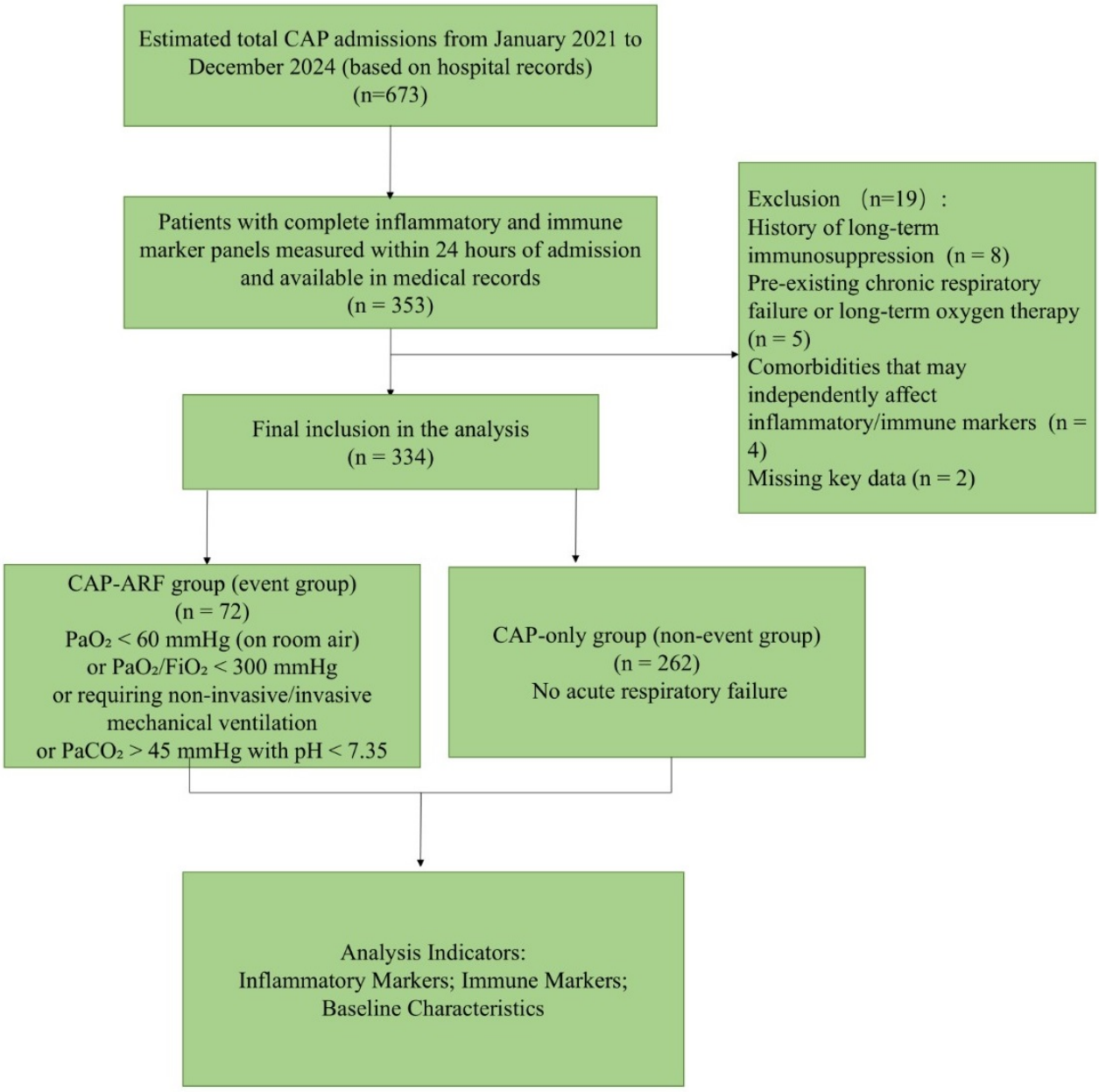

Fig. 1. Flowchart of patient selection and study design. CAP, community-acquired pneumonia; ARF, acute respiratory failure; PaO_2/FiO_2, arterial partial pressure of oxygen to fraction of inspired oxygen.

inflammatory and immune markers, patients in the event group exhibited significantly higher white blood cell count, lymphocyte count, neutrophil count, and tumor necrosis factor-α (TNF-α) (all $p < 0.05$), while complement C3 and C4 levels, as well as IgA and IgG levels, were significantly lower than those observed in the non-event group (all $p < 0.05$). These findings suggest that dysregulated inflammatory activation and immune response imbalance may be closely associated with the development of respiratory failure in CAP patients.

3.2 Results of Univariate Regression Analysis

To preliminarily identify factors associated with respiratory failure in patients with community-acquired pneumonia, univariate logistic regression analysis was performed. The results indicated that among the inflammatory and immune markers evaluated, white blood cell count, neutrophil count, tumor necrosis factor-α, complement C3, complement C4, IgG, and IgA were all significantly associated with the development of respiratory failure (all $p < 0.05$), suggesting that these markers may serve as potential risk or protective factors. Conversely, smoking history, gender, age, BMI, lymphocyte count, comorbidities, early

Table 1. Baseline characteristics of study participants.

Variables	Non-event group (n = 262)	Event group (n = 72)	Statistic	*p*-value
Age (years)	55.77 (48.02, 62.53)	54.65 (48.73, 63.71)	$Z = -0.380$	0.704
BMI (kg/m^2)	26.38 ± 3.73	26.58 ± 3.41	$t = -0.418$	0.676
Gender, n (%)			$\chi^2 = 0.066$	0.797
Female	112 (42.75)	32 (44.44)		
Male	150 (57.25)	40 (55.56)		
Comorbidities, n (%)			-	0.148
Hypertension	48 (18.32)	17 (23.61)		
COPD	30 (11.45)	13 (18.06)		
Diabetes mellitus	14 (5.34)	3 (4.17)		
Heart disease	2 (0.76)	2 (2.78)		
Early treatment factors, n (%)				
Broad-spectrum antibiotic use	183 (69.85)	46 (63.89)	$\chi^2 = 0.930$	0.335
Guideline-concordant therapy	213 (81.30)	53 (73.61)	$\chi^2 = 2.058$	0.151
Smoking status, n (%)			$\chi^2 = 0.029$	0.864
Never	99 (37.79)	28 (38.89)		
Current/Former	163 (62.21)	44 (61.11)		
WBC (×10^9/L)	6.78 ± 0.94	7.41 ± 1.00	$t = -5.015$	<0.001
Neutrophil count (×10^9/L)	4.81 ± 1.00	5.24 ± 1.01	$t = -3.257$	0.001
Lymphocyte count (×10^9/L)	2.64 (2.52, 2.76)	2.69 (2.61, 2.79)	$Z = -2.064$	0.039
IL-6 (pg/mL)	59.60 (54.70, 68.01)	61.88 (54.14, 68.48)	$Z = -0.084$	0.933
IL-8 (pg/mL)	4.66 ± 0.86	4.69 ± 0.94	$t = -0.296$	0.767
CRP (mg/L)	131.61 ± 19.89	126.61 ± 18.09	$t = 1.926$	0.055
TNF-α (pg/mL)	17.14 (13.65, 20.49)	18.30 (15.49, 22.64)	$Z = -2.582$	0.010
C3 (g/L)	1.51 ± 0.29	1.22 ± 0.28	$t = 7.653$	<0.001
C4 (g/L)	0.49 (0.34, 0.62)	0.41 (0.28, 0.56)	$Z = -2.411$	0.016
IgM (g/L)	1.15 ± 0.28	1.15 ± 0.25	$t = -0.074$	0.941
IgA (g/L)	2.73 ± 0.73	2.52 ± 0.65	$t = 2.226$	0.027
IgG (g/L)	9.84 (8.35, 11.11)	9.53 (8.24, 10.65)	$Z = -2.947$	0.003

BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; IL, interleukin; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; Ig, immunoglobulin; C3, complement component 3; C4, complement component 4.

treatment factors, IL-6, IL-8, CRP, and IgM were not statistically significant (Table 2).

3.3 Results of Multivariate Regression Analysis

To further control for potential confounding and identify independent predictors, variables that were significant in the univariate analysis were entered into a multivariate logistic regression model. The results (Table 3) confirmed the independent predictive value of several indicators. Notably, WBC (OR = 1.922, 95% CI: 1.363–2.709, $p < 0.001$) and neutrophil count (OR = 1.643, 95% CI: 1.172–2.304, $p = 0.004$) were independently associated with an increased risk of respiratory failure. In contrast, complement C3 (OR = 0.033 per 1 g/L increase, 95% CI: 0.010–0.108, $p < 0.001$) and complement C4 (OR = 0.071 per 1 g/L increase, 95% CI: 0.010–0.500, $p = 0.008$) showed strong protective effects. Similarly, immunoglobulin IgA (OR = 0.561, 95% CI: 0.353–0.893, $p = 0.015$) and IgG (OR = 0.752, 95% CI: 0.577–0.980, $p = 0.035$) were identified as independent protective factors. Furthermore, elevated levels of the inflammatory cytokine TNF-α were independently associated with increased risk (OR = 1.103, 95% CI: 1.030–1.181, $p = 0.005$). The variance inflation factor (VIF) values for all variables included in the final model ranged from 1.005 to 1.050, which are substantially below the threshold of 10, indicating no evidence of clinically relevant multicollinearity.

3.4 ROC Curve

To further evaluate the combined predictive value of the independent predictive factors identified above, the seven indicators from the multivariate analysis, including WBC, neutrophil count, TNF-α, C3, C4, IgA, and IgG, were analyzed collectively using ROC curve analysis to assess their overall predictive performance. As shown in Fig. 2, the combined model demonstrated strong discriminatory capacity for respiratory failure in patients with community-acquired pneumonia, with an area under the curve of 0.853 (95% CI: 0.802–0.903). At the optimal cut-off value of 0.246, the model achieved a sensitivity of 79% and a specificity of 82%. These results indicate that the composite

Table 2. Univariate logistic regression analysis of factors associated with acute respiratory failure.

Variables	β	SE	Z	*p*-value	OR (95% CI)
Smoking					
Never					1.000 (Reference)
Current/Former	–0.047	0.273	–0.171	0.864	0.954 (0.559–1.631)
Gender					
Female					1.000 (Reference)
Male	–0.069	0.268	–0.257	0.797	0.933 (0.552–1.578)
Comorbidities					
Hypertension	0.316	0.320	0.987	0.324	1.372 (0.7321–2.569)
COPD	0.529	0.363	1.458	0.145	1.697 (0.833–3.454)
Diabetes mellitus	–0.247	0.651	–0.379	0.705	0.782 (0.218–2.798)
Heart disease	1.327	1.009	1.315	0.189	3.768 (0.521–27.233)
Early treatment factors					
Broad–spectrum antibiotic use	–0.269	0.280	–0.963	0.336	0.764 (0.441–1.322)
Guideline–concordant therapy	–0.444	0.311	–1.427	0.153	0.64 2(0.349–1.180)
Age	0.003	0.014	0.232	0.817	1.003 (0.976–1.031)
BMI	0.015	0.036	0.419	0.675	1.015 (0.945–1.091)
WBC	0.707	0.152	4.637	<0.001	2.028 (1.504–2.734)
Neutrophils	0.448	0.142	3.167	0.002	1.566 (1.186–2.066)
Lymphocytes	1.476	0.791	1.865	0.062	4.374 (0.928–20.620)
IL-6	–0.005	0.015	–0.320	0.749	0.995 (0.966–1.025)
IL-8	0.045	0.153	0.297	0.766	1.046 (0.776–1.412)
CRP	–0.013	0.007	–1.911	0.056	0.987 (0.973–1.000)
TNF-α	0.082	0.029	2.807	0.005	1.086 (1.025–1.150)
C3	–3.538	0.551	–6.425	<0.001	0.029 (0.010–0.086)
C4	–2.201	0.826	–2.663	0.008	0.111 (0.022–0.559)
IgG	–0.227	0.108	–2.111	0.035	0.797 (0.645–0.984)
IgM	0.037	0.491	0.075	0.940	1.037 (0.396–2.715)
IgA	–0.412	0.187	–2.200	0.028	0.662 (0.459–0.956)

SE, standard error; OR, odds ratio; CI, confidence interval.

Table 3. Multivariate logistic regression analysis of factors associated with acute respiratory failure .

Variables	β	SE	Z	*p*-value	OR (95% CI)	VIF
WBC	0.653	0.175	3.728	<0.001	1.922 (1.363–2.709)	1.041
Neutrophils	0.497	0.172	2.880	0.004	1.643 (1.172–2.304)	1.027
TNF-α	0.098	0.035	2.810	0.005	1.103 (1.030–1.181)	1.006
C3	–3.398	0.600	–5.665	<0.001	0.033 (0.010–0.108)	1.050
C4	–2.649	0.998	–2.654	0.008	0.071 (0.010–0.500)	1.009
IgG	–0.285	0.135	–2.108	0.035	0.752 (0.577–0.980)	1.005
IgA	–0.578	0.237	–2.439	0.015	0.561 (0.353–0.893)	1.009

VIF, variance inflation factor. Odds ratios for C3, C4, IgA, and IgG are expressed per 1 g/L increase.

model incorporating these inflammatory and immune indicators provides robust discriminative performance for early identification of CAP patients at high risk of respiratory failure.

4. Discussion

This retrospective study systematically evaluated the predictive value of inflammatory and immune markers for acute respiratory failure in patients with community-acquired pneumonia. The findings demonstrated that white blood cell count, neutrophil count, TNF-α, complement C3 and C4, and immunoglobulin IgA and IgG levels were independent predictors of CAP progression to ARF. Furthermore, when these markers were combined, the combined model exhibited strong discriminative performance (area under the curve [AUC] = 0.853). These findings suggest that excessive systemic inflammatory activation, accompanied by immune dysregulation, represents a core pathophysiological mechanism underlying CAP progression, and that an integrated assessment of inflammatory and immune

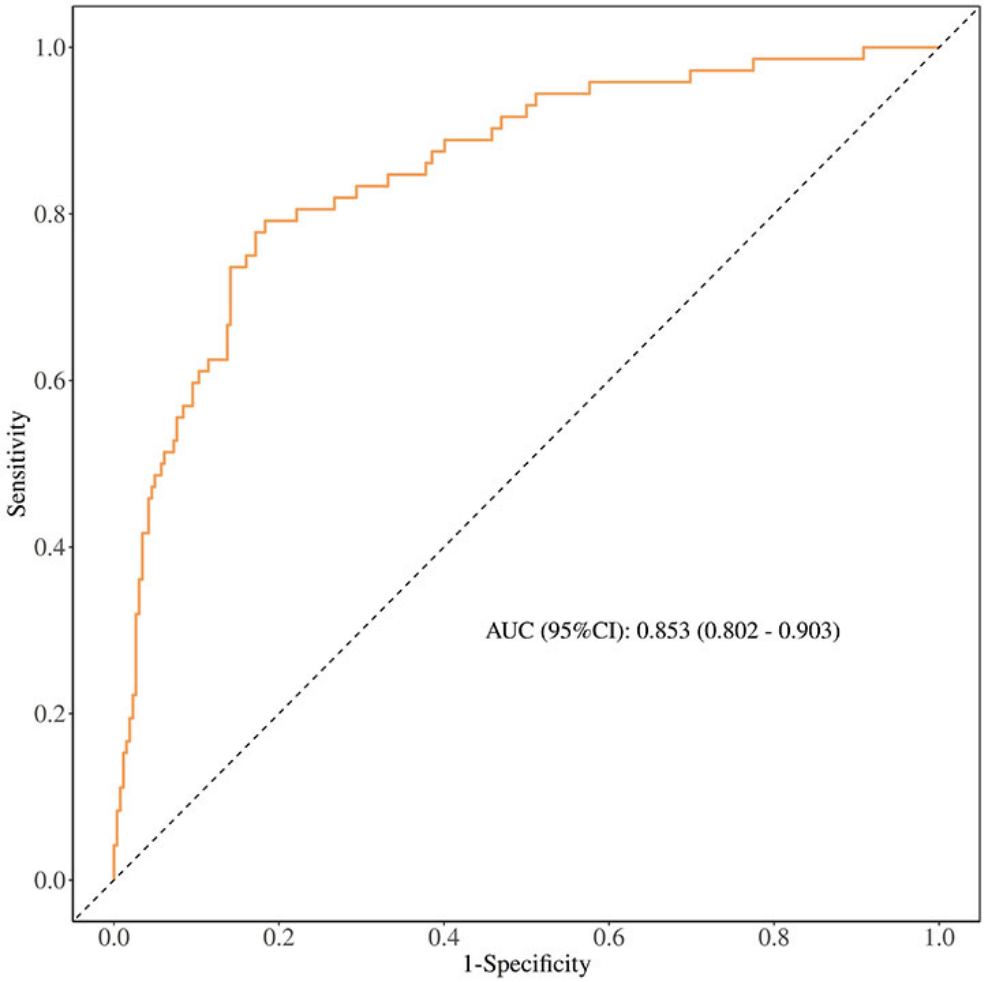

Fig. 2. Receiver operating characteristic (ROC) curve. AUC, area under the curve.

markers may provide clinically relevant evidence for the early identification of high-risk patients.

White blood cell and neutrophil counts represent key inflammatory parameters associated with the progression of community-acquired pneumonia. In the present study, significantly elevated peripheral WBC and neutrophil levels were observed in patients with acute respiratory failure, and remained statistically significant after multivariate adjustment, consistent with established inflammatory pathophysiology. As critical components of the innate immune response, excessive activation and recruitment of neutrophils lead to the release of reactive oxygen species, proteases, and pro-inflammatory mediators, which directly damage alveolar epithelial cells and capillary endothelium, increase vascular permeability, and contribute to the development of acute lung injury and ARF [21]. These findings further suggest that even among unstratified hospitalized patients with general CAP, elevated WBC and neutrophil counts may serve as early indicators of disease progression toward respiratory failure.

In the present study, the inflammatory cytokine TNF-α was identified as an independent risk factor for ARF, with elevated levels significantly associated with increased risk. TNF-α, as an early and central mediator in the inflammatory cascade, can activate endothelial cells, promote the release of downstream inflammatory mediators (such as IL-1β and IL-6), and induce neutrophil adhesion and aggregation within the pulmonary microvasculature, ultimately contributing to tissue injury and organ dysfunction [13,22]. Our findings are consistent with previous studies by Yesildag et al. [23] and Dao et al. [24] on pneumonia, highlighting the pivotal role of upstream inflammatory mediators in driving progression from CAP to severe disease. Targeted monitoring and modulation of these key inflammatory pathways may therefore represent a promising direction for future therapeutic interventions.

Notably, this study found that levels of complement components C3 and C4 were significantly reduced in CAP patients who developed acute respiratory failure, and were independently associated with a protective effect in the multivariate model (i.e., decreased C3 and C4 levels were associated with an increased risk of ARF). It is important to emphasize that the reported odds ratios correspond to a change of 1 g/L, which represents a relatively large increment com-

pared with the interquartile range observed in our cohort. Accordingly, although indicating a strong inverse relationship, the OR values likely reflect a more moderate protective effect across the physiological range of patients. This observation is consistent with current understanding of the dual role of the complement system in pulmonary infection and acute lung injury: during the early stages of infection, complement exerts a protective role by promoting pathogen clearance and enhancing phagocytosis; however, under conditions of excessive infection or inflammatory activation, the complement cascade is extensively activated, generating large amounts of active fragments (such as C3a and C5a), which may exacerbate local inflammation and tissue damage, and may also lead to depletion of measurable components such as C3 and C4 in circulation [16,25].

Reduced levels of C3 and C4 may therefore have clinical relevance, reflecting previous excessive complement system activation, and may also indicate a state of complement depletion or relative immune dysfunction, thus associated with poorer outcomes. Mechanistic studies have shown that complement activation products can directly promote neutrophil aggregation, increase vascular permeability, and induce the release of inflammatory cytokines. At the same time, complement depletion may impair the capacity of the host to clear pathogens, which may explain why reduced C3 and C4 levels were inversely associated with ARF risk in this study [26,27]. A previous study by Shaldoum [28] has shown that in various pulmonary diseases, patients often exhibit decreased C3 and C4 levels, either independently or concurrently. In other pneumonia-related infections, high-risk patients have also demonstrated significantly lower C3 and C4 levels compared with control groups, consistent with the findings of this study [29]. Therefore, decreased complement levels may serve as a measurable and biologically significant marker of dysregulated immune and inflammatory responses in patients with severe infections.

Furthermore, combining complement markers with inflammatory indicators (e.g., WBC and TNF-α) may provide a more comprehensive representation of the immunopathological processes underlying the progression of CAP to ARF. Excessive inflammatory activation, together with relative immune insufficiency, may jointly contribute to the outcome of CAP progressing to ARF. A study by Rademaker et al. [30] has also reported decreased immunoglobulin levels in severe cases, consistent with the present findings. Therefore, this study integrated indicators representing these two processes (e.g., WBC, TNF-α, C3, and IgG) into a multivariate model. The resulting composite model demonstrated strong predictive performance (AUC = 0.853), suggesting that a combined assessment that captures both inflammatory activation and immune response may improve risk stratification. This approach provides a more systematic perspective for understanding the complex immunopathological mechanisms underlying CAP progression to severe disease. Additionally, the area under the ROC curve reached 0.853, indicating that this combination of indicators has the potential to develop into a clinically applicable early warning tool. Such a model may assist clinicians in identifying potentially high-risk individuals early in the disease course, thereby facilitating timely escalation of monitoring and therapeutic interventions.

The findings of this study should be interpreted in light of several limitations. First, the single-center retrospective design may introduce selection bias, and the generalizability of the findings requires validation in multi-center, prospective studies. Second, although the overall sample size was adequate, the number of outcome events (ARF, n = 72) was relatively modest. Larger cohorts would yield more stable effect estimates. Third, the inclusion criterion requiring completion of a full biomarker panel within 24 hours may have introduced selection bias, as such comprehensive testing is more likely to be performed in patients perceived as having greater disease severity. This may bias the study population toward moderate-to-severe CAP and limit the applicability of the model to the broader CAP population, particularly patients with milder disease. Fourth, all biomarkers were measured only once at admission, precluding assessment of their dynamic changes over time. Fifth, potential confounding variables, such as the initial antibiotic treatment regimens and etiological data, were not incorporated into the analysis, which may have influenced the observed associations. Sixth, the predictive model based on early laboratory biomarkers was not directly compared with established clinical severity scores, such as CURB-65 or Pneumonia Severity Index (PSI), which are widely validated for mortality prediction. Although these scoring systems serve different primary purposes, future comparative analyses may help clarify the complementary roles and potential integration of clinical and biomarker-based assessment tools. Seventh, although a rigorous multi-source verification process for CAP case identification was applied and data quality control measures, including double-entry verification of a random sample, were implemented, some degree of data extraction error cannot be excluded. However, such errors are likely to be non-differential and would tend to bias the results toward the null. Future studies should adopt prospective designs that incorporate etiological data and longitudinal monitoring of biomarkers to further optimize predictive models and explore the clinical value of more specific immune biomarkers, such as complement activation products.

5. Conclusion

This study demonstrates that elevated white blood cell count, neutrophil count, and TNF-α levels are independent risk factors for acute respiratory failure in patients with community-acquired pneumonia, while decreased levels of complement C3 and C4, as well as IgA and IgG,

are independently associated with a protective effect. The combined predictive model based on these indicators exhibits strong discriminative performance, facilitating the early identification of high-risk patients. These findings suggest that, in the clinical management of CAP, both inflammatory activation and immune status should be evaluated concurrently, and that risk stratification based on multiple indicators may provide more comprehensive evidence to support early intervention and improve patient outcomes.

Key Points

• This single-center retrospective cohort study, involving 334 patients with community-acquired pneumonia (CAP), systematically evaluated the predictive value of early-measured inflammatory and immune markers for the development of acute respiratory failure (ARF) within 24 hours of admission.

• Multivariate analysis identified elevated white blood cell count, neutrophil count, and TNF-α levels as independent risk factors for ARF, while decreased levels of complement C3 and C4, and IgA and IgG, were identified as independent protective factors.

• A combined predictive model incorporating these seven indicators demonstrated strong discriminatory performance (AUC = 0.853), indicating its potential utility for early risk stratification in clinical practice.

• The findings underscore the central role of concurrent systemic inflammatory activation and immune dysregulation in the pathogenesis of CAP progression to respiratory failure.

• While providing a pathophysiologically grounded framework for early identification of high-risk patients, the study acknowledges limitations including its retrospective design and potential selection bias, warranting further validation in prospective, multi-center studies.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

JPS and JZ designed the research study. JPS performed the research. JZ analyzed the data. JPS drafted the article. Both authors contributed to the important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Zhuji Sixth People's Hospital (approval number: 2025-06), and all procedures followed the principles of the Declaration of Helsinki. Given that this study employed a retrospective design, used anonymized data, and posed minimal risk to participants, the Ethics Committee of Zhuji Sixth People's Hospital waived the requirement for individual informed consent.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Martin-Loeches I, Reyes LF, Rodriguez A. Severe community-acquired pneumonia (sCAP): advances in management and future directions. Thorax. 2025; 80: 565–575. https://doi.org/10.1136/thorax-2024-222296

[2] Vaughn VM, Dickson RP, Horowitz JK, Flanders SA. Community-Acquired Pneumonia: A Review. JAMA. 2024; 332: 1282–1295. https://doi.org/10.1001/jama.2024.14796

[3] Aliberti S, Cruz CSD, Amati F, Sotgiu G, Restrepo MI. Community-acquired pneumonia. The Lancet. 2021; 398: 906–919. https://doi.org/10.1016/S0140-6736(21)00630-9

[4] Liu YN, Zhang YF, Xu Q, Qiu Y, Lu QB, Wang T, et al. Infection and co-infection patterns of community-acquired pneumonia in patients of different ages in China from 2009 to 2020: a national surveillance study. The Lancet. Microbe. 2023; 4: e330–e339. https://doi.org/10.1016/S2666-5247(23)00031-9

[5] Chaudhuri D, Nei AM, Rochwerg B, Balk RA, Asehnoune K, Cadena R, et al. 2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia. Critical Care Medicine. 2024; 52: e219–e233. https://doi.org/10.1097/CCM.0000000000006172

[6] Ullah AR, Masood A, Amin S, Ali I. Predictive factors and outcomes of severe community acquired pneumonia in patients with respiratory failure. Pakistan Journal of Medical Sciences. 2022; 38: 1031–1037. https://doi.org/10.12669/pjms.38.4.5312

[7] Pan J, Bu W, Guo T, Geng Z, Shao M. Development and validation of an in-hospital mortality risk prediction model for patients with severe community-acquired pneumonia in the intensive care unit. BMC Pulmonary Medicine. 2023; 23: 303. https://doi.org/10.1186/s12890-023-02567-5

[8] Ferriero AM, Di Lella R, Farroni C, Aiello A, Giarratano A, Todaro M, et al. Host-pathogen interaction in community-acquired pneumonia: a focus on the immune response. Frontiers in Cellular and Infection Microbiology. 2026; 16: 1731074. https://doi.org/10.3389/fcimb.2026.1731074

[9] Niederman MS, Torres A. Severe community-acquired pneumonia. European Respiratory Review. 2022; 31: 220123. https://doi.org/10.1183/16000617.0123-2022

[10] Fan L, Xu N, Guo Y, Li L. Enhanced insights into the neutrophil-driven immune mechanisms during *Mycoplasma pneumoniae* infection. Heliyon. 2024; 10: e38950. https://doi.org/10.1016/j.heliyon.2024.e38950

[11] Chai DD, Wang XM, Xing B. Predictive value of systemic immunity index for sepsis in low-medium risk community-acquired pneumonia. Journal of Hainan Medical University. 2024; 30: 113–119. (In Chinese)

[12] Viasus D, Simonetti AF, Estupiñan-Bohórquez AF, Carratalà J. Effects of age and comorbidities on serum levels of inflammatory markers in community-acquired pneumonia. European Journal of Clinical Investigation. 2021; 51: e13480. https://doi.org/10.1111/eci.13480

[13] Rombauts A, Abelenda-Alonso G, Cuervo G, Gudiol C, Carratalà J. Role of the inflammatory response in community-acquired pneumonia: clinical implications. Expert Review of Anti-infective Therapy. 2022; 20: 1261–1274. https://doi.org/10.1080/14787210.2021.1834848

[14] Wang J, Pei L, Zhao T, Liu X, Wang Q, Zhang S, et al. $CD4^+$ T cells related to disease severity in elderly and frailty community-acquired pneumonia patients: A retrospective cohort study. Immunity, Inflammation and Disease. 2023; 11: e1009. https://doi.org/10.1002/iid3.1009

[15] Kuikel S, Pathak N, Poudel S, Thapa S, Bhattarai SL, Chaudhary G, et al. Neutrophil-lymphocyte ratio as a predictor of adverse outcome in patients with community-acquired pneumonia: A systematic review. Health Science Reports. 2022; 5: e630. https://doi.org/10.1002/hsr2.630

[16] Xu Z, Hou XF, Feng CM, Zheng L, Xu DX, Zhao H, et al. The association between serum complement C3a and severity in patients with community-acquired pneumonia. Frontiers in Immunology. 2023; 14: 1034233. https://doi.org/10.3389/fimmu.2023.1034233

[17] Dv P, Ov M, Iu V P, Ln S. Community-acquired pneumonia: immune and metabolic disorders before and after treatment. Journal of Pharmaceutical Negative Results. 2022; 13.

[18] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clinical Infectious Diseases. 2007; 44: S27–S72. https://doi.org/10.1086/511159

[19] Rochwerg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. The European Respiratory Journal. 2017; 50: 1602426. https://doi.org/10.1183/13993003.02426-2016

[20] Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. Journal of Clinical Epidemiology. 1995; 48: 1503–1510. https://doi.org/10.1016/0895-4356(95)00048-8

[21] Grudzinska FS, Brodlie M, Scholefield BR, Jackson T, Scott A, Thickett DR, et al. Neutrophils in community-acquired pneumonia: parallels in dysfunction at the extremes of age. Thorax. 2020; 75: 164–171. https://doi.org/10.1136/thoraxjnl-2018-212826

[22] Nutautiene R, Aleksa I, Janulaityte I, Skrodeniene E, Bieksiene K, Zaliaduonyte D, et al. Role of Inflammatory Markers as a Risk Factor for Community-Acquired Pneumonia Management. Medicina. 2025; 61: 1078. https://doi.org/10.3390/medicina61061078

[23] Yesildag M, Bakdık B, Balasar B, Eroğlu E. Evaluation of the relationship between biomarkers and disease severity in patients with community-acquired pneumonia. European Journal of Therapeutics. 2024; 30: 354–361.

[24] Dao BN, Le HDT, Nguyen KX, Viet TT, Tran CT, Luong TC, et al. Relationship between serum TNF-α, IL-6, and IL-10 levels and disease severity, and changes in the cytokines after treatment in patients with bacterial community-acquired pneumonia. Pneumon. 2023; 36: 1–8. https://doi.org/10.18332/pne/170181

[25] Jayaraman A, Walachowski S, Bosmann M. The complement system: A key player in the host response to infections. European Journal of Immunology. 2024; 54: 2350814. https://doi.org/10.1002/eji.202350814

[26] Wang H, Liu M. Complement C4, Infections, and Autoimmune Diseases. Frontiers in Immunology. 2021; 12: 694928. https://doi.org/10.3389/fimmu.2021.694928

[27] Wang Y, Huang X, Li F, Jia X, Jia N, Fu J, et al. Serum-integrated omics reveal the host response landscape for severe pediatric community-acquired pneumonia. Critical Care. 2023; 27: 79. https://doi.org/10.1186/s13054-023-04378-w

[28] Shaldoum F. C3 and C4 in Patients Suffering from Lung Diseases. Sciences. 2016; 6: 559–566.

[29] Zinellu A, Mangoni AA. Serum Complement C3 and C4 and COVID-19 Severity and Mortality: A Systematic Review and Meta-Analysis With Meta-Regression. Frontiers in Immunology. 2021; 12: 696085. https://doi.org/10.3389/fimmu.2021.696085

[30] Rademaker E, Vernooij LM, van der Poll T, Bonten MJM, Leavis H, Cremer OL, et al. Longitudinal assessment of immunoglobulin response and disease progression in critically ill patients with community acquired pneumonia. Critical Care. 2024; 28: 405. https://doi.org/10.1186/s13054-024-05197-3