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Diagnostic Value of the Combination of Serum T_H1/T_H2 Cytokines, Procalcitonin, and High-sensitivity C-reactive Protein for Predicting the Severity of Pneumonia

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ABSTRACT

T helper 1 (T_H1) and T helper 2 (T_H2) cells can secrete various proinflammatory and anti-inflammatory factors, which can serve as indicators for predicting the severity of pneumonia. However, they are rarely used in combination with procalcitonin (PCT) and high-sensitivity C-reactive protein (hsCRP) detection to predict the severity of pneumonia. The purpose of this study is to investigate the combination of serum T_H1/T_H2 cytokines, PCT, and hsCRP for predicting the severity of community-acquired pneumonia (CAP).

This study observed 58 inpatients with CAP. Analyses were conducted on the serum levels of T_H1/T_H2 cytokines, PCT, and hsCRP; imaging examination results; underlying diseases; pathogens; and the pneumonia severity index (PSI).

The severe pneumonia group showed significantly higher PSI scores, age, and complication rates. Serum IL-2 was notably elevated in severe cases, while a combination of PCT, IL-4, TNF-α, and IFN-γ effectively predicted severe pneumonia, with an AUC of 0.712. Specific alterations in cytokines and biomarkers were identified as risk factors for higher PSI, complications, and prolonged hospitalization.

The combined detection of PCT, IL-4, TNF-α, and IFN-γ provides a potential tool for predicting severe CAP, and distinct biomarker profiles are associated with different clinical outcomes.

Keywords: Community-acquired pneumonia; High-sensitivity C-reactive protein; Procalcitonin; Serum T_H1/T_H2 cytokines

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INTRODUCTION

Community-acquired pneumonia (CAP) is a common infectious disease of the respiratory system. Approximately 5% to 20% of CAP cases progress to

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severe pneumonia (SP), for which the 30-day mortality rate in the intensive care unit (ICU) is 23%–47%.[1] Research has demonstrated that the positivity rate of etiological testing is minimal, and anti-infection protocols based on etiological results alone postpone treatment for the majority of patients.

Procalcitonin (PCT) and high-sensitivity C-reactive protein (hsCRP) are commonly used in medical settings as markers for identifying infectious illnesses. However, they are not precise markers for assessing the severity of pneumonia. Some studies have shown that serum T helper 1 (T_H1)/T helper 2 (T_H2) cytokines may play an important role in this regard.[2] T_H1 cytokines are secreted by T_H1 cells and mainly include interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), which are up-regulated during bacterial or viral infection. These cytokines can promote the elimination of intracellular pathogens by activating macrophages and are mainly involved in the process of cellular immune response.[3,4]

T_H2 cells secrete T_H2 cytokines such as interleukin-4 (IL-4), interleukin-6 (IL-6), and interleukin-10 (IL-10), which boost the humoral immune response of B cells and are important for eliminating parasites and extracellular pathogens, as well as triggering allergic reactions.[5] These cytokines are classified as either proinflammatory (TNF-α, IFN-γ, IL-2, IL-4, IL-6) or anti-inflammatory (IL-10) and play a significant role in immune regulation. The maintenance of immune homeostasis is highly dependent on the equilibrium of cytokines. If the cytokine balance is disrupted, immune function can become imbalanced, which leads to the progression of diseases.[6,7] This study assessed the diagnostic significance of the combination of serum T_H1/T_H2 cytokines, PCT, and hsCRP for CAP and explored its relationship with the severity of pneumonia according to the widely employed Pneumonia Severity Index (PSI).

MATERIALS AND METHODS

Study Participants

During the period spanning from September 2021 to December 2023, a total of 58 individuals diagnosed with CAP were selected as participants for this retrospective study. The participants were recruited from the Department of Respiratory and Critical Care Medicine at Shenzhen Hospital of Southern Medical University. Patients aged between 14 and 93 years of both genders were included in the study. Clinical information was gathered within 24 hours of admission and 3 days post-treatment, including imaging results, complications, preexisting conditions, identified pathogens, PSI scores, and the serum levels of T_H1/T_H2 cytokines, PCT, and hsCRP. The criteria for inclusion and grouping were determined according to the guidelines outlined by the American Thoracic Society and the Infectious Diseases Society of America. CAP was diagnosed in 49 patients (84.48%), while severe pneumonia was diagnosed in 9 patients (15.52%). We also analyzed the relationship between changes in serum T_H1/T_H2 cytokines, PCT, and hsCRP levels and length of hospital stay.

Serum Analyses

A quantity of 4 mL of venous blood was acquired from patients with CAP to measure the levels of T_H1/T_H2 cytokines (specifically TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-10), PCT, and hsCRP in the serum. The blood sample was obtained using a vacuum blood-collection tube that contained a gel for separation and then incubated at a temperature of 37°C for 30 minutes. Following the incubation period, the sample was centrifuged at 1000 *g* for a duration of 10 minutes. Then, the serum was immediately separated.

The separated serum was frozen at −70°C for the detection of PCT, hsCRP, and serum T_H1/T_H2 cytokines. A Roche cobas e 411 automatic electrochemiluminescence immunoassay analyzer was used to measure PCT. The reagents used were provided by Roche, and the normal reference range is 0–0.046 ng/mL.

hsCRP was measured using the latex-enhanced immune scattering immunoturbidimetry method, a CRP-M100 protein immunoassay analyzer, and a Mindray hsCRP assay kit. The normal reference range is 0–5 mg/L. A CBA human T_H1/T_H2 cytokine detection kit (ACEA) was used to measure TNF-α, IFN-γ, IL-2, IL-4, IL-6, and IL-10 with an ACEA NovoCyte flow cytometer. Each cytokine had a standard curve that was obtained using the standard substance provided in the kit. Six cytokine levels can be obtained for each test. The tests were performed according to the manufacturer's instructions, and the results ranged from 2.4 to 10 000 pg/mL.

Statistical Analysis

Statistical analysis was performed using the software SPSS 27.0. Quantitative data are expressed as the means±standard deviations, and an independent-sample

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t test was used for comparisons between groups. Categorical data were expressed as frequencies (%), and the chi-squared test was used for comparisons between groups. Linear regression was used to evaluate the correlation between each variable and the PSI, and backward stepwise regression was performed based on the AIC criteria. The prognostic value of each variable was evaluated by analyzing the receiver operating characteristic (ROC) curve. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Patient Clinical Information and Findings

This study included 58 individuals with CAP, who were divided into two groups: a common pneumonia group (49 patients; 84.48%) and a severe pneumonia group (9 patients; 15.52%). No significant differences in sex, pathogen, or chest CT results were observed between these groups (p>0.05). Age, the rates of underlying diseases and complications, and PSI values were significantly higher in the severe pneumonia group than in the common pneumonia group (Table 1).

Serum Levels in Different Groups

Within 24 hours after admission, the severe pneumonia group exhibited notably elevated serum IL-2 levels compared to the common pneumonia group (p<0.05). No significant variances were observed in the remaining parameters between the two groups (Table 2).

After excluding two instances of Mycoplasma pneumonia and one instance of Candida pneumonia, a total of 55 patients were included in the analyses. Patients with bacterial pneumonia were compared to patients with viral pneumonia. The results are shown in Figure 1. Levels of IL-6, IFN-γ, PCT, hsCRP, and neutrophil percentage were higher in the bacterial pneumonia group, whereas levels of IL-2, IL-4, IL-10, and TNF-α were higher in the viral pneumonia group. The white blood cell (WBC) count and PCT levels were significantly different between the two groups (p<0.05).

Table 1. Comparison of general data between the common pneumonia group and the severe pneumonia group

Variables	All patients (N=58)	Common pneumonia (N=49)	Severe pneumonia (N=9)	*p*
Age, y	59.8 ± 21.70	56.8 ± 21.70	76.4 ± 12.70	0.001
Sex				1.000
Male	31 (53.40%)	26 (53.10%)	5 (55.60%)	
Female	27 (46.60%)	23 (46.90%)	4 (44.40%)	
Pathogen				0.529
Bacteria	46 (79.30%)	40 (81.60%)	6 (66.70%)	
Virus	10 (17.20%)	7 (14.30%)	3 (33.30%)	
Mycoplasma	2 (3.45%)	2 (4.08%)	0 (0.00%)	
Underlying diseases				0.002
≥ 2	19 (32.80%)	12 (24.50%)	7 (77.80%)	
1	16 (27.60%)	14 (28.60%)	2 (22.20%)	
0	23 (39.70%)	23 (46.90%)	0 (0.00%)	
Complications				<0.001
0	41 (70.70%)	41 (83.70%)	0 (0.00%)	
≥1	17 (29.30%)	8 (16.30%)	9 (100%)	
Chest CT				1.000
Patchy	41 (70.70%)	34 (69.40%)	7 (77.80%)	
GGO	8 (13.80%)	7 (14.30%)	1 (11.10%)	
Other	9 (15.50%)	8 (16.30%)	1 (11.10%)	
PSI	92.50 ± 39.40	81.40 ± 28.80	153 ± 34.80	<0.001

CT: computed tomography; GGO: ground-glass opacity; PSI: pneumonia severity index.

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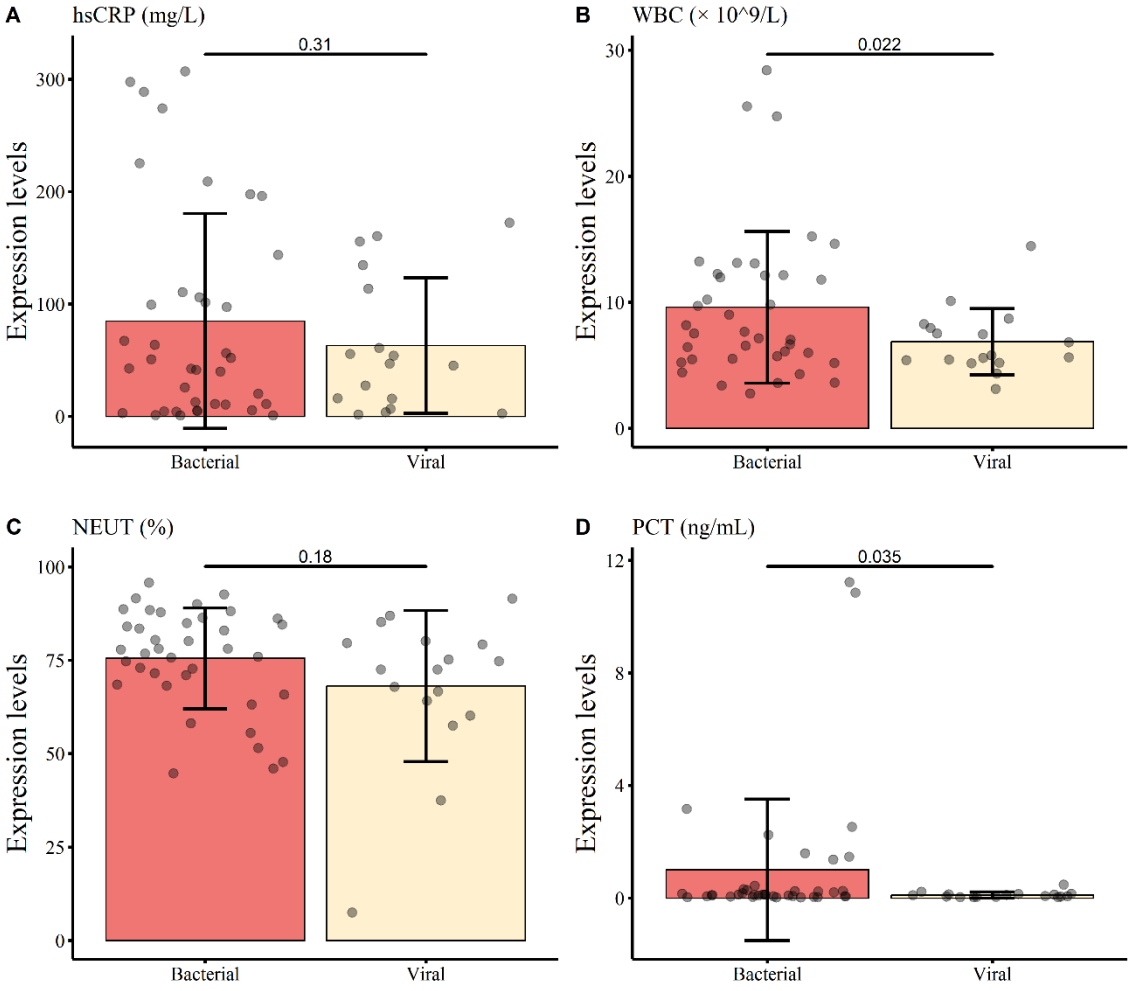
Table 2. Comparison of various indices between the common pneumonia group and the severe pneumonia group

Indicators	All patients (N=58)	Common pneumonia (N=49)	Severe pneumonia (N=9)	*p*
hsCRP, mg/L	77.80 ± 84.10	72.50 ± 80.50	107 ± 102	0.367
WBC, × 10^9/L	8.75 ± 5.23	8.53 ± 4.38	9.96 ± 8.80	0.645
NEUT, %	73.3 ± 15.60	72.10 ± 15.60	80.1 ± 14.90	0.170
PCT, ng/mL	0.70 ± 2.07	0.52 ± 1.64	1.68 ± 3.63	0.370
IL-2, pg/mL	0.99 ± 1.92	1.10 ± 2.07	0.40 ± 0.25	0.026
IL-4, pg/mL	2.43 ± 3.78	2.61 ± 4.05	1.47±1.58	0.157
IL-6, pg/mL	78.3 ± 239	39.70 ± 66.10	289±566	0.224
IL-10, pg/mL	5.27 ± 10.20	4.93 ± 10.70	7.13±6.47	0.417
TNF-α, pg/mL	9.89 ± 12.10	9.72 ± 11.80	10.80±14.40	0.835
IFN-γ, pg/mL	33.70 ± 90.80	38.10 ± 98.20	9.76±13.00	0.059

hsCRP: high-sensitivity C-reactive protein; IFN: interferon; IL: interleukin; NEUT: neutrophil; PCT: procalcitonin; TNF: tumor necrosis factor; WBC: white blood cell.



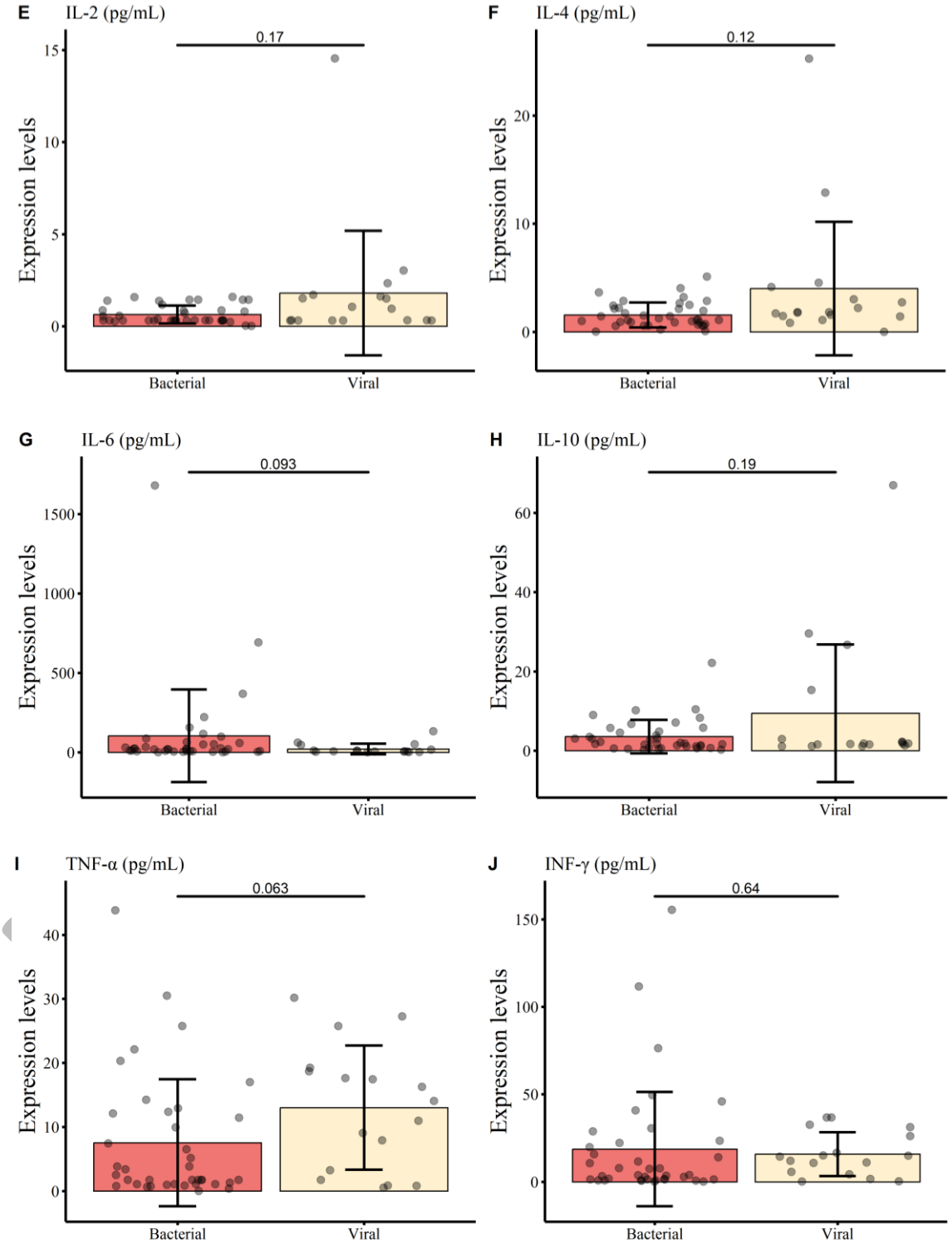


Figure 1. Comparison of various indices between the bacterial pneumonia group and the viral pneumonia group

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Correlations

Linear regression analysis was conducted with the PSI as the dependent variable and the serum T_H1/T_H2 cytokines, PCT, and hsCRP as the independent variables. The results of stepwise regression showed that increases in PCT and TNF-α and decreases in IL-4 and IFN-γ were associated with increases in the PSI (Table 3).

ROC curves were plotted according to the multivariate model, and the results showed that when the Youden index was maximized, the area under the curve (AUC) of the combination of PCT, IL-4, TNF-α, and IFN-γ was 0.712 (95% confidence interval (CI): 0.517–0.907). The sensitivity and specificity were 66.67% and 71.43%, respectively (Figure 2).

Ordinal logistic regression analysis was performed with the rate of complications as the dependent variable and age, sex, and serum indices as independent variables. The results of stepwise regression showed that the increase in complications in pneumonia patients was associated with older age, increased neutrophil percentage, and decreased WBC and IL-10 levels (Table 4).

Linear regression analysis was performed with hospitalization time as the dependent variable and changes in serum indices as the independent variable. The results of stepwise regression showed that increases in IL-4 and decreases in IL-2 and TNF-α at 3 days after admission were risk factors for longer hospitalization time (Table 5).

Table 3. Risk factors for patients' disease severity

Variables	Univariate linear regression			Multivariate linear regression		
	Beta	Standard Error	*p* value	Beta	Standard Error	*p*
PCT	0.55	0.33	0.103	3.61	2.38	0.136
IL-4	−1.47	2.74	0.594	−2.82	1.49	0.064
TNF-α	0.35	0.52	0.494	0.88	0.51	0.094
IFN-γ	−0.16	0.44	0.708	−0.15	0.06	0.017
hsCRP	0.07	0.06	0.232	-	-	-
NEUT%	0.24	1.01	0.810	-	-	-
IL-2	3.87	2.49	0.126	-	-	-
IL-6	−2.40	1.35	0.082	-	-	-
IL-10	0.02	0.02	0.354	-	-	-

hsCRP: high-sensitivity C-reactive protein; IFN: interferon; IL: interleukin; NEUT: neutrophil; PCT: procalcitonin; TNF: tumor necrosis factor.

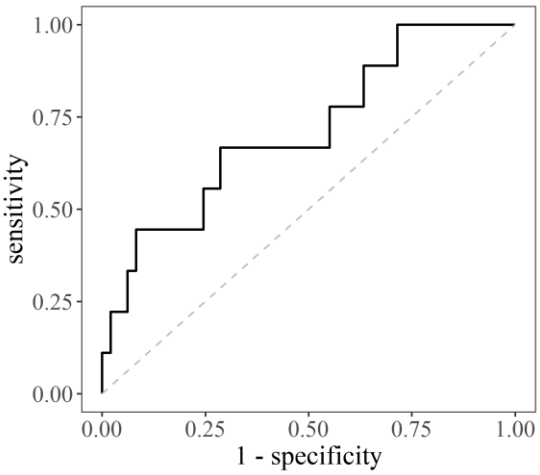

Figure 2. ROC curve of PCT, IL-4, TNF-α, and IFN-γ for predicting the incidence of severe pneumonia.

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Table 4. Risk factors for complications in patients with pneumonia

Variables	Univariate ordinal logistic regression		Multivariate ordinal logistic regression	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.10 (1.06 to 1.14)	<0.001	1.13 (1.08 to 1.19)	<0.001
WBC	0.98 (0.90 to 1.07)	0.625	0.74 (0.59 to 0.95)	0.016
NEUT%	1.03 (0.99 to 1.06)	0.104	1.06 (1.01 to 1.11)	0.016
IL-2	0.62 (0.29 to 1.33)	0.221	0.72 (0.36 to 1.44)	0.351
IL-6	1.00 (0.99 to 1.01)	0.835	1.00 (1.00 to 1.01)	0.076
IL-10	0.95 (0.89 to 1.03)	0.206	0.87 (0.77 to 0.98)	0.023
TNF-α	0.97 (0.92 to 1.02)	0.183	0.95 (0.88 to 1.02)	0.127
Sex	0.72 (0.28 to 1.88)	0.503	-	-
hsCRP	1.00 (1.00 to 1.01)	0.615	-	-
PCT	1.14 (0.90 to 1.44)	0.269	-	-
IL-4	0.77 (0.56 to 1.05)	0.100	-	-
IFN-γ	0.99 (0.98 to 1.00)	0.174	-	-

CI: confidence interval; hsCRP: high-sensitivity C-reactive protein; IFN: interferon; IL: interleukin; NEUT: neutrophil; OR: odds ratio; PCT: procalcitonin; TNF: tumor necrosis factor; WBC: white blood cell.

Table 5. Risk factors for hospitalization time

Serum indicators	Univariate ordinal logistic regression			Multivariate ordinal logistic regression		
	Beta	Standard Error	*p*	Beta	Standard error	*p*
PCT	3.446	0.973	0.001	1.514	0.840	0.077
IL-2	0.123	1.008	0.903	−4.239	1.006	<0.001
IL-4	1.088	0.494	0.032	3.492	0.571	<0.001
TNF-α	−0.565	0.280	0.049	−1.720	0.320	<0.001
hs-CRP	0.030	0.030	0.326	-	-	-
WBC	0.231	0.308	0.455	-	-	-
NEUT%	0.010	0.091	0.913	-	-	-
IL-6	0.007	0.011	0.562	-	-	-
IL-10	0.045	0.134	0.737	-	-	-
IFN-γ	0.017	0.039	0.663	-	-	-

IL: interleukin; PCT: procalcitonin.

DISCUSSION

The annual incidence and mortality rates of CAP are increasing worldwide, and the condition can lead to multiple organ dysfunction or death.[8] Appropriate monitoring is important to reduce the risk of common pneumonia progressing to severe pneumonia or death. In this study, there were no differences in sex, pathogens, and chest CT findings between the common pneumonia group and the severe pneumonia group. The small

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number of cases could be the cause of this absence of distinctions. However, the severe pneumonia group had significantly greater age, rates of underlying illnesses and complications, and PSI values than the common pneumonia group.

The findings indicated a significant increase in the serum IL-2 level among individuals with severe pneumonia compared to those with common pneumonia. Activated T lymphocytes produce IL-2, which binds to the IL-2 receptor expressed by lymphocytes.[9] Research has demonstrated that IL-2 has the ability to decrease the production of proinflammatory cytokines such as IL-1β and TNF-α.[10] Moreover, excessive expression of TNF-α can contribute to the progression of inflammation, which has a detrimental impact on human health.[11] This phenomenon also partly explains why a decrease in IL-2 is a risk factor for increased complications among patients with pneumonia.

No statistical differences were found in other biochemical indicators, such as IL-4. This lack of differences could also be attributed to the limited sample size. Nevertheless, the results in Table 2 demonstrate that compared to the common pneumonia group, PCT, hsCRP, IL-6, TNF-α, IL-10, and neutrophil levels were greater in the severe pneumonia group, while the levels of IL-4 and IFN-γ were lower. This is consistent with many international research results.[12–14] The reason for these differences may be that the appropriate expression of IL-6 and IL-10 offers protective effects against pulmonary infection,[15,16] while IFN-γ has the opposite effect.[17]

Table 4 shows that advanced age, a higher neutrophil percentage, as well as lower WBC count and IL-10 levels, are associated with pneumonia complications. Research has demonstrated that IFN-γ can be used to treat COVID-19.[18] These findings may seem a little contradictory, but it may be that various cytokines should be in a state of equilibrium and that the overexpression of a particular cytokine may lead to adverse effects.

The linear regression analysis results indicated that greater PSI values were associated with a rise in PCT and TNF-α, as well as a decrease in IL-4 and IFN-γ (Table 3). The ROC curve analysis revealed that the combined AUC of PCT, IL-4, TNF-α, and IFN-γ was 0.712. When the Youden index was maximized, the sensitivity for this combination was 66.67%, and the specificity was 71.43%. Consequently, this combination of indicators could be used to predict the occurrence of severe pneumonia.

This study compared groups with bacterial pneumonia and viral pneumonia. The positive rate of sputum culture of CAP was low in clinical work.[19] We identified bacterial cases based on clinical symptoms of pneumonia, chest CT infection lesions characterized by patchy consolidation, and effective antibiotic treatment, while viral pneumonia was characterized by clinical symptoms of pneumonia, chest CT infection lesions characterized by ground glass changes, and symptoms improving without antibiotic treatment (most of these cases involved COVID-19).

The findings in Figure 1 suggest that the levels of PCT, WBC, hsCRP, and IFN-γ, as well as the proportion of neutrophils, were elevated in the bacterial pneumonia cohort compared to the viral pneumonia cohort. Statistically significant differences were observed in WBC count and PCT between the two groups ($p < 0.05$), while the differences in IL-2, IL-4, IL-10, and TNF-α were insignificant. These results align with clinical recommendations and the majority of global research outcomes.[20,21]

After 3 days of treatment, serum T_H1/T_H2 cytokines, PCT, and hsCRP concentrations were measured again, and linear regression analysis was performed. The results of the stepwise regression showed that increases in IL-4 and decreases in IL-2 and TNF-α were risk factors for longer hospital stays. The presence of elevated IL-4 levels could potentially explain the increased severity of infections, which leads to longer hospital stays. Adequate production of IL-2 and TNF-α can contribute to protecting against lung infections.

In summary, our findings demonstrate that the combination of PCT, IL-4, TNF-α, and IFN-γ serves as a reliable predictor for severe pneumonia. Beyond this predictive model, the study reveals distinct inflammatory profiles associated with disease severity and etiology: elevated PCT and TNF-α alongside reduced IL-4 and IFN-γ levels correlate with higher PSI scores and greater severity, while older age, increased neutrophil percentage, and decreased WBC and IL-10 concentrations are linked to a higher risk of complications. Furthermore, elevated PCT and IL-4 combined with decreased IL-2 and TNF-α levels are associated with prolonged hospitalization. These results collectively underscore the interplay between specific inflammatory mediators and clinical outcomes, highlighting the potential of cytokine profiling not only in early risk stratification but also in anticipating complications and resource use in pneumonia

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management. Unfortunately, due to various factors, the data volume in this study is relatively small, resulting in certain deviations in the research results. In the future, large-scale, multicenter studies need to be established to further validate these research findings.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Shenzhen Hospital of Southern Medical University in accordance with the Helsinki Declaration (No. SZYYEC2021R113).

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Due to ethical restrictions, the raw data cannot be made publicly available. However, de-identified data may be obtained from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

This manuscript does not involve any artificial intelligence.

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