

# Construction and Verification of Risk Predictive Nomogram in Patients of Connective Tissue Disease with Severe Pneumonia

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**Purpose:** To construct Risk Predictive Nomogram in patients of connective tissue disease (CTD) with severe pneumonia.

**Methods:** Eighty CID patients with severe pneumonia in rheumatology and respiratory department of chongqing University Three Gorges hospital from January 2020 to December 2022 were retrospectively reviewed and analyzed. Independent risk factors for severe pneumonia in CTD were screened by univariate and binomial logistic regression analysis. The nomogram was constructed by R software. Area under the curve (AUC) of receiver operating characteristic (ROC) was used to evaluate the nomogram's discrimination, and the calibration curve and Hosmer–Lemeshow test were used to reflect the nomogram's calibration.

**Results:** The study cohort was including 48 patients in the general pneumonia group and 32 patients in the severe pneumonia group. The model variables included Ln CD4/CD8, Ln CRP, Ln PCT and Ln IFN- $\gamma$ . Hosmer–Lemeshow test P value less than 0.05 ( $\chi^2 = 7.753$ ,  $P = 0.458$ ), the area under ROC curve of nomogram was 0.9084 (95% CI: 0.8461–0.9707), and the optimal cutoff value of nomogram was 0.490, the sensitivity was 0.872, the specificity was 0.848. In a retrospective study design, 50 patients with CTD complicated with pneumonia admitted to the same hospital from January to June 2023 were selected to verify the model. The nomogram verification results showed Hosmer–Lemeshow test ( $\chi^2 = 7.1171$ ,  $P = 0.5241$ ), AUC value was 0.8958 (95% CI: 0.808–0.9837), and optimal cutoff value was 0.664, the sensitivity was 0.988, the specificity was 0.812.

**Conclusion:** The prediction nomogram in this study is helpful for clinical staffs to screen high-risk patients with severe pneumonia in CTD, and has high clinical application value.

**Keywords:** connective tissue disease, severe pneumonia, prediction model, nomogram

## Introductions

Severe pneumonia is a common acute and critical disease in clinical practice, characterized by acute onset, rapid progression, multiple complications and high mortality rate. It is a major disease threatening human life and health worldwide. Although the diagnosis and treatment of severe pneumonia are constantly updated and standardized with advances in medical care, the patient mortality rate can still be as high as about 30%.<sup>1</sup>

Connective tissue disease (CTD) is a group of systemic diseases characterized by autoimmune mediated organ dysfunction. It mainly includes systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, inflammatory myopathy and so on. CTD patients are susceptible to complications of infections due to endogenous immune imbalance, glucocorticoid and immunosuppressive drug use leading to immunocompromised patients. Some studies have shown that pulmonary infections account for the first place of infections in CTD hospitalized patients.<sup>2</sup> Unlike ordinary patients, patients with CTD often have atypical symptoms of lung infection, which can be easily overlooked in the early stage, and the disease progresses more rapidly, which can easily develop into severe pneumonia if not treated in time. Severe pneumonia is the most common cause of hospitalization and ICU admission in CTD patients, and is one of the main causes of death in CTD patients.<sup>3</sup> Current studies have shown that timely and effective therapeutic measures for CTD



patients complicated with severe pneumonia can significantly improve the prognosis.<sup>4</sup> Therefore, early identification of high-risk patients and taking active intervention measures are urgent problems for clinicians to solve. It is necessary to identify independent risk factors for CTD-complicated severe pneumonia and further construct a logistic regression prediction model to early identify patients with CID-complicated severe pneumonia, so as to facilitate early screening of high-risk groups, early intervention, and improvement of prognosis, thereby reducing the mortality rate.

Sex and age were routine baseline characteristics of the included patients. Biomarkers such as white blood cell count (WBC), neutrophil percentage (NEU%), platelet count (PLT), lymphocyte count (LY), C-reactive protein (CRP), procalcitonin (PCT), CD4+ T lymphocyte count, CD8+ T lymphocyte count, and CD4/CD8 ratio can represent immune-inflammatory responses and are often associated with the severity of the disease. Additionally, pro-inflammatory factors such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ),<sup>5,6</sup> interferon- $\gamma$  (IFN- $\gamma$ ),<sup>7</sup> interleukin-4 (IL-4),<sup>6</sup> interleukin-6 (IL-6),<sup>5</sup> and interleukin-17A (IL-17A)<sup>8</sup> have been proven to be upregulated in the serum of patients with severe pneumonia. Hence, we collected the data of the aforementioned variables for research. Nomograms are seldom utilized for predicting the risk of severe pneumonia in patients with connective tissue diseases (CTD). Our objective was to develop a nomogram capable of accurately predicting the occurrence risk of severe pneumonia in CTD patients. In this study, we retrospectively assessed the clinical characteristics and representative biomarkers of CTD patients complicated with severe pneumonia and identified the independent risk factors for CTD patients complicated with severe pneumonia. Eventually, a dynamic nomogram model comprising four independent risk factors was successfully constructed, which demonstrated excellent calibration and discrimination.

## Object and Method

### Research Object

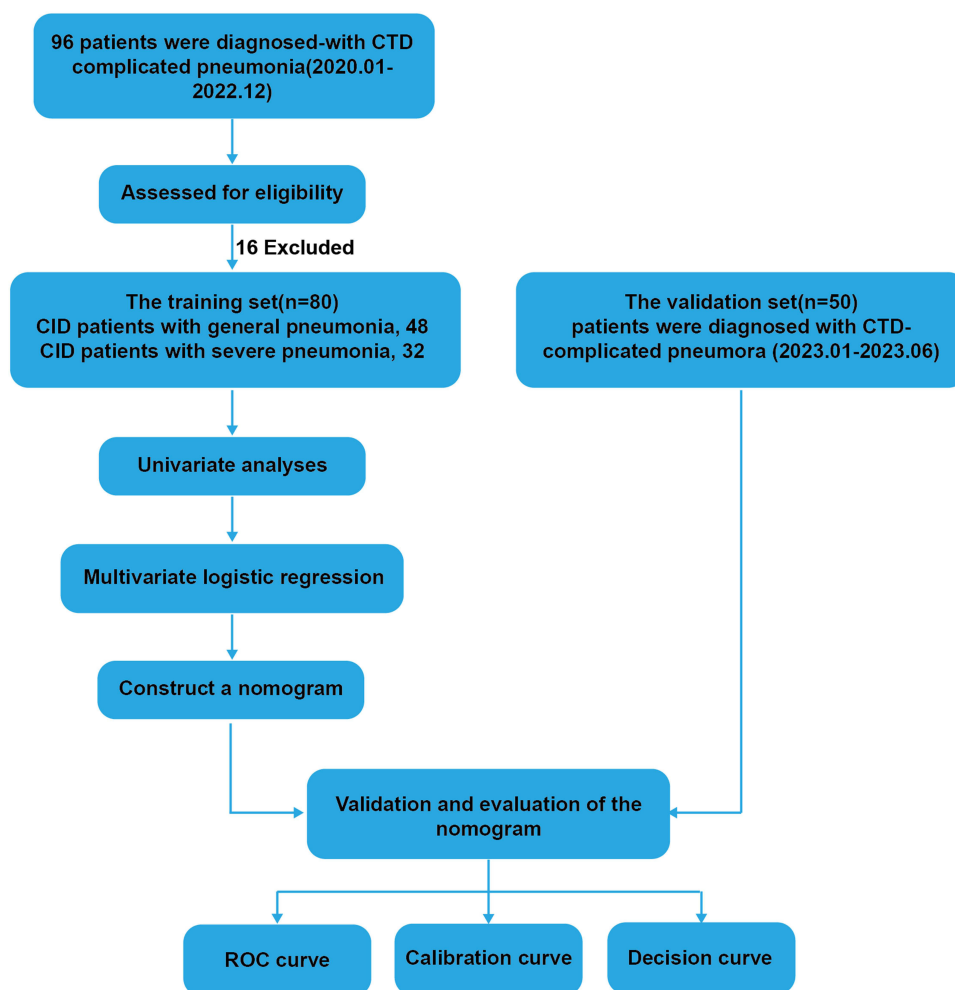
A total of 130 patients with CTD complicated with pneumonia admitted to the Rheumatology and Immunology Department of the Chongqing University Three Gorges Hospital from January 2020 to June 2023 were selected as the study objects. Patients admitted from January to December 2020 were selected as the training group, and patients from January to June 2023 were selected as the validation group. For details, refer to [Figure 1](#). CTD patients included patients with rheumatoid arthritis, systemic lupus erythematosus, idiopathic inflammatory myopathy, and Sjogren's syndrome. Inclusion criteria: (1) age over 18 years old with radiologically confirmed pneumonia; (2) case data of HIS system were complete. Exclusion criteria: (1) incomplete case data in HIS system; (2) persons under the age of 18; (3) pregnant women; (4) non-infectious pneumonia, such as diffuse alveolar hemorrhage, acute lupus pneumonia, interstitial pneumonia, etc. This study had passed the ethical review of the Chongqing University Three Gorges Hospital (Review Opinion: No. 165 in 2022).

### Diagnostic Criteria

The diagnosis of rheumatoid arthritis was based on the RA classification criteria issued by the European/Anti-Rheumatic League of the American Association of Rheumatology in 2010,<sup>9</sup> and the diagnosis of systemic lupus erythematosus and idiopathic inflammatory myopathy was based on the corresponding diagnostic criteria formulated by the rheumatology Branch of the Chinese Medical Association.<sup>10,11</sup> The diagnosis of Sjogren's syndrome was based on the 2016 ACR/EULAR Primary Sjogren's Syndrome classification diagnostic criteria,<sup>12</sup> and severe pneumonia was based on the Chinese Adult Hospital Acquired Pneumonia and Ventilator-associated Pneumonia Diagnosis and Treatment Guidelines.<sup>13</sup>

### Data Collection

General information and laboratory tests: Gender, age, white blood cell count (WBC), neutrophil percentage (NEU%), platelet count (PLT), lymphocyte count (LY), C-reactive protein (CRP), procalcitonin (PCT), CD4+ T lymphocyte count, and CD8+ T lymphocyte count, CD4/CD8, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-4 (IL-4), Interleukin-6 (IL-6), Interleukin-17A (IL-17A).



**Figure 1** Flow chart of the study process.

## Statistical Analysis

The R Programming Language (4.3.3) was used for statistical analysis. Kolmogorov–Smirnov test was used to analyze the normality of continuous variables. The measurement data of normal distribution were described by mean (standard deviation) and compared by Mann–Whitney *U*-test. The measurement data of skewness distribution were described by M (P25, P75) and compared by Wilcoxon rank sum test. The count data were all described by frequency, percentage or proportion. The  $\chi^2$  test (with Yates' continuity correction applied when appropriate) and Fisher's Exact test were used for comparison among groups. Wilcoxon rank sum test was used for comparison of rank data. The variables that entered the model, CRP, PCT, CD4/CD8, TNF- $\alpha$ , IFN- $\gamma$ , IL-4, IL-6, and IL-17A, were normalized by natural logarithm transformation. Binary Logistic regression analysis was used to screen independent risk factors for severe pneumonia. First, univariate Logistic regression was performed, and variables with significant differences were entered into multivariable Logistic regression model. After multivariable Logistic regression test, variables with significant differences were used to construct the nomogram prediction model of "rms" package. The area under receiver operator characteristic (ROC) curve was used to evaluate the differentiation of the model. The calibration curve and Hosmer–Lemeshow test were used to reflect the calibration degree of the model. Decision curve analysis assesses clinical utility by considering the possible range of patient risks and benefits.  $P < 0.05$  indicated that the difference was statistically significant.

## Results

### Patient General Data

A total of 130 patients with CTD complicated with pneumonia were included in this study, 80 patients were in the training group and 50 patients were in the validation group. There was no statistical significance in the general data between the two groups ( $P > 0.05$ ) (Table 1).

### Univariate and Multivariable Regression Results of CTD Complicated with Severe Pneumonia

The natural logarithms of 8 variables, CD4/CD8, CRP, PCT, TNF- $\alpha$ , IFN- $\gamma$ , IL-4, IL-6 and IL-17A, were normalized. Univariate Logistic regression analysis showed that NEU% increased, LY decreased, Ln CD4/CD8, Ln CRP, Ln PCT, Ln

**Table 1** Results of Baseline Data Comparison Between Training Group and Validation Group

Variate	All (n=130)	Training Group (n=80)	Validation Group (n=50)	P value
Age	61.88 (12.24)	63.45 (9.43)	59.36 (15.52)	0.064
Gender (%)				
Male	56 (43.1)	40 (50.0)	16 (32.0)	0.067
Female	74 (56.9)	40 (50.0)	34 (68.0)	
WBC ( $\times 10^9/L$ )				
<9.5	85 (65.4)	54 (67.5)	31 (62.0)	0.651
>9.5	45 (34.6)	26 (32.5)	19 (38.0)	
Neu (%)				
<75	46 (35.4)	28 (35.0)	18 (36.0)	1
>75	84 (64.6)	52 (65.0)	32 (64.0)	
LY ( $\times 10^9/L$ )				
<0.5	47 (36.2)	28 (35.0)	19 (38.0)	0.874
>0.5	83 (63.8)	52 (65.0)	31 (62.0)	
PLT ( $\times 10^9/L$ )				
<350	109 (83.8)	68 (85.0)	41 (82.0)	0.836
>350	21 (16.2)	12 (15.0)	9 (18.0)	
CRP (mg/L)	33.95 [14.05, 84.15]	33.95 [16.75, 79.95]	32.80 [9.17, 90.25]	0.977
PCT (ng/mL)	0.16 [0.05, 1.05]	0.11 [0.04, 0.73]	0.32 [0.06, 1.66]	0.074
CD4/CD8	1.42 [0.85, 2.12]	1.43 [0.96, 2.14]	1.35 [0.71, 1.98]	0.147
TNF- $\alpha$ (pg/mL)	3.57 [2.40, 7.04]	3.76 [2.10, 9.70]	3.43 [2.46, 5.81]	0.698
IFN- $\gamma$ (pg/mL)	4.60 [3.19, 12.83]	4.15 [3.37, 15.99]	3.95 [3.17, 13.00]	0.089
IL-4 (pg/mL)	2.44 [1.44, 5.78]	2.42 [1.39, 6.18]	2.46 [1.73, 3.80]	0.856
IL-6 (pg/mL)	24.51 [12.03, 59.02]	24.51 [11.67, 62.55]	25.27 [14.03, 56.91]	0.863
IL-17A (pg/mL)	17.66 [7.02, 25.59]	16.77 [3.64, 25.35]	18.42 [15.10, 27.40]	0.135

IFN- $\gamma$ , Ln IL-6 were statistically significant in severe pneumonia group compared with common pneumonia group ( $P < 0.05$ ). The factors with statistical significance in univariate analysis were taken as independent variables to conduct multivariable Logistic regression analysis. The results showed that the decrease of Ln CD4/CD8 and the increase of Ln CRP, Ln PCT and Ln IFN- $\gamma$  were the independent risk factors of CTD complicated with severe pneumonia ( $P < 0.05$ ) (Table 2). As shown in [Supplementary Figure 1](#), in order to avoid multicollinearity among variables, Spearman correlation analysis was conducted, which shows that four factors are independent risk factors.

## Nomogram Construction

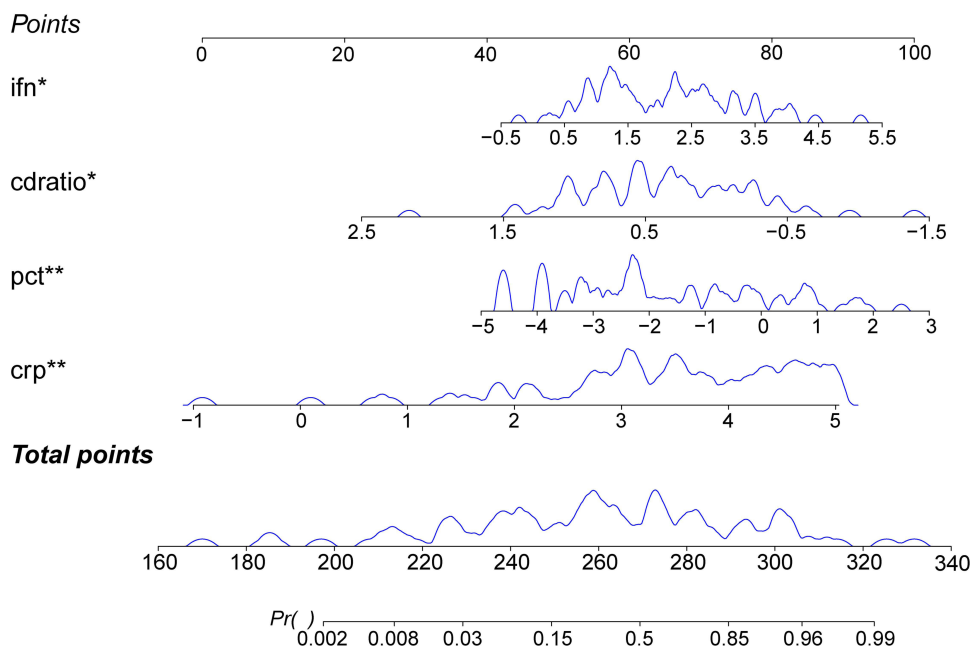
Finally, four factors with statistical significance in multivariable Logistic regression analysis, Ln CD4/CD8, Ln CRP, Ln PCT and Ln IFN- $\gamma$ , were included as predictors, and a column-graph model was established. The column-graph was assigned scores according to variables, and the scores of each variable were added to obtain the total score. The predicted probability of severe pneumonia in CTD can be obtained (Figure 2). The area under the ROC curve of this model is 0.9084 (95% CI: 0.8461–0.9707) (Figure 3A). As shown in Figure 3B, calibration curve of the model was close to the 45 degree Angle, and the Hosmer–Lemeshow test showed a good fit ( $\chi^2 = 7.753$ ,  $P = 0.458$ ).

## Nomogram Validation

A retrospective study design was adopted to conveniently select 50 CTD patients with pneumonia admitted to the same hospital from January to June 2023 were conveniently selected as the validation group research subjects for internal model validation. Inclusion and exclusion criteria, as well as diagnostic criteria, are modeled together. Among 50 pneumonia patients, there were 16 males and 34 females. The model used a probability threshold of 0.664, meaning that patients with a predicted probability above this value were classified as having severe pneumonia. Based on this threshold, the model predicted 29 cases of severe pneumonia, while in reality, 33 cases of severe pneumonia occurred. The area under the ROC curve of the external validation group is 0.8958 (0.808–0.9837) (Figure 3C). The calibration curve closely follows a 45 degree angle, and the Hosmer Lemeshow test has a chi square of 7.1171 and a P-value of

**Table 2** Univariate and Multivariable Logistic Regression Analysis of CTD Complicated with Severe Pneumonia

	Univariate Analysis OR (95% CI)	P value	Multivariable Analysis OR (95% CI)	P value
Age	1.02 (0.97–1.07)	0.424		
Female	0.90 (0.37–2.20)	0.820		
WBC elevation	1.35 (0.52–3.48)	0.537		
Neu elevation	3.96 (1.44–12.22)	0.010	3.27 [0.61–21.74]	0.186
LY reduce	0.29 (0.11–0.74)	0.011	0.42 [0.09–1.75]	0.241
PLT elevation	0.42 (0.09–1.56)	0.225		
Ln CD4/CD8	0.09 (0.01–0.41)	0.004	0.02 [0.00–0.32]	0.009
Ln CRP	2.43 (1.47–4.38)	0.001	3.25 [1.37–9.40]	0.015
Ln PCT	5.73 (2.06–20.55)	0.003	16.14 [2.47–207.62]	0.013
Ln TNF- $\alpha$	0.61 (0.34–1.04)	0.081		
Ln IFN- $\gamma$	3.15 (1.80–6.09)	<0.001	2.66 [1.24–6.57]	0.019
Ln IL-4	0.71 (0.36–1.33)	0.299		
Ln IL-6	1.60 (1.05–2.52)	0.034	0.98 [0.50–1.90]	0.941
Ln IL-17A	1.30 (0.83–2.08)	0.264		



**Figure 2** Prognostic nomogram for severe pneumonia risk stratification in CTD patients. This nomogram integrates four clinically actionable predictors to estimate the probability of severe pneumonia development in CTD patients. Each variable corresponds to a scoring axis: ifn, IFN- $\gamma$ ; cdratio, CD4/CD8; pct, Procalcitonin; crp, C - reactive protein; All scales display log-transformed values. Statistical significance: \* $p < 0.05$ , \*\* $p < 0.01$ . The blue density plots in each sub - graph represent the distribution of the corresponding variable.

0.5241 (Figure 3D). It indicates that the model has good goodness of fit. When the Youden index calculates the optimal critical value of 0.4900738 for this model, the accuracy rate is 80%.

## Clinical Benefit Analysis of Nomogram

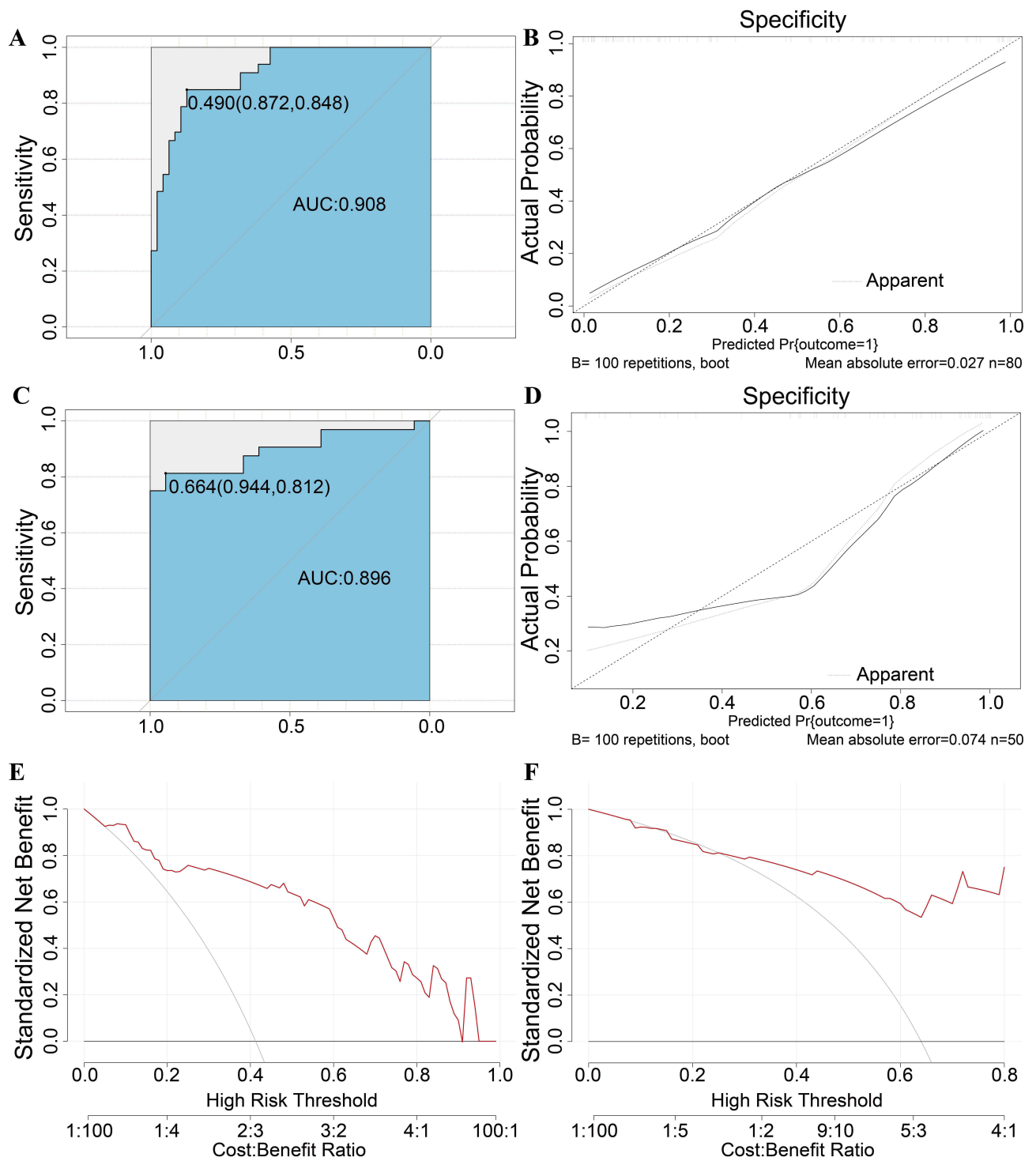
R4.3.3 software was used to draw decision curves for the training group and the validation group respectively, and the results showed that Nomogram had good clinical benefits both in the training group (Figure 3E) and in the validation group (Figure 3F).

## Discussion

Connective tissue diseases (CTDs) are a group of autoimmune-mediated chronic inflammatory diseases, and apart from the activity of the disease itself, infections are a major cause of death among CTD patients. Among all infections, pulmonary infections account for the highest proportion, at around 78%.<sup>14</sup> Notably, aspiration pneumonia exhibits particularly high mortality rates (30–50%) in immunocompromised populations.<sup>15</sup>

Furthermore, due to the use of steroids and immunosuppressants, CTD patients have low immunity and are prone to severe pneumonia, which poses a serious threat to their lives. Therefore, early identification of patients with severe pneumonia and prompt intervention can improve their prognosis to some extent. This study aims to analyze the risk factors for severe pneumonia in CTD patients and construct a receiver operating characteristic (ROC) model to predict the risk of CTD patients developing severe pneumonia, with the goal of improving patient outcomes.

This study shows that a decreased CD4+/CD8+T lymphocyte ratio, elevated levels of IFN- $\gamma$ , CRP, and PCT are independent risk factors for the development of severe pneumonia in patients with CTD. The immune response state plays an important role in the development of severe pneumonia, and T lymphocyte-mediated immune dysregulation and cytokine storm directly lead to the transformation of pulmonary infection from mild to severe and tissue damage.<sup>16</sup> Calvet et al<sup>17</sup> found that the CD4+/CD8+T lymphocyte ratio was significantly lower in patients with severe COVID-19 pneumonia compared to those with non-severe disease, and that this ratio was negatively correlated with the severity of COVID-19. Lin et al<sup>18</sup> reported that the CD4+/CD8+ ratio of children with bacterial pneumonia in the severe group was lower than that of the normal group, which could be used as a reference for predicting the severity of the disease.



**Figure 3** Evaluation of the validity and reliability of the nomogram. The ROC curves of the training set (**A**) and the validation set (**C**); the calibration curves of the training set (**B**) and the validation set (**D**), The apparent curve represents the model's performance on the training data, while the bootstrap-corrected curve is based on 100 resampled validations; the DCA curves of the training set (**E**) and the validation set (**F**). Decision Curve Analysis demonstrates the standardized net benefit of using the CTD-pneumonia nomogram across risk thresholds, weighing true positives (timely intensive therapies) against false positives (unnecessary interventions). The cost: benefit ratio quantifies threshold probabilities where treatment utility (reduced mortality) justifies resource expenditure (antibiotic overuse, invasive procedures). Reference Curves: Treat All (red): Universal intensive therapy; Treat None (gray): Standard care only.

T lymphocyte subpopulation imbalance will also lead to abnormal expression of downstream regulated cytokines, resulting in upregulation of Th1-related cytokine IFN- $\gamma$  and triggering an inflammatory response.<sup>19</sup> IFN- $\gamma$  can act as an antigen-presenting cell and lymphocyte proliferation differentiation regulator to participate in cellular inflammatory responses. Our study found that the level of IFN- $\gamma$  in the peripheral blood of patients with CTD and severe pneumonia was significantly higher. Guo et al<sup>20</sup> compared the levels of IFN- $\gamma$  in the peripheral blood of 64 patients with severe pneumonia and 101 patients with common pneumonia and found that the level of IFN- $\gamma$  in the peripheral blood of patients with severe pneumonia was significantly higher than that of patients with common pneumonia, and that the level of IFN- $\gamma$  in patients with poor prognosis of severe pneumonia was higher than that of patients with good prognosis. PCT and CRP are the most widely used inflammatory acute phase reactants in clinical practice. Procalcitonin is secreted by the thyroid C cells and has a very low concentration in the blood of healthy people. Inflammation stimulation, especially bacterial infection or sepsis, causes various cell types in various tissues of the body to produce PCT and release it into the bloodstream, causing a sharp increase in PCT levels.<sup>21</sup> Zhang et al<sup>22</sup> found that the serum PCT level of patients with poor prognosis severe pneumonia was significantly higher, suggesting that PCT has a high clinical application value in evaluating the prognosis of patients with severe pneumonia. C-reactive protein is mainly synthesized by the liver and plays a pro-inflammatory role by promoting the expression of MCP-1, endothelin-1, and IL-6, etc.<sup>23</sup> It has important roles in evaluating the severity of various inflammatory diseases, prognosis, and efficacy assessment.<sup>24</sup>

## Conclusions

In this study, four factors with statistically significant results in multivariable Logistic regression analysis were ultimately included as predictor variables to establish a receiver operating characteristic (ROC) model. The ROC model assigns scores to variables and adds the scores of each variable to obtain a total score. The higher the score, the greater the risk of developing severe pneumonia in patients with CTD. At the same time, the model was validated externally, and the results showed that the model had good predictive performance, calibration, and clinical value, which is worth clinical promotion and application.

This study is a single-center retrospective study, with certain limitations, including an incomplete range of clinical features. The conclusions drawn from this study may be biased due to the insufficient sample size, and further studies are needed to expand the sample size and include more clinical indicators for a more comprehensive analysis.

## Data Sharing Statement

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study strictly adheres to the ethical principles of the Declaration of Helsinki (2013 revision) and its later amendments. All individuals provided informed consent to participate in this study and approval was provided by Scientific Research Ethics Committee of the Chongqing University Three Gorges Hospital (Review Opinion: No. 165 in 2022).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no potential conflicts of interest in this work.

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