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Original Article

Predictive role of inflammatory markers in characterizing the progression of interstitial lung disease: a retrospective analysis

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Abstract: Objectives: To evaluate the association between inflammatory markers and interstitial lung disease (ILD) progression in order to enhance disease monitoring and risk stratification. Methods: This retrospective cohort study analyzed the clinical data from 172 ILD patients admitted to Nanjing Jiangbei Hospital between January 2021 and December 2023. Patients were categorized into two groups: progressive ILD (PILD; n=95) and rapidly progressive ILD (RPILD; n=77), based on changes in symptoms and pulmonary function within six months. PILD was defined by a ≥10% relative decline in predicted Forced Vital Capacity (ppFVC) or related clinical criteria. RPILD was defined by acute symptom worsening and significant pulmonary function deterioration. Inflammatory markers assessed included C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII). Results: CRP, NLR, PLR, and SII levels were significantly higher in the RPILD group, while LMR was significantly lower (all P<0.05). Multivariate logistic regression identified CRP, NLR, LMR, and SII as independent predictors of ILD progression. ROC analysis showed NLR had the highest individual predictive value (AUC=0.757). A composite model combining all five markers achieved an AUC of 0.842, indicating improved predictive accuracy. Conclusions: Inflammatory markers, particularly NLR, are independently associated with ILD progression. A composite model incorporating multiple markers offers enhanced predictive performance, potentially supporting clinical decision-making and early intervention strategies.

Keywords: Interstitial lung disease, inflammatory markers, disease progression, neutrophil to lymphocyte ratio, retrospective study, predictive modeling

Introduction

Interstitial lung disease (ILD) encompasses a heterogeneous group of pulmonary disorders characterized by varying degrees of inflammation and fibrosis of lung tissue, often leading to impaired respiratory function and reduced overall health [1-3]. Although ILD includes diverse subtypes-such as idiopathic pulmonary fibrosis and connective tissue disease-associated ILD, they share key pathological features, notably progressive scarring of the interstitium and compromised gas exchange [4, 5]. Understanding the mechanisms and risk factors influencing ILD progression is crucial, given the considerable variability in clinical course: some patients experience rapid deterioration, while others maintain stable lung function over prolonged periods.

Despite recent advances in treatment, the prognosis of ILD remains poor due to the unpredictable nature of disease progression and the limited efficacy of current therapies in halting fibrotic changes [6, 7]. Consequently, research has increasingly focused on identifying reliable biomarkers to aid in early diagnosis, prognostic evaluation, and treatment monitoring in ILD patients [8-10]. In this context, systemic inflammation has been recognized as a major contributor to disease progression, highlighting the potential utility of blood-based inflammatory markers in clinical practice [11].

Markers such as neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and platelet-to-lymphocyte ratio (PLR) have gained attention for their roles in chronic inflammatory conditions, including cardiovascular diseases and

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malignancies [12-14]. These indicators reflect systemic immune responses and may offer insight into ILD pathogenesis. For example, NLR reflects both innate and adaptive immune activation; CRP is a well-established acute-phase reactant; and PLR integrates platelet activity and lymphocyte-mediated immunity, both of which are implicated in immune dysregulation [15-18].

Given the potential involvement of systemic inflammation in ILD progression, examining the relationship between these markers and disease severity represents a promising research direction. Prior studies have linked elevated inflammatory markers to poor outcomes in various respiratory diseases, suggesting a potential role in ILD exacerbation as well [19-21]. However, comprehensive investigations specifically addressing these associations in ILD populations remain limited.

Therefore, the present study aims to explore the correlation between selected blood inflammatory markers and the progression of ILD. By retrospectively analyzing data from patients admitted to a tertiary care hospital, we assessed the prognostic value of baseline levels of NLR, CRP, PLR, and other relevant inflammatory indices. This investigation seeks to clarify their role in ILD pathogenesis and progression, with the ultimate goal of informing more effective clinical management strategies.

Materials and methods

Study design and participants

This retrospective cohort study investigated the association between inflammatory markers and the progression of ILD. Clinical data were collected from 172 ILD patients admitted to Nanjing Jiangbei Hospital between January 2021 and December 2023. Based on disease progression within six months of admission, patients were classified into two groups: progressive ILD (PILD; n=95) and rapidly progressive ILD (RPILD; n=77). Baseline data at the time of admission were extracted from the hospital's electronic medical record system for analysis.

The study was approved by the Ethics Committee of Nanjing Jiangbei Hospital and conducted in accordance with ethical standards for retrospective research.

Inclusion and exclusion criteria

Inclusion Criteria for PILD: Patients were required to have centrally reviewed high-resolution computed tomography (HRCT) showing >10% parenchymal fibrosis, with fibrosis predominating over emphysema throughout the lungs. In addition, disease progression within the past 24 months had to be confirmed by at least one of the following: (1) A relative percent predicted forced vital capacity (ppFVC) decline ≥10%; A ppFVC decline of 5-10% accompanied by radiologic evidence of increased fibrosis on HRCT compared to previous imaging; (2) Clinical symptoms of progression alongside increased fibrosis on HRCT.

Inclusion Criteria for RPILD: Patients met RPILD criteria if, within three months of disease onset, any of the following were observed: (1) Worsening dyspnea on exertion; (2) HRCT showing increased ILD extent; (3) Pulmonary function test indicating an FVC decline ≥10%, or FVC decline of 1-5% with a concurrent diffusion capacity of the lung for carbon monoxide (DLCO) decrease ≥15%; (4) Arterial blood gas analysis showing a ≥10 mmHg reduction in PaO_2.

Exclusion Criteria: (1) Incomplete medical records, including missing demographic, historical, or clinical data; (2) Coexisting pulmonary diseases such as chronic obstructive pulmonary disease, asthma, or active lung infections; (3) Immunocompromised status, including HIV infection, immunosuppressive therapy, or organ transplantation history; (4) Pregnancy, due to potential influence on inflammatory markers and disease course; (5) Age under 18 years.

Data collection

Primary indicators: Inflammatory markers including CRP, NLR, PLR, lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammation index (SII).

Secondary indicators: Complete blood count, arterial blood gas parameters, and pulmonary function test results.

Baseline characteristics

Baseline data collected for all participants included demographic information, medical history, disease duration, and the Interstitial Lung Disease-Gender, Age, Physiology (ILD-GAP) score [22]. These data were extracted from electronic health records and hospital databases to provide a comprehensive assessment of each patient's status at the time of admission.

Blood tests

Complete blood count: A 3 mL venous blood sample was collected from each patient eight hours after admission. Samples were processed using a fully automated hematology analyzer (Nanjing Beyden Medical Co., Ltd., China) to measure red blood cell count (RBC), white blood cell count (WBC), neutrophils (NEUT), lymphocytes (LYM), eosinophils (EOS), basophils (BASO), hemoglobin (Hb), platelets (PLT), and monocytes (MON). Whole blood was anticoagulated with ethylenediaminetetraacetic acid (EDTA). Erythrocyte sedimentation rate (ESR) was determined using a TEST 1 automated analyzer (ALIfax, Italy). CRP was measured via rate nephelometry using the Synchron LX20 biochemical analyzer (Beckman Coulter, USA), with manufacturer-provided reagents.

Derived inflammatory indices were calculated as follows: NLR = NEUT/LYM, PLR = PLT/LYM, LMR = LYM/MON, SII = PLT × NEUT/LYM.

Blood gas analysis: A 2 mL arterial blood sample was collected at any time point and analyzed using a blood gas analyzer (Beckman Coulter, USA). Parameters recorded included pH, arterial oxygen partial pressure (PaO_2), and arterial carbon dioxide partial pressure ($PaCO_2$), which were compared between the PILD and RPILD groups.

Pulmonary function tests

Testing was conducted using a full-range lung function analyzer (Vyaire Medical, Bodnegg, Germany). Measurement specifications included a volume range of 0-10 liters with an accuracy of ±3% or 0.05 L (whichever was greater), and a flow range of 0-16 L/s with an accuracy of ±5% or 0.2 L/s. The following indices were recorded: FVC, forced expiratory volume in the first second (FEV_1), FEV_1/FVC ratio, DLCO, maximal voluntary ventilation (MVV), vital capacity (VC), residual volume (RV), total lung capacity (TLC), and RV/TLC ratio.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. For comparisons between two groups, independent samples t-tests were applied to normally distributed variables, and the Mann-Whitney U test was used for non-normal distributions. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. For comparisons among multiple groups, one-way ANOVA followed by Tukey's HSD test was used for normally distributed data, and the Kruskal-Wallis test followed by Dunn's post-hoc test was applied for non-parametric data.

Correlations between inflammatory markers and ILD progression were evaluated using Spearman's rank correlation coefficients. Univariate logistic regression was performed to assess associations between individual inflammatory markers and the risk of disease progression. Multivariate logistic regression was subsequently conducted, adjusting for confounding factors including age, sex, body mass index (BMI), smoking status, alcohol consumption, medical history, and ILD-GAP score, to identify independent predictors.

Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of each inflammatory marker. The area under the ROC curve (AUC), sensitivity, specificity, and Youden index were calculated. A composite predictive model incorporating CRP, NLR, PLR, LMR, and SII was developed to assess overall prognostic utility. A two-sided *P*-value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

Baseline characteristics of participants in the PILD and RPILD groups are summarized in **Table 1**. There were no significant differences

Table 1. Comparison of baseline characteristics

Parameters	PILD group (n=95)	RPILD group (n=77)	t/x^2	*P* value
Age (years)	56.72 ± 6.24	58.11 ± 7.75	1.269	0.206
Gender (M/F)	51/44	43/34	0.08	0.777
BMI (kg/m^2)	23.98 ± 2.64	24.06 ± 3.12	0.182	0.856
Smoking history (pack-years)	17.72 ± 5.24	18.04 ± 6.55	0.343	0.732
Alcohol intake (g/week)	11.65 ± 2.53	12.03 ± 2.85	0.934	0.352
Past Medical History				
History of gastroesophageal reflux (Yes/No)	15/80	20/57	2.722	0.099
History of acute coronary syndrome (Yes/No)	17/78	22/55	2.765	0.096
History of diabetes (Yes/No)	12/83	10/67	0.005	0.945
History of osteoporosis (Yes/No)	13/82	19/58	3.393	0.065
Use of anti-rheumatic drugs (Yes/No)	24/71	25/52	1.084	0.298
Use of steroids (Yes/No)	21/74	24/53	1.809	0.179
Duration of disease (months)	15.57 ± 6.24	14.76 ± 6.83	0.81	0.419
ILD-GAP score [n (%)]			6.056	0.109
0-1	36 (37.89%)	19 (24.68%)		
2-3	36 (37.89%)	27 (35.06%)		
4-5	20 (21.05%)	28 (36.42%)		
>5	3 (3.16%)	3 (3.90%)		

PILD, Progressive Interstitial Lung Disease; RPILD, Rapidly Progressive Interstitial Lung Disease; M/F, male/female; BMI, Body Mass Index; ILD-GAP, Interstitial Lung Disease-Gender, Age, Physiology Index.

Table 2. Comparison of routine blood parameters

Parameters	PILD group (n=95)	RPILD group (n=77)	t	*P* value
ESR (mm/h)	27.91 ± 7.28	29.44 ± 8.64	1.265	0.208
RBC (10^12/L)	4.52 ± 0.47	4.48 ± 0.49	0.538	0.591
WBC (10^9/L)	7.12 ± 1.56	7.91 ± 2.01	2.826	0.005
NEUT (10^9/L)	4.21 ± 1.02	4.82 ± 1.34	3.267	0.001
LYM (10^9/L)	2.01 ± 0.56	1.98 ± 0.58	0.333	0.74
EOS (10^9/L)	0.10 ± 0.03	0.10 ± 0.03	0.738	0.462
BASO (10^9/L)	0.09 ± 0.03	0.09 ± 0.03	0.271	0.787
Hb (g/L)	132.1 ± 14.7	131.8 ± 15.1	0.132	0.895
PLT (10^9/L)	230.1 ± 56.2	224.4 ± 59.3	0.645	0.52
MON (10^9/L)	0.61 ± 0.18	0.65 ± 0.16	1.555	0.122

PILD, Progressive Interstitial Lung Disease; RPILD, Rapidly Progressive Interstitial Lung Disease; ESR, Erythrocyte Sedimentation Rate; RBC, Red Blood Cell Count; WBC, White Blood Cell Count; NEUT, Neutrophil Count; LYM, Lymphocyte; EOS, Eosinophil Count; BASO, Basophil Count; Hb, Hemoglobin; PLT, Platelet Count; MON, Monocyte.

between the two groups in age, sex distribution, BMI, smoking status, alcohol consumption, history of diabetes, use of anti-rheumatic drugs, or corticosteroid usage (all P>0.05). Similarly, disease duration did not differ significantly (*P*=0.419).

Regarding comorbidities, the incidences of gastroesophageal reflux (*P*=0.099), acute coronary syndrome (*P*=0.096), and osteoporosis (*P*=0.065) tended to be higher in the RPILD group, although these differences did not reach statistical significance. The distribution of ILD-GAP scores showed a higher proportion of patients in the RPILD group with scores of 4-5 PILD, though this difference was also not statistically significant (P=0.109).

Comparison of routine blood parameters

Table 2 summarizes the routine blood parameters in the PILD and RPILD groups. No significant differences were found in ESR (*P*=0.208), RBC (*P*=0.591), LYM (*P*=0.74), EOS (*P*=0.462), BASO (*P*=0.787), Hb (*P*=0.895), PLT (*P*=0.52), or MON (*P*=0.122). In contrast, WBC (P=0.005) and NEUTPILDPILD (P=0.001) levels were sig-

Table 3. Comparison of inflammatory markers

Inflammatory marker	PILD group (n=95)	RPILD group (n=77)	t	*P* value
CRP (mg/L)	10.67 ± 5.54	12.98 ± 5.75	2.672	0.008
NLR	2.97 ± 1.32	4.32 ± 1.47	6.332	<0.001
PLR	158.47 ± 35.38	171.26 ± 36.45	2.327	0.021
LMR	2.53 ± 0.91	2.14 ± 0.96	2.736	0.007
SII	564.28 ± 126.47	647.11 ± 124.32	4.303	<0.001

PILD, Progressive Interstitial Lung Disease; RPILD, Rapidly Progressive Interstitial Lung Disease; CRP, C-Reactive Protein; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; LMR, Lymphocyte to Monocyte Ratio; SII, Systemic Immune-Inflammation Index.

Table 4. Comparison of blood gas indices

Inflammatory marker	PILD group (n=95)	RPILD group (n=77)	t	*P* value
pH	7.43 ± 0.04	7.43 ± 0.03	1.106	0.27
PO_2 (mmHg)	68.21 ± 12.34	65.78 ± 10.12	1.392	0.166
PCO_2 (mmHg)	37.12 ± 6.54	39.02 ± 7.89	1.723	0.087

PILD, Progressive Interstitial Lung Disease; RPILD, Rapidly Progressive Interstitial Lung Disease; PO_2, Partial Pressure of Oxygen; PCO_2, Partial Pressure of Carbon Dioxide.

Table 5. Pulmonary function indicators

Parameters	PILD Group (n=65)	RPILD Group (n=57)	t	*P* value
FVC (%)	78.43 ± 10.23	73.54 ± 12.17	2.864	0.005
FEV1 (%)	75.32 ± 11.65	70.12 ± 13.42	2.717	0.007
FEV1/FVC	0.78 ± 0.06	0.77 ± 0.07	0.916	0.361
DLCO (%)	65.32 ± 15.43	55.42 ± 17.65	3.923	<0.001
MVV (%)	75.56 ± 12.34	69.45 ± 14.56	2.98	0.003
VC (%)	75.83 ± 11.12	71.34 ± 13.21	2.42	0.017
TLC (%)	87.12 ± 10.23	82.34 ± 12.34	2.781	0.006
RV (%)	110.23 ± 15.34	116.12 ± 17.45	2.353	0.020
RV/TLC	0.45 ± 0.06	0.46 ± 0.06	0.656	0.513

PILD, Progressive Interstitial Lung Disease; RPILD, Rapidly Progressive Interstitial Lung Disease; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in 1 second; DLCO, Diffusing Capacity for Carbon Monoxide; MVV, Maximal Voluntary Ventilation; VC, Vital Capacity; TLC, Total Lung Capacity; RV, Residual Volume; RV/TLC, Ratio of Residual Volume to Total Lung Capacity.

nificantly elevated in the RPILD group compared to the PILD group.

Comparison of inflammatory markers

As shown in **Table 3**, significant differences were observed in multiple inflammatory markers. CRP levels were significantly higher in the RPILD group than in the PILD group (P=0.008). The RPILD group also showed significantly higher NLR (P<0.001), PLR (P=0.021), and SII (P<0.001), while LMR was significantly lower (P=0.007).

Comparison of blood gas parameters

Table 4 presents the comparison of arterial blood gas parameters between the two groups. There were no significant differences in pH (P=0.270), PaO_2 (P=0.166), or $PaCO_2$ (P=0.087) between the PILD and RPILD groups.

Comparison of pulmonary function parameters

Pulmonary function test indicators for participants in the PILD are shown in **Table 5**. Several key parameters were significantly worse in the RPILD group. FVC PILD (P=0.005), FEV_1 (P=0.007), DLCO (P<0.001), MVV (P=0.003), VC (P=0.017), and TLC (P=0.006) were all significantly lower in RPILD patients. Conversely, RV was significantly higher in the RPILD group (P=0.020). No significant differences were found in the FEV_1/FVC ratio (P=0.361) or RV/TLC ratio (*P*=0.513).

Correlation analysis between clinical parameters and ILD progression

Figure 1 illustrates the correlation between clinical parameters and ILD progression. Positive correlations were observed for WBC (rho=0.247, *P*=0.001), NEUT (rho=0.225, *P*=0.003), CRP (rho=0.191, *P*=0.012), NLR (rho=0.442, *P*<0.001), PLR (rho=0.191, *P*=0.012), SII (rho=0.306, *P*<0.001), and RV (rho=0.173, *P*=0.024), suggesting that higher levels of these markers are associated with accelerated ILD progression.

Negative correlations were found for LMR (rho=-0.215, *P*=0.005), FVC (rho=-0.193, *P*=

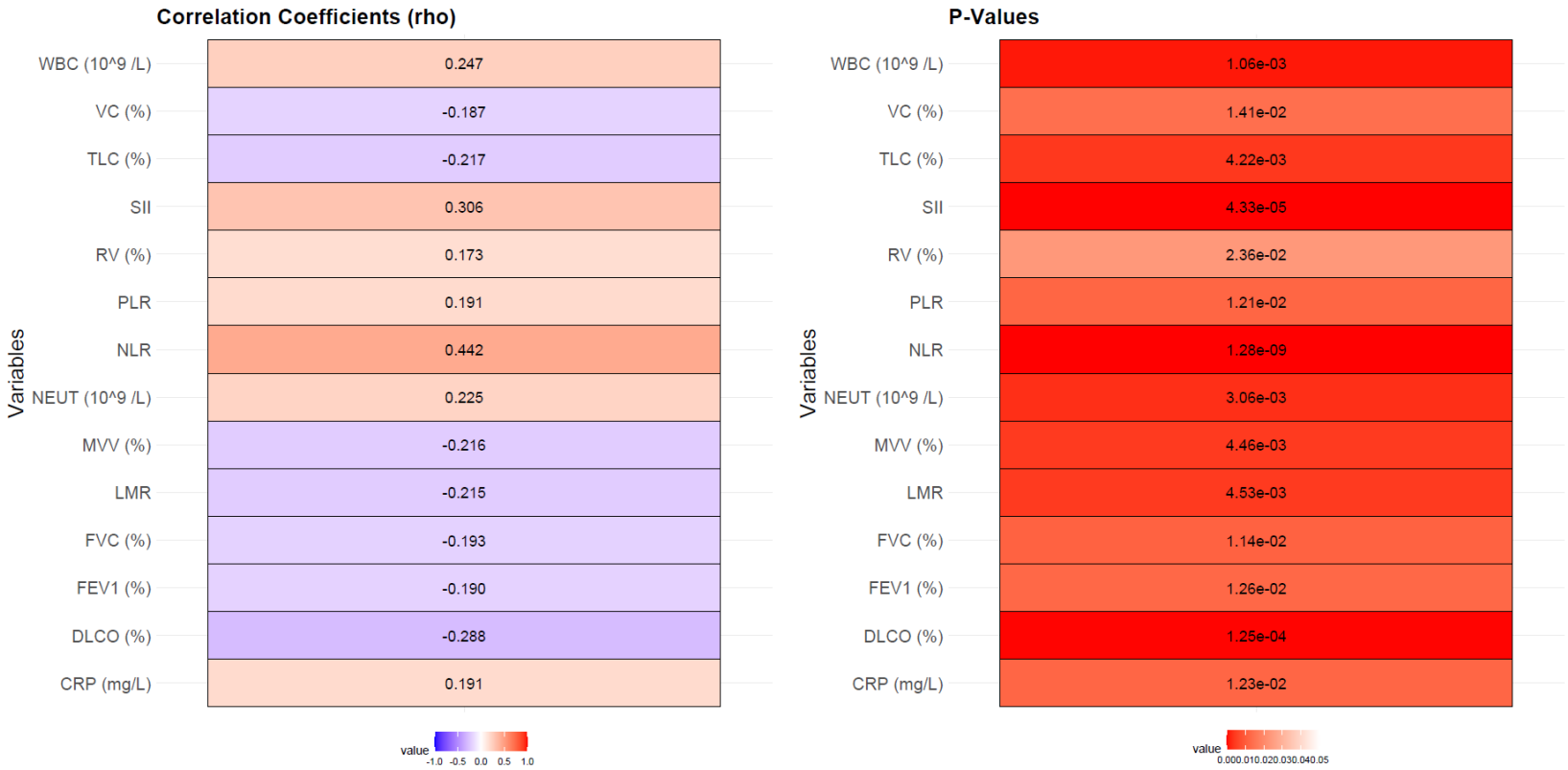

Figure 1. The correlation analysis between various variables and the ILD progression. ILD, Interstitial Lung Disease; WBC, White Blood Cell Count; VC, Vital Capacity; TLC, Total Lung Capacity; SII, Systemic Immune-Inflammation Index; RV, Residual Volume; PLR, Platelet to Lymphocyte Ratio; NLR, Neutrophil to Lymphocyte Ratio; NEUT, Neutrophil Count; MVV, Maximal Voluntary Ventilation; LMR, Lymphocyte to Monocyte Ratio; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in 1 second; DLCO, Diffusing Capacity for Carbon Monoxide; CRP, C-Reactive Protein.

Table 6. Univariate logistic regression analysis of inflammatory markers for ILD progression

Parameters	Coefficient	Std Error	Wald	*P* value	OR (95% CI)
CRP	0.073	0.028	2.588	0.010	1.076 (1.019-1.139)
NLR	0.691	0.132	5.225	<0.001	1.996 (1.561-2.627)
PLR	0.010	0.004	2.274	0.023	1.010 (1.002-1.019)
LMR	-0.452	0.171	2.645	0.008	0.636 (0.451-0.883)
SII	0.005	0.001	3.918	<0.001	1.005 (1.003-1.008)

ILD, Interstitial Lung Disease; OR, Odds Ratio; CI, Confidence Interval; CRP, C-Reactive Protein; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; LMR, Lymphocyte to Monocyte Ratio; SII, Systemic Immune-Inflammation Index.

Table 7. Multivariate logistic regression analysis of inflammatory markers for ILD progression

Parameters	Coefficient	Std Error	Wald	*P* value	OR (95% CI)
CRP	0.081	0.035	2.299	0.022	1.084 (1.012-1.162)
NLR	0.768	0.152	5.056	<0.001	2.156 (1.601-2.904)
PLR	0.008	0.005	1.550	0.121	1.008 (0.998-1.019)
LMR	-0.537	0.218	-2.466	0.014	0.584 (0.381-0.896)
SII	0.006	0.002	3.891	<0.001	1.006 (1.003-1.010)

ILD, Interstitial Lung Disease; OR, Odds Ratio; CI, Confidence Interval; CRP, C-Reactive Protein; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; LMR, Lymphocyte to Monocyte Ratio; SII, Systemic Immune-Inflammation Index.

0.011), FEV1 (rho=-0.190, *P*=0.013), DLCO (rho=-0.288, *P*<0.001), MVV (rho=-0.216, *P*=0.004), VC (rho=-0.187, *P*=0.014), and TLC (rho=-0.217, *P*=0.004), indicating that lower pulmonary function and LMR are associated with slower disease progression.

Among all markers, NLR showed the strongest correlation (rho=0.442, *P*<0.001), underscoring its potential as a key predictor of disease progression. The marked negative correlation of DLCO (rho=-0.288, *P*<0.001) also highlights its clinical relevance in assessing lung function decline.

Univariate logistic regression analysis of inflammatory markers for ILD progression

Table 6 presents the results of the univariate logistic regression analysis assessing the association between inflammatory markers and ILD progression. Elevated CRP levels were significantly associated with an increased risk of disease progression (OR=1.076; 95% CI: 1.019-1.139; P=0.010). NLR emerged as the strongest individual predictor, demonstrating a robust positive association with ILD progression (OR=1.996, 95% CI: 1.561-2.627, *P*<0.001). PLR demonstrated a modest but significant correlation (OR= 1.010, 95% CI: 1.002-1.019, *P*=0.023). Conversely, LMR was inversely associated with ILD progression, indicating that lower LMR values conferred a higher risk (OR=0.636, 95% CI: 0.451-0.883, *P*=0.008). SII was also significantly associated with disease progression (OR=1.005, 95% CI: 1.003-1.008, *P*<0.001).

Multivariate logistic regression analysis

Table 7 summarizes the multivariate logistic regression results after adjusting for potential confounders. CRP remained a significant predictor of ILD progression (OR=1.084, 95% CI: 1.012-1.162, *P*=0.022), and NLR continued to exhibit a strong positive association (OR=2.156, 95% CI: 1.601-2.904, *P*<0.001). PLR, however, did it not retain statistical significance in the adjusted model (OR=1.008, 95% CI: 0.998-1.019, *P*=0.121). LMR maintained its inverse association, with lower values indicating a higher risk of progression (OR=0.584, 95% CI: 0.381-0.896, *P*=0.014). SII also remained significantly associated with disease progression (OR=1.006, 95% CI: 1.003-1.010, *P*<0.001).

Predictive value of inflammatory markers for ILD progression

Table 8 and **Figure 2** evaluate the predictive performance of inflammatory markers through ROC curve analysis. Among the individual markers, NLR exhibited the highest predictive accuracy with an AUC of 0.757 (sensitivity: 0.597; specificity: 0.832; Youden index: 0.429), indicating good discriminatory power.

CRP and PLR each demonstrated an AUC of 0.611, with CRP yielding a sensitivity of 0.688 and specificity of 0.516 (Youden index: 0.204),

Table 8. Predictive value of inflammatory markers for the ILD progression

Parameters	Sensitivities	Specificities	AUC	Youden index
CRP	0.688	0.516	0.611	0.204
NLR	0.597	0.832	0.757	0.429
PLR	0.662	0.558	0.611	0.22
LMR	0.584	0.642	0.625	0.226
SII	0.597	0.716	0.678	0.313

ILD, Interstitial Lung Disease; AUC, Area Under the Curve; CRP, C-Reactive Protein; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio; LMR, Lymphocyte to Monocyte Ratio; SII, Systemic Immune-Inflammation Index.

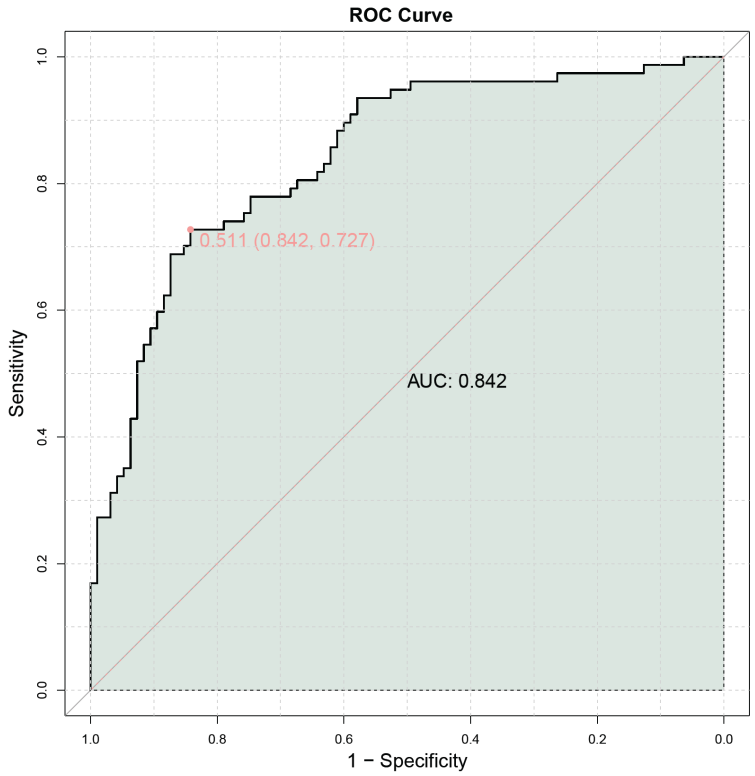

Figure 2. ROC curve analysis of composite inflammatory markers for predicting the ILD progression. ROC, Receiver Operating Characteristic; ILD, Interstitial Lung Disease; AUC, Area Under the Curve.

and PLR showing a sensitivity of 0.662 and specificity of 0.558 (Youden index: 0.220).

LMR had an AUC of 0.625 (sensitivity: 0.584; specificity: 0.642; Youden index: 0.226), while SII yielded an AUC of 0.678 (sensitivity: 0.597; specificity: 0.716; Youden index: 0.313).

A composite model integrating CRP, NLR, PLR, LMR, and SII achieved an enhanced AUC of 0.842, as illustrated in **Figure 2**, indicating superior predictive performance over any single marker.

These findings suggest that combining multiple inflammatory indicators may provide a more robust tool for identifying patients at higher risk of ILD progression, offering enhanced support for clinical decision-making.

Discussion

In this retrospective cohort study, we aimed to elucidate the relationship between inflammatory markers and the progression of ILD. Our findings offer important insights into the interplay between systemic inflammation and ILD progression, identifying specific inflammatory markers as potential predictors of disease trajectory.

One of the most notable findings is the strong association between the NLR and ILD progression. This is supported by NLR's high predictive value, with a superior AUC of 0.757 in ROC analysis. As a simple and cost-effective biomarker, NLR shows considerable promise for clinical application in risk stratification. The mechanistic basis of this association likely lies in NLR's reflection of systemic inflammatory status [23, 24]. An elevated NLR typically signifies neutrophilia and relative lymphopenia-features commonly observed in chronic inflammatory states, including fibrotic lung diseases [25, 26]. Neutrophils contribute to tissue damage and fibrosis through the release of proteolytic enzymes and reactive oxygen species, while lymphopenia may reflect an impaired adaptive immune response, potentially exacerbating fibrotic processes [27]. Collectively, these findings emphasize NLR's value as a predictive marker and underscore the contribution of systemic inflammation to ILD progression.

CRP, a well-established acute-phase protein synthesized in response to pro-inflammatory

cytokines such as IL-6, also demonstrated predictive relevance [12]. Its elevation in the RPILD group reflects the inflammatory burden associated with more aggressive disease phenotypes. Notably, CRP remained an independent predictor of ILD progression in the multivariate model. Mechanistically, CRP may participate in immune modulation through opsonization, complement activation, and the recruitment of immune cells to sites of inflammation [28-30]. While its predictive value was moderate, CRP's consistent association with disease progression supports its utility as a supplementary biomarker in clinical evaluation.

The PLR and the SII further reinforce the role of immune dysregulation in ILD progression [31, 32]. The elevated PLR in RPILD patients may reflect platelet-mediated contributions to inflammation and tissue remodeling. Beyond their role in hemostasis, platelets release pro-inflammatory cytokines and growth factors, which may facilitate fibrotic progression. SII, a composite index incorporating neutrophil, lymphocyte, and platelet counts, provides a more integrated view of the inflammatory landscape. Its significant association with disease progression underscores the importance of coordinated activation of these cellular components in ILD pathogenesis [33-35]. Together, PLR and SII serve as useful markers for identifying patients at risk of rapid disease advancement.

An inverse relationship was observed between LMR and ILD progression, consistent with the known role of monocytes in fibrotic diseases [36]. Elevated monocyte levels and their differentiation into pro-fibrotic macrophages promote fibrosis through the secretion of transforming growth factor-beta and matrix metalloproteinases, which contribute to extracellular matrix remodeling [16, 26, 37]. The lower LMR observed in RPILD patients likely reflects a shift toward monocyte-dominant inflammation, impairing the resolution of inflammation and accelerating fibrotic progression. Thus, the inverse association between LMR and disease progression highlights monocyte-driven inflammation as a key mechanism in ILD pathogenesis.

Our findings have important implications for understanding ILD pathogenesis, highlighting systemic inflammation as a key driver of disease progression and a potential target for therapeutic intervention. Pharmacological modulation of inflammatory pathways could potentially slow disease progression. Specifically, therapies designed to reduce neutrophilic inflammation or inhibit platelet activation may hold clinical promise. The identification of these inflammatory markers as predictors of progression suggests that targeting systemic inflammation may represent a novel strategy in ILD management.

Despite the strengths of this study-including a well-defined patient cohort and comprehensive statistical analyses, several limitations should be acknowledged. The retrospective design limits causal inference between inflammatory markers and ILD progression. Additionally, reliance on previously recorded clinical data may introduce selection bias and reduce control over confounding factors, although multivariate models were employed to mitigate these effects. Furthermore, while significant associations were identified, the underlying biological mechanisms remain speculative and require further experimental validation. Therefore, although the study provides valuable insights, its retrospective nature and dependence on existing data must be considered when interpreting the findings.

Future research should focus on validating these results in prospective studies with larger and more diverse populations to improve generalizability. Integration of advanced omics approaches, such as genomics and proteomics, may help elucidate the molecular pathways linking systemic inflammation to ILD progression and uncover new therapeutic targets. Additionally, longitudinal studies assessing dynamic changes in these inflammatory markers could inform their potential role in monitoring disease activity, treatment response, or exacerbations. Continued research in these areas will be crucial to further understanding the mechanistic links between inflammation and ILD and to developing more effective, individualized treatment strategies.

In conclusion, our study underscores the pivotal role of systemic inflammation in the progression of ILD and identifies several inflammatory markers as potential prognostic tools. These biomarkers could enhance clinical decision-making by enabling early risk stratification and supporting personalized therapeutic approach-

es. As research advances, integrating these markers into multifactorial diagnostic and prognostic models may significantly improve the management of ILD and patient outcomes.

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Disclosure of conflict of interest

None.

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