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ORIGINAL RESEARCH

Interleukin-6 as a Biomarker for Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Retrospective Study

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Objective: This study aims to assess the predictive value of interleukin-6 (IL-6) as a biomarker in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Methods: A total of 361 RA patients (236 RA non-ILD and 125 RA-ILD patients) are included in the study, and stratified analysis is performed according to age and gender. The RA-ILD group is divided into mild ILD, moderate ILD, and severe ILD groups based on HRCT score. Using logistic regression analysis to investigate the risk association between IL-6 and rheumatoid arthritis-associated interstitial lung disease (RA-ILD), and employing receiver operating characteristic (ROC) to determine the value of IL-6 for distinguishing RA-ILD. Pearson's analysis and linear regression are used to analyze the association between IL-6 and RA disease activity, High-Resolution Computed Tomography (HRCT) scores, and Krebs Von den Lungen-6 (KL-6).

Results: The level of IL-6 in the RA-ILD group is higher than that in the RA non-ILD group ($p < 0.001$). The OR of IL-6 associated with the risk of ILD is 1.03 ($p < 0.001$). IL-6 demonstrated significant diagnostic utility in distinguishing RA-ILD patients from RA patients without ILD, with an area under the receiver operating characteristic curve (AUC) of 0.810 (95% CI: 0.767–0.854; $p < 0.001$). At the best cutoff value of 8.87 pg/mL, IL-6 exhibited a sensitivity of 94.4% and specificity of 63.6%. There is no statistically significant difference in IL-6 among the ILD subgroups ($p > 0.05$). Pearson correlation analysis and multiple linear regression analysis show that IL-6 is significantly positively correlated with Disease Activity Score-28 (DAS28), but does not significantly correlate with HRCT score and KL-6.

Conclusion: IL-6 may be used as a new peripheral blood biomarker to predict RA-ILD.

Keywords: IL-6, RA-ILD, biomarker, inflammation, cytokine

Introduction

Rheumatoid arthritis (RA) is a systemic, chronic, autoimmune disease,[1] which is mainly characterized by symmetric synovitis, and rheumatoid arthritis. Among the joints of the whole body, the metacarpophalangeal joints, proximal interphalangeal joints, and metatarsophalangeal joints are most commonly involved.[2]

In addition to systemic joint involvement, RA has many extra-articular manifestations (EAMs), with the lungs, eyes, cardiovascular system, and nerves being the main target organs involved.[3,4] EAMs are usually associated with high mortality in RA patients, among which RA-ILD is a common EAM and one of the most common causes of death in RA patients, and the prevalence of interstitial lung disease (ILD) is about 39.8% in Chinese RA patients.[5–7] Patients with RA-ILD have a significantly increased risk of death compared to RA patients without ILD, with one study showing that patients with RA-ILD have a 3-fold higher risk of death than RA patients without ILD, and the median survival after RA-ILD diagnosis is only 2.6 years.[8] Therefore, the management and early diagnosis of EAMs are of great interest, and the search for a biomarker that is clinically appropriate and provides a reliable predictive value for the development of ILD in RA patients is an extremely important aspect.

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Although previous studies have investigated potential diagnostic biomarkers for RA-ILD, including uric acid, KL-6, and D-dimer,[9,10] their clinical utility remains limited. These limitations include suboptimal sensitivity, modest diagnostic accuracy (as reflected by AUC values), and inadequate sample sizes. Moreover, it is well known that KL-6, as a classic ILD biomarker, typically begins to rise after ILD has developed, making it more diagnostic than predictive. Therefore, we are seeking a new biomarker with predictive value, and IL-6 may hold such potential.

IL-6 is a pleiotropic pro-inflammatory cytokine. Its deregulation is associated with chronic inflammation and multifactorial autoimmune disorders.[11] In response to inflammatory tissue injury, cell surface and intracellular Toll-like receptors (TLRs) are activated in monocytes and macrophages and induce IL-6 transcription via nuclear factor-κB (NF-κB).[12] In RA, IL-6 creates an inflammatory environment conducive to ILD formation by affecting CD4+ T cell differentiation and stimulating B cell proliferation.[13] It mediates its biological roles through a hexameric complex composed of IL-6 itself, its receptor IL-6 receptor (IL-6R), and glycoprotein 130 (IL-6/IL-6R/gp130).[11] It has been shown that IL-6 binding to IL-6R/gp130 receptor activates the Janus kinases (JAK)/signal transducers and activators of transcription (STAT) signaling pathway and induces epithelial-mesenchymal transition (EMT) and fibroblast-mesenchymal transition (FMT), leading to ILD.[14,15] In the constructed RA-ILD mouse model, its serum levels of IL-6 were elevated,[16,17] and in other connective tissue-associated interstitial lung diseases (CTD-ILD), such as desiccation syndrome, IL-6 has also been shown to be highly correlated with ILD occurrence.[18] However, the potential utility of IL-6 as a diagnostic and predictive biomarker for RA-ILD remains understudied, with limited clinical validation studies available to date.

Therefore, we conducted a retrospective study to assess the predictive value of IL-6 as a biomarker in patients with rheumatoid arthritis-associated interstitial lung disease.

Materials and Methods

Patients

This study was performed according to the tenets of the Declaration of Helsinki. Moreover, informed consent was obtained from the subjects. Given that the data has been fully anonymized and the study is a purely observational analysis, the risk to participants' privacy is extremely low, and no foreseeable harm will be caused to their well-being or rights. In accordance with internationally accepted ethical guidelines (eg, the Declaration of Helsinki) and the relevant regulations of our institution's Ethics Committee, studies with such extremely low risks generally meet the criteria for exemption from ethical review. After careful evaluation and confirmation with the Ethics Committee of the Second Affiliated Hospital of Nanchang University, Jiangxi, China, this study is exempt from the requirement for ethical review and approval. This study reviewed the medical records of 843 patients attending RA with the Second Affiliated Hospital of Nanchang University from January 2019 to November 2023, and 361 patients were finally included in this study. The 361 enrolled patients met the 1987 American College of Rheumatology criteria or the 2010 American College of Rheumatology or European League Against Rheumatism (EULAR) criteria for RA, and the DAS28 system was used to evaluate the patients' disease activity.[19,20] Divided 361 patients into female and male subgroups, followed by subcategorization based on age (≤64 years and >64 years subgroups)"). The diagnosis of ILD relies on chest HRCT: All HRCT images of RA patients were independently interpreted by two radiologists and reviewed by two senior pulmonologists. Those meeting radiographic criteria for ILD (including ground-glass opacities, pleural irregularities, interlobular septal thickening, pleural lines, reticular patterns, and honeycombing) were included in the RA-ILD group (n = 125); the remaining patients were assigned to the RA non-ILD group (n = 236).

Patients with any combination of non-rheumatoid arthritis-related interstitial lung diseases, severe acute infections, chronic infections, chronic respiratory diseases such as chronic bronchitis, emphysema, bronchial asthma, bronchiectasis, and other chronic respiratory diseases, combination of hematologic disorders, various types of neoplasms and histories of radiation, chemotherapy, and immunotherapy, etc., and chronic cardiac insufficiency were excluded from this study. Informed consent was obtained from all patients and healthy volunteers involved in the study (Figure 1).

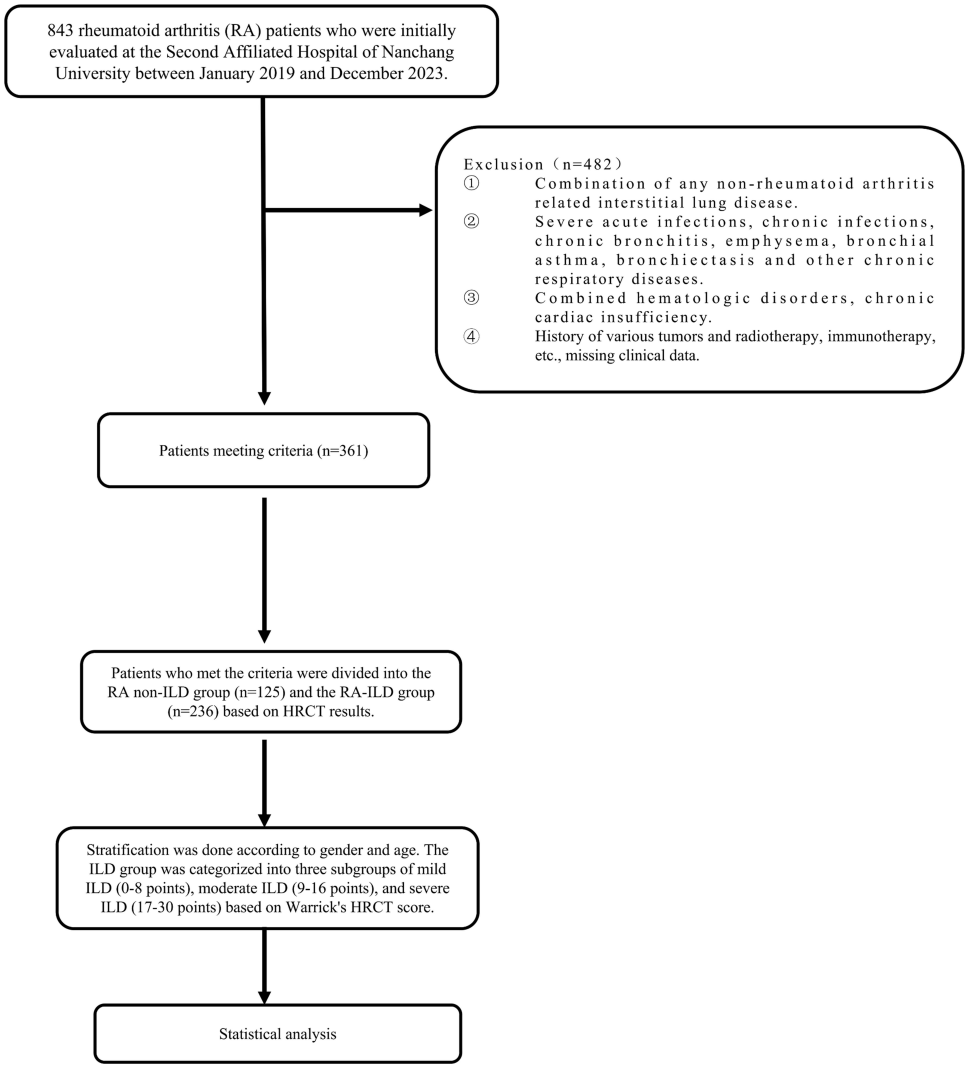

Figure 1 Screening process for research subjects.

Data Collection

Data on all patients of age, sex, and body mass index (BMI). Neutrophil count (Net), lymphocyte count (Lym), Rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA), erythrocyte sedimentation rate (ESR), and KL-6 were measured by standard methods in the laboratory of the Department of Laboratory Medicine, the Second Affiliated Hospital of Nanchang University. All ILD patients completed pulmonary function tests in the Pulmonary Function Laboratory of the Department of Respiratory and Critical Care Medicine, the Second Affiliated Hospital of Nanchang University. Warrick's HRCT score (0–30) was assigned to the degree and extent of lung lesions in RA-ILD patients[21] (Table 1). Grouping was based on scores, with ≤8 categorized as mild ILD, ≤16 categorized as moderate ILD, and 17–30 categorized as severe ILD.[22]

Measurement of Serum IL-6 Levels

The peripheral blood samples in the patients' medical records were collected within 24 hours of admission. Serum IL-6 levels in patients were measured by the laboratory of the Second Affiliated Hospital of Nanchang University using an ELISA kit (Shenzhen Dakowe Biotechnology Co., Ltd). The laboratory's normal reference range is 0–5 pg/mL. The procedure strictly followed the instructions for the serum IL-6 level assay.

DAS28 Score Calculation Formula

$$DAS28 = 0.56 \times \ln(TJC28) + 0.28 \times \ln(SJC28) + 0.70 \times \ln(ESR) + 0.014 \times VAS$$

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Table 1 Warrick's HRCT Scores

HRCT Performance	Scores (Point)
Ground-glass opacity	1
Pleural irregularity	2
Interlobular septal thickening or subpleural line	3
Reticular pattern	4
Honeycombing	5
Number of lung segments involved	
1–3	1
4–9	2
>9	3
Total score	30

Note: Score Calculation = Total HRCT Pattern Score + Segmental Involvement Score of Each Pattern (Total score: 30 points).

TJC28 is the number of swollen joints; SJC28 is the number of pressure-painful joints; and VAS is the patient's subjective pain level (0–100, with a score of 0 indicating no pain and 100 indicating severe pain).

Statistical Analysis

Statistical analyses are performed using SPSS 27.0 (IBM-SPSS, Chicago, IL, USA) software, and variables that conformed to normal distribution are analyzed using the *t*-test, and the results are expressed as the mean ± standard deviation (SD), while those that did not conform to normal distribution are analyzed using a nonparametric test (Kruskal–Wallis), and the results are expressed as the "Median (IQR) (upper quartile, lower quartile)" form. Indicators with statistically significant differences (two-sided p-value < 0.05) are considered as suspected risk factors for inclusion in univariate and multivariate logistic regression analyses to determine whether or not the indicator is an independent risk factor for RA-ILD. ROC analysis is used to assess the best cutoff value for diagnosing RA-ILD. Pearson's analysis and linear regression are used to analyze the association of IL-6 with RA disease activity, HRCT scores, and KL-6.

Results

Demographics and Clinical Characteristics

There is no statistically significant difference between the RA non-ILD group and the RA-ILD group in terms of BMI and age. The RA non-ILD group is higher than the RA-ILD group in terms of female composition ratio ($p < 0.001$), while the male composition ratio is higher in the RA-ILD group than in the RA non-ILD group ($p < 0.001$). The level of Net, IL-6, ESR, RF, ACPA, and DAS28 is higher in the RA-ILD group than in the RA non-ILD group ($p < 0.001$) (Figure 2). The RA non-ILD group and RA-ILD patients' demographics and clinical characteristics are shown in Table 2.

Stratification Analysis of IL-6

Study population demographics analysis shows a difference in the gender composition ratio among the RA non-ILD group and RA-ILD group, and as the literature indicates that age is a risk factor for RA-ILD.[14] The RA-ILD group is categorized into female and male subgroups, followed by subcategorization based on age (≤64 years and >64 years subgroups)") to perform a hierarchical analysis. It shows that IL-6 level is also higher in the RA-ILD group than in the RA non-ILD group ($p < 0.05$). Stratification analysis of IL-6 is shown in Table 3.

Risk Factors for RA-ILD

Using univariate and multivariate logistic regression analysis to identify IL-6 as an independent risk factor for RA-ILD. Univariate logistic regression analysis showed that male, high level of IL-6, ESR, RF, ACPA, and DAS28 are suspected risk factors for RA-ILD ($p < 0.05$). Further, after correcting for confounders by multifactorial logistic regression analysis, it was confirmed that male (OR [95% CI]: 2.29 [1.25–4.18], $p < 0.001$), high level of ACPA (OR [95% CI]: 1.00

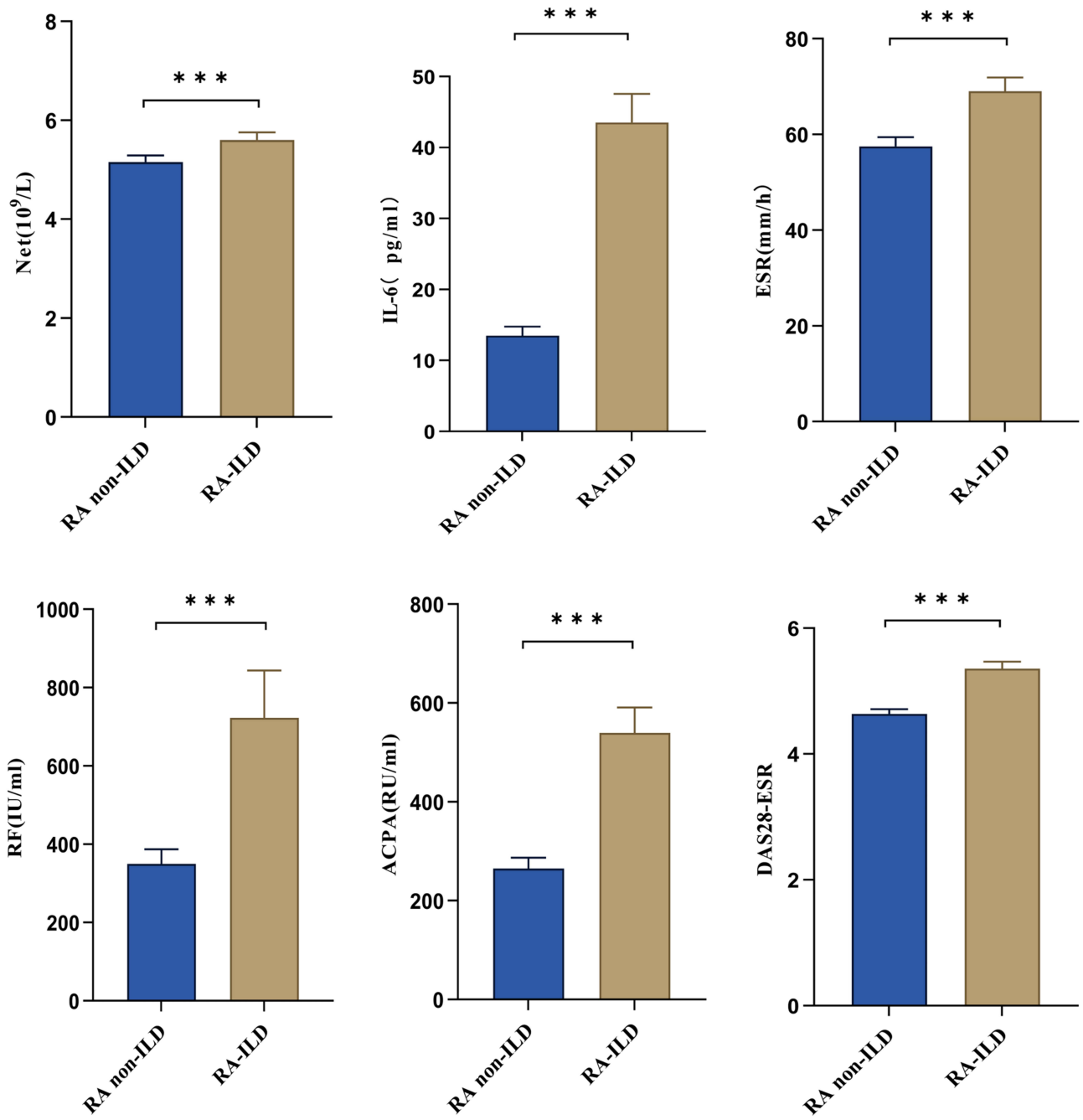

Figure 2 The difference of Net, IL-6, ESR, RF, ACPA, and DAS28-ESR between RA-ILD and RA non-ILD. Significance levels are indicated as follows: ***p < 0.001.

[1.00–1.00], $p = 0.007$), and IL-6 (OR [95% CI]: 1.03 [1.02–1.05], $p < 0.001$) are independent risk factors for RA-ILD. The results of univariate and multifactor logistic regression analyses are shown in Table 4.

Receiver Operating Characteristic Analysis

The predictive value of IL-6 for RA-ILD was assessed using ROC analysis. IL-6 demonstrated significant diagnostic utility in distinguishing RA-ILD patients from RA patients without ILD, with an AUC of 0.810 (95% CI: 0.767–0.854; p < 0.001). At the best cutoff value of 8.87 pg/mL, IL-6 exhibited a sensitivity of 94.4% and specificity of 63.6% (Table 5). The AUC of IL-6 for RA-ILD and the best cutpoint were shown in Figure 3.

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Table 2 Demographic Characteristics and Laboratory Parameters of the Study Population

Characteristic	Groups		*p*-value
	RA non-ILD, N = 236	RA-ILD, N = 125	
Age (years)	65 (57, 72)	65 (59, 72)	0.9212
BMI (Kg/m^2)	22.47 ± 2.57	22.24 ± 2.52	0.4033
Gender			<0.001
Female	198 (83.9%)	71 (56.8%)	
Male	38 (16.1%)	54 (43.2%)	
Plt (10^9/L)	276 (230, 342)	274 (217, 329)	0.4802
Net (10^9/L)	4.68 (3.72, 6.13)	5.29 (4.43, 6.62)	0.0052
Lym (10^9/L)	1.46 (1.15, 1.82)	1.55 (1.14, 1.97)	0.4562
IL-6 (pg/mL)	5 (2, 18)	22 (13, 69)	<0.001
ESR (mm/h)	61 (32, 76)	72 (49, 94)	<0.001
RF (IU/mL)	132 (35, 333)	282 (74, 804)	<0.001
ACPA (RU/mL)	106 (23, 378)	291 (79, 800)	<0.001
DAS28	4.75 (3.88, 5.52)	5.33 (4.47, 6.47)	<0.001

Table 3 Stratification Analysis of IL-6

Characteristic	Groups		*p*-value
	RA non-ILD, N =236	RA-ILD, N = 125	
IL-6 (pg/ml)			
Female			
>64	4 (2, 16)	22 (13, 55)	<0.001
≤64	5 (2, 13)	16 (13, 20)	<0.001
Male			
>64	22 (5, 39)	58 (13, 87)	0.002
≤64	7 (2, 18)	28 (16, 78)	0.002

Table 4 Univariate and Multifactor Logistic Regression Analyses of RA-ILD

Characteristic	Univariable			Multivariable		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (years)	1	0.98, 1.02	0.949	0.99	0.97, 1.01	0.226
BMI (Kg/m^2)	0.96	0.88, 1.05	0.404	0.93	0.84, 1.04	0.197
Gender						
Female	—	—		—	—	
Male	3.96	2.41, 6.51	<0.001	2.29	1.25, 4.18	0.007
IL-6 (pg/mL)	1.04	1.03, 1.05	<0.001	1.03	1.02, 1.05	<0.001
ESR (mm/h)	1.01	1.00, 1.02	<0.001	0.99	0.98, 1.01	0.28
RF (IU/mL)	1	1.00, 1.00	<0.001	1	1.00, 1.00	0.05
ACPA (RU/mL)	1	1.00, 1.00	<0.001	1	1.00, 1.00	<0.001
DAS28	1.76	1.43, 2.17	<0.001	1.29	0.92, 1.80	0.134

Table 5 Diagnostic and Predictive Value of IL-6 in RA-ILD

Predictor	AUC	Best Cutoff Value	Sensitivity	Specificity	95% CI	*p*-value
IL-6 (pg/mL)	0.810	8.87	94.40%	63.60%	0.767–0.854	<0.001

Correlation Analysis

RA-ILD Subgroup Analysis

The RA-ILD group is categorized into three subgroups based on HRCT scores: mild ILD, moderate ILD, and severe ILD, to compare the differences in laboratory parameters among the groups. The results show no statistically significant differences in Age, Plt, Net, Lym, IL-6, ESR, DAS28, RF, ACCPA, and FEV1 among the ILD subgroups ($p > 0.05$). However, the DLCO, FVC, and KL-6 differences between subgroups were significant ($p < 0.05$). Table 6 shows the characterization of laboratory indicators between ILD subgroups. Figure 4 demonstrates the differences in DLCO (%), FEV1 (%), FVC (%), IL-6, and KL-6 levels between ILD subgroups.

Pearson Correlation Analysis and Linear Regression Analysis

Subgroup analysis reveals no statistically significant differences in IL-6 levels across varying severity grades of RA-ILD. Furthermore, both Pearson correlation analysis and linear regression analysis confirm the absence of a significant association between IL-6 level and RA-ILD severity (Table 7). However, IL-6 level shows significant positive correlations with both DAS28-ESR ($r = 0.169$, $p < 0.001$) and ACPA ($r = 0.477$, $p < 0.001$) (Table 8). Figure 5 illustrates linear correlations between serum IL-6 levels and DLCO, KL-6, and DAS28.

Discussion

According to some previous studies, RA-ILD is the leading cause of death in RA patients.[23–25] Complications of ILD greatly affect the prognosis of RA because the progression of RA-ILD is usually progressive and currently leaves limited treatment options for patients and physicians, therefore, early identification and diagnosis of RA-ILD has become increasingly important, but patients with ILD usually do not have clinically significant symptoms in the early stage, therefore, we conducted a retrospective study to evaluate the predictive value of peripheral blood markers such as IL-6 in RA-ILD patients.

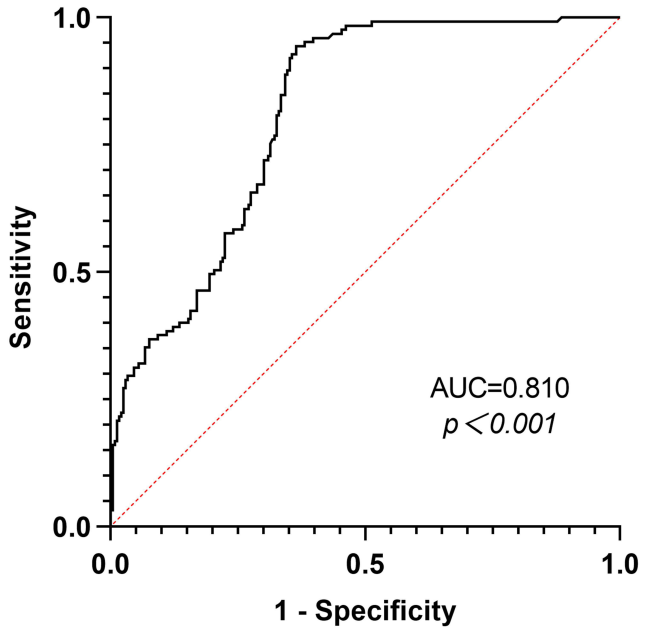

Figure 3 Characterization of the ROC curve for IL-6.

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Table 6 Characterization of Laboratory Indicators Between ILD Subgroups

Characteristic	ILD severity			*p*-value
	Mild ILD, N = 51	Moderate ILD, N = 57	Severe ILD, N = 17	
Age (years)	64 (56, 70)	65 (61, 72)	68 (64, 69)	0.281
BMI (Kg/m^2)	21.60 (20.13, 23.17)	22.31 (20.58, 24.22)	22.58 (20.41, 24.84)	0.091
Plt (10^9/L)	296 (242, 335)	251 (207, 330)	271 (260, 302)	0.337
Net (10^9/L)	5.31 (4.32, 5.98)	5.29 (4.56, 6.89)	5.29 (4.87, 6.78)	0.506
Lym (10^9/L)	1.41 (1.09, 1.77)	1.60 (1.24, 2.03)	1.56 (1.18, 2.16)	0.275
IL-6 (pg/mL)	19 (13, 69)	22 (14, 69)	22 (10, 64)	0.708
ESR (mm/h)	70 (46, 96)	68 (49, 94)	79 (56, 86)	0.821
RF (IU/mL)	231 (45, 785)	303 (100, 804)	287 (59, 1250)	0.734
ACPA (RU/mL)	351 (90, 895)	276 (103, 846)	87 (10, 585)	0.171
DAS28	5.21 (4.27, 6.44)	5.24 (4.67, 6.31)	6.34 (4.26, 6.53)	0.806
DLCO (%)	79 (66, 92)	64 (54, 78)	58 (51, 66)	<0.001
FEV1 (%)	94 ± 18	89 ± 18	83 ± 15	0.054
FVC (%)	85 (76, 95)	81 (68, 90)	78 (67, 84)	0.014
KL-6 (U/mL)	243 (188, 322)	410 (321, 664)	815 (395, 916)	<0.001

Notes: FEV1%: Forced expiratory volume in 1 second (percentage of predicted value). FVC%: Forced vital capacity (percentage of predicted value). DLCO%: Diffusing capacity of the lungs for carbon monoxide (percentage of predicted value).

IL-6 is an important pro-inflammatory factor in the cytokine network that contributes to the development of comorbidities. It mainly derived from macrophages and fibroblast-like synoviocytes (FLS), which is a prototypical cytokine with pleiotropic and redundant functional activity that binds to the common IL-6 signaling gp130 receptor to elicit a cascade of inflammation, in addition to this, IL-6 also affects CD4+ T cell differentiation and stimulates B cell proliferation to maintain inflammation,[26,27] those ongoing inflammation is key to the formation of ILD.

IL-6 can induce EMT and FMT through activation of the JAK/STAT signaling pathway. When IL-6 binds to the gp130 receptor, it induces JAK dimerization, and then JAK is activated and phosphorylates the tail tyrosine residues to form p-JAK. These phosphorylated tyrosine residues act as docking sites for STAT and bind to it via their SH2 structural domains. Upon phosphorylation of STAT by the SH2 structural domains, p-JAK activates phosphorylated STAT to form p-STAT, which subsequently becomes dimerized and translocates from the cytoplasm to the nucleus, where it acts as a transcription factor leading to increased expression of the cytokine IL-6 in the lung, which activates FMT and mediates EMT leading to extracellular matrix deposition (ECM) in the lungs and ultimately causes the development of ILD.[14,28–30] In a prospective study reported by Dilek Tezcan et al, the IL-6 levels were significantly higher in patients with CTD and CTD-ILD than in controls.[31]

In our study, we observed that the level of IL-6 (22 (13, 69) vs 5 (2, 18), $p < 0.001$) was significantly higher in the RA-ILD group than in the RA non-ILD group. A significant risk association between IL-6 with RA-ILD was confirmed by logistic regression. IL-6 was found to be effective in differentiating RA-ILD and RA non-ILD patients by ROC analysis (AUC = 0.810 (95% CI: 0.767–0.854; p < 0.001; Optimal cutoff value = 8.87)"to"(AUC = 0.810 (95% CI: 0.767–0.854; p < 0.001; Optimal cutoff value = 8.87). A significant proportion of clinical evidence suggests that tocilizumab, an IL-6R antagonist, may attenuate the progression of RA-ILD and potentially prevent ILD development in RA patients.[32,33] This may partly corroborate the value of IL-6 as a predictive marker for RA-ILD.

Additionally, we also found a significant positive correlation between IL-6 and the severity of RA in our study, which is similar to previous reports by Choe, J.Y., Almeida-Santiago et al.[34,35] This means that the severity of RA may be related to the development of RA-ILD. The high disease activity has also been reported to be an independent risk factor for comorbid ILD in patients with RA in a previous study.[14]

Finally, Warrick's semi-quantitative HRCT score is a measure of the degree and extent of lung involvement in patients with interstitial lung disease and has been widely used in other previous studies of CTD-ILD.[21,36,37] To further investigate the relationship between IL-6 levels and ILD severity, we performed a Pearson correlation analysis of IL-6 levels with HRCT score and KL-6 level. The results showed no significant correlation between IL-6 and HRCT score and KL-6. This implies that there is no significant correlation between the level of IL-6 and the severity of ILD in RA-ILD

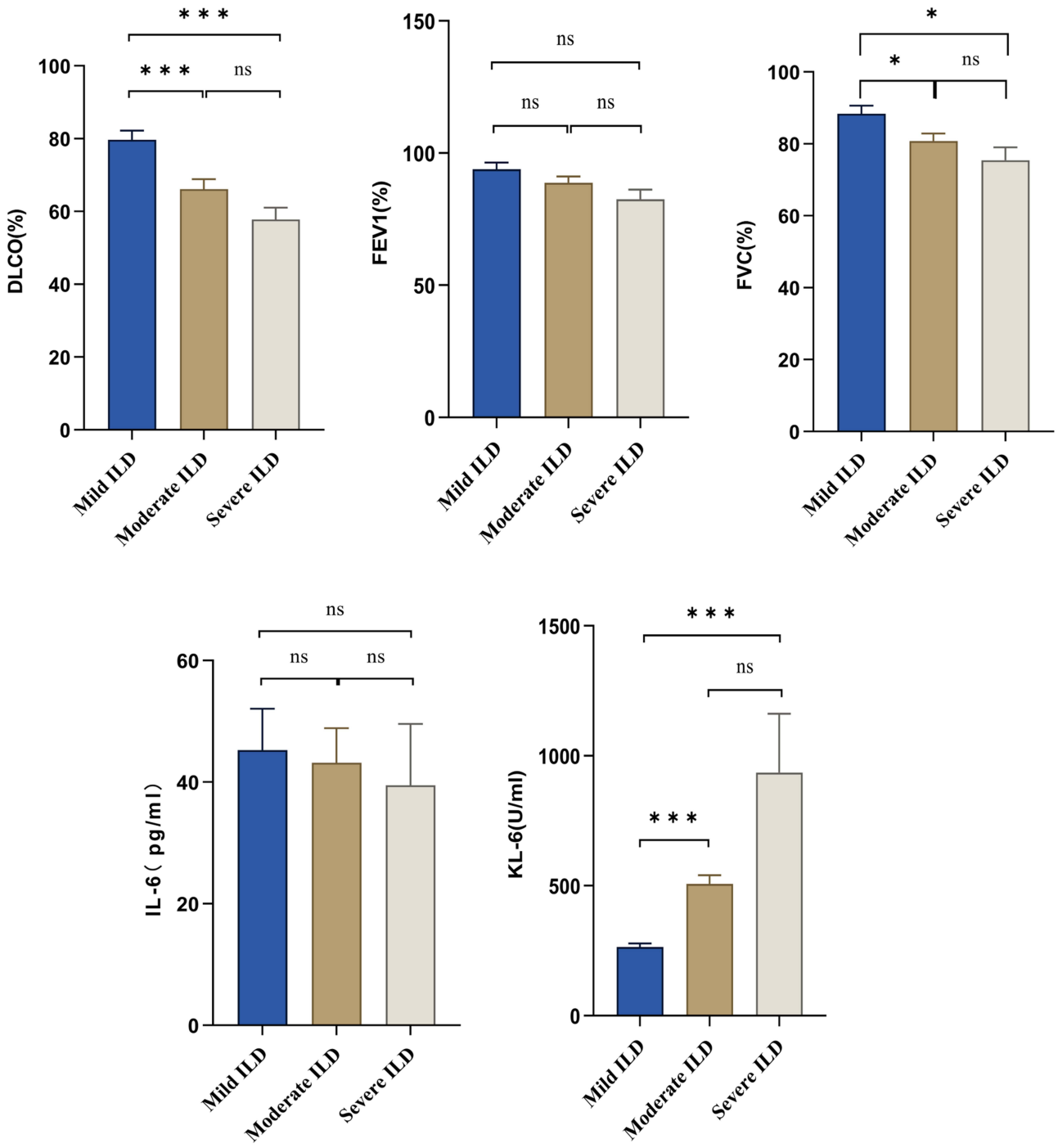

Figure 4 The differences in DLCO (%), FEV1 (%), FVC (%), IL-6, and KL-6 level between ILD subgroups. Significance levels are indicated as follows: *p < 0.05, ***p < 0.001; ns, not significant.

patients. The precise mechanisms underlying this phenomenon remain incompletely characterized, and current literature provides limited explanatory insights. Based on our findings, we hypothesize that the following pathophysiological factors may contribute. Firstly, since ILD takes a long time to continue to progress, whereas the progression time for non-progressive RA-ILD may be measured in years,[38] and, in our previous work, an acute-phase inflammatory marker, IL-6, is predominantly secreted by B lymphocytes, fibroblasts, and M1 macrophages during early RA inflammation.[39] However, pulmonary fibrosis typically manifests at later disease stages, when lymphopenia often occurs due to apoptosis-

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Table 7 Association Between IL-6 Levels and Pulmonary Function Parameters

Predictor	Pearson			Multiple Linear Regression		
	r	95% CI	*p*-value	B	95% CI	*p*-value
DLCO (%)	0.068	−0.109–0.240	0.454	0.228	−0.239–0.696	0.335
FEV1 (%)	−0.058	−0.231–0.119	0.524	−0.198	−1.148–0.752	0.681
FVC (%)	−0.043	−0.217–0.134	0.633	−0.078	−1.158–1.002	0.886
KL-6 (U/mL)	0.066	−0.111–0.239	0.466	0.013	−0.009–0.034	0.252
HRCT Score	−0.025	−0.199–0.152	0.786	−0.521	−2.410–1.368	0.586

Notes: FEV1%: Forced expiratory volume in 1 second (percentage of predicted value). FVC%: Forced vital capacity (percentage of predicted value). DLCO%: Diffusing capacity of the lungs for carbon monoxide (percentage of predicted value).

Table 8 Association of IL-6 with Other Laboratory Indicators

Predictor	Pearson			Multiple Linear Regression		
	r	95% CI	*p*-value	B	95% CI	*p*-value
Plt (10^9/L)	0.186	0.084–0.284	<0.001	0.011	−0.023–0.045	0.528
Net (10^9/L)	0.129	0.026–0.229	0.014	0.947	−0.750–2.643	0.273
Lym (10^9/L)	−0.097	−0.198–0.006	0.065	−3.071	−8.338–2.197	0.252
ESR (mm/h)	0.366	0.273–0.452	<0.001	0.064	−0.076–0.205	0.368
RF (IU/mL)	0.089	−0.014–0.190	0.092	−0.002	−0.005–0.002	0.305
ACPA (RU/mL)	0.169	0.066–0.267	0.001	0.012	0.005–0.019	<0.001
DAS28	0.477	0.394–0.553	<0.001	11.63	8.009–15.251	<0.001

mediated lymphocyte depletion[40]—a phenomenon consistently reported in our studies and by Chen et al.[41] This aligns with the higher PLR observed in RA-ILD patients. Second, while M1 macrophages drive initial inflammation, their transition to M2 phenotypes and fibroblasts transition to myofibroblasts in later stages, whose primary role is to secrete large amounts of ECM and Th2 cytokines, rather than producing significant quantities of IL-6, which promotes fibrosis, explaining the dissociation between IL-6 levels and fibrotic severity.[39] Finally, some RA-ILD patients experience joint-specific flares without respiratory symptoms. In such cases, HRCT-detected ILD may be early-stage, and elevated IL-6 primarily reflects articular disease activity rather than pulmonary fibrosis progression.

This study has several limitations. First, its cross-sectional retrospective design with a small sample size inherently restricts causal inference. The review of cases may not have accounted for all potential confounders affecting serum IL-6 levels, such as undetected inflammation at other sites. Moreover, the identified best IL-6 cutoff value (8.87 pg/mL) lies close to the upper normal limit, which may result in heightened sensitivity and a potentially elevated false-positive rate, thereby weakening the evidence for a causal link with interstitial lung disease progression. Second, treatment heterogeneity among patients, arising from the unavailability of specific therapies during the data collection period, introduced a confounding bias that could not be adequately controlled, partially affecting the validity of the findings. Third, as

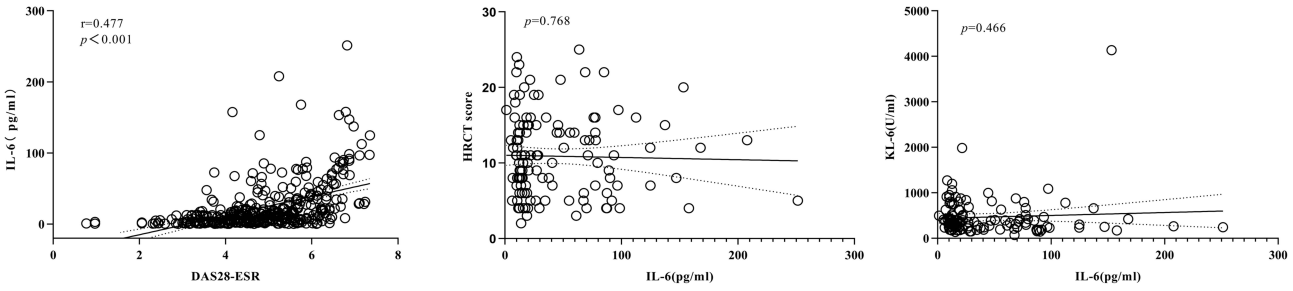

Figure 5 Linear correlations between serum IL-6 levels and DLCO, KL-6, DAS28.

research on IL-6 as a diagnostic and prognostic biomarker for CTD-ILD remains limited, this study lacks external cross-validation. Our conclusions rely primarily on existing pathophysiological rationale and the documented efficacy of IL-6 inhibitors. Thus, further prospective studies are warranted to confirm these results.

In conclusion, an elevated level of IL-6 may be an independent risk factor for RA-ILD, which is associated with an increased risk of RA-ILD. IL-6 may become an important predictive indicator for the diagnosis and prediction of RA-ILD.

Conclusions

We found that elevated IL-6 levels correlate with increased RA-ILD risk and show a significant positive correlation with disease activity. Patients with rheumatoid arthritis exhibiting high disease activity are more prone to developing interstitial lung disease. Furthermore, the decoupling relationship between IL-6 levels and RA-ILD severity partially suggests a causal link between IL-6 and RA-ILD. Specifically, elevated IL-6 in RA patients may trigger the development of interstitial lung disease, rather than being a consequence of the disease—a fundamental distinction from the classic biomarker KL-6. In summary, IL-6 demonstrates more predictive value and may serve as a predictive biomarker for RA-ILD, guiding the clinical application of IL-6-targeted therapeutics.

Data Sharing Statement

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

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Disclosure

This work had been read and approved by all co-authors. No part of this work has been published and is being considered for publication elsewhere. All the authors of this article report no conflicts of interest.

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