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ORIGINAL ARTICLE

Analysis of risk factors for the progression and prognosis of connective tissue disease-associated interstitial lung disease

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ABSTRACT

Objectives: This study aimed to investigate the risk factors of lung progression in patients with connective tissue disease-associated interstitial lung disease (ILD).

Patients and methods: A total of 91 ILD patients (28 males, 63 females; mean age: 54.9±11.3 years; range, 30 to 77 years) were included in the prospective follow-up study conducted throughout 2020. They were divided into progressors (n=27) and nonprogressors (n=64) according to whether the pulmonary disease progressed during a six-month follow-up period. The clinical data of the two groups were analyzed, and a logistic regression model was constructed to analyze the risk factors of the progression of ILD in all patients.

Results: Univariate analysis revealed significant differences ($p<0.05$) between the two groups in smoking history, serum ferritin, FVC% (the percentage of forced vital capacity), DLCO% (the percentage of diffusion capacity for carbon monoxide), and computed tomography involvement range. Further application of a logistic regression model revealed that increased serum ferritin level was an independent risk factor for ILD progression (odds ratio=1.002, 95% confidence interval: 1.000-1.003, $p=0.004$). The optimal critical value of serum ferritin was 303.25 ng/mL, the sensitivity and specificity were 81.5% and 54.7%, respectively, and the area under the curve was 0.747.

Conclusion: The level of serum ferritin may be an independent predictor for ILD progression.

Keywords: Connective tissue disease, interstitial, lung disease, progression, serum ferritin.

Connective tissue disease (CTD) is a systemic autoimmune disease characterized by multiple organ damage. The lungs are among the most vulnerable organs affected by CTD. Here, the disease can manifest as interstitial lung disease (ILD), pulmonary hypertension, and pleurisy, among which ILD is the most common.[1] Progressive ILD changes rapidly and has a poor prognosis, causing it to be one of the main causes of death in CTD patients.[2] ILD is often associated with systemic sclerosis (SSc), inflammatory myopathy, rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS), and systemic lupus erythematosus (SLE).[3] The severity and response to treatment of those with ILD can vary greatly.[4] For some patients, the disease progresses rapidly, treatment induces a poor response, and there is a high chance they experience respiratory failure, but in others, the disease develops much more slowly, and they respond to treatment positively. Thus, there is a question of whether different CTD-ILDs have common predictors. In this study, a statistical model was constructed to analyze the possible risk factors that affect how CTD-ILDs progress.

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PATIENTS AND METHODS

This prospective follow-up study was conducted at the Zhangzhou Affiliated Hospital of Fujian Medical University, Department of Rheumatology and Immunology with 91 patients (28 males, 63 females; mean age: 54.9±11.3 years; range, 30 to 77 years) selected from a follow-up study, with data prospectively collected throughout 2020. The patients were grouped as progressors (n=27) and nonprogressors (n=64) according to whether the ILD progressed during a six-month follow-up period. According to the American Thoracic Society/European Respiratory Society classification guidelines for idiopathic interstitial pneumonia,[5] progression of ILD is defined as the fulfillment of one of the following parameters upon a six-month follow-up: *(i)* relative decrease in predicted forced vital capacity (FVC%) ≥15%; *(ii)* relative decrease in predicted FVC% ≥10% and predicted diffusion capacity for carbon monoxide (DLCO%) ≥15%; *(iii)* high-resolution computed tomography (HRCT) revealing new pulmonary infiltrating lesions, though conditions must exclude infection, heart failure, and fluid overload. All of the patients subject to this study met at least one of the following criteria: SSc as defined by the 2013 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria; RA according to the 2010 ACR/EULAR; SLE according to the 2019 ACR/EULAR classification criteria; pSS according to the 2016 ACR/EULAR classification criteria; idiopathic inflammatory myopathy (IIM) according to the 2019 ACR/EULAR classification criteria: ANCA (antineutrophil cytoplasmic antibody)-associated vasculitis according to the 2017 ACR/EULAR classification criteria (draft): mixed connective tissue disease according to 1987 Alarcon-Segovia criteria. Interstitial lung disease can be diagnosed when related clinical symptoms and signs appear, combined with HRCT findings (reticular opacity, tractive bronchiectasis, and honeycomb alternation) and pulmonary function (restricted ventilation dysfunction and reduced diffusion function). Symptoms include but are not limited to dry cough, chest tightness, shortness of breath after activity, cyanosis, clubbing fingers, or bursting sound from the bottom of the lungs. Exclusion criteria were as follows: patients with a malignant tumor, infection, pregnancy, pulmonary lesions caused by occupational, drug, genetic and environmental factors, familial idiopathic pulmonary fibrosis, pulmonary hypertension, congenital heart disease, pulmonary vein occlusion, chronic obstructive pulmonary disease, and left heart failure.

The clinical data of all subjects were recorded, including their sex, age, course of the disease, smoking history, arthritis, and the type of CTD. Laboratory samples were collected at the time of the initial illness, including serum ferritin, serum albumin (ALB), serum Krebs von den Lungen-6 (KL-6), erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein, immunoglobulin G, and complement C3. Baseline pulmonary function indexes were recorded, including the percentage of FVC% in the predicted value and the percentage of DLCO% in the predicted value. The HRCT was read by two experienced radiologists. According to the percentage of interstitial fibrosis observed (from the findings of reticular opacity, tractive bronchiectasis, and honeycombing) in the total lung volume, the patients were divided into mild (affected range <10%), moderate (affected range 10 to 30%), and severe ILD groups (affected range ≥30%). The medication regimens of the two groups of patients were recorded. When the diagnoses were established, the subjects were treated with corresponding glucocorticoids and immunosuppressants by an experienced rheumatic immunologist from the same department as the authors.

Statistical analysis

Statistical analysis was performed by IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). If the measured data followed a normal distribution, it was expressed by mean ± standard deviation (SD), and the two groups were compared by the independent samples t-test. The median and interquartile range were used for other variables, and the Wilcoxon rank sum test was used to compare results generated by the two groups. The categorical data were then expressed as the number of cases and percentages, and a chi-square test was carried out for a comparison between groups. Logistic regression analysis was applied

Table 1. Comparisons of the general information between CTD-ILD patients with and without progression at baseline

	Progressors (n=27)			Non-progressors (n=64)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Onset age (year)			56.8±10.7			54.0±11.5	0.286
Sex							0.400
Male	10			18			
Female	17			46			
Disease course (month)	15	3.48		7.5	3.24		0.193
Smoking (%)	10	37.4		9	14.1		0.014
Arthritis/arthralgia (%)	12	27		37	64		0.243
CTD subtype (%)							
SLE	0			8	12.5		-
pSS	1	3.7		11	17.2		0.02
IIM	12	44.4		18	28.1		0.728
RA	2	7.4		6	9.4		0.001
SSc	4	14.8		6	9.4		0.002
MCTD	5	18.5		5	7.8		0.002
AAV	0	0		2	3.1		-
Overlap syndrome	3	11.1		8	12.5		0.007

CTD: Connective tissue disease; ILD: Interstitial lung disease; SD: Standard deviation; SLE: Systemic lupus erythematosus; pSS: Primary Sjögren's syndrome; IIM: Idiopathic inflammatory myopathy; RA: Rheumatoid arthritis; SSc: Systemic sclerosis; MCTD: Mixed connective tissue disease; AAV: ANCA (Antineutrophil cytoplasmic antibody)-associated vasculitis.

for risk factors analysis, and the optimal cut-off value was determined through receiver operating characteristics curve analysis. A *p* value <0.05 was considered statistically significant.

RESULTS

First, it should be noted that no deaths occurred among the 91 patients involved in this study during the six-month follow-up period. Among these patients, the most common type of CTD was IIM, with 30 cases, followed by pSS, with 14 cases. Twenty-seven (29.7%) patients who showed ILD progression at the six-month follow-up were classified as progressors, while 64 (70.3%) cases were stable and did not meet these criteria; they were thus classified as nonprogressors. There was no significant difference between the numbers of IIM cases in each group (p=0.728). However, there were significant differences in the numbers of other CTD types, such as pSS, RA, SSc, mixed CTD, and overlap syndrome (p<0.05). Furthermore, there were no significant differences between the groups in sex, age, course of the disease, and incidence of arthritis; however, progressors were comprised of a higher proportion of smokers (p<0.05). The patient characteristics are shown in Table 1.

Laboratory indicators including serum KL-6 level, ALB, ESR, high-sensitivity C-reactive protein, immunoglobulin G, and complement C3 were shown to be of similar general trends across all patients. However, the level of serum ferritin was substantially higher in progressors (p<0.05). Moreover, there was a marked difference in FVC% and DLCO% between the two groups, with those of the progressors being lower (p<0.05). Similarly, there was a notable contrast in the computed tomography (CT) range between the two groups at baseline (p<0.05), as demonstrated in Table 2.

All 91 patients were treated with glucocorticoid after diagnosis, of whom 86 (94.5%) were treated with a combination of immunosuppressants. There was no significant difference in the types of immunosuppressants and antifibrotic agents used between the two groups (p>0.05). The relevant data is presented in Table 3.

Table 2. Comparisons of clinical features between CTD-ILD patients with and without progression at baseline

	Progressors (n=27)					Non-progressors (n=64)					
Variables	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
KL-6 (U/L)				1041	530,1569				878	575,1282	0.599
ALB (g/L)			33.2±5.0					34.5±5.8			0.290
ESR (mm/h)			41.7±27.3					47.2±28.2			0.322
hsCRP (mg/L)				7.8	2.7,39.1				4.7	1.1,20.7	0.173
IgG (g/L)				16.9	11.5,18.0				16.6	13.4,21.8	0.260
Low-C3 (g/L)	7	25.9				15	23.4				0.800
Serum ferritin (ng/L)				678.1	323.0,1342.1				255.6	132.45,492.6	0.000
FVC%			65.5±18.1					76.2±13.4			0.009
DLCO%			57.3±17.1					65.1±16.8			0.047
CT range (%)											
<10	1	3.7				11	17.2				
10-30	7	25.9				26	40.6				
>30	19	70.4				27	42.2				

CTD: Connective tissue disease; ILD: Interstitial lung disease; SD: Standard deviation; KL-6: Krebs von den Lungen-6; ALB: Albumin; ESR: Erythrocyte sedimentation rate; hsCRP: Hypersensitivity C-reactive protein; IgG: Immunoglobulin; C3: Complement 3; FVC: Forced vital capacity; DLCO: Diffusion capacity for carbon monoxide; CT: Computed tomography.

Table 3. Comparisons of treatments between CTD-ILD patients with and without progression

	Progressors (n=27)		Non-progressors (n=64)		
Treatment	n	%	n	%	*p*
Corticosteroid alone	2	7.4	3	4.7	
Corticosteroid + immunosuppressant	25	92.6	61	95.3	0.987
+ Cyclophosphamide	10	37.0	30	46.9	0.079
+ Cyclosporine/tacrolimus	6	22.2	11	17.2	0.110
+ Azathioprine	6	22.2	13	20.3	0.311
+ Hydroxychloroquine	3	11.1	20	31.3	0.652
+ Tripterygium wilfordii	5	18.5	11	17.2	0.080
Anti-fibrotic agents	6	22.2	10	15.6	0.071

CTD: Connective tissue disease; ILD: Interstitial lung disease.

Table 4. Logistic analysis of CTD-ILD patients with progression

Variables	B	S.E.	Wald	*p*	OR	95% CI
Serum ferritin	0.02	0.001	8.108	0.004	1.002	1.000-1.003
Smoking (yes)	0.797	0.629	1.609	0.205	2.220	0.647-7.613
FVC%	-0.22	0.024	0.795	0.372	0.979	0.934-1.026
DLCO%	-0.002	0.019	0.011	0.915	0.998	0.962-1.036
CT range (%)						
10-30†	0.666	1.201	0.307	0.580	1.946	0.185-20.499
>30‡	1.114	1.197	0.867	0.352	3.048	0.292-31.817

CTD: Connective tissue disease; ILD: Interstitial lung disease; B: Regression coefficient; S.E.: Standard error; OR: Odds ratio; CI: Confidence interval; FVC: Forced vital capacity; DLCO: Diffusion capacity for carbon monoxide; CT: Computed tomography; † (CT range 10%-30%)/(CT range <10% + CT range >30%); ‡ (CT range >30%)/(CT range ≤30%); FVC, DLCO: Note the same as table 2.

Analysis of the risk factors affecting ILD progression was conducted by logistic regression. For univariate analysis, the factors with a statistical difference between the two groups, including smoking history, serum ferritin, FVC%, DLCO%, and CT involvement range, were considered independent variables. The results suggested that elevated serum ferritin was an independent risk factor for ILD progression (odds ratio=1.002, 95% confidence interval [CI]: 1.000-1.003, p=0.004, Table 4). Further comparisons were made between the serum ferritin levels of IIM and non-IIM patients at baseline, which yielded no significant difference between the two groups observed in this study (Table 1). The serum ferritin levels in each CTD subtype were also recorded, and there were no discernable differences between progressors and nonprogressors (Table 2).

High serum ferritin levels in CTD-ILD patients indicated they were prone to pulmonary progression. The optimal cut-off value was

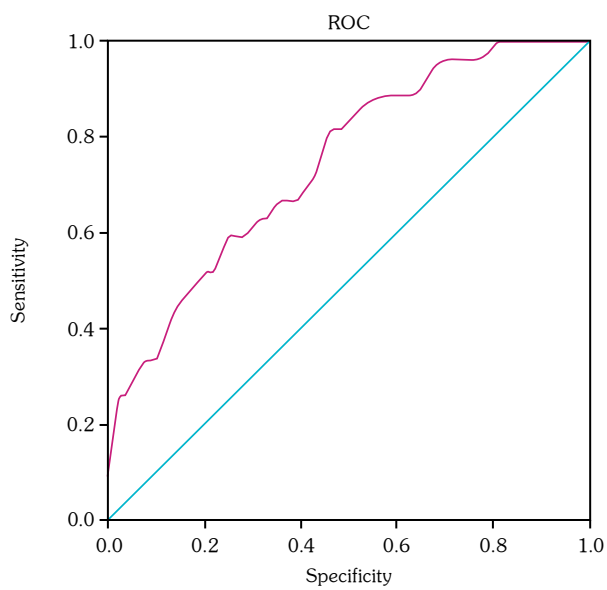

Figure 1. Working characteristic curve of serum ferritin in predicting the progression of connective tissue disease associated interstitial lung disease.
ROC: Receiver operating characteristic.

303.25 ng/mL, the sensitivity and specificity were 81.5% and 54.7%, respectively, and the area under the curve was 0.747 (Figure 1).

DISCUSSION

In this study, the outcomes of 91 CTD-ILD patients were monitored for six months, with the goal of determining prognostic factors that affected the progression of the disease in the patients' lungs. We focused on all CTD-ILD patients, including both the rapidly progressive (RP)-ILD and chronic ILD. This is in contrast to other research that has mainly focused on IIM or SSc, particularly on patients with RP-ILD.

High-resolution computed tomography is one of the most convenient methods to diagnose interstitial lung disease. The sensitivity and specificity it provides in the diagnosis of ILD can reach up to 90%,[6] and it is also one of the main means of monitoring the disease's effects and predicting any curative potential at the same time.[7] Higher variability in the size of lesions detected by HRCT and an increase in the incidence of consolidation indicate an escalation in the severity of the condition.[7] In a previous cohort study of patients with dermatomyositis, it was found that the involvement of the area below the pulmonary vein with positive anti-MDA5 (melanoma differentiation-associated gene 5) or anti-ARS (aminoacyl tRNA synthase antibody) was an independent risk factor for RP-ILD.[8] The results of this study showed at baseline that the range of HRCT involvement was >30% in progressors, while in nonprogressors, it was ≤30%. However, the range of HRCT involvement at baseline failed to predict the occurrence of the exacerbation of ILD. As a noninvasive examination, the pulmonary function test is mainly used to assess restrictive ventilatory dysfunction and reduced diffusion function in CTD-ILD patients.[1] It is also an important means to evaluate the severity of ILD. In this study, there were significant differences in FVC% and DLCO% between the two groups at baseline. However, further regression analysis found that pulmonary function parameters could not be used as a predictor for the progression of ILD. The average level of lung function of the subjects, which was in the mild to moderate range, has not been able to predict the progression of ILD, which is consistent with a cohort study on mild SSc-ILD.[9] Long-term smokers are prone to pulmonary interstitial fibrosis,[10] as was shown in the present study, though it should be noted that the number of smokers among progressors was significantly higher than among nonprogressors. Even so, any smoking habits, whether past or present, did not suggest the predictive value related to the progression of ILD.

In addition, many serum markers have been developed for CTD-ILD, among which KL-6 is strongly correlated with the occurrence of ILD. The serum KL-6 level of CTD-ILD patients is significantly higher than patients without ILD,[11] which can reflect the severity of the disease and can suggest a poor prognosis.[12] Two studies showed that baseline serum KL-6 concentrations >800 u/mL (hazard ratio= 2.91, 95% CI: 1.04-8.10, p=0.022) and >1000 u/mL (odd ratio= 2.02, 95% CI: 1.2-3.41, p=0.0083) were independent predictors for the acute exacerbation of ILD.[13,14] However, its clinical significance in CTD-ILD patients has not been fully clarified, and there is still some controversy regarding it. Indeed, many scholars believe it is difficult to establish a specific cut-off value of KL-6 to accurately reflect the severity of ILD disease and evaluate the prognosis. Dynamic monitoring of the changes in the KL-6 level has more guiding significance for clinical efficacy determination and disease outcome.[15] In our study, the level of KL-6 in progressors was higher than in non-progressors at baseline, but the difference was not statistically significant and was not further included in the regression analysis. Among other serological markers, serum ferritin showed better disease predictive value. Ferritin is secreted by activated macrophages and dendritic cells, plays a crucial role in sequestering potentially harmful reactive iron molecules, and activates the Th1 response.[16] Research has shown that the increase in serum ferritin level is significantly correlated with the expression of cytokines IL-18, IL-6, IL-8, IL-10, and TNF-α in patients with polymyositis/dermatomyositis-related ILD.[17] Related to this, Matsuda et al.[18] reported that the 24-week follow-up survival rate of polymyositis/dermatomyositis patients with serum ferritin levels ≥450 ng/mL at baseline

was significantly less than in those with lower ferritin levels. A study conducted at the Shanghai Renji Hospital reported that the HRCT score and serum ferritin level were correlated with a poor prognosis of clinically amyopathic dermatomyositis combined with RP-ILD, and a serum ferritin level ≥1,810 ng/mL (hazard ratio= 1.001, 95% CI: 1.002-1.007, p=0.010) was an independent risk factor for death within one year.[19] A study with a six-month follow-up showed that the survival rate after the onset of ILD was substantially higher among the patients treated with tofacitinib compared to the traditional treatment.[20] Furthermore, the level of serum ferritin also decreased significantly with the improvement of the disease. As is already known, different types of CTD have inconsistent pathological processes. For example, SLE-and pSS-related ILD progresses slowly, while IIM progresses rapidly. Idiopathic inflammatory myopathy-ILD often causes high levels of ferritin, but no significant difference in serum ferritin levels between IIM and non-IIM patients at baseline was observed in this study. There was also no notable difference in the distribution of IIM between the two groups (p>0.05). Subsequently, statistical analysis was carried out for the serum ferritin levels in each CTD subtype, though the results showed no statistical difference between progressors and nonprogressors due to the small sample size. Since ferritin is an acute-phase protein that increases with inflammation, elevated ferritin levels may be associated with rheumatologic disease activity, either in local organs or generalized.[21,22] It was speculated that ferritin could also be useful for non-IIM-ILD. Due to the small number of cases in this study and the lack of dynamic monitoring of ferritin, it would need further investigation to confirm its potential. It was observed that patients with serum ferritin ≥303.25 ng/mL were prone to ILD progression, but the cut-off value indicated by the results was lower than reported in other studies. This may be due to the subjects of this study having CTD types that may develop ILD. Consequently, the criterion of serum ferritin levels ≥303.25 ng/mL may be concluded to be the lowest predictive limit of pulmonary progression in all CTD-ILDs.

The evaluation of CTD-ILD required collaboration among multiple disciplines, and there were many individual differences in the selection of treatment schemes. However, there was no significant contrast between the treatment schemes of the two groups; therefore, their impact on the outcomes could be excluded. Some mild cases of ILD can be maintained in a stable condition during the potentially extensive duration of the disease, but in other instances, it can develop into progressive pulmonary fibrosis with serious damage to pulmonary function and even become life threatening.[23] For CTD patients with only mild ILD in its early stages, there is no clear and effective index to predict the possible occurrence of progressive pulmonary fibrosis.[9] Although serum ferritin level is known to reflect ILD disease activity, there are few reports describing this association. This study observed that serum ferritin levels could be used as a serum marker to predict whether CTD is complicated by ILD progression. However, analysis, as detailed in the work presented here, has limitations due to the small sample size and the brief follow-up duration. Further verification is required by additional, longer-term, and larger-scale cohort studies in the future.

In conclusion, an elevated serum ferritin level is a prominent factor associated with a poor prognosis in patients with CTD-ILD. Those with serum ferritin levels ≥303.25 ng/mL formed a group at risk of pulmonary progression in this study. However, whether this data point can be used to predict the progression of ILD in those diagnosed with CTD-ILD remains to be further studied.

Ethics Committee Approval: The study protocol was approved by the Zhangzhou Affiliated Hospital of Fujian Medical University Ethics Committee (date: 18.05.2020, no: 2020LWB077). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Study design: T.Z., H.P.C.; Data collection: T.Z., F.A.L.; Statistical analysis: T.Z.; manuscript writing by all authors.

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