



Risk factors for progression and prognosis of rheumatoid arthritis–associated interstitial lung disease: single center study with a large sample of Chinese population

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Abstract

Background Factors associated with progression and survivals in rheumatoid arthritis–associated interstitial lung disease (RA-ILD) have not been described in a large center China cohort.

Methods Seven-hundred and ninety-one consecutive RA patients who completed lung HRCT were considered as potential participants in this retrospective cohort study. Determinants of ILD progression were identified through multivariable logistic analysis. Cox hazards analysis was used to determine significant variables associated with survival.

Results Of 307 patients diagnosed with RA-ILD, 266 were finally included. The 3-year survival rate of RA-ILD patients was 81.24%, and the 5-year survival rate was 69.71%. A total of 82 deaths occurred during follow-up, of which 56 died of respiratory failure due to ILD progression and/or pneumonia while 14 with malignancies (8 with lung cancer). Logistic regression analysis showed that anti-CCP antibody high titer positive (OR: 4.03, 95% CI: 1.04–15.69) and DLCO% < 45% (OR: 8.31, 95% CI: 2.17–31.75) were independent risk factors for the ILD progression. Cox hazards analysis revealed that advanced age (> 60 years old) of RA-ILD diagnosis (HR: 2.32, 95% CI: 1.27–4.25) and extensive lung involvement on HRCT (HR: 2.19, 95% CI: 1.24–3.87) were associated with worse survival. Treatment with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69) was associated with better survival.

Conclusions In RA-ILD patients, anti-CCP antibody high titer positive and DLCO% < 45% are risk factors for ILD progression. Advanced age and extensive lung involvement on HRCT, rather than the baseline UIP pattern, independently predict mortality after controlling for potentially influential variables. Furthermore, cyclophosphamide treatment helps to improve the prognosis in real-world experience.

Keywords Interstitial lung disease · Prognosis · Progression · Rheumatoid arthritis · Risk factor

Introduction

Rheumatoid arthritis (RA) is a systemic, chronic autoimmune disease. Interstitial lung disease (ILD) is one of the most common extra-articular manifestations among RA patients [1–3]. The estimate of prevalence and incidence of rheumatoid arthritis–associated interstitial lung disease (RA-ILD) is variable, which depends on the diagnostic method and selected population [2, 3]. Studies demonstrated that elderly, men, smoking, an increased RF, and anti-CCP antibody titer are predictors for the development of RA-ILD, while small sample studies showed that one-third of patients with interstitial lung disease had progressed within 2 years [4, 5]. Poor prognosis has been shown in RA-ILD patients. Previous studies have reported a median survival of only 3 years after diagnosis of RA-ILD [6]. A recent large population-based cohort study revealed that 5-year mortality was 39.0% in RA-ILD patients, which was significantly higher than RA patients with non-ILD [7]. Factors associated

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with ILD progression or RA-ILD patients' survivals have not been previously described in a large center China cohort.

We designed the present study to investigate the risk factors for interstitial lung disease progression and explore the prognostic factors for survival in patients with RA-ILD.

Materials and methods

Patients

We performed a retrospective cohort study involving patients who received medical care at Chao-Yang Hospital, Capital Medical University. The patients were enrolled in our study consecutively from May 2008 to January 2014. The inclusion criterion for RA in this study was the fulfillment of 1987 ACR or 2010 ACR-EULAR classification criteria for RA [8, 9]. Exclusion criteria were other autoimmune or infectious diseases, neoplasm, lung surgery, and other respiratory diseases. Taking lung high-resolution CT (HRCT) results into consideration, a work-group which included experienced rheumatologists and radiologists comprehensively assessed the absence/presence of RA-ILD. Of 791 consecutive RA patients who completed lung HRCT, 307 had RA-ILD. Twenty-nine patients refused to participate in the study, 12 patients could not be contacted, and 266 RA-ILD patients were finally included (Fig. 1). Follow-up of those 266 patients was finished, but not all test or examination results were available.

The medical records of the cases were obtained from the medical record database. Demographic characteristics, clinical features, inspection, and test data were extracted from the database. Patients' medical treatment was defined as the medication regularly taken under doctors' advice for more than 3 months. RF and anti-CCP antibody high titer positive were defined as a threefold increase in titer greater than normal. Anti-CCP was quantified by ELISA using commercial kits (Euro Diagnostica, SWEDEN). Survival time (measured in month) was calculated

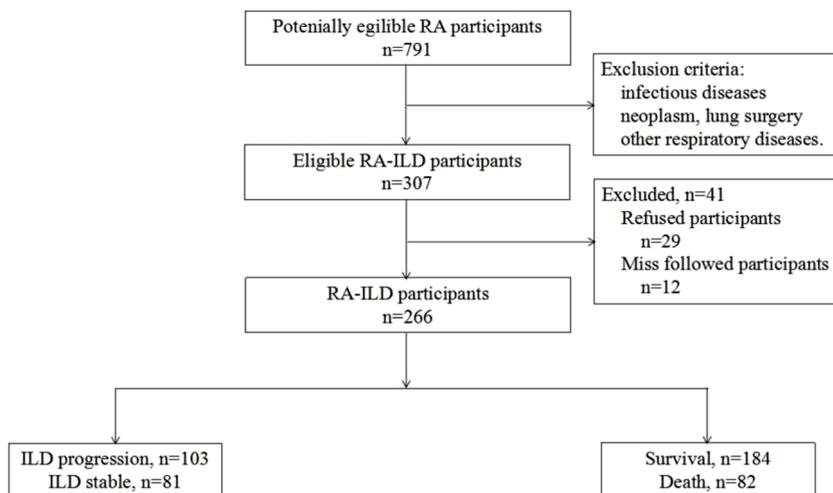
from the date of the first diagnosis of RA-ILD to either the date of death or the date of the latest updated data (August 2017). The research received ethical approval from Ethics Committee in Chao-Yang Hospital, Capital Medical University and the principles of the Declaration of Helsinki were followed throughout the study. All participants gave written informed consent.

Pulmonary function tests and HRCT

Pulmonary function tests were performed according to American Thoracic Society standards/European Respiratory Society guidelines [10], using Master Screen PFT System (JAEGER, Germany). We collected the data on baseline forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO), which were both expressed as a percentage of predicted values. In the univariate analysis, the cut off value of FVC and DLCO were defined as 70% and 45% [4, 11].

All patients had completed HRCT imaging scan of chest, using 1–2 mm-thickness cuts. The HRCT scans were performed during end inspiration in the supine positions, and those images were evaluated in a blinded manner by two experienced radiologists. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists. HRCT results were analyzed for both subtypes (UIP, NSIP, OP, LIP, or indeterminate) and extent of lung involvement [12, 13]. Cellular NSIP (c-NSIP) and fibrotic NSIP (f-NSIP) were evaluated as described by MacDonald (2001) [14]. Cellular NSIP: on the basis of NSIP characteristics, a fine reticular pattern was presented, but the dominant finding was ground-glass opacity. Fibrotic NSIP: Superimposed ground-glass opacity within the reticular pattern, and characteristic features of UIP (e.g., honeycombing) were absent. We defined disease extent based on the percentage of lung involved as assessed by HRCT (< 10% = limited, 10–30% = moderate, > 30% = extensive). The ILD score of HRCT

Fig. 1 Study flow diagram



(ILDS) was also used to evaluate the severity and extent of ground-glass opacity, reticular pattern, and honeycombing in the six lung zones, with a maximum possible total score of 24. Interstitial lung disease progression was defined as meeting any of the followings: a decrease of FVC > 10% or DLCO > 15% predicted, worsening of ILDS or death from respiratory failure due to ILD and/or pneumonia [4, 15]. Lung stable was defined as not meeting the above conditions. Pulmonary function test and HRCT data assessment were collected at the time of baseline and at the most recent follow-up.

Statistical analysis

Continuous variables were presented in terms of the mean and standard deviation for normally distributed data or the median (range) for non-normally distributed data. Categorical variables were indicated as percentages. Continuous variables were compared using the Student's *t* test or Mann-Whitney *U* test, whereas chi-square test was used for comparing categorical data. Interobserver agreement on HRCT pattern was analyzed using the κ statistic test. To identify independent risk factors for interstitial lung disease progression, multivariate logistic regression analyses were used. Survival was evaluated using the Kaplan-Meier method and the log-rank test according to the observation period. Cox hazards analysis was used to determine significant variables associated with survival. Any variable with a *P* value of < 0.1 on bivariate analysis were included in multivariate analysis. Statistical analyses were performed by SPSS19.0 (SPSS Inc., Chicago, IL, USA) software. All *P* values were 2-tailed and *P* < 0.05 was considered to be statistically significant.

Results

Patient characteristics

The baseline characteristics of 266 patients with RA-ILD were shown in Table 1. Among them, 162 (60.90%) were females. The mean age at diagnosis of RA-ILD was 64.80 ± 10.71 years old, and 67.67% of patients were older than 60 years old. 81.95% of patients with RA before the onset of ILD, and 80.27% of patients with ILD occur within 10 years of RA diagnosed. A total of 108 patients (40.60%) had a history of smoking. Smoking was significantly more frequent among males (75.92%) than females (24.07%).

Usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP) pattern were the common types of RA-ILD, accounting for 37.22% and 25.94%, respectively. Interobserver agreement between both radiologists was moderate (κ statistic test, $\kappa = 0.46$). Of 99 UIP pattern, 46 were definite UIP and 53 were possible UIP. There were 49 c-NSIP and 20 f-NSIP in 69 NSIP pattern.

Table 1 Baseline characteristics of the 266 patients with RA-ILD

Characteristics	<i>n</i> (%)
Age at RA-ILD diagnosis, mean (S.D.), years	64.80 (10.71)
Advanced age (> 60 years old)	180/266 (67.67%)
RA onset earlier than ILD	218/266 (81.95%)
ILD occurs within 10 years of RA diagnosed	175/218 (80.27%)
Female patient	162/266 (60.90%)
Ever smoker	108/266 (40.60%)
Males ever	82/108 (75.92%)
Females ever	26/108 (24.07%)
Follow-up time, median (range), month	51.02 (2.66–104.79)
RF positive	212/266 (79.69%)
RF high titer positive	179/266 (67.29%)
Anti-CCP antibody positive	236/266 (88.72%)
Anti-CCP antibody high titer positive	203/266 (76.32%)
ESR, mean (S.D.)	52.65 (28.34)
CRP, median (range)	2.20 (1.07–6.11)
DAS28, mean (S.D.)	5.56 (1.68)
HRCT pattern of ILD	
UIP	99/266 (37.22%)
Definite UIP	46/266 (17.29%)
Possible UIP	53/266 (19.92%)
NSIP	69/266 (25.94%)
c-NSIP	49/266 (18.84%)
f-NSIP	20/266 (7.52%)
OP	11/266 (4.14%)
LIP	2/266 (0.75%)
indeterminate	85/266 (31.95%)
Extent of lung involvement	
Limited (< 10% of lung involvement)	130/266 (48.87%)
Moderate (10–30% of lung involvement)	67/266 (25.19%)
Extensive (> 30% of lung involvement)	69/266 (25.94%)
FVC (% predicted), mean (S.D.) ^a	84.69 (22.63)
DLCO (% predicted), mean (S.D.) ^a	54.99 (23.07)

^a Only 165 patients had baseline pulmonary function test results

RA rheumatoid arthritis, ILD interstitial lung disease, RF rheumatoid factor, Anti-CCP antibody anti-cyclic citrullinated peptide antibody, ESR erythrocyte sedimentation rate, CRP C-reactive protein, DAS disease activity score, UIP usual interstitial pneumonia, NSIP non-specific interstitial pneumonia, OP organized pneumonia, LIP lymphocytic interstitial pneumonia, FVC forced vital capacity, DLCO diffusion capacity of the lung for carbon monoxide

Extent of lung involvement analysis showed that limited was predominant (130/266, 48.87%), with smaller numbers of moderate (67/266, 25.19%), and extensive (69/266, 25.94%) lung involvement. Only 165 patients had baseline pulmonary function test results. The average FVC% was 84.69 ± 22.63%, and DLCO% was 54.99 ± 23.07% (Tables 2, 3, and 4).

Table 2 Univariate analysis of the baseline clinical characteristics between RA-ILD patients with and without ILD disease progression

Characteristics	RA-ILD patients who had lung progression (n = 103)	RA-ILD patients with stable lung (n = 81)	
Advanced age (> 60 years old)	75/103 (72.81%)	50/81 (61.73%)	0.10
Male patient	45/103 (43.69%)	31/81 (38.27%)	0.54
<i>ILD occurs within 10 years of RA diagnosed</i>	<i>58/103 (56.31%)</i>	<i>60/81 (74.07%)</i>	<i>0.01</i>
Ever smoker	45/103 (43.69%)	29/81 (35.80%)	0.29
RF high titer positive	73/103 (70.87%)	52/81 (64.19%)	0.35
<i>Anti-CCP antibody high titer positive</i>	<i>95/103 (92.23%)</i>	<i>59/81 (72.84%)</i>	<i>0.00</i>
<i>UIP pattern in HRCT</i>	<i>48/103 (46.60%)</i>	<i>22/81 (27.16%)</i>	<i>0.01</i>
Extensive lung involvement	31/103 (30.09%)	20/81 (24.69%)	0.51
Treatment for RA-ILD			
Corticosteroid	41/103 (39.81%)	37/81 (45.68%)	0.46
<i>CYC</i>	<i>38/103 (36.89%)</i>	<i>43/81 (53.08%)</i>	<i>0.04</i>
MTX	28/103 (27.18%)	32/81 (39.51%)	0.08
Tripterygium ^a	45/103 (43.69%)	34/81 (41.97%)	0.88
FVC% < 70%	20/72 (27.78%)	11/57 (19.29%)	0.35
<i>DLCO% < 45%</i>	<i>31/72 (43.05%)</i>	<i>9/57 (15.78%)</i>	<i>0.00</i>

^a Tripterygium is an extract of *Tripterygium wilfordii*, a traditional Chinese medicine, which has immunosuppression effects

RA rheumatoid arthritis, ILD interstitial lung disease, RF rheumatoid factor, Anti-CCP antibody anti-cyclic citrullinated peptide antibody, UIP usual interstitial pneumonia, CYC cyclophosphamide, MTX methotrexate, FVC forced vital capacity, DLCO diffusion capacity of the lung for carbon monoxide

The entries in italics in Table 2 means it has statistically significant ($P < 0.05$)

The follow-up of RA-ILD patients

The median observation period was 51.02 months (range 2.66–104.79 months) (Table 1). The 3-year survival rate was 81.24%, and the 5-year survival rate was 69.71%. During the follow-up period, 82 patients died, and 49 (59.76%) died within 3 years after diagnosis. As showed in Table 5, 56 of 82 (68.29%) patients died of respiratory failure due to ILD progression and/or pneumonia. Fourteen of 82 (17.07%) patients were complicated with malignancies (eight cases with lung cancer). Nine patients died of cardiovascular and cerebrovascular diseases (myocardial

infarction in four cases, cerebral hemorrhage in four cases, and cerebral infarction in one case), of which three had a history of hypertension and one case of coronary heart disease (Table 5).

We have collected the medications of the 266 patients after being diagnosed as RA-ILD. Patients' medical treatment was defined as the medication regularly taken under doctors' advice for more than 3 months. In our research, 14 patients have used biological agents: 10 of them used biosimilar products of TNF- α inhibitor (made in China), two with adalimumab, and two with infliximab. Only five of those patients have baseline and follow-up data for comparison, which did not associate

Table 3 Logistic regression analysis of predictors for ILD disease progression

Characteristics	OR	95%CI	P value
Advanced age(> 60 years old)	1.12	0.43–2.91	0.81
ILD occurs within 10 years of RA diagnosed	0.47	0.18–1.22	0.12
Ever smoker	1.02	0.39–2.64	0.97
<i>Anti-CCP antibody high titer positive</i>	<i>4.03</i>	<i>1.04–15.69</i>	<i>0.04</i>
UIP pattern in HRCT	1.48	0.57–3.85	0.42
CYC	0.96	0.37–2.47	0.93
MTX	0.72	0.25–2.08	0.54
FVC% < 70%	0.67	0.19–2.29	0.52
<i>DLCO %< 45%</i>	<i>8.31</i>	<i>2.17–31.75</i>	<i>0.00</i>

RA rheumatoid arthritis, ILD interstitial lung disease, Anti-CCP antibody anti-cyclic citrullinated peptide antibody, UIP usual interstitial pneumonia, CYC cyclophosphamide, MTX methotrexate, FVC forced vital capacity, DLCO diffusion capacity of the lung for carbon monoxide

The entries in italics in Table 3 means it has statistically significant ($P < 0.05$)

Table 4 Cox hazard analysis of prognostic factors for death in RA-ILD patients

Characteristics	Bivariate		Multivariate		
	χ^2	P value	HR	95% CI	P value
<i>Advanced age(> 60 years old)</i>	<i>12.54</i>	<i>0.00</i>	<i>2.32</i>	<i>1.27–4.25</i>	<i>0.01</i>
Sex, male	5.84	0.02	1.72	0.99–2.97	0.05
Ever smoker	2.37	0.12	0.85	0.49–1.45	0.54
RF high titer positive	3.49	0.06	1.34	0.78–2.28	0.28
Anti-CCP antibody high titer positive	8.03	0.01	1.92	0.81–4.53	0.14
UIP pattern in HRCT	9.89	0.00	1.16	0.71–1.93	0.56
<i>Extensive lung involvement</i>	<i>5.75</i>	<i>0.02</i>	<i>2.19</i>	<i>1.24–3.87</i>	<i>0.01</i>
Treatment for RA-ILD					
<i>CYC</i>	<i>13.95</i>	<i>0.00</i>	<i>0.43</i>	<i>0.26–0.69</i>	<i>0.00</i>
MTX	3.82	0.05	0.58	0.33–1.01	0.05
Tripterygium	3.74	0.05	1.49	0.94–2.37	0.09

RA rheumatoid arthritis, ILD interstitial lung disease, Anti-CCP antibody anti-cyclic citrullinated peptide antibody, UIP usual interstitial pneumonia, CYC cyclophosphamide, MTX methotrexate, FVC forced vital capacity, DLCO diffusion capacity of the lung for carbon monoxide

The entries in italics in Table 2 means it has statistically significant ($P < 0.05$)

with malignancy. Two of them had no progression in lung HRCT, other two patients died of respiratory failure due to ILD progression and/or pneumonia, and one patient had lung progression in HRCT. Only two patients used MMF and both of them had no progression in lung HRCT.

During follow-up period, eight RA-ILD patients (8/266, 3.01%) were diagnosed as lung cancer, all of whom died within 3 years after diagnosis. Among them, three were females, five were males and 75.0% of patients were older than 60 years old. A total of four patients (50.0%) had a history of smoking, and were males. Five patients (5/8, 62.50%) with UIP pattern on HRCT (four definite UIP and one possible UIP), and half of the lung involvement was limited. Only

two patients underwent surgical lung biopsy, and the pathological findings were adenocarcinoma.

Risk factors for interstitial lung disease progression

Due to the lack of data on lung HRCT and pulmonary function test during the follow-up period, some patients could not be evaluated. Finally, a total of 103 RA-ILD patients were identified as interstitial lung disease (ILD) progression, and 81 participants were stable. On univariate analysis, ILD occurs within 10 years of RA diagnosed, anti-CCP antibody high titer positive, treatment with cyclophosphamide, DLCO % < 45% and UIP pattern on HRCT was associated with ILD progression in RA-ILD patients ($P < 0.05$, Table 2). Considering that the history of smoking and FVC% reduction may be related to the progression of ILD, so both factors were also included in the Logistic regression analysis. Logistic regression modeling demonstrated that anti-CCP antibody high titer positive (OR: 4.03, 95% CI: 1.04–15.69, $P < 0.05$) and DLCO% < 45% (OR: 8.31, 95% CI: 2.17–31.75, $P < 0.01$) were independent risk factors for the ILD progression (Table 3).

Prognostic factors for survival in RA-ILD patients

Considering the number of missing values, pulmonary function test results were not included within the survival analysis. On bivariate analysis in RA-ILD patients, advanced age (> 60 years old) of RA-ILD diagnosis, males, anti-CCP antibody high titer positive, treatment with cyclophosphamide, extensive lung involvement, and UIP pattern on HRCT were associated with survival ($P < 0.05$). Cox hazards modeling revealed that advanced age (> 60 years old) of RA-ILD diagnosis (HR: 2.32, 95% CI: 1.27–4.25, $P < 0.05$) and extensive

Table 5 Causes of deaths in 82 patients with RA-ILD

Cause of death	n (%)
Respiratory failure (ILD progression and/or pneumonia)	56/82 (68.29%)
Malignancies	14/82 (17.07%)
Lung cancer	8/82 (9.75%)
Hematological malignancies	2/82 (2.44%)
Breast cancer	1/82 (1.22%)
Colon cancer	1/82 (1.22%)
Esophagus cancer	1/82 (1.22%)
Gallbladder carcinoma	1/82 (1.22%)
Other diseases	12/82 (14.63%)
Myocardial infarction	4/82 (4.88%)
Cerebral hemorrhage	4/82 (4.88%)
Cerebral infarction	1/82 (1.22%)
Abdominal aortic dissection aneurysm	1/82 (1.22%)
Gastrointestinal bleeding	1/82 (1.22%)
Acute renal failure	1/82 (1.22%)

lung involvement on HRCT (HR: 2.19, 95% CI: 1.24–3.87, $P < 0.05$) were associated with worse survival. Treatment with cyclophosphamide (HR: 0.43, 95% CI: 0.26–0.69, $P < 0.01$) was associated with better survival.

Discussion

Interstitial lung disease (ILD) is the most common extra-articular manifestation of RA patients, and the risk of death for RA-ILD is three times higher than in RA patients without ILD [1, 6]. This is the largest retrospective cohort study in China to analyze the risk factors for interstitial lung disease progression and prognosis in RA-ILD patients. Our research included 266 RA-ILD patients from 791 consecutive RA patients who completed lung HRCT. The 3-year survival rate was 81.24%, and the 5-year survival rate was 69.71%.

Progression of interstitial lung disease in RA-ILD patients can be manifested by a worsening of respiratory symptoms and/or decreased activity endurance, with developed ground-glass opacity, reticular pattern, and honeycombing on lung HRCT images, and the corresponding pulmonary function impairment. Previous study reported that one-third of patients had interstitial lung disease progressed within 2 years [4], and ILD progression had a serious impact on survival [16]. Due to the lack of data on lung HRCT and pulmonary function test during the follow-up period, some patients could not be evaluated; however, 103 RA-ILD patients were identified as interstitial lung disease progressed at least. When age, smoking history, and HRCT data entering the multivariate logistic regression model, the results showed that anti-CCP antibody high titer positive and DLCO% < 45% were independent risk factors for the ILD progression.

Anti-CCP antibody positive can be earlier than the emergence of joint symptoms in RA patients, and has been demonstrated to be a risk factor for the development of RA-ILD [2]. Moreover, our findings indicated that anti-CCP antibody high titer positive has a predictive value for ILD progression. Studies found that tobacco smoking mostly plays a role in the development of RA through tissue protein citrullination, which may be the source of anti-CCP antibodies in early stage RA patients [17]. In our research, although the frequency of tobacco smoking was higher among the ILD progression group than patients with lung stable, no significant difference was shown. Those results demonstrated that exist other factors stimulate the sustained rise of anti-CCP antibodies. Impaired DLCO is a common pathophysiological change in the early stage of ILD. DLCO decline can reflect the severity of lung damage, but also one of the most sensitive indicators. Previous studies have shown that DLCO reduction is a useful factor not only for the development of RA-ILD, but also for the ILD progression [2, 4]. Our results revealed that DLCO < 45% of

the predicted value is a ponderable predictor of ILD progression.

The use of HRCT in defining the subtype of ILD disease is now well established. The present study confirms that UIP and NSIP patterns were the common types of RA-ILD, accounting for 37.22% and 25.94%, respectively. Previous researches have shown that UIP pattern on HRCT has been associated with a worse outcome than other subtypes [18, 19]. On bivariate analysis, UIP pattern on HRCT was associated with survival in our study. Moreover, we used multivariate analytical method to identify clinical predictors of mortality. In a model controlling for sex, smoking, and HRCT pattern, advanced age (> 60 years old) of RA-ILD diagnosis and extensive lung involvement on HRCT were independently associated with an increased risk of death. Solomon et al. found that pulmonary function impairment, rather than the baseline HRCT pattern, independently predicted mortality after controlling for potentially influential variables [20]. Rojas-Serrano et al. reported that the severity of ILD, but not the HRCT pattern, is associated with mortality and older patients have worse prognosis [21]. Sathi et al. studied 29 patients with RA-ILD, followed 13 to 15 years, revealed that patients with extensive RA-related ILD (> 25% lung involvement) have a poor prognosis [5]. These data support the present findings. It is necessary to take both HRCT pattern and extent of lung involvement into consideration.

Treatment of ILD is challenging given the lack of robust data regarding the therapies used [22]. Treatment decisions are often made clinically, based on exacerbating or mitigating factors such as functional impairment and comorbidity burden. Tripterigium is an extract of *Tripterigium wilfordii*, a traditional Chinese medicine, which has immune-suppression effects [23]. Tripterigium is widely used in the treatment of RA-ILD in China; however, in our study, current data analysis does not suggest that Tripterigium can help improve disease progression and prognosis in patients with RA-ILD, so dose corticosteroids 38.72% (103/266) patients have used corticosteroids. After controlling for possible influences, the multivariable analysis found that there was no statistical difference among the two groups. A double-blind, randomized, placebo-controlled trial has demonstrated that cyclophosphamide had a significant but modest beneficial effect on clinical symptoms and lung function in patients with symptomatic scleroderma-related interstitial lung disease [24]. Our real-world study also revealed that cyclophosphamide helps to improve the prognosis in RA-ILD patients. We'll further our exploration in following researches.

A total of 82 RA-ILD patients died during the follow-up period. The main cause of death was respiratory failure due to ILD progression and/or pneumonia. It is noteworthy that 14 patients were complicated with malignancies, of which eight cases of lung cancer (8/266, 3.01%). Literature meta-analysis showed that RA patients had an increased risk of lung cancer

compared with the general population. A retrospective study of 1685 idiopathic pulmonary fibrosis (IPF) patients in Korea found that the incidence of lung cancer with IPF was 6.8%, and lung cancer was an independent risk factor for the pulmonary fibrosis prognosis [25]. The incidence of lung cancer in China general population was about 0.73% [26]. Reported by a cohort study of 23,644 RA patients in Taiwan, China, the standardized incidence of lung cancer was 1.36% [27]. In this study, the incidence of lung cancer with RA-ILD was 3.01% by following up, which is significantly higher than those general population and RA patients reported in the literature. Furthermore, among the RA-ILD patients with lung cancer, older, smoking and male patients were common. The most prevalent HRCT pattern was UIP, with limited and moderate lung involvement, and all lung cancer patients died within 3 years. We should pay more attention to the screening for cancer in this population.

Our research does have some inevitable limitations. This cohort study was designed and enrolled patients in a single medical care center retrospectively. Due to the lack of adequate pulmonary function test results at baseline and follow-up periods, those data were not included within the survival analysis; however, this is the largest cohort study in China to analyze the risk factors for interstitial lung disease progression and prognosis in RA-ILD patients. This study has a good regional representation, and some practical points are useful for clinicians.

Conclusions

In summary, this cohort study revealed that anti-CCP antibody high titer positive and DLCO% < 45% are independent risk factors for the ILD progression. Advanced age and extensive lung involvement on HRCT, rather than the baseline UIP pattern, independently predict mortality after controlling for potentially influential variables. Cyclophosphamide treatment helps to improve the prognosis in real-world experience. Furthermore, patients with RA-ILD are at high risk for malignancies (especially lung cancer), and clinicians should pay more attention to the tumor screening.

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Author contributions Yi Zheng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Qiang Fu, Li Wang, and Yi Zheng were involved in the design of the study; Qiang Fu, Luling Li, Yifan Li, and Ran Liu selected the patients and acquired the data; Qiang Fu and Li Wang analyzed and interpreted the data; authors Qiang Fu and Li Wang jointly completed the writing, and Luling Li, Yifan Li, Ran Liu, and Yi Zheng were substantially involved in revising the article.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no competing interests.

Disclosures None.

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