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ORIGINAL ARTICLE

A preliminary study of lung abnormalities on HRCT in patients of rheumatoid arthritis–associated interstitial lung disease with progressive fibrosis

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Abstract

Objective This retrospective study evaluates lung abnormalities on high-resolution CT (HRCT) and clarifies which abnormality can predict the progressive fibrosis of rheumatoid arthritis (RA)–associated interstitial lung disease (ILD).

Objects and methods We identified 1096 RA patients, and enrolled 213 patients with a diagnosis of RA-ILD who underwent serial chest HRCT. Clinical data of the patients were obtained. The presence, extent, and distribution of lung abnormalities were assessed on CT scans. Logistic regression analysis was used to determine positive indicators with predictive value for progressive fibrosis, and 2 × 2 contingency tables were constructed to assess their diagnostic efficiency.

Result Of 213 RA-ILD patients, 106 (49.8%) were diagnosed as progressive fibrosis. The rates of advanced age, male, smoking history, shortness of breath, and anti-CCP antibody high titer positive were higher, and RA duration was shorter in progressive fibrosis patients. Reticular pattern (RP), peribronchovascular interstitium (PBVI) thickening, interlobular septal thickening, and traction bronchiolectasis were more common in the progressive fibrosis group (84.9% vs 42.1%, $P < 0.001$; 79.3% vs 45.8%, $P < 0.001$; 74.5% vs 43.9%, $P < 0.001$; 67.0% vs 40.2%, $P < 0.001$; respectively). Lung abnormalities demonstrated subpleural predominance, and the subpleural RP and/or interlobular septal thickening had a wide distribution in the progressive fibrosis group (71.7% vs 14.0%, $P < 0.001$). The overall extent of lung abnormalities was more extensive in the progressive fibrosis group (18.4% vs 14.2%, $P < 0.05$). Logistic regression analysis showed that a wide distribution of subpleural RP and/or interlobular septal thickening (OR, 18.15) and PBVI thickening (OR, 4.98) were independent risk factors predictive of progressive fibrosis. For the combination of these two CT abnormalities, sensitivity was 63.2%, specificity was 92.5%, positive likelihood ratio was 8.5, and negative likelihood ratio was 0.4 in predicting progressive fibrosis.

Conclusions A wide distribution of subpleural RP and/or interlobular septal thickening and PBVI thickening on HRCT appear predictive of progressive fibrosis in RA-ILD. The combined evaluation of these two CT abnormalities has a good judgment value.

Key Points

- *We designed this study to investigate the risk factors for progressive fibrosis in patients with RA-ILD. Factors including clinical, physiological, radiological and therapeutic variables were all included in the data analysis.*
- *Our results showed HRCT abnormalities, rather than other parameters, appeared predictive of progressive fibrosis in RA-ILD.*
- *The methods and results of image evaluation in this article would provide reference to rheumatologists in identifying early stage of progressive fibrosis which helps to improve poor prognosis of RA-ILD.*

Keywords Interstitial lung disease · Lung abnormalities · Progressive fibrosis · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects approximately 0.5~1% of the population, and pulmonary involvement is common, affecting all the components of the lung, such as the airways, parenchyma, pleura, and pulmonary vasculature [1, 2]. Interstitial lung disease (ILD) is the primary pulmonary manifestation of RA, and associated with high morbidity and mortality [3–5]. Natural course of RA-ILD varied from long-term stability to rapid progression, even acute exacerbation in a short time [6–8]. At present, there is no effective method to predict the clinical course of RA-ILD, which has attracted the attention of clinicians. Therefore, in this study, we retrospectively analyzed the high-resolution CT (HRCT) data of 213 RA-ILD patients with sequential imaging data, and visually assessed the lung abnormalities on CT scans. We further determined CT abnormalities predictive of progressive fibrosis, which will be beneficial in identifying patients at risk and with early stage of progressive fibrosis, as well as providing references for identification and development of clinical strategies.

Materials and methods

Patients and diagnoses

This is a retrospective study. Data of 1096 RA patients who admitted to Beijing Chao-Yang hospital, Capital Medical University, from October 2008 to October 2017 were retrospectively reviewed, and 421 patients were diagnosed with RA-ILD. Diagnosis criteria for RA were those fulfilled 1987 ACR or 2010 ACR-EULAR classification criteria for RA [9, 10]. Exclusion criteria were other autoimmune and infectious diseases, tumors, lung surgery, and other respiratory diseases. ILD was proved on HRCT. Progressive fibrosis was defined as a new development or an increase in the extent of reticular pattern (RP) and/or honeycombing (HC) on follow-up CT [11]. Rapidly progressive fibrosis was considered to be present when progressive fibrosis occurred within 6 months. Finally, 213 RA-ILD patients who underwent serial chest HRCT were included.

The medical records of the cases were obtained from the medical record database. Demographic characteristics, clinical features, inspection, test, and therapeutic data were extracted from the database. RF and anti-CCP antibody high titer positive were defined as a threefold increase in titer greater than normal. 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. Not all test or examination results were available. This research received ethical approval from Ethics Committee in Beijing Chao-Yang Hospital, Capital Medical University, and the principles of the Declaration of Helsinki were followed throughout the study.

High-resolution CT image acquisition

All patients underwent HRCT scans. HRCT was performed using various CT scanners. Scans were obtained at the end of inspiration and in supine position from the lung apices to the bases. Image data were reconstructed by using a high spatial-frequency (bone) algorithm, with a slice thickness of 0.6 mm, slice spacing of 0.6 mm, and slice number of about 400–460, or with a slice thickness of 1.0 mm, slice spacing of 1.0 mm, and slice number of about 240–270. The number of slices varied with the slice thicknesses and the sizes of the lungs of different patients. All images were viewed with a PACS workstation at window settings appropriate for viewing the lung parenchyma (window level, − 600 to − 700 HU; window width, 1200–1500 HU) and the mediastinum (window level, − 20 to − 40 HU; window width, 350–400 HU).

Image evaluation

HRCT images were evaluated in a blinded manner by two chest radiologists (with 10 and 6 years of HRCT interpretation experience respectively). Inconsistencies between the two observers were resolved by common discussions. Both observers evaluated the presence of various abnormalities: ground-glass opacity (GGO), RP, HC, interlobular septal thickening, peribronchovascular interstitium (PBVI) thickening, traction bronchiectasis, traction bronchiolectasis, and emphysema/bulla. The distribution of lung abnormalities was recorded, and the extent of GGO, RP, and HC was quantitatively assessed.

GGO was defined as hazy increased attenuation of lung, with preservation of bronchial and vascular margins; RP was defined as innumerable interlacing lines, suggestive of mesh (synonym, reticulation); HC was considered to be present when clustered cystic airspaces of 3–10 mm in diameter with shared well-defined walls were identified; interlobular septal thickening was considered to be present when visible linear opacities was seen to outline the pulmonary lobules (Fig. 1) [12–14]. In this article, GGO referred to pure GGO and GGOs adjacent to or overlying a region of RP/HC. Subpleural abnormalities referred to abnormalities in contact with pleura and within 2 cm from the pleural surface [11], including subpleural GGO, subpleural RP, subpleural HC, and subpleural interlobular septal thickening (Fig. 1). Subpleural septal lines tend to be straight with 1–2 cm in length, and are usually seen extending to the pleural surface and being roughly perpendicular to the pleura.

PBVI thickening was defined as an increase in bronchial wall thickness or an increase in the diameter of pulmonary arteries; traction bronchiectasis and traction bronchiolectasis were respectively defined as irregular bronchial and

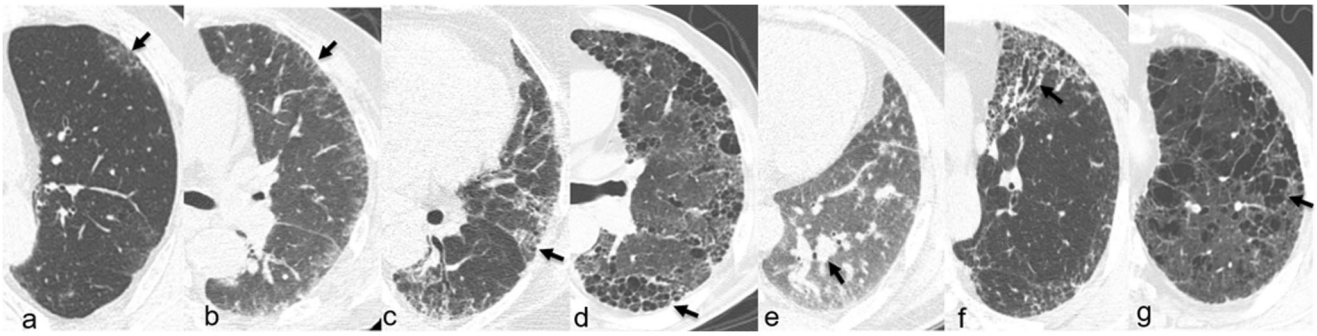

Fig. 1 Lung abnormalities on HRCT in RA-ILD patients. Transverse high-resolution CT images show lung abnormalities (arrows) as follow: subpleural ground-glass opacity **a**, subpleural interlobular septal thickening **b**, subpleural reticular pattern **c**, subpleural honeycombing **d**, peribronchovascular interstitium thickening **e**, traction bronchiectasis **f**, and emphysema **g**. Subpleural septal lines tend to be straight with 1–2 cm in length **b**, and are usually seen extending to the pleural surface and being roughly perpendicular to the pleura.

bronchiolar dilatation caused by surrounding retractile pulmonary fibrosis; emphysema was defined as areas of decreased attenuation, usually without visible walls; bulla was defined as a rounded focal lucency or area of decreased attenuation, bounded by a thin wall (Fig. 1) [12, 13, 15].

The transverse distribution was classified as subpleural (2 cm from the pleural surface), peribronchovascular (along the bronchovascular bundles), or random distribution. The coronal distribution of lung abnormalities was classified as upper-lobe (above hilum) predominant or lower-lobe (below hilum) predominant [11].

The lungs were divided into six zones (upper, middle, and lower zones in both lungs), and each zone was evaluated separately. The upper zone was defined as the area above the level of the carina; the lower zone was the area below the level of the inferior pulmonary vein; and the middle zone was the area between the upper and lower zones [16, 17]. The extent of GGO, RP, and HC was evaluated visually for each lung zone, and the final percentage of involvement was obtained by averaging the six zones. The percentage of lung abnormalities was estimated to the nearest 10% of parenchymal involvement.

The distribution ranges of subpleural abnormalities were particularly assessed in this study. A full chest was non-anatomically divided into six zones (upper, middle, and lower lung zones) by the levels of trachea carina and inferior pulmonary vein, as mentioned above. For each subpleural abnormality, wide distribution was defined as ≥ 4 lung zones involvement and total subpleural range > 50%, and local distribution was defined as ≤ 3 lung zones involvement or total subpleural range $\leq 50\%$.

Statistical analysis Statistical analysis was performed using the SPSS 19.0. The normal distribution data were expressed as the mean ± standard deviation. Measurement data were analyzed by Student's *t* test. Categorical data were analyzed by chi-square test or Fisher's exact test. Interobserver agreement on the distribution ranges of subpleural abnormalities was analyzed using the κ statistic test. Logistic regression was performed by stepwise method. All P values < 0.05 were considered statistically significant. The following indicators of the performance of lung abnormalities for the prediction of progressive fibrosis were calculated: sensitivity, specificity, positive likelihood ratio (LR), negative LR, false negative rate, and false positive rate.

Results

Patient characteristics

The baseline characteristics of 213 RA-ILD patients were shown in Table 1. Among them, 119 (55.9%) were females. The mean age at baseline was 64.9 ± 11.4 years, and 67.6% of patients were older than 60 years. A total of 86 patients (40.4%) had a history of smoking. The mean duration of RA was 24 months (range 0–712), and 77.5% of patients were diagnosed with RA before the onset of ILD. Respiratory symptoms were presented in 119 (55.9%) patients, and shortness of breath was the most common symptom (88/213, 41.3%).

The median HRCT intervals were 25 months (range1–127) (Table 1). In total, 106 of 213 (49.8%) RA-ILD patients were diagnosed with progressive fibrosis by the follow-up HRCT. Among them, progressive fibrosis occurred in 3 cases (2.8%) within 1 months, 9 cases (8.5%) during 1 to 6 months, 16 cases (15.1%) during 7 to 12 months, 19 cases (17.9%) during 13 to 24 months, 59 cases (55.7%) 24 months later.

We have collected therapeutic medications of the 213 patients during the time of initial and latest CT examinations (Table 1). In our research, glucocorticoid (GC) was the most frequently prescribed drug (44.1%), followed by tripterygium (42.7%), hydroxychloroquine (HCQ) (35.7%), leflunomide (LEF) (31.5%), methotrexate (MTX) (30.1%), cyclophosphamide (CYC) (19.7%), sulfasalazine (SASP) (5.2%), biological agents (3.3%),

Table 1 Baseline characteristics of RA-ILD patients with and without progressive fibrosis

Characteristics	RA-ILD ($n = 213$)	Progressive fibrosis ($n = 106$)	Non-progressive fibrosis ($n = 107$)	P value
Age at baseline, years	64.96 ± 11.40	67.47 ± 11.91	62.48 ± 10.33	0.001
Advanced age (> 60 years) at baseline	144 (67.6%)	79 (74.5%)	65 (60.8%)	0.032
Male patient	94 (44.1%)	56 (52.8%)	38 (35.5%)	0.011
Ever smoker	86 (40.4%)	52 (49.1%)	34 (31.8%)	0.010
RA duration at baseline, months	24 (4, 84)	12 (2, 60)	36 (6, 120)	0.009
RA onset earlier than ILD	165 (77.5%)	77 (72.6%)	88 (82.2%)	0.094
CT intervals, months	25 (1–127)	27 (12, 42)	24 (12, 37)	0.828
DAS28	4.69 ± 1.91	4.59 ± 2.13	4.79 ± 1.71	0.516
Respiratory symptoms				
Shortness of breath	88 (41.3%)	51 (48.1%)	37 (34.6%)	0.045
Dry cough	65 (30.5%)	31 (29.3%)	33 (30.8%)	0.799
RF high titer positive	146 (68.6%)	72 (67.9%)	74 (69.2%)	0.846
Anti-CCP antibody high titer positive	160 (75.1%)	86 (81.1%)	74 (69.2%)	0.043
FVC (% predicted)	83.81 ± 21.91	80.92 ± 22.59	86.34 ± 21.17	0.208
DLCO (% predicted)	53.70 ± 20.06	51.10 ± 21.92	56.08 ± 18.07	0.197
Treatment for RA-ILD				
Irregular medication	18 (8.5%)	11 (10.4%)	7 (6.5%)	0.314
Corticosteroid	95 (44.6%)	48 (45.3%)	47 (43.9%)	0.842
CYC	42 (19.7%)	19 (17.9%)	23 (21.5%)	0.513
MTX	64 (30.1%)	28 (26.4%)	36 (33.7%)	0.250
LEF	67 (31.5%)	32 (30.2%)	35 (32.7%)	0.692
Tripterygium[a]	91 (42.7%)	48 (45.3%)	43 (40.2%)	0.452
HCQ	76 (35.7%)	36 (34.0%)	40 (37.4)	0.602
SASP	11 (5.2%)	4 (3.8%)	7 (6.5%)	0.361
TNF inhibitors	7 (3.3%)	2 (1.9%)	5 (4.7%)	0.254
Pirfenidone	3 (1.41%)	1 (0.94%)	2 (1.87%)	0.566
Mycophenolate	2 (0.94%)	1 (0.94%)	1 (0.94%)	0.995
Azathioprine	1 (0.47%)	0 (0%)	1 (0.94%)	0.318

RA rheumatoid arthritis, *ILD* interstitial lung disease, *RF* rheumatoid factor, *Anti-CCP* antibody anti-cyclic citrullinated peptide antibody, *DAS* disease activity score, *FVC* forced vital capacity, *DLCO* diffusion capacity of the lung for carbon monoxide, *CYC* cyclophosphamide, *MTX* methotrexate, *LEF* leflunomide, *HCQ* hydroxychloroquine, *SASP* sulfasalazine, *TNF* tumor necrosis factor

[a] Tripterygium is an extract of *Tripterygium wilfordii*, a traditional Chinese medicine, which has immunesuppression effects

pirfenidone (1.4%), mycophenolate (0.9%), and azathioprine (0.5%). Eighteen patients were considered as irregular medication for they only have received drug therapy during hospitalization with refusal of medication after discharge.

On univariate analysis, advanced age (> 60 years), male, smoking history, shortness of breath, anti-CCP antibody high titer positive, and short duration of RA disease were associated with the progressive fibrosis of RA-ILD ($P < 0.05$, Table 1). No significant difference was found for baseline FVC, DLCO, and treatment for RA-ILD, such as GC, LEF, MTX, CYC, or irregular medication ($P > 0.05$).

Lung abnormalities on initial HRCT

Presence of lung abnormalities The presence of lung abnormalities in RA-ILD patients was shown in Table 2. The most common abnormality on HRCT in 213 RA-ILD patients was GGO, followed by RP, PBVI thickening, interlobular septal thickening, traction bronchiolectasis, traction bronchiectasis, emphysema/bulla, and HC. Among them, RP was the most common abnormality in the progressive fibrosis group, and GGO was the most common abnormality in the non-progressive fibrosis group.

RP, PBVI thickening, interlobular septal thickening, and traction bronchiolectasis were more common in the

progressive fibrosis group (84.9% vs 42.1%, $P < 0.001$; 79.3% vs 45.8%, $P < 0.001$; 74.5% vs 43.9%, $P < 0.001$; 67.0% vs 40.2%, $P < 0.001$; respectively). No significant difference was found for other lung abnormalities, including GGO, traction bronchiectasis, HC, and emphysema/bulla ($P > 0.05$).

Distribution of lung abnormalities

Lung abnormalities of 213 RA-ILD patients demonstrated bilateral infiltration (93.4%), with lower predominance (93.4%) and subpleural predominance (77.9%). The abnormalities of the two separate groups appeared the similar distribution. The upper predominance, peribronchovascular predominance, and unilateral infiltration were all uncommon in both groups.

Extent of lung abnormalities

The extent of lung abnormalities was shown in Table 3. The overall extent of lung abnormalities was more extensive in the progressive fibrosis group (18.4% vs 14.2%, $P < 0.05$). No other significant difference was identified in the extent of GGO, RP, and HC individually between the two groups.

Subpleural abnormalities

As the transverse distribution of lung abnormalities in RA-ILD patients showed subpleural predominance, in this article, we paid extra attention to the subpleural abnormalities and made detailed evaluation. The most frequent subpleural abnormality in 213 RA-ILD patients was subpleural RP, followed by subpleural GGO, subpleural interlobular septal thickening, subpleural HC. Subpleural interlobular septal thickening and subpleural RP were more common in the progressive fibrosis group (43.4% vs 33.6%, $P < 0.001$; 80.2% vs 33.6%, $P < 0.001$; respectively), and no significant difference was found for subpleural GGO and subpleural HC between the two groups (Table 2).

The distribution ranges of subpleural abnormalities on HRCT were shown in Table 4. In view of the mixed existence of RP and interlobular septal thickening in subpleural areas on HRCT, in this study, we combined the two subpleural abnormalities when evaluating the distribution ranges (Table 4). Interobserver agreement between both radiologists was good (κ statistic test, $\kappa = 0.785$). The wide distribution of subpleural RP and/or interlobular septal thickening was more common in the progressive fibrosis group (71.7% vs 14.0%, $P < 0.001$). No other significant difference was identified in the distribution ranges of subpleural GGO and subpleural HC between the two groups.

Rapidly progressive fibrosis

A total of 12 patients (12/106, 11.3%) were considered to be present with rapidly progressive fibrosis. A wide distribution of subpleural RP and/or interlobular septal thickening appeared on HRCT in 10 patients (10/12, 83.3%), and PBVI

Table 2 Lung abnormalities on initial HRCT of RA-ILD patients

Parameter	RA-ILD ($n = 213$)	Progressive fibrosis ($n = 106$)	Non-progressive fibrosis ($n = 107$)	P value
GGO				
GGO	152 (71.4%)	75 (70.8%)	77 (72.0%)	0.845
Subpleural GGO	115 (54.0%)	62 (58.5%)	53 (49.5%)	0.190
Interlobular septal thickening				
Interlobular septal thickening	126 (59.2%)	79 (74.5%)	47 (43.9%)	0.000
Subpleural interlobular septal thickening	104 (48.8%)	68 (43.4%)	36 (33.6%)	0.000
RP				
RP	135 (63.4%)	90 (84.9%)	45 (42.1%)	0.000
Subpleural RP	121 (56.8%)	85 (80.2%)	36 (33.6%)	0.000
HC				
Subpleural HC [a]	49 (23.0%)	30 (28.3%)	19 (17.8%)	0.067
Traction bronchiolectasis	114 (53.5%)	71 (67.0%)	43 (40.2%)	0.000
Traction bronchiectasis	60 (28.2%)	36 (34.0%)	24 (22.4%)	0.061
PBVI thickening	133 (62.4%)	84 (79.3%)	49 (45.8%)	0.000
Emphysema/bulla	52 (17.8%)	30 (20.8%)	22 (15.0%)	0.189

RA rheumatoid arthritis, *ILD* interstitial lung disease, *GGO* ground-glass opacity, *RP* reticular pattern, *HC* honeycombing, *PBVI* peribronchovascular interstitium

[a] All HCs demonstrated subpleural distribution

Table 3 Extent of lung abnormalities on initial HRCT of RA-ILD patients

Parameter	Progressive fibrosis ($n = 106$)	Non-progressive fibrosis ($n = 107$)	P value
Overall extent of lung abnormalities	18.4 ± 14.3	14.2 ± 15.5	0.042
GGO			
Any GGO	14.1 ± 16.2	13.8 ± 15.2	0.879
Subpleural GGO	6.8 ± 5.0	7.4 ± 4.5	0.633
RP			
Any RP	10.9 ± 8.3	9.1 ± 6.9	0.201
Subpleural RP	8.5 ± 5.0	7.0 ± 5.5	0.128
HC			
Subpleural HC[a]	9.2 ± 8.6	14.3 ± 11.9	0.082

Data are percentage of lung parenchyma

RA rheumatoid arthritis, *ILD* interstitial lung disease, *GGO* ground-glass opacity, *RP* reticular pattern, *HC* honeycombing

[a] All HCs demonstrated subpleural distribution

thickening appeared in all the patients (12/12, 100%). The increase in bronchial wall thickness or the increase in the diameter of pulmonary arteries visually was more severe.

Logistic regression analysis

Eight CT parameters which significantly associated with progressive fibrosis in univariate analysis were included in the regression model (Table 5). To adjust for possible confounding factors, clinical, and laboratory variables ($P < 0.05$) were also included in the logistic regression analysis. Finally, the logistic regression analysis showed that a wide distribution of subpleural RP and/or interlobular septal thickening (OR value of 18.15) and PBVI thickening (OR value of 4.98) were independent risk factors for the progressive fibrosis of RA-ILD.

2 × 2 contingency tables were constructed to assess the performance of CT abnormalities for predicting progressive fibrosis of RA-ILD (Table 6). When a wide distribution of subpleural RP and/or interlobular septal thickening alone was used for predicting progressive fibrosis, sensitivity was 73.6%, specificity was 86.0%, positive likelihood ratio (LR) was 5.3, and negative LR was 0.3. When PBVI thickening alone was used for predicting progressive fibrosis, sensitivity was 84.0%, specificity was 49.5%, positive LR was 1.7, and negative LR was 0.3. When both lung abnormalities were presented on HRCT, sensitivity was 63.2%, specificity was 92.5%, positive LR was 8.5, and negative LR was 0.4 in predicting progressive fibrosis.

Discussion

ILD is the most important pulmonary manifestation of rheumatoid disease, being the commonest pulmonary cause of death in RA and a significant contributor to morbidity. The previous researches indicated that pulmonary fibrosis was associated with worse prognosis, and a progression of pulmonary fibrosis on serial CT scans was a prognostic factor predictive of poor survival duration [18–20]. Thus, our study promptly focused on radiology by evaluating HRCT

Table 4 Distribution ranges of subpleural abnormalities on initial HRCT of RA-ILD patients

Parameter	RA-ILD ($n = 213$)	Progressive fibrosis ($n = 106$)	Non-progressive fibrosis ($n = 107$)	P value
Subpleural GGO				
Wide distribution	31 (14.6%)	19 (17.9%)	12 (11.2%)	0.165
Local distribution	94 (44.1%)	53 (50.0%)	41 (38.3%)	0.086
Subpleural RP and/or subpleural interlobular septal thickening				
Wide distribution	89 (41.8%)	75 (70.8%)	15 (14.0%)	0.000
Local distribution	68 (31.9%)	28 (26.4%)	40 (37.4%)	0.086
Subpleural HC				
Wide distribution	15 (7.0%)	8 (7.6%)	7 (6.5%)	0.774
Local distribution	34 (16.0%)	22 (20.8%)	12 (11.2%)	0.057

RA rheumatoid arthritis, *ILD* interstitial lung disease, *GGO* ground-glass opacity, *RP* reticular pattern, *HC* honeycombing

Table 5 Logistic regression analysis of predictors for progressive fibrosis in RA-ILD patients

Independent variables	OR	95% CI	*P* value
Advanced age (> 60 years)	1.034	0.445–2.401	0.938
Male patient	0.879	0.326–2.369	0.798
Ever smoker	1.337	0.502–3.564	0.561
RA duration at baseline, months	1.001	0.997–1.004	0.714
Shortness of breath	1.637	0.684–3.917	0.269
Anti-CCP antibody high titer positive [a]	2.082	0.776–5.585	0.145
Overall extent of lung abnormalities	0.984	0.953–1.017	0.335
RP	2.859	0.527–15.526	0.224
Subpleural RP	1.104	0.190–6.429	0.912
Interlobular septal thickening	1.330	0.368–4.805	0.663
Subpleural interlobular septal thickening	1.463	0.404–5.297	0.562
Subpleural RP and/or interlobular septal thickening			0.000
Local distribution	2.549	0.625–10.390	0.192
Wide distribution	18.147	3.574–92.147	0.000
PBVI thickening	4.984	2.040–12.174	0.000
Traction bronchiolectasis	0.661	0.267–1.639	0.372

RA rheumatoid arthritis, *ILD* interstitial lung disease, *Anti-CCP* antibody anti-cyclic citrullinated peptide antibody, *RP* reticular pattern, *PBVI* peribronchovascular interstitium, *OR* odds ratio

abnormalities of RA-ILD patients, and aimed at identifying early signs of progressive fibrosis. In 213 RA-ILD patients of our research, progressive fibrosis occurred in nearly 50%, of whom 47 cases (44.3%) occurred within 2 years. This was a retrospective study, so whether to perform a CT reexamination may be affected by the disease severity, patient compliance and other factors, which may account for the relatively high proportion of progressive fibrosis patients.

Considering the risks of drug-related lung toxicity and possible exacerbation of underlying ILD [21], so in this study, the medications during CT intervals were collected and analyzed. All factors that may affect progressive fibrosis, including clinical, laboratory, physiological, and radiological variables were also included in the data analysis. Our results showed that treatments with GC, MTX, LEF, and CYC were not associated with the progressive fibrosis of RA-ILD. And none of the clinical and laboratory variables, which in the univariable analysis had a P value < 0.05, presented significant difference in the regression model. Although the results just represented the features of the 213 participants, which need to be further verified, it still illustrated the importance of image evaluation, rather than other parameters, in predicting progressive fibrosis of RA-ILD.

HRCT has become the criterion standard for the radiologic evaluation of pulmonary fibrosis, and is capable of detecting the early stages of ILD in patients with or without respiratory symptoms. Meanwhile, a RA patient with respiratory presentation may represent ILD, infection, chronic obstructive pulmonary disease (COPD), tumors, and even no lesion. Therefore, all RA participants had performed HRCT in our study to identify the presence and characteristics of lung abnormalities.

Characteristics of HRCT in RA are now well defined [22]. In our research, GGO, RP, and PBVI thickening were the three most frequent abnormalities of RA patients. GGO and RP have been studied more, representing early stage of alveolar inflammation and middle stage of fibrosis respectively, while less attention has been paid to the PBVI thickening. Peribronchovascular interstitium (PBVI) is a system of fibers that invests bronchi and pulmonary arteries. PBVI and the centrilobular interstitium correspond to the "axial fiber system" described by Weibel, which extends peripherally from the pulmonary hila to the level of the alveolar ducts and sacs [14]. Because the thickening of PBVI cannot be distinguished from the underlying opacity of the bronchial wall or pulmonary artery, this abnormality is perceived at CT as an increase in bronchial wall thickness or an increase in the diameter of pulmonary arteries [15]. PBVI thickening can be seen in a wide variety of diseases, such as pulmonary fibrosis, sarcoidosis, pulmonary lymphangitic carcinomatosis, and lung cancer [15].

PBVI thickening is an important manifestation of ILD [23]. Our research found PBVI thickening was more common in the progressive fibrosis group, and was a risk factor for progressive fibrosis, indicating that PBVI thickening may play an important role in the process of fibrosis, although the specific mechanism was not clear yet. Within the lung parenchyma, bronchi and pulmonary arteries are closely associated with the surrounding tissues, and PBVI thickening may reflect pathological changes of both axial interstitium and nearby tissues

Table 6 Comparative performance of CT abnormalities for predicting progressive fibrosis of RA-ILD

Parameter	CT abnormalities		
	A wide distribution of subpleural RP and/or interlobular septal thickening	PBVI thickening	A wide distribution of subpleural RP and/or interlobular septal thickening plus PBVI thickening
False negative rate (%)	26.4 (28/106)	16.0 (17/106)	36.8 (39/106)
False positive rate (%)	14.0 (15/107)	50.5 (54/107)	7.5 (8/107)
Sensitivity (%)	73.6 (0.7–0.8)	84.0 (0.8–0.9)	63.2 (0.5–0.7)
Specificity (%)	86.0 (0.8–0.9)	49.5 (0.4–0.6)	92.5 (0.9–1.0)
Positive LR	5.3 (3.4–8.2)	1.7 (1.4–2.0)	8.5 (4.3–16.7)
Negative LR	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.4 (0.3–0.5)

Values for sensitivity/specificity and positive LR/negative LR are the percent and ratio (95% confidence interval), respectively

RP reticular pattern, *PBVI* peribronchovascular interstitium, *LR* likelihood ratio

[15, 23]. PBVI thickening with a distorted or stiff shape, indicative of pulmonary fibrosis, is the combined result of the proliferation of axial interstitium and the traction of surrounding interstitial fibrosis. Although PBVI thickening alone does not allow reliable diagnosis for ILD, it may possess a certain value for predicting progressive fibrosis, according to our results.

The linear and reticular opacities occur in different interstitial lung diseases and may help refine the differential diagnosis and clinical strategies. The linear opacities without evident lung architecture distortion suggest the active process, and the reticular opacities with evident lung distortion suggest the presence of irreversible fibrosis [24]. In this study, we found RP and interlobular septal thickening were more common in the progressive fibrosis group, and a wide distribution of subpleural RP and/or interlobular septal thickening was a risk factor for progressive fibrosis.

Unlike in the idiopathic interstitial pneumonias (IIPs), a surgical lung biopsy is usually not sought in RA-ILD. In this study, transbronchial lung biopsy was performed in 13 of 213 RA-ILD patients, but the obtained pathology samples were inadequate to reflect the pathological changes of peripheral lung tissue. Wu et al. analyzed radiographic-histopathologic correlation of early idiopathic pulmonary fibrosis (IPF), and noted 2 patients with a definite UIP pattern proven by biopsy had a manifestation of RP and/or interlobular septal thickening with predominantly subpleural distribution on HRCT [25]. The pathological changes of subpleural tissues were pleura thickening and subpleural interstitium proliferation, which was composed by the proliferation of parallel arranged fiber cells or irregular distributed fibroblasts, while rare inflammatory cells. Although these results were derived from IPF cases complicated with lung cancer, it does suggest that subpleural RP and/or interlobular septal thickening may represent active fibrosis, and may be an early sign of definite UIP. Thus, patients with these CT abnormalities should be monitored closely.

The overall extent of lung abnormalities was more extensive in the progressive fibrosis group, but with no predictive value in logistic model. Our previous research revealed extensive lung involvement on HRCT was associated with worse survival in RA-ILD patients [26]. Other studies also found overall extent of lung fibrosis on the baseline CT scans appeared predictive of survival [6, 11]. These results indicated that, although the extent of lung involvement was not a predictor of progressive fibrosis, it may be a risk factor for mortality and needs regular follow-up. Additionally, our study found traction bronchiolectasis was more common in the progressive fibrosis group. Traction bronchiolectasis related to ILD is caused by surrounding retractile pulmonary fibrosis, thus its predictive value is limited on account of secondary abnormality.

RA-ILD is a common disease with great variability in the disease course. The diagnosis of progressive fibrosis will lead to the increase of CT examinations, economic costs, adverse drug effects, and so on. Therefore, it is necessary to select parameters with high positive LR as predictors to ensure diagnostic accuracy. Our results showed that when a wide distribution of subpleural RP and/or interlobular septal thickening and PBVI thickening, meanwhile, were presented on HRCT, specificity was 92.5%, and positive LR was 8.5 in predicting progressive fibrosis, both figures were higher than that of any single abnormality, indicating the combined evaluation has a higher predictive value.

Furthermore, our study found that in patients with progressive fibrosis occurring within 6 months, the extent of the above two predictive abnormalities was visually heavier, which reminds that the intervals of chest CT examinations and pulmonary function tests for these patients should be shortened. However, it should be

pointed out that all above lung abnormalities for ILD such as RP and PBVI thickening could not be reliably identified when RA patients were complicated with infection, COPD, tumors, and other conditions, which had already been excluded in our study at baseline and need to be carefully differentiated in clinical practice.

This study has some limitations. It is a retrospective study designed at a single medical care center. Selection bias and time bias were two inevitable biases in the design. Further studies, particularly prospective ones, including a multicenter cohort should be planned for the validation and broader generalization of our study results.

In conclusion, our study reveals that a wide distribution of subpleural RP and/or interlobular septal thickening and PBVI thickening on HRCT are risk factors for progressive fibrosis in RA-ILD patients. The combined evaluation of the two significant CT abnormalities has a high value in predicting progressive fibrosis. The research of RA-ILD should focus not only on mortality, but also on preventing or slowing down the progress of the disease. We hope some of our findings can help to alter the profile and outcome of this disease.

Compliance with ethical standards

Disclosures None.

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