Impact of cigarette smoking on rheumatoid arthritis-associated lung diseases: a retrospective case control study on clinical and radiological features and prognosis

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Abstract
Our study aimed to investigate the clinical and radiological features and prognosis of male smoker patients with rheumatoid arthritis (RA). We consecutively enrolled male inpatients with RA who received chest HRCT during hospitalization in Peking University Third Hospital from Jan 1st, 2012 to August 1st, 2021. 154 male patients with RA were eligible for analysis, of whom 76.6% (n = 118) were current smokers or had a history of cigarette smoking. Compared to never-smokers, smoker patients had more respiratory symptoms, including cough (31.4% vs 5.6%, p = 0.002) and sputum production (26.3% vs 2.8%, p = 0.002), and a higher positive rate of rheumatoid factor (RF) (77.6% vs 58.8%, p = 0.030). A higher percentage of smoker patients showed emphysema (45.8% vs 16.7%, p = 0.002) and signs of lung fibrosis (51/54, 94.4% vs 7/13, 53.8%, p < 0.001) in those with interstitial lung disease (ILD, n = 67) on chest HRCT. The overall survival rate was different between smoker and never-smoker patients (p = 0.031), but instead of cigarette smoking, lung fibrosis on HRCT was the risk factor for survival of our patients. In conclusion, male patients with RA who were current smokers or had a history of cigarette smoking presented more respiratory symptoms and a higher positive rate of RF. They also showed more emphysema and signs of lung fibrosis on chest HRCT. Cigarette smoking impacted on the overall survival as a confounding factor in this cohort of male patients with RA.

Keywords Rheumatoid arthritis · Cigarette smoking · Lung diseases · Prognosis

Introduction
Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by joint inflammation and damage. Lung involvement is one of the most common extra-articular manifestations of RA, and can affect as high as 60% of the patients during the course of the disease [1]. RA-associated lung diseases may involve any lung compartments, including the large and small airways, interstitia, pleura and pulmonary vessels, resulting in a variety of radiological manifestations, such as interstitial lung diseases (ILDs, including honeycombing, reticular changes, ground glass opacity, and/or consolidation), nodules or masses, bronchiectasis, pleural effusion, and signs of pulmonary hypertension [1].

Several factors have been shown to be associated with increased risk of RA-associated lung diseases, such as cigarette smoking, male gender, duration of RA, high disease activity, positivity of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) [1, 2]. Cigarette smoking could cause injury to alveolar epithelial cells, promote production of inflammatory mediators, and lead to generation of citrullinated proteins by induction of peptidylarginine deiminase enzymes in lung alveolar cells, resulting in the break of immune tolerance and hence autoimmunity in genetically susceptible individuals [3–5]. Smoking patients...
with RA tend to develop both airway and parenchymal lung diseases, and have an increased risk of developing autoimmune disease, indicating that there exists an interaction among cigarette smoke exposure, inflammation and autoimmune reaction in the lung [1, 2, 6, 7].

Previous studies have shown that cigarette smoking is associated with the prevalence of RA-ILD, combined pulmonary fibrosis and emphysema, rheumatoid nodules [1], and a poorer prognosis in both RA patients [8] and RA-ILD patients [9, 10]. However, the impact of cigarette smoking on different patterns of lung involvements has not been studied in well-matched cohorts of RA patients. Our study was therefore aimed to investigate the clinical and chest radiological features and prognosis of male smoker patients with RA as compared with their never-smoker counterparts.

Methods

Patients and data collection

We consecutively enrolled RA patients admitted to the Department of Rheumatology and Immunology and the Department of Respiratory and Critical Care Medicine in Peking University Third hospital from Jan 1st, 2012 to August 1st, 2021. The inclusion criteria were: (1) diagnosis fulfilled the 2010 ACR/EULAR RA classification criteria [11]; (2) male; (3) age ≥ 18 years; (4) chest HRCT performed during hospitalization. The exclusion criteria were: (1) patients without HRCT; (2) patients whose HRCT could not be evaluated due to diffuse bacterial pneumonia; (3) patients who were diagnosed with COVID-19. The study was approved by the Clinical Research Ethics Committees of Peking University Third Hospital (S2018193), on Aug 16th, 2018, and exception from informed consent was applied.

The RA cases were identified and manually reviewed from the electronic medical record system of the hospital. The clinical data included demographics, smoking history and the amount of cigarettes smoked, disease duration of RA, joint manifestations (morning stiffness, swollen joint counts (SJC), tender joint counts (TJC)), and respiratory symptoms (cough, sputum, dyspnea). RA-associated complications, comorbidities and treatment were also recorded. The laboratory data included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF, anti-cyclic citrullinated peptide (anti-CCP) antibody, antinuclear antibody (ANA), and immunoglobulins (IgG, IgM, IgA). Pulmonary hypertension was reported by echocardiography as defined by 2015 ESC/ERS Guidelines [12]. Lung function measurements, hand x-ray, and echocardiography performed within 12 months before or after hospitalization were used for analysis.

To collect the outcome of all the patients, medical records were reviewed on Mar 24th, 2022. For patients with a death record, the date and cause of death were recorded. For those without, we made telephone calls to the patients or their family members to confirm whether they were alive, and for those who were dead, the date and cause of death were recorded. For those who did not answer the phone, we recorded the last time they visited the hospital as they were alive.

Evaluation of chest HRCT

Two pulmonary physicians evaluated the CT scan without knowing the patient’s clinical data. They independently completed the assessment and differences in readings were resolved through their final consensus. As for ILD, fibrosis (reticular changes, honeycombing and traction bronchiectasis), ground glass opacity (GGO), and consolidation were identified according to the diagnostic criteria of Hiromitsu et al. [13] and the Fleischner Society [14]. The patterns of ILD were classified as defined by the ATS/ERS statement [15]: usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP) and unclassifiable. As for evaluation of pulmonary emphysema, the modified Goddard scoring system [16] was used. Each image was classified as normal (score 0), ≤ 5% affected (score 0.5), ≤ 25% affected (score 1), ≤ 50% affected (score 2), ≤ 75% affected (score 3) and > 75% affected (score 4). For identification of bronchiectasis, the Fleischner Society’s criteria [14] were used, and traction bronchiectasis related to pulmonary fibrosis was excluded. The degree of bronchiectasis on each lobe was scored, according to the scoring system proposed by Smith [17]: normal (score 0), ≤ 25% affected (score 1), ≤ 50% affected (score 2), ≤ 75% affected (score 3) and > 75% affected (score 4). Patients with a score of 1 were considered normal because mild bronchiectasis in only one lobe may be seen in a significant proportion of healthy people. Nodules, cavities, pleural lesions (pleural thickening and/or effusion), and signs of previous tuberculosis (PTB) [14, 18] in every lobe were also recorded.

Statistical analysis

All data were analyzed using SPSS (version 26.0, IBM, USA) and R statistical software (version 4.1.2). The sample size was estimated as the mortality in non-smoker RA patients being 20%, OR = 3, α = 0.05, β = 0.2. The Shapiro–Wilk method was used to test whether the data were normally distributed. Normally distributed data were presented as mean ± SD and compared by Student’s t test. Data not distributed normally were expressed as median (interquartile range, IQR) and differences were tested by the Mann–Whitney U test. The chi-square test was used to
compare categorical data and percentages between groups. Kaplan–Meier survival curve was used to observe the survival of the two groups, and log rank method was used to compare the survival between the two groups. The least absolute shrinkage and selection operator (LASSO) Cox model was performed to select the most predictive variables from the preselected potential candidate variables. Cox proportional-hazards model was used to develop the model and estimate the coefficients associated with each predictor. Missing data were treated as censored data. \( p \) value < 0.05 was considered to be statistically significant.

**Results**

**Clinical characteristics of the cohort**

A total of 239 male inpatients diagnosed with RA were identified. After excluding seventy-eight patients without HRCT and seven patients whose HRCT could not be evaluated due to diffuse bacterial pneumonia, 154 patients were included for analysis in the study. Thirty-six (23.4%) patients had never smoked and 118 (76.6%) were current or former smokers, among whom, 66 (55.9%) were currently smoking, as shown in supplementary Table 1. The age of the patients was 66.6 \( \pm \) 12.47 years. The duration of RA was 24 (6, 120) months, and the interval between chest HRCT scanning and the diagnosis of RA was 12 (0, 108) months. Concurrently, clinical diagnosis of ILD \( (n = 57, 37.0\%) \), COPD \( (n = 15, 9.7\%) \), asthma \( (n = 3, 1.9\%) \), bronchiectasis \( (n = 12, 7.8\%) \), lung cancer \( (n = 5, 3.2\%) \) and active or previous pulmonary tuberculosis \( (n = 17, 11.0\%) \) were recorded in this cohort. Chest HRCT evaluation showed emphysema in 60 (39.0%), ILD in 67 (43.5%), bronchiectasis in 24 (15.6%), single or multiple nodules in 23 (14.9%), pleural lesions in 25 (16.2%), previous tuberculosis in 25 (16.2%), and cavities in 6 (3.9%) cases, as shown in Fig. 1.

**Comparison of demographic, clinical, and laboratory features between smoker and never-smoker patients with RA**

Compared to never-smoker patients with RA, smoker patients were more likely to have cough (31.4% vs 5.6%, \( p = 0.002 \)) and sputum production (26.3% vs 2.8%, \( p = 0.002 \)). There were no statistical differences in age, BMI,
duration of RA, articular manifestations, disease activity score (DAS), and RA-associated complications and comorbidities between the two groups. Smokers had a higher ESR (40 (16, 60) vs 23 (11, 44) mm/h, \( p = 0.028 \)), but not CRP. The positive rate of RF was higher in smoker patients (77.6% vs 58.8%, \( p = 0.030 \)), and the positive rate of anti-CCP antibody tended to be higher in the smoker group. There were no statistical differences in joint space narrowing and bone erosion by X-ray of the hand joints. Interestingly, more smoker patients were found to have pulmonary hypertension (26.4% vs 9.4%, \( p = 0.043 \)) by echocardiography. See supplementary Table 2.

### Comparison of chest CT features and lung function between smoker and never-smoker patients with RA

As shown in Table 1, supplementary Tables 3 and 4, supplementary Figs. 1, 2 and 3, CT emphysema was more common in smokers compared to never-smokers (45.8% (54/118) vs 16.7% (6/36), \( p = 0.002 \)), more remarkably in current smokers (51.5% (34/66), \( p = 0.003 \)) and smokers who had smoked more than 25 pack-years (52.9% (36/68), \( p = 0.001 \)). It was notable that 16.7% of the never-smoker patients also had emphysema. Emphysema predominantly involved the upper lobes (56/60, 93.3%). Smoker and heavy smoker patients tended to have more severe emphysema, though the differences were not statistically significant.

ILD was evident on chest CT in 43.5% (67/154) of the whole cohort, 45.8% (54/118) in the smoker group and 36.1% (13/36) in the never-smoker group, the difference

### Table 1 Chest HRCT features of male patients with RA grouped by smoking status

|                     | Total n = 154 | Smoker n = 118 | Never-smoker n = 36 | OR (95%CI)* | \( p \) value |
|---------------------|---------------|----------------|---------------------|------------|---------------|
| Age (mean ± SD, years) | 66.6 ± 12.47  | 66.6 ± 10.54   | 66.8 ± 17.57 | 0.929      |               |
| Emphysema           | 60/154, 39.9% | 54/118, 45.8%  | 6/36, 16.7%  | 4.22 (1.71, 10.38) | 0.002 |
| Upper lobes         | 56/60, 93.3%  | 50/54, 92.6%  | 6/6, 100.0% | 0.490       |               |
| Middle/lingula lobes| 37/60, 61.7%  | 33/54, 61.1%  | 4/6, 66.7%  | 0.791       |               |
| Lower lobes         | 21/60, 35.0%  | 19/54, 35.2%  | 2/6, 33.3%  | 0.928       |               |
| ILD                 | 67/154, 43.5% | 54/118, 45.8% | 13/36, 36.1% | 1.49 (0.68, 3.22) | 0.307 |
| Type of ILD         |               |               |               |             |               |
| UIP                 | 41/67, 61.2%  | 32/54, 59.3%  | 9/13, 69.2%  | 0.65 (0.18, 2.35) | 0.538 |
| NSIP                | 10/67, 14.9%  | 9/54, 16.7%  | 1/13, 7.7%  | 2.40 (0.29, 19.69) | 0.366 |
| OP                  | 2/67, 3.0%    | 1/54, 1.9%    | 1/13, 7.7%  | 0.23 (0.02, 311) | 0.094 |
| Unclassifiable      | 14/67, 20.9%  | 12/54, 22.2%  | 2/13, 15.4% | 12.57 (0.31, 8.00) | 0.046 |
| Fibrosis            | 58/67, 86.8%  | 51/54, 94.4%  | 7/13, 53.8% | 14.57 (3.73, 56.92) | 0.001 |
| Upper lobes         | 24/58, 41.4%  | 20/51, 39.2%  | 4/7, 57.1%  | 0.366       |               |
| Middle/lingula lobes| 24/58, 41.4%  | 21/51, 41.2%  | 3/7, 42.9%  | 0.933       |               |
| Lower lobes         | 56/58, 96.6%  | 50/51, 98.0%  | 6/7, 85.7%  | 0.094       |               |
| Ground glass opacity| 12/67, 17.9%  | 6/54, 11.1%  | 6/13, 46.2% | 0.15 (0.04, 0.52) | 0.003 |
| Upper lobes         | 5/12, 41.7%   | 2/6, 33.3%    | 3/6, 50.0%  | 0.558       |               |
| Middle/lingula lobes| 7/12, 58.3%  | 3/6, 50.0%    | 4/6, 66.7%  | 0.558       |               |
| Lower lobes         | 7/12, 58.3%  | 3/6, 50.0%    | 4/6, 66.7%  | 0.558       |               |
| Consolidation       | 3/67, 4.5%    | 3/54, 5.6%    | 0, 0%      | 0.385       |               |
| Bronchiectasis      | 24/154, 15.6% | 19/118, 16.1% | 5/36, 13.9% | 1.19 (0.41, 3.45) | 0.749 |
| Upper lobes         | 5/24, 20.8%   | 4/19, 21.1%   | 1/5, 20.0%  | 0.959       |               |
| Middle/lingula lobes| 11/24, 45.8%  | 9/19, 47.4%   | 2/5, 40.0%  | 0.769       |               |
| Lower lobes         | 17/24, 70.8%  | 14/19, 73.7%  | 3/5, 60.0%  | 0.549       |               |
| Single nodule       | 10/154, 6.5%  | 8/118, 6.8%  | 2/36, 5.6%  | 1.24 (0.25, 6.09) | 0.794 |
| Multiple nodules    | 13/154, 8.4%  | 10/118, 8.5%  | 3/36, 8.3%  | 1.02 (0.26, 3.92) | 0.979 |
| Pleural lesions     | 24/154, 15.6% | 17/118, 14.4% | 7/36, 19.4% | 0.79 (0.26, 1.84) | 0.466 |
| Previous tuberculosis| 25/154, 16.2% | 20/118, 16.9% | 5/36, 13.9 | 1.27 (0.44, 3.65) | 0.663 |

\( p < 0.05 \) are in bold

OR odd ratio, CI confidence interval, ILD interstitial lung disease, UIP usual interstitial pneumonia, NSIP nonspecific interstitial pneumonia, OP organizing pneumonia, PTB previous tuberculosis

*OR (95%CI) of smoke status in different lung involvements
being not significant. The pattern of UIP tended to be more frequent in never-smokers, while NSIP tended to be more frequent in smokers. Signs of fibrosis was more prevalent in smokers (94.4% (51/54) vs 53.8% (7/13), $p < 0.001$) among the patients with ILD. Fibrosis was predominantly distributed in lower lobes (96.6%, 56/58). GGO was evident in 17.9% (12/67) of the patients with ILD, and was more common (11.1% (6/54) vs 46.2% (6/13), $p = 0.003$) in never-smokers. Non-traction bronchiectasis occurred in 15.6% (24/154) of the patients, predominantly distributed in lower lobes (70.8%, 17/24). The frequency, distribution and severity of bronchiectasis showed no differences between smoker and never-smoker groups.

Of the 154 patients with RA, only 42 underwent pulmonary function tests within one year before or after chest CT scanning. FEV$_1$/FVC was lower in the smoker group ([72.28 ± 8.184] % vs [83.8 ± 3.342] %, $p = 0.004$). FEV$_1$%pred was lower and RV/TLC was higher in the smoker group, but the differences did not reach statistical significance.

**Survival of male patients with RA**

All but one patients were followed until Mar 24th, 2022. The median follow-up time was 37 (17.8 to 64.1) months, with the longest up to 123 months. The all-cause mortality was 23.4% (36/153). The overall survival rate was significantly different between smoker and never-smoker groups ($p = 0.031$), as shown in Fig. 2. LASSO model was used to select the most predictive variables from the 34 preselected potential candidate variables as shown in Fig. 3, among which 14 candidates were included in the Cox proportional-hazards model, as shown in Table 2. The result showed that fibrosis on chest CT, but not cigarette smoking, was an independent risk factor for survival in male patients with RA.

**Discussion**

The present study, to our knowledge, was the first to have comprehensively investigated the potential impact of cigarette smoking on the prevalence, distribution and severity of lung involvements in a cohort of male RA patients with a high proportion of ever-smokers. It was interesting to note that, although the prevalence of ILDs was not different between smoker and non-smoker patients, signs of lung fibrosis were more common in the former, and lung fibrosis,
but not cigarette smoking per se, was an independent risk factor for survival in this cohort.

ILDs are the most common lung diseases in RA patients. RA-ILD could be one of the progressive-fibrosing interstitial lung diseases [19] which are associated with worsening respiratory symptoms, lung function decline and decreased quality of life. UIP accounts for the most proportion of RA-ILD and is associated with poorer survival [9, 20, 21]. Cigarette smoking is a risk factor for the incidence [21, 22] and the progression of RA-ILD [9, 23]. In the present study, we firstly found that smoker patients with RA showed more signs of fibrosis, including honeycombing and reticular changes, but less GGO, on chest HRCT as compared to their non-smoker counterparts, indicating that cigarette smoking was associated with lung fibrosis in RA patients. In line with this, more non-smoker patients showed GGO on chest CT in our cohort, which may be partly explained by the shorter disease course of RA in these patients, as GGO is often an earlier manifestation of ILD [21]. Cigarette smoking could directly cause injury to alveolar epithelial cells, promoting the release of pro-fibrotic mediators, such as chemokines, proteases, transforming growth factor-beta (TGF-β), and could also stimulate citrullination of proteins, leading to the production of ACPA, both of which may initiate the fibrotic process of the lung [22, 24].

In our study, 39.9% of the patients showed CT emphysema, which was more frequent in current smokers and heavy smokers (> 25 pack-years), but was also seen in never-smokers. Cigarette smoking has been shown to be a common risk factor for both RA and COPD. A meta-analysis showed that RA patients had a significantly increased risk of incident COPD, with a pooled RR of 1.82, and the pooled prevalence of COPD in RA patients was 6.2% [25]. Interestingly, screening for preclinical parenchymal lung diseases in RA revealed a high prevalence of radiological emphysema in never-smoker patients (47%) [26]. Another study reported that CT emphysema was also present in 27% of never-smoking patients with RA-ILD [27]. The underlying mechanisms for emphysema in RA may be varied. Pre-RA ACPA positivity was associated with increased COPD risk [28], suggesting that autoimmunity may play a role in the pathogenesis of emphysema and COPD. Furthermore, RA is typically accompanied by systemic inflammation affecting multiple organs. Chronic inflammation in the lung may cause destruction of the normal airway structure and increase the susceptibility to COPD.

Bronchiectasis is another important lung disease in RA patients, and symptomatic bronchiectasis has been estimated to be between 2 and 12%, while the prevalence of subclinical bronchiectasis detected by HRCT reached 30%–50% [29]. Cigarette smoking was not considered to be associated with bronchiectasis, while chronic infection, age, low BMI, RF, ACPA [1, 29, 30] and cystic fibrosis transmembrane conductance regulator (CFTR) mutations [31] were. In our cohort, non-traction bronchiectasis, predominantly distributed in lower lobes, was present in 15.6% of the patients, and no association was found between cigarette smoking and bronchiectasis.

RA-related extra-articular manifestations and comorbidities are associated with exacerbated outcomes of the patients. Studies have demonstrated that respiratory diseases, cardiovascular diseases and neoplasms are the primary causes of death in RA patients [32–34]. The 1-year,

| Risk prediction model of enrolled factors for male patients with RA |
| --- |
| **β coefficient** | **Hazard ratio** | **95%CI** | **p** |
| Age | 0.056 | 1.058 | 0.990–1.129 | 0.095 |
| Cough | 0.788 | 2.200 | 0.710–6.811 | 0.172 |
| Cigarette smoke | 0.101 | 1.106 | 0.266–4.597 | 0.889 |
| DAS28-ESR | −0.312 | 0.732 | 0.480–1.117 | 0.148 |
| Positivity of anti-CCP antibody | 0.639 | 1.894 | 0.429–8.373 | 0.400 |
| Positivity of ANA | −0.922 | 0.398 | 0.106–1.492 | 0.172 |
| Anemia | 0.443 | 1.557 | 0.522–4.639 | 0.427 |
| Diabetes | 0.739 | 2.094 | 0.511–8.583 | 0.304 |
| Malignancy | 1.553 | 4.724 | 0.617–36.188 | 0.135 |
| Erosion of joints | 1.075 | 2.931 | 0.763–11.254 | 0.117 |
| Bronchiectasis on HRCT | −1.765 | 0.171 | 0.021–1.424 | 0.102 |
| Fibrosis on HRCT | 1.633 | 5.122 | 1.174–22.343 | **0.030** |
| Single nodule on HRCT | 0.417 | 1.517 | 0.135–17.033 | 0.735 |
| Cavity on HRCT | 0.652 | 1.919 | 0.187–19.837 | 0.585 |

*p < 0.05 is in bold

RA rheumatoid arthritis, DAS disease activity score, ESR erythrocyte sedimentation rate, CCP cyclic citrullinated peptide, ANA anti-nuclear antibodies.
5-year and 10-year mortality of RA-associated ILD was 13.9%, 39.0% and 60.1% in a population-based cohort study [35]. In our cohort of male patients with RA, the all-cause mortality was 23.4%. We found that the overall survival rate was different between smoker and non-smoker patients, but instead of cigarette smoking, fibrosis on chest HRCT was the risk factor for survival in these patients, suggesting that cigarette smoking works as a confounding factor for lung fibrosis.

A number of studies have investigated the influence of cigarette smoking on manifestations of arthritis, but the results are inconsistent. Some studies found that cigarette smoking was associated with more SJC, TJC, higher VAS for pain and disease activity score [36, 37], positivity of RF [37, 38] and ACPA [38], more severe joint damage progression [37, 39], and poorer response to first-line DMARDs [40]. But there were also contrary results from different cohorts [8]. In our study, smokers were characterized by a higher ESR and a higher positive rate of RF. The positive rate of anti-CCP antibodies tended to be higher in the smoker group. However, SJC, TJC and DAS-28, and articular injury on X-ray showed no difference between the smoker and non-smoker groups.

There were some limitations in our study. RA patients who did not have respiratory symptoms might not take HRCT, and those with COVID-19 were not admitted to our hospital, which may lead to underestimation of the prevalence of lung diseases in our cohort. Due to the retrospective nature of the study, the onset and duration of lung diseases on chest HRCT could not be evaluated. Information of passive smoking, a potential confounder in non-smoker patients, was not recorded. Lung function tests were available in only a proportion of the patients. As smokers in female patients with RA were rare in the Chinese population, to avoid the bias of gender, we did not enroll female patients in the study. As HRCT was not a routine examination for outpatients, we only enrolled hospitalized RA patient with moderate disease-active score, and patients who were in remission were not evaluated.

Conclusion

In conclusion, in this single-center cohort of male patients with RA, ever-smokers, including current smokers and those who had a history of cigarette smoking, presented more respiratory symptoms and a higher positive rate of RF. They also showed more emphysema and signs of lung fibrosis on chest HRCT. Cigarette smoking impacted on the overall survival as a confounding factor. Larger scale and prospective studies are warranted to further delineate the impact of cigarette smoking on the manifestations and outcomes of RA-associated lung diseases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-022-05219-9.

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Authors contribution All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. JR: Formal analysis; Investigation; Writing—Original Draft; YD: Data Curation; JZ: Resources; YS: Conceptualization; Data Curation; Writing—Review & Editing; Supervision. All authors take full responsibility for the integrity and accuracy of all aspects of the work.

Data availability All data generated or analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest Jiaqi Ren, Yanling Ding, Jinxia Zhao, Yongchang Sun declare that they have no conflict of interest.

Ethical statement The study was approved by the Clinical Research Ethics Committees of Peking University Third Hospital (S2018193).

References

1. Wang D, Zhang J, Lau J et al (2019) Mechanisms of lung disease development in rheumatoid arthritis. Nat Rev Rheumatol 15(10):581–596. https://doi.org/10.1038/s41584-019-0275-x
2. Demoruelle MK, Wilson TM, Deane KD (2020) Lung inflammation in the pathogenesis of rheumatoid arthritis. Immunol Rev 294(1):124–132. https://doi.org/10.1111/imr.12842
3. Makrygiannakis D, Hermansson M, Ulfgren AK et al (2008) Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis 67(10):1488–1492. https://doi.org/10.1136/ard.2007.075192
4. Lugli EB, Correia RE, Fischer R et al (2015) Expression of citrulline and homocitrulline residues in the lungs of non-smokers and smokers: implications for autoimmunity in rheumatoid arthritis. Arthritis Res Ther 17:9. https://doi.org/10.1186/s13075-015-0520-x
5. Polacheck A, VreeEgberts W, Fireman E et al (2018) Sputum anticitrullinated protein antibodies in patients with long-standing rheumatoid arthritis. J Clin Rheumatol 24(3):122–126. https://doi.org/10.1097/RHU.0000000000000619
6. Kadura S, Raghu G (2021) Rheumatoid arthritis-Interstitial lung disease: manifestations and current concepts in pathogenesis and management. Eur Respir Rev. https://doi.org/10.1183/16000617.0011-2021
7. Akiyama M, Kaneko Y (2022) Pathogenesis, clinical features, and treatment strategy for rheumatoid arthritis-associated interstitial lung disease. Autoimmun Rev 21(5):103056. https://doi.org/10.1016/j.autrev.2022.103056
8. Wieczorek M, Gwninnut JM, Ransay-Colle M et al (2022) Smoking, alcohol consumption and disease-specific outcomes in rheumatic and musculoskeletal diseases (RMDs): systematic reviews informing the 2021 EULAR recommendations for lifestyle
improvements in people with RMDs. RMD Open. https://doi.org/10.1136/rmdopen-2021-002170

9. Solomon JJ, Chung JH, Cosgrove GP et al (2016) Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 47(2):588–596. https://doi.org/10.1183/13993003.00357-2015

10. Kim HC, Lee JS, Lee EY et al (2020) Risk prediction model in rheumatoid arthritis-associated interstitial lung disease. Respirology 25(12):1257–1264. https://doi.org/10.1111/resp.13848

11. Aletaha D, Neogi T, Silman AJ et al (2010) 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against rheumatism collaborative initiative. Arthritis Rheum 62(9):2569–2581. https://doi.org/10.1002/art.27584

12. Galie N, Humbert M, Vachiery JL et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: association for European Paediatric and congenital cardiology (AEPC). Eur Heart J 37(1):67–119. https://doi.org/10.1093/eurheartj/eht317

13. Sumikawa H, Johkoh T, Colby TV et al (2008) Computed tomography findings in pathological usual interstitial pneumonia: relationship to survival. Am J Respir Crit Care Med 177(4):433–439. https://doi.org/10.1164/rccm.200611-1696OC

14. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Remy J (2008) Fleischner Society: glossary of terms for thoracic imaging. Radiology 246(3):697–722. https://doi.org/10.1148/radiol.2462070712

15. Travis WD, Costabel U, Hansell DM et al (2013) An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 188(6):733–748. https://doi.org/10.1164/rccm.201308-1483ST

16. Makita H, Nasuhara Y, Nagai K et al (2007) Characterisation of phenotypes based on severity of emphysema in chronic obstructive pulmonary disease. Thorax 62(11):932–937. https://doi.org/10.1136/thx.2006.072777

17. Smith JE, Jurriaans E, Diederich S, Ali N, Shneerson JM, Flower CD (1996) Chronic sputum production: correlations between clinical features and findings on high resolution computed tomo-graphic scanning of the chest. Thorax 51(9):914–918. https://doi.org/10.1136/thx.51.9.914

18. (2000) Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. Am J Respir Crit Care Med, 161(4 Pt 1):1376–1395, doi: https://doi.org/10.1164/ajrccm.161.4.16141

19. Cottin V, Hirani NA, Hotchklin DL et al (2018) Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev. https://doi.org/10.1183/16000617.0076-2018

20. Yunt ZX, Chung JH, Hobbs S et al (2017) High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. Respir Med 126:100–104. https://doi.org/10.1016/j.rmed.2017.03.027

21. Kelly CA, Saravanan V, Nisar M et al (2014) Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. Rheumatology (Oxford) 53(9):1676–1682. https://doi.org/10.1093/rheumatology/keu165

22. Johnson C (2017) Recent advances in the pathogenesis, prediction, and management of rheumatoid arthritis-associated interstitial lung disease. Curr Opin Rheumatol 29(3):254–259

23. Mena-Vazquez N, Rojas-Gimenez M, Romero-Barco CM et al (2021) Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. J Clin Med 10(4):874. https://doi.org/10.3390/jcm10040874

24. Richeldi L, Collard HR, Jones MG (2017) Idiopathic pulmonary fibrosis. Lancet 389(10082):1941–1952. https://doi.org/10.1016/S0140-6736(17)30866-8

25. Ma Y, Tong H, Zhang X et al (2019) Chronic obstructive pulmonary disease in rheumatoid arthritis: a systematic review and meta-analysis. Respir Res 20(1):144. https://doi.org/10.1186/s12931-019-1123-x

26. Esposito AJ, Sparks JA, Gill RR et al (2022) Screening for preclinical parenchymal lung disease in rheumatoid arthritis. Rheumatology (Oxford) 61(8):3234–3245. https://doi.org/10.1093/rheumatology/keab891

27. Jacob J, Song JW, Yoon HY et al (2018) Prevalence and effects of emphysema in never-smokers with rheumatoid arthritis interstitial lung disease. EBioMedicine 28:303–310. https://doi.org/10.1016/j. ebiom. 2018. 01. 038

28. Zaccardelli A, Liu X, Ford JA et al (2021) Elevated anti-citrullinated protein antibodies prior to rheumatoid arthritis diagnosis and risks for chronic obstructive pulmonary disease or asthma. Arthritis Care Res (Hoboken) 73(4):498–509. https://doi.org/10.1002/acr.24140

29. Duarte AC, Porter J, Leandro MJ (2020) Bronchiectasis in rheumatoid arthritis. A clinical appraisal. Joint Bone Spine 87(5):419–424. https://doi.org/10.1016/j.jbspin.2019.12.006

30. McDermott G, Gill R, Gagne S et al (2022) Demographic, lifestyle, and serologic risk factors for rheumatoid arthritis-associated bronchiectasis: role of RA-related autoantibodies. J Rheumatol. https://doi.org/10.3899/jrheum.211242

31. Puechel X, Bienvenu T, Dusser D (2019) Rheumatoid arthritis-associated bronchiectasis. Lancet 393(10185):2035–2036. https://doi.org/10.1016/S0140-6736(19)30020-0

32. Kerola AM, Kazemi A, Rollefstad S et al (2022) All-cause and cause-specific mortality in rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis: a nationwide registry study. Rheumatology (Oxford). https://doi.org/10.1093/rheumatology/keac210

33. Kim YJ, Shim JS, Choi CB, Bae SC (2012) Mortality and incidence of malignancy in Korean patients with rheumatoid arthritis. J Rheumatology (Oxford). https://doi.org/10.1093/rheumatology/keab891

34. Shah NN, Wass S, Hajarji J et al (2022) Proportionate cardiovascular mortality in chronic inflammatory disease in adults in the united states from 1999 to 2019. J Clin Rheumatol 28(2):97–103. https://doi.org/10.1097/RHU.0000000000001818

35. Hylldgaard C, Hilberg O, Pedersen AB et al (2017) Fibrosis and risks for chronic obstructive pulmonary disease or asthma. Thorax 72(9):746–750. https://doi.org/10.1136/thoraxjnl-2017-211138

36. Manfredsdottir VF, Vikingsdottir T, Jonsson T et al (2006) The prevalence of malignancy in Korean patients with rheumatoid arthritis. J Rheumatol 39(2):226–232. https://doi.org/10.3899/jrheum.110704

37. Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifitaki N, Drosos AA (2005) Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients? Clin Exp Rheumatol 23(6):861–866
38. Krol A, Garred P, Heegaard NH et al (2015) Interactions between smoking, increased serum levels of anti-CCP antibodies, rheumatoid factors, and erosive joint disease in patients with early, untreated rheumatoid arthritis. Scand J Rheumatol 44(1):8–12. https://doi.org/10.3109/03009742.2014.918651

39. de Rooy DP, van Nies JA, Kapetanovic MC et al (2014) Smoking as a risk factor for the radiological severity of rheumatoid arthritis: a study on six cohorts. Ann Rheum Dis 73(7):1384–1387. https://doi.org/10.1136/annrheumdis-2013-203940

40. Daien CI, Hua C, Combe B, Landewe R (2017) Non-pharmacological and pharmacological interventions in patients with early arthritis: a systematic literature review informing the 2016 update of EULAR recommendations for the management of early arthritis. RMD Open 3(1):e000404. https://doi.org/10.1136/rmdopen-2016-000404

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