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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

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with RA tend to develop both airway and parenchymal lung diseases, and have an increased risk of developing autoimmunity, 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 $\geq$ 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 exeption 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), $\leq$ 5% affected (score 0.5), $\leq$ 25% affected (score 1), $\leq$ 50% affected (score 2), $\leq$ 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), $\leq$ 25% affected (score 1), $\leq$ 50% affected (score 2), $\leq$ 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, $\alpha = 0.05$, $\beta = 0.2$. The Shapiro–Wilk method was used to test whether the data were normally distributed. Normally distributed data were presented as mean $\pm$ 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 ± 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,

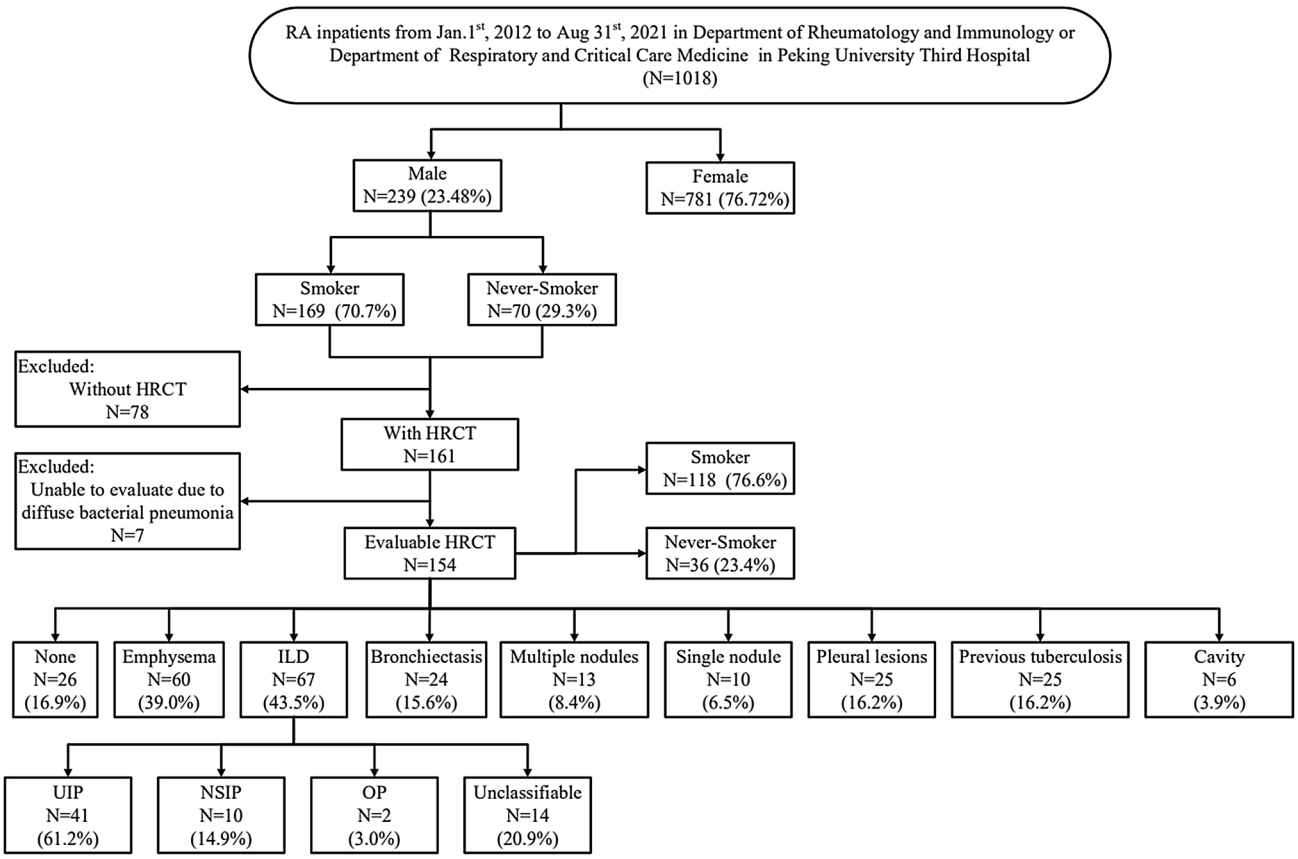

Fig. 1 Inclusion criteria of RA patients and the design of the study

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)	
OP	2/67, 3.0%	1/54, 1.9%	1/13, 7.7%	0.23 (0.02, 311)	
Unclassifiable	14/67, 20.9%	12/54, 22.2%	2/13, 15.4%	12.57 (0.31, 8.00)	
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%		**0.046**
Consolidation	3/67, 4.5%	3/54, 5.6%	0, 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.

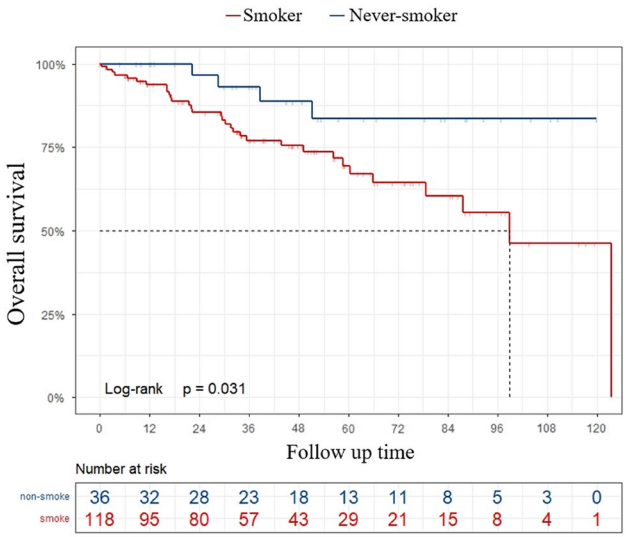

Fig. 2 Kaplan–Meier survival curves of RA patients grouped by smoking status

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,

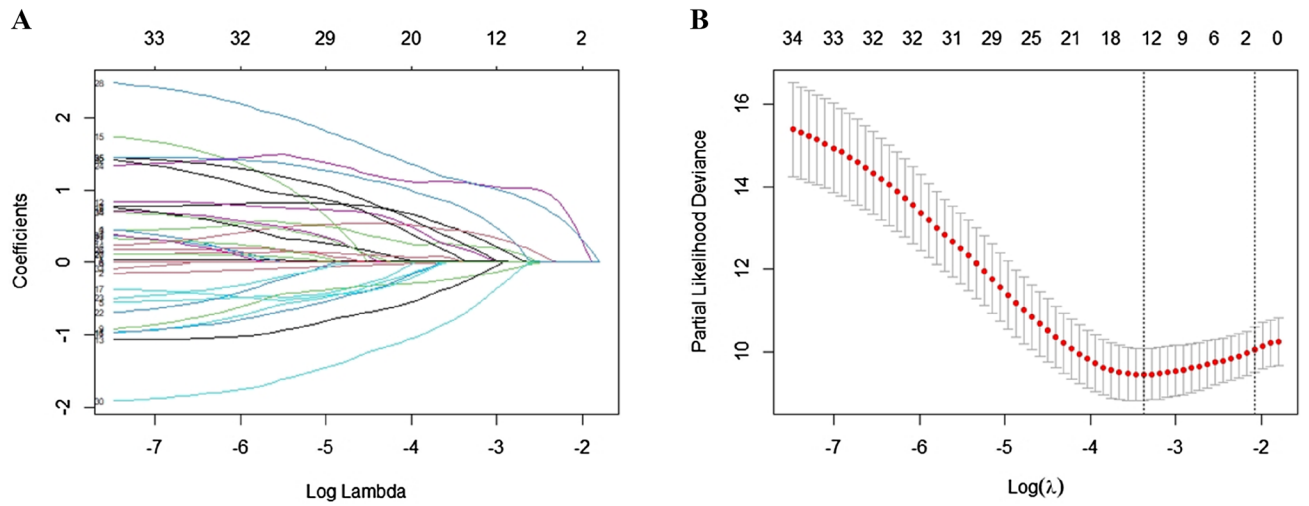

Fig. 3 Variable selection using the LASSO Cox regression mode

Table 2 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

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, but this observation still needs further study for verification. 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,

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).

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