RESEARCH

Lung involvement prevalence in patients with early rheumatoid arthritis without known pulmonary disease: a multicentric cross sectional study

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Abstract

Background: Clinically evident interstitial lung disease (ILD) affects between 10 and 42% of the patients with rheumatoid arthritis (RA). Airway involvement seems to be even more common. Most of the available evidence comes from studies performed in established RA patients. The aim of our study was to know the prevalence of non-diagnosed lung disease (airway and interstitial involvement) in patients with early RA and look for associated factors.

Methods: We designed an observational, multicenter, cross-sectional study, and included patients with RA of less than two years since diagnosis. We performed a structured questionnaire, HRCT and lung functional tests looking for lung disease, together with joint disease evaluation. We analyzed which variables were associated with the presence of lung disease on HRCT.

Results: We included 83 patients, 83% females. The median (IQR) of time since RA diagnosis was 3 (1–6) months. In the HRCT, 57 patients had airway compromisea (72%), and 6 had interstitial abnormalities (7.5%). The most common altertion found in lung functional tests was a reduced DLCO (14%). The presence of at least one abnormality in the physical exam was associated with lung involvement on HRCT [13 (21.6%) vs 0 (0%); $p = 0.026$]. Also, patients with lung involvement presented significantly lower values of FVC% and DLCO%, and higher values of RV/TLC. No variable related to joint involvement was found associated with alterations in HRCT.

Conclusion: Our study shows that a large proportion of early RA patients has abnormal findings in HRCT. Further studies are required to confirm these findings.

Keywords: Rheumatoid arthritis, Interstitial lung disease, Early rheumatoid arthritis, Airway disease

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Background

Rheumatoid Arthritis (RA) is the most common autoimmune disease in adults with a prevalence ranging from 0.4 to 1.3% in the general population [1]. Although joint involvement is the most prevalent and known manifestation, extra-articular manifestations represent an important issue due to the implications it may have patients´ quality-of-life and survival. In the last years, a change has been seen in the pattern of extra-articular disease occurrences because of changes in treatments and closer follow-ups [2]. Among them, the lung involvement implies one of the most relevant ones given its various manifestations and the impact it may have in the course of this disease. Lung may be affected in all its components: pleura, airway, interstitium and blood vessels, with an estimated prevalence near 30% according to different series [3]. Treatment of the articular component has experienced an important progress due to the emergence of an increasing number of agents, both biological and non-biological [4]. However, this better management of the joint disease has not been accompanied by an improvement in the course of the lung involvement, which currently represents the second cause of death after the cardiovascular disease [5]. The most severe form of lung involvement is the interstitial lung disease (ILD). The clinically evident ILD affects between 10 and 42% of the patients in different series, mainly based on the method used for its study [6, 7]. Patients with RA and ILD show a threefold higher mortality rate, and ILD is the leading cause in 7% of RA-related deaths [8, 9]. Median survival in these patients is between 3.2–6.6 years, depending on the patterns found in the High-Resolution Computerized Tomography (HRCT) or histology [10]. Airway involvement seems to be more common than ILD (up to 92% in a series), even though available evidence about it is limited [11]. Forms of airway involvement may vary, affecting the proximal as well as the small airway [3]. Patients with lung involvement seem to have elevated anti-cyclic citrullinated peptides antibodies (ACPAs) values and ACPAs have been involved not only as a marker of disease but also in the pathogenesis of severe RA [12–14]. The presence of ACPAs has been detected in patients without articular involvement. However, taking in account their pathogenicity, the organ injury could have started previously. A group of investigators showed that the active monitoring of lung disease with HRCT in RA patients may show interstitial abnormalities in 33% of the cases [15]. This scenario was defined as subclinical ILD characterized by the presence of interstitial abnormalities in HRCT in a group of asymptomatic patients or with symptoms not attributed to an ILD. 34–57% of patients with sub-clinical ILD are known to show disease progression during its course in the HRCT [15, 16]. However, this information

comes from studies that included patients with established RA (with more than two years of disease duration). Therefore, we consider that the conduction of a study to evaluate the importance of an active screening of lung disease (both ILD and airway involvement) in patients with early RA is justified. Thus, the aim of our study was to know the prevalence of non-diagnosed lung disease (airway and interstitial involvement) in patients with early RA.

As a secondary objective, we propose to determine which demographic, clinical, functional and laboratory factors are associated with undiagnosed lung disease.

Materials and methods

We designed an observational, multicenter, cross-sectional study and included patients older than 18 years, with diagnosis of RA according to ACR/EULAR 2010 criteria [17]. We excluded patients with more than 2 years since the diagnosis of RA, patients previously diagnosed with RA-related lung disease, and patients that were under biologics or synthetic targeted therapies.

Patients were consecutively recruited between December 2017 and February 2020 in two rheumatology outpatient clinics and assessment of clinimetric variables related to the joint involvement was done. Patients were subsequently referred to pulmonologists for a clinical and functional respiratory evaluation. Also, a chest HRCT was performed. Data was collected in a structured form during patients' evaluation, and included: demographics (age, gender), time from diagnosis of RA (months), treatments received, erythrocyte sedimentation rate (ESR) and c reactive protein (CRP) at the time of assessment, number of tender joints, number of swollen joints, visual analog scale (VAS) for pain, VAS for activity, VAS for the rheumatologist, Disease Activity Score for 28 joints (DAS28) and CDAI (Clinical Disease Activity Index) scores, presence of extra-articular manifestations xerophthalmia, xerostomia, rheumatoid nodules), smoking history, accumulated pack/year, time and degree of dyspnea (mMRC), time of cough, presence of clubbing, presence of velcro crackles, presence of added sounds in airways (wheeze or rhonchus), saturation by pulse oximeter, lung functional parameters as FVC (liters and % theoretical value), FEV_1 (liters and % theoretical value), FEV_1/FVC (%) ratio, TLC (liters and % theoretical value), DLCO (absolute and % value). Immunology laboratory were also studied, including antinuclear antibodies (ANA) Hep2(immunofluorescence), rheumatoid factor (RF, immunoturbidimetry), and ACPAs (ELISA).

All the High Resolution Computed tomography's (HRCTs) were performed in the same center and were analyzed centrally by the same reader. The primary outcome (the presence of lung involvement) was classified

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into two types: interstitial abnormalities and airway disease. In the first group (interstitial abnormalities) we included the presence of honeycombing, septal thickening, reticular pattern, consolidation resembling organizing pneumonia, or ground glass opacities. In the second type (airway disease) we included the presence of centrilobular nodules, mosaic pattern or bronchiectasis.

Patients were recruited following good clinical practices (GCP) and after the signature of an ethical informed consent. The protocol was evaluated by an Ethic Committee.

Statistical analysis

Categorical variables were described based on their frequency and the continuous variables with mean and standard deviation (SD) or median and interquartile range depending on the presence of normal distribution or not. We analyzed which variables were associated with the presence of lung disease on HRCT. For comparison of categorical variables, a Chi square test or a Fisher´s test was used. For continuous variables, Student´s test or Wilcoxon´s test were used based on distribution.

Lung compromise on HRCT was divided in two different outcomes: ILD and airway involvement.

Results

We included 83 patients, 69 (83%) females, with a mean (SD) of age of 46.49 (17.09) years. Characteristics of the cohort are shown in Table 1. In the group of ever smokers (past or current smokers) the median (IQR) of pack years was 10 (5–30). The median (IQR) of time since RA diagnosis was 3 (1–6) months. Regarding symptoms referred by patients, 25 (30%) presented at least one, with cough as the most frequent (18%). Twenty patients (25%) referred a previously diagnosed respiratory disease, not related to RA. Nine patients referred a previous diagnosis of asthma, 4 referred tuberculosis, 3 recurrent pneumonia. Thirteen patients (15%) had at least one abnormal finding in the physical exam. The most common alteration found in lung functional tests was a reduced DLCO (14%). Regarding auto antibodies prevalence, 89% of patients were positive for ACPAs, 86% for RF, and 75% for ANA.

Four patients could not perform HRCT. In the HRCT, 57 patients had airway compromise (72%), and 6 had interstitial abnormalities (7.5%). In the last group, we found two patients with a pattern compatible with usual interstitial pneumonia, one with a subtle reticular pattern, one with isolated septal thickening, one with organizing pneumonia, and one with ground glass and cysts compatible with lymphoid interstitial pneumonia. From the 57 patients whose HRCT showed airway compromise, 42 showed air trapping, 18 centrilobular

Table 1 General characteristics of the population of patients with early RA without known related pulmonary disease

Age, mean (SD)	46.49 (17.09)
Female gender, n (%)	69 (83.1)
Comorbidities	
Past or current somker, n (%)	42 (50.6)
Previous respiratory disease, n (%)	20 (25%)
Cariovascular disease, n (%)	4 (4.82)
Symptoms	
Dyspnea greater than I mMRC, n (%)	12 (15.6)
Months with dyspnea, median (IQR)	
Cough, n (%)	15 (18.7)
Any symptom, n (%)	25 (30.12)
Physical exam	
Ronchus, n (%)	2 (2.5)
Wheezing, n (%)	2 (2.5)
Crackles, n (%)	6 (7.5)
Digital clubbing, n (%)	6 (7.5)
Abnormal physical exam, n (%)	13 (15.6)
Lung function tests	
FVC%, mean (SD)	90.4 (13.9)
FVC% < 80, n (%)	7 (8.42)
FEV1/FVC < 70%, n (%)	5 (6.02)
TLC%, mean (SD)	107.6 (15.3)
TLC% < 80, n (%)	1 (1.2%)
RV/TLC% > 120, n (%)	12 (14.4)
DLCO%, mean (SD)	104.9 (24.42)
DLCO% < 80, n (%)	12 (14.4)
HRCT findings	
Airway compromise, n (%)	57/79 (72.15)
Interstitial compromise, n (%)	6/79 (7.5)
Emphysema, n (%)	10/79 (12.6)
Auto-antibodies and inflammatory parameters	
ANA, n (%)	48/64 (75)
ACPAs, n (%)	61/68 (89.7)
RF, n (%)	59/68 (86.7)
ESR, median (IQR)	28.5 (21–48)
CRP, median (IQR)	1.64 (0.74–8)
Articular evaluation	
CDAI, median (IQR)	18 (11–24)
DAS28, mean (SD)	4.53 (1.35)
HAQ, mean (SD)	1.38 (0.8)
Extra articular compromise	
Sicca syndrome, n (%)	18 (21.95)
Rheumatoid nodules, n (%)	1 (1.22)
Treatment	
Methotrexate, n (%)	50 (60.9)
Leflunomide, n (%)	7 (8.5)

nodules and 6 bronchiectasis. We compared the group of patients with interstitial abnormalities with those

patients who showed airways disease in the HRCT. We did not found statistically significant differences in the median (IQR) of age [57.5 (52–61) vs 49 (42–57); $p = 0.138$], proportion of female gender [6 (100%) vs 45 (83%); $p = 0.278$], proportion of ever smokers [4 (66.6%) vs 33 (45%); $p = 0.311$], mean (SD) of FVC% [87.3 (12.4) vs 98.4(13.1); $p = 0.05$], mean (SD) of DLCO [88.1 (18.7) vs 105.1 (23.9); $p = 0.095$], median (IQR) of DAS28 [4.24 (3.3–6.2) vs 4.53 (3.6–5.1); $p = 0.94$], ANA positivity [6 (100%) vs 42 (72.4%); $p = 0.137$], ACPAs positivity [5(83.3%) vs 55(91.67%); $p = 0.49$], and proportion of patients with extra articular manifestations [3 (50%) vs 57 (78%); $p = 0.122$]. However, the analysis showed that patients with interstitial abnormalities tend to be older, with worse values of FVC% and DLCO%, without reaching statistical significance.

With respect to the variables associated with the presence of lung compromise on HRCT (Table 2), we found that the presence of at least one abnormality in the physical exam was associated with lung involvement [13 (21.6%) vs 0 (0%); $p = 0.026$]. Also, patients with lung involvement presented significantly lower values of FVC% and DLCO%, and higher values of RV/TLC than patients without lung compromise. No variable related to joint involvement was found associated with alterations in HRCT.

Given its putative association with the presence of secondary Sjögren syndrome, which also could be associated with lung disease, we analyzed separately the presence of anti Ro antibody. The anti Ro antibody was tested in 57 patients and was positive in 11 (19.3%). Of them, 8 patients were positive for Ro60 alone, 3 were positive for both Ro60 and Ro52, and no patient was positive for Ro52 alone. The Ro antibody was more frequent in patients with interstitial abnormalities [3 (50%) vs 8 (15.6%); $p = 0.044$]. The association between Anti Ro and interstitial abnormalities was also observed in patients with Ro52 [2 (33%) vs 1(1.9%); $p = 0.001$] and those with Ro60 [3 (50%) vs 8 (15.6%); $p = 0.044$]. However, we found no association between anti Ro and the presence of lung involvement, when we included airways compromise and interstitial abnormalities together (Table 2).

Table 2 Comparison of characteristics of patients with and without interstitial or airway abnormalities on HRCT

	Interstitial or airway abnormalities on HRCT (n = 60)	Absence of Interstitial or airway abnormalities on HRCT (n = 19)	P value
Age, median (IQR)	50 (42–58)	45 (33–53)	0.17
Female gender, n (%)	51 (85)	15 (78.9)	0.53
Month since RA diagnosis, median (IQR)	3 (1–7)	2 (0–5)	0.22
Smoking status (past or current), n (%)	32 (53.3)	10 (52.6)	0.95
Dyspnea and/or cough, n (%)[a]	21 (35)	4 (21)	0.25
Abnormal physical examination, n (%)[b]	13 (21.6)	0 (0)	0.026
FVC%, mean (SD)	95.6 (1.69)	103.6 (2.91)	0.022
FVC% < 80, n (%)	7 (11.6)	0 (0)	0.119
VEF1/FVC% < 70, n (%)	2 (10.53)	3 (5)	0.38
TCL%, mean (SD)	106.5 (12.05)	110.1 (23.4)	0.39
TLC < 80%, n (%)	1 (1.67)	0 (0)	0.57
RV/TLC%, mean (SD)	99.83 (31.5)	82.05 (30.08)	0.044
RV/TLC% > 120, n (%)	12 (20)	0 (0)	0.034
DLCO%, mean (SD)	91.05 (21.42)	107.6 (23.4)	0.009
DLCO < 80%, n (%)	7 (11.67)	5 (26.3)	0.121
ANA, n (%)	39 (78)	9 (64.29)	0.29
RF, n (%)	44 (86.2)	14 (93.3)	0.46
ACPA, n (%)	44 (88)	16 (100)	0.146
Anti Ro, n (%)	7/44 (15.9)	4/13 (30.7)	0.233
ESR, median (IQR)	31 (22–53)	27 (15–40)	0.113
RCP, median (IQR)	1.8 (0.7–8)	2 (1–12)	0.71
CDAI, median (IQR)	18 (11–24)	18 (12–24)	0.69
DAS28, median (IQR)	4.55 (3.81–5.4)	4.4 (3.37–4.95)	0.48
HAQ, median (IQR)	1.37 (0.7–2)	1 (0.6–1.2)	0.81
Extra articular manifestations, n (%)	12 (21.6)	6 (31.5)	0.37

[a] Dyspneagreater the I mMRC

[b] Rochus, wheezing or crackles on auscultation, or digital clubbing on examination

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Discussion

In this study we found a low prevalence of interstitial compromise and high prevalence of airway involvement in a population of patients with early RA, without known related pulmonary disease. Also, we found that the presence of any type of lung involvement in the HRCT was associated with abnormalities in the physical exam, and abnormal functional tests. Also, we found that the presence of anti-Ro antibody was associated with interstitial abnormalities in the HRCT.

It has been reported that the prevalence of ILD is 10–42% among RA patients. The prevalence varies depending on detection methods and the selected patients in each publication [18]. Regarding clinically significant RA-ILD, it is identified in 2% to 10% of patients with RA, but reported estimates also vary due to the heterogeneity of RA, genetic susceptibility, and differences in disease definition and diagnostic methods [19]. Although our results showed a low interstitial lung disease prevalence compared with other studies, a possible explanation for this finding is that our studied population was compound only by early RA patients. This is an interesting point to highlight from the study. Wilsher et al. published an article which included 60 patients with early RA. Compared with our results, they found a higher prevalence of lung involvement, with ground glass opacities in HRTC in 18% of patients and reticular changes in 12%. Bronchiectasis were observed in 35% and bronchial wall thickening in 50% of the cases [20].

When we analyzed the presence of all types of lung compromise, this cohort of early RA patients showed a great proportion of airway involvement. This fact cannot be dissociated from the high prevalence of smoking found in our sample (past or current smoking near 50%), that may explain itself the airways compromise. However, this finding is consistent with studies showing the presence of RA associated antibodies evidencing an underlying autoimmune phenomenon before the appearance of clinical manifestations, in some cases several years (10 or 15) before [21]. In opposition to what we supposed, we did not find association between the smoking status and the presence of lung compromise in the HRCT. This fact may be related to the high prevalence of smoking in both groups (with and without lung disease), which can be expected in patients with RA, given the role of smoking in this disease pathogenesis. Demoruelle et al. evaluated the presence of lung abnormalities in 42 seropositive patients (RF or ACPA positive) without inflammatory arthritis (IA) [11]. They found airway compromise in 76% of the patients (thickening of bronchial wall, bronchiectasis, centrilobular opacities and air trapping) using HRCT as screening method. These findings suggest that the airway mucosa could be the place where the autoimmune response begins and highlights the importance of the lung in the development of autoantibodies and clinical RA.

The relationship between lung disease and high levels of ACPAs has been proposed by many authors, but the results are still inconclusive. Rocha-Muñoz et al. compared titers of ACPAs in 39 patients with RA-ILD vs 42 patients without RA-ILD [22]. They found a significative relationship between high ACPAs titers and interstitial compromise but the relation with prognosis couldn´t be established. A meta-analysis was conducted regarding this topic by Zhu et al. [23]. They analyzed seven observational studies (243 patients with lung disease and 1442 RA controls) and showed that the ACPA positivity was associated with RA-pulmonary related disease with a pooled OR of 2.6 (95% CI 1.561–4.403; $p < 0,001$). In our study this relationship hasn´t been demonstrated probably because, as near 90% of our patients were seropositive, this high prevalence likely precludes detection of an association.

Functional tests in our study showed that patients with lung involvement presented significantly lower values of FVC% and DLCO%, and higher values of RV/TLC than patients without lung compromise. Also, we found that patients with interstitial abnormalities tend to be older, with worse values of FVC% and DLCO% than those with airways disease, but without reaching statistical significance. This fact may be explained by a low power of detection due to small number of included patients. Chung et al. found that certain tomographic patterns (mosaic attenuation) were significatively related with lower values of FEF 25–75% [24]. Salaffi et al. conducted a trial that showed DLCO as the most sensitive parameter to predict ILD on HRCT [25]. They performed HRCT in 151 RA patients with established disease, and a mean of seven years of disease duration. The prevalence of ILD was 19.2% in that population. Values of DLCO and FVC in the group with ILD were statistically lower, with a mean of DLCO% of 74.8 and a mean of FVC% of 86.77. Despite the difference with our results regarding ILDs prevalence, these results are consistent with our findings.

The main feature related with lung disease in our study was the presence of at least one abnormality in the physical exam. This finding was statistically associated with any type of lung involvement. In a trial published by the British Rheumatoid Interstitial Lung (BRILL) Network that analyzed ILD-RA proved by HRCT in 25 medical centers over a 25-year period, they found that seropositivity was related with ILD, as well as male gender, age of onset, and smoking [26]. The association that we found between the presence of lung involvement in the HRCT and an abnormal physical examination has been recently

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reported in a retrospective study that included patients with stablished RA, conducted by Kawano Dourado and coworkers, and has important implications in clinical practice [27, 28].

The association of anti-Ro antibody (in particular Ro52) with the presence of ILD has been reported in other diseases (i.e., inflammatory myopathies) [27, 28]. Our results suggests that this antibody could be a marker of interstitial involvement in RA, a fact that may have important clinical implications. However, the anti-Ro antibody could just be a marker of Sjogren Syndrome that could itself be associated with ILD, and thus, this finding needs to be confirmed by new studies, powered to detect this association.

We consider as strengths of our study that it included patients with early AR, from two rheumatology reference centers, that both HRCT and the lung functional tests together with the immunological laboratory were performed centrally with expert evaluators blind to other data. Our suggests that early lung screening with HRCT and lung functional tests can detect incipient alterations in a large number of patients. This represents an opportunity to start early treatment when indicated.

However, this study has limitations. First: the number of patients included was relatively small to estimate a real prevalence. Second: although we have considered in the analyses and reported the smoking status and the antecedent of a previous pulmonary diseases, an ideal cohort should consist of nonsmokers and patients without that conditions. Finally, the study has a cross-sectional design that does not allow us to arrive conclusions regarding causality. The longitudinal follow up of this cohort, with a larger number of patients, will allow us to elucidate this question, and to know if the prevalence of pulmonary involvement increases over time, which patients with lung disease experience a deterioration of functional parameters in the follow up, and how the different treatments influences lung disease evolution.

Conclusion

In conclusion, our study shows that a large proportion of newly diagnosed RA patients has abnormal findings in HRCT with or without clinical symptoms, and suggests that early screening for lung disease could be useful in patients with RA. Most of them are airway patterns, probably related with the pathophysiology of RA, but a significant number has interstitial pattern on HRCT. As expected, an abnormal clinical examination is associated with the presence of HRCT abnormalities, a fact with important implications in clinical practice. Further studies are needed to confirm these conclusions.

Authors' contributions
FP designed the study, made the statistical analysis, and wrote the first draft of the manuscript together with AS. MF, FC and LA made the pulmonary evaluation. JJRM made the lung function tests. FB, AC, PS made the rheumatologic evaluation. SR and PO analyzed the HRCTs. GC and FI made the immunologic laboratory. MCV edited the manuscript and contributed to define the design of the study. All authors read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Patients were recruited following good clinical practices and after the signature of an ethical informed consent. The protocol was evaluated and approved by an external Ethic Committee (Independent ethic committee, technical report number PR-0000001644/2017).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests related to the content of this manuscript.

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References
1. Rooney BK, Silman AJ. Epidemiology of the rheumatic diseases. Curr Opin Rheumatol. 1999;11(2):91–7.
2. Myasoedova E, Crowson CS, Turesson C, et al. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995–2007 versus 1985–1994: a population-based study. J Rheumatol. 2011;38(6):983–9.
3. Antin-Ozerkis D, Evans J, Rubinowitz A, et al. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med. 2010;31(3):451–78.
4. Singh JA, Furst DE, Bharat A, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(5):625–39.
5. Young A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford). 2007;46(2):350–7.
6. Zou Y-Q, Li Y-S, Ding X-N, et al. The clinical significance of HRCT in evaluation of patients with rheumatoid arthritis-associated interstitial lung disease: a report from China. Rheumatol Int. 2012;32(3):669–73.
7. Richman NC, Yazdany J, Graf J, et al. Extraarticular manifestations of rheumatoid arthritis in a multiethnic cohort of predominantly Hispanic and Asian patients. Medicine (Baltimore). 2013;92(2):92–7.
8. Olson AL, Swigris JJ, Sprunger DB, et al. Rheumatoid arthritis—interstitial lung disease—associated mortality. Am J Respir Crit Care Med. 2011;183:372–8.
9. Bongartz T, Nannini C, Medina-velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population based study. Arthritis Rheum. 2010;62(6):1583–91.

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10. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010;35(6):1322–8.

11. Demoruelle MK, Weisman MH, Simonian PL, et al. Airways abnormalities and rheumatoid arthritis-related autoantibodies in subjects without arthritis: early injury or initiating site of autoimmunity? Arthritis Rheum. 2012;64(6):1756–61.

12. Yin Y, Liang D, Zhao L, et al. Anti-cyclic citrullinated peptide antibody is associated with interstitial lung disease in patients with rheumatoid arthritis. PLoS ONE. 2014;9(4):1–6.

13. Rocha-Muñoz AD, Ponce-Guarneros M, Gamez-Nava JI, et al. Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis. J Immunol Res. 2015;2015:1–10.

14. Young A. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. Rheumatology (Oxford). 2014;53(9):1676–82.

15. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med. 2008;168(2):159–66.

16. Dawson JK, Fewins HE, Desmond J, et al. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. Ann Rheum Dis. 2002;61(6):517–21.

17. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569–81. https://doi.org/10.1002/art.27584.

18. Dai Y, Wang W, Yu Y, et al. Rheumatoid arthritis–associated interstitial lung disease an overview of epidemiology, pathogenesis and management. Clin Rheumatol. 2021. https://doi.org/10.1007/s10067-020-05320-z.

19. Bendstrup E, Møller J, Kronborg-White S, et al. Interstitial lung disease in rheumatoid arthritis remains a challenge for clinicians. J Clin Med. 2019;2038:1–21. https://doi.org/10.3390/jcm8122038.

20. Wilsher M, Voight L, Milne D, et al. Prevalence of airway and parenchymal abnormalities in newly diagnosed rheumatoid arthritis. Respiratory Med. 2012;106(10):1441–6.

21. Nielen MM, van Schaardenburg D, Reesink HW, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004;50(2):380–6. https://doi.org/10.1002/art.20018.

22. Rocha-Muñoz AD, Ponce-Guarneros M, Gamez-Nava JI, et al. Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis. J Immunol Res. 2015. https://doi.org/10.1155/2015/151626.

23. Zhu J, Zhou Y, Chen X, et al. A meta analysis of the increased risk of rheumatoid arthritis-related pulmonary disease as a result of serum anticitrullinated protein antibody positivity. J Rheumatol. 2014;41:1282–9.

24. Chung MH, Lee HL, Kwon SS, et al. Air obstruction in rheumatoid arthritis: CT manifestations correlated with pulmonar function testing. Yonsei Medi J. 2004;45(3):443–52.

25. Salaffi F, Carotti M, Di Carlo M, et al. High-resolution computed tomography of the lung in patients with rheumatoid arthritis. Medicine. 2019;98:38.

26. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study. Rheumatology. 2014;53:1676–82.

27. Kawano-Dourado L, Doyle TJ, Bonfiglioli K, et al. Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. Chest. 2020;158(4):1546–54. https://doi.org/10.1016/j.chest.2020.04.061.

28. Schulte-Pelkum J, Fritzler M, Mahler M. Latest update on the Ro/SS-a autoantibody system. Autoimmunity Rev. 2009;8(7):632–7. https://doi.org/10.1016/j.autrev.2009.02.010.

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