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ORIGINAL RESEARCH ARTICLE

Risk factors for rheumatoid arthritis-associated interstitial lung disease: a retrospective study

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ABSTRACT

Background: The objective of this study was to assess clinical and imaging features of rheumatoid arthritis (RA) associated with interstitial lung disease (ILD), (RA-ILD) group, in comparison to RA without ILD (RA-C) and to identify the associated factors to ILD.

Methods: This was a retrospective comparative study (from June 2015 to March 2022) including RA patients aged ≥18 years. The RA-C control group was matched according to age (±2 years), gender, and RA duration (±2 years). General data, RA characteristics, ILD features, and treatment modalities were recorded. Statistical analysis was performed to determine the predictive factors of ILD.

Results: A total of 104 patients were included (52 RA-ILD and 52 RA-C); sex ratio was 0.36. Mean age was 66.3±11 years (RA-ILD) *versus* 65.6±10.8 years (RA-C) (p=0.72). In comparison to RA-C, RA-ILD patients were significantly higher smokers (p=0.01) and physically inactive (p=0.01). Regarding RA features, RA-ILD patients have significantly increased positive anti-citrullinated peptide antibody (ACPA) (p=0.01), ACPA rate (p<0.001), erosive disease (p<0.001), and disease activity score (p<0.001). Mean time to ILD diagnosis was 5.85±7.16 years. Chest high-resolution computed tomography (HRCT) patterns of disease were identified: nonspecific interstitial pneumonia (NSIP) (28.8%), usual interstitial pneumonia (UIP) (17.3%), organizing pneumonia (OP) (25%), acute interstitial pneumonia (13.5%), and respiratory bronchiolitis (3.8%). Multivariate analysis identified smoking, high baseline DAS28 (disease activity score 28) and ACPA positivity as predictive factors of ILD.

Conclusion: Our results confirmed the reported associated factors of ILD in RA (smoking, higher disease activity, ACPA positivity). Thus, we need to target the modifiable factors by supporting and educating RA patients to quit smoking and intensify disease modifying anti-rheumatoid drugs (DMARD) to reach remission.

Key words: Rheumatoid arthritis; interstitial lung disease; risk factors.

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

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Introduction

Rheumatoid arthritis (RA) is the most prevalent rheumatic inflammatory disease [1]. Extraarticular features constitute the hallmark of the systemic character of the disease [2]. Thanks to modern imaging, interstitial lung disease (ILD) is going more described in RA. The reported prevalence of ILD associated with RA (RA-ILD) ranged between 20 and 50% [3,4]. ILD accounts for among the main causes of morbidity and mortality in RA [2]. Although the definition of ILD was based on histopathological criteria, diagnosis can be established nowadays using high-resolution computed tomography (HRCT) backed by pulmonary function and clinical symptoms [3]. Mastering its diagnosis and management features can significantly change the RA prognosis. However, specific predictive biomarkers of ILD are still lacking, and lead to delay diagnosis [4,5]. On the other hand, the role of disease-modifying antirheumatic drugs (DMARD)'sdrug toxicity in the onset or worsening of ILD is also controversial [6,7]. Thus, early screening of RA patients for ILD is mandatory.

The objective of the study was to assess clinical and imaging features of RA-ILD patients in comparison to RA patients without ILD and to identify the associated factors to ILD.

Methods

Study design and population

This was a retrospective comparative study extended over a 7-year period (June 2015-March 2022). Patients aged ≥18 years and diagnosed with RA according to the American College of Rheumatology and European League of Rheumatology (ACR/EULAR) 2010 RA criteria were included [8]. Sample size was composed of 2 groups: RA-ILD group and control group of RA without ILD (RA-C). The control group (RA-C) was matched to RA-ILD patients according to gender, age (±2 years) and RA duration (±2 years). RA-ILD fulfilled the Clinical-Radiologic-Pathologic Diagnosis (New ATS/ERS Classification) [9]. ILD categories such as those drug-induced, associated with occupational or environmental exposure, collagen vascular disease, and granulomatous lung disorders were not included.

Data collection

General data were collected: age, gender, tuberculosis history, physical activity, smoking habits, anthropometric measures andthe presence of concurrent comorbidities. Regular physical activity corresponded to at least 150 minutes a week of moderate-intensity physical activity [10]. RA characteristics including age at onset of RA, disease duration, extra-articular features, erosions/joint damage were assessed *via* X-ray, and serologic status: positive for rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA), and their rate. Disease parameters were recorded at the diagnosis of ILD: number of nocturnal awakenings, morning stiffness duration, VAS pain, disease activity score $(DAS)_{28}$, and C-reactive protein (CRP).

ILD features at diagnosis (baseline) were noted: diagnosis delay since onset of, RA clinical symptoms, spirometry, imaging findings (chest radiographs, chest HRCT), and ILD classification: usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), acute interstitial pneumonia (AIP), respiratory bronchiolitis, desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia (LIP). Therapeutic data were detailed: list of DMARD at diagnosis of ILD, and change in medication after ILD confirmation. The last evaluation of spirometry and HRCT was also recorded. We considered disease progression (deterioration) as: a decline of 15% in gas transfer from baseline and/or imaging worsening in follow up HRCT.

Statistical analysis

Statistical package for social sciences (SPSS) version 26.0 was used to perform statistical analysis. The quantitative variables were summarized as mean and standard deviation (SD). The qualitative variables were expressed as percentages and frequencies. Comparisons between quantitative variables were made using ANOVA test. The Chi-square test was used to analyse categorical data. Multivariate analysis with multiple logistic regression was performed to identify the predictive factors of ILD; odds ratio (OR), their 95% confidence intervals, and the significance level were reported. The level of significance was set at $p<0.05$.

Results

Patients' and RA characteristics

A total of 104 patients were included (52 RA-ILD and 52 RA-C); 76(73%) were females in the 2 groups. Mean age was 66.3±11 years (RA-ILD) *versus* 65.6±10.8 years (RA-C), (p=0.72). In comparison to RA-C, RA-ILD patients were significantly higher current smoking (p=0.01) and physical inactivity (p=0.01). There was no significant statistical difference according to number of comorbidities between 2 groups (p=0.85). Patients' characteristics were summarized in Table 1.

Table 1. General data of the sample size (RA-ILD, RA-C).

	RA-ILD	RA-C	p
Sex ratio	0.36	0.36	-
Mean age, years (±SD)	66.3 (±11)	65.6 (±10.8)	0.72
Smoking, n (%)	19 (37)	7 (13)	0.01
BMI, mean (±SD)	27.5 (±6.04)	26.5 (±4.41)	0.41
Physical activity, n (%)			0.01
Regular	23 (55.7)	38 (73)	
Sedentary	23 (44.3)	17 (27)	
Medical comorbidities			
Diabetes	10 (19.2)	9 (17.3)	
Hypertension	13 (25)	15 (28.8)	
Dysthroidism	2 (3.8)	4 (7.6)	
Cardiac comorbidities	1 (2)	2 (3.8)	

RA, rheumatoid arthritis; ILD, interstitial lung disease; RA-C, control group; BMI, body mass index.

The mean age at onset of RA was 47.2±13.5 years (RA-ILD) versus 48±12.8 (RA-C), (p=0.76). Mean RA duration was 13.3±7.8 (RA-ILD) *versus* 12.2±7.4 (RA-C), (p=0.44). RA-ILD patients, comparison to RA-C, have significantly increased positive ACPA (p=0.01), ACPA rate (p<0.001), erosive disease (p<0.001), extra-articular features (p=0.027), and Sjogren's syndrome (p=0.021). Disease activity was significantly higher in the RA-ILD group in terms of VAS pain (p<0.001), number of nocturnal awakenings (p=0.033), morning stiffness duration (p<0.001), and DAS_{28}CRP (p<0.001). Table 2 represented RA features of the 2 groups.

Interstitial lung disease

Mean time to ILD diagnosis was 5.85years±7.16; ILD preceded RA diagnosis in 4 patients. Baseline evaluation showed: breathlessness (44%), cough (23%), restrictive (75%)/obstructive (2%) patterns on spirometry, and peripheral reticular opacity (82.7%) on chest radiographs. Chest HRCT patterns of disease were identified: NSIP (28.8%), UIP (17.3%), organizing pneumonia (25%), acute interstitial pneumonia (13.5%), and respiratory bronchiolitis (3.8%). The last spirometry evaluation demonstrated worsening of restrictive disorder (55%), sustainability (26%), and improvement (19%).

Regarding treatment for ILD, 25% received glucocorticoids mean daily dose 9.2±3.4 mg (5-25)], 15% inhaled steroids, and 4% one course of cyclophosphamide 1 g. As for change in DMARD prescription: discontinuation MTX (24%), sulfasalazine (40%), and leflunomide (100%); switch from TNF inhibitors to rituximab (n=9), switch from csDMARD to rituximab (n=11), and prescription of tocilizumab (n=4). Assessment of last chest HCRT imaging recorded was detailed in Table 3.

Predictive factors of RA-ILD

Multivariate analysis identified smoking, high baseline DAS28 and ACPA positivity as predictive factors of ILD (Table 4).

Discussion

This study compared two RA patients with and without ILD. The 2 groups were comparable according to age (±2years), sex and RA duration (±2 years). We highlighted that RA-ILD patients have significantly higher severe disease (erosive, high ACPA rate), and active disease (DAS_{28}, patient reported outcomes).

ATS/ERS (American Thoracic Society/ European Respiratory Society) classification criteria are currently the most used for diagnosis, evaluation and follow up of ILD. These were initially established in 2000, reviewed in 2012 and more recently in 2018 [9,10]. They are based on a variety of arguments (history, clinical, imaging, spirometry and histology if necessary). In our study, HRCTs were assessed by expert radiologists, no one underwent a lung biopsy. NSIP was more common than OP and both were more

Table 2. Comparative disease features between RA-ILD and RA-C.

	RA-ILD	RA-C	p
Mean age of onset of RA, (years ±SD)	47.2±13.5	48±12.8	0.76
RA duration, (years ±SD)	13.3±7.8	12.2 ±7.49	0.44
Positive ACPA, n (%)	44 (84.6)	32(61.5)	0.01
Mean ACPA rate at diagnosis, (UI/ml ±SD)	271±181	132±109	<0.001
Positive RF, n (%)	37(71)	33(64)	0.4
Erosive disease, n (%)	50(96)	34(65)	<0.001
Mean DAS_{28}CRP ±SD	4.55±1.22	3.60 ± 0.94	<0.001
Mean CRP, (mg) ±SD	40±43	31.3 ± 26	0.18
VAS pain ±SD	7.16±1.37	4.1±1.68	<0.001
Nocturnal awakenings, n (%)	2.87 (1.3)	1(1)	0.033
Mean morning stiffness, (min ±SD)	92.21 ±74.7	18.37±20	<0.001
AAL, n (%)	6 (12)	1(2)	0.11
Coxitis, n (%)	7 (13)	3 (5.8)	
Extra-articular features, n (%)	52 (100)	46 (88)	0.027
Ocular	34 (65)	30 (58)	0.42
Sjogren syndrome	31 (60)	25 (48)	0.021
Renal	3 (5.8)	6 (12)	0.49
Cardiovascular	6 (12)	3 (5.5)	0.49
Osteoporosis	22(42)	6 (12)	0.5
csDMARD			
Methotrexate, n (%)	38 (73)	43 (82)	
Sulfasalazine, n (%)	15 (29)	8 (27.5)	
Leflunomide, n (%)	1 (0.02)	0	
bDMARD			
TNF inhibitors, n (%)	6 (12)	8 (27.5)	
Rituximab, n (%)	3(5.8)	9 (17.3)	
Tocilizumab, n(%)	2 (3.9)	2 (3.9)	

RA, rheumatoid arthritis; ILD, interstitial lung disease; RA-C, control group; BMI, body mass index; ACPA, anti-citrullinated protein antibodies RF, rheumatoid factor; DAS28, disease activity index 28; CRP, c-reactive protein; VAS, visual analogue scale; AAL, atlantoaxial dislocation; csDMARD, synthetic disease modifying anti-rheumatoid drugs; bDMARD, biologic disease modifying anti-rheumatoid drugs.

common than UIP. This finding that was not in concordance with previous reports which described UIP as the most prevalent category of ILD [10,11].

Despite a good knowledge of the RA pathophysiological mechanisms, determining the RA-ILD predictive factors remains challenging. Male sex, advanced age, smoking status, ACPA positivity, DMARDs and high disease activity have all been suggested as putative risk factors [12-15].

A recent systematic review and meta-analysis including 29 records concluded that both the presence and higher titers of ACPA were suggested to be significantly associated with an increased risk of RA-ILD [4,11,16,17]. Pursuant to that, our results were in line with literature data: ACPA positivity and rate were significantly higher in RA-ILD than in RA without ILD, and the absence of ACPA was a protective factor from RA-ILD (OR=0.294; p=0.03).

In line with previous reports, smoking was identified in our work as a predictive factor of RA-ILD [18,19]. Smoking is the most studied predisposing factor for the occurrence of joint and extra-articular manifestations of RA [1]. Saag *et al*. showed an odds ratio of 3.8 was found with patients smoking over 25 pack/years for RA-ILD patients [20]. RA-specific autoimmunity antibodies may be triggered by external factors such as smoking to generate an immunological interaction in the lung tissues and leading to pulmonary damage such as ILD [19].

In our study, higher disease activity score was also a predictive factor of ILD. Interestingly, selection criteria of 2 groups, especially in terms of disease duration, allowed to avoid confounded factors. Many studies had showed association between higher disease activity and ILD [4,12,21,22], however the study design must be reviewed.

Demographic factors were not associated to ILD in our study as previously reported. In fact, advanced age was considered as a risk factor [14,15] and a predictor of mortality [23,24]. Male sex was also identified as a RA-ILD risk factor even though the female susceptibility for developing RA [25,26].

Despite new advances in RA treatment, the management of RA-ILD patients remains fairly vague. Unlike RA, no clear guidelines were established after ILD diagnosis. In our study, previous and current treatments were not associated with ILD occurrence or progression. These results are in occurrence with literature data. Perez and al demonstrated that csDMARDs was not associated with spirometry, HRCT incomes in RA-ILD regardless the type of drugs [27].

Moreover, it has been hypothesized that MTX, the most commonly recommended treatment for RA in first line, can cause ILD as an adverse effect. This affirmation has been controversial over the past 10 years, proving that there was no further increased risk of ILD or respiratory failure with MTX. In accordance with these findings, a Danish nationwide population-based study found no increased risk with MTX at each the 1-, 5- or 10-years' follow up [28]. Otherwise, a meta-analysis of 22 randomized controlled trials showed a small but increased risk of MTX compared with other DMARD or biologic agents for overall respiratory events but not for non-infectious pulmonary events [29].

A recent review published in 2021 had assessed treatment strategy in RA-ILD [30]. Authors concluded that csDMARDs still is used as first approach regardless their controversial role in ILD occurrence. Corticosteroids are the mainstay of therapy in ILD, particularly for cases of NSIP or OP where they may lead to potential clinical and imaging improvement. Similar to csDMARDs, controversy regarding TNFα inhibitors is showing improvement and others demonstrating development or progression of ILD. The management approach still leaved to physician common sense and on a case-by-case basis. Among the drugs panel for RA, rituximab and abatacept demonstrated promising results better than other biologicals, such as TNF blockers, in terms often achieving stabi-

Table 3. **ILD evolution in patients following treatment change.**

	Not evaluated	Sustainability	Aggravation	Improvement	Total
bDMARD					
Rituximab	5 (25%)	6 (30%)	2 (10%)	7 (35%)	20
Tocilizumab	3 (50%)	0	2 (33%)	1 (17%)	6
TNF inhibitor	3 (20%)	0	11 (73%)	1 (7%)	15
CsDMARD					
None	4	0	6	0	10
Methotrexate	9 (29%)	8 (26%)	5 (16%)	9 (29%)	31
Sulfasalazine	1 (14%)	2 (28%)	3 (43%)	1 (14%)	7

bDMARD, biologic disease modifying anti-rheumatoid drugs; csDMARD, synthetic disease modifying anti-rheumatoid drugs.

Table 4. **Predictive factors of interstitial lung disease.**

Variables	Modality	OR (CI at 95%)	p
Intercept		0.0423 (0.00458-0.300)	<0.01
Smoking	Yes	4.76 (1.52-16.8)	0.01
Physical activity	None	1.90 (0.651-5.74)	0.25
	Regular	0.364 (0.0885-1.33)	0.14
ACPA	Positive	-	-
	Negative	0.294 (0.0916-0.857)	0.03
DAS_{28} CRP	-	2.13 (1.38-3.51)	<0.01
R^2 de Nagelkerke = 34.9%			

OR, odds ratio; CI, confidence interval; ACPA, anti-citrullinated protein antibodies; DAS_{28}, disease activity index 28; CRP, C-reactive protein.

lization and improvement of ILD in patients with RA [31].

In this work, results related to our population were mostly in concordance with studies and literature results and support other authors finding in matter of diagnosis, prognosis and management of ILD. Despite the restrict number of patients, our description may insure us that international recommendations are applicable to our population particularities.

However, this study has some limitations. The retrospective design did not allow to conclude about the causal relationship between RA and ILD.Further longitudinal cohort studies involving larger samples are necessary to confirm our results. Second, the time of the last evaluation of spirometry and HCRT was not the same. Interestingly, our patients were homogenous in terms of age, gender and disease duration which can eliminate some interpretation bias.

Conclusion

RA-ILD remains a real clinical and therapeutic challenge and it is associated with poor survival rate. This study tried to highlight the importance of disease's assessment to predict prognosis and improve patient management: we discerned smoking, positive ACPA and high disease activity as the most common predictive factors of ILD. Despite a large variety of treatment, progression of ILD on HRCT was seen in 18,2% of cases in this study. Improvements in RA therapy in recent years did help to reduce mortality of lung affection.

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