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Assessment of risk factors in patients with rheumatoid arthritis-associated interstitial lung disease

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ABSTRACT

Objective: To assess the risk factors for interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA) and to evaluate the association of ILD with the use of methotrexate as well as with joint disease activity. **Methods:** A retrospective, cross-sectional study conducted between March and December 2019 at a tertiary healthcare center, in a follow-up of RA patients who had undergone pulmonary function tests (PFT) and chest computed tomography. We evaluated the tomographic characteristics, such as the presence of ILD and its extension, as well as joint disease activity. Functional measurements, such as forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), were also assessed. After this, a multivariate logistic regression analysis was applied in order to identify risk factors associated with ILD. **Results:** We evaluated 1.233 patients, of which 134 were eligible for this study. The majority were female (89.6%), with a mean age of 61 years old and with a positive rheumatoid factor (86.2%). RA-associated ILD (RA-ILD) was detected in 49 patients (36.6%). We found an association of RA-ILD with age ≥= 62 year, male sex, smoking history and fine crackles in lung auscultation and a decreased DLCO. The indicators of being aged ≥ 62 years old and having moderate or high RA disease activity were both independent factors associated with RA-ILD, with an odds ratio of 4.36 and 3.03, respectively. The use of methotrexate was not associated with a higher prevalence of ILD. **Conclusion:** Age and RA disease activity are important risk factors associated with RA-ILD. Methotrexate was not associated with the development of RA-ILD in the present study.

Keywords: Rheumatoid arthritis; Interstitial lung disease; Rheumatoid arthritis-associated interstitial lung disease.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease with a prevalence rate ranging from 0.3 to 1% of the population, with a higher incidence in women aged between 30 and 50 years old.[1]

Although join manifestations are more prevalent, extra-articular manifestations of RA may occur in about 40% of patients, usually presenting with rheumatoid nodules, secondary Sjögren's syndrome and lung disease.[2]

The association of lung disease with RA was first described in 1948.[3] Since then, a wide range of pulmonary involvement due to this illness have been well described, such as pleurisy/pleural effusion, rheumatoid nodules, Caplan syndrome, pulmonary hypertension, bronchiolitis, bronchiectasis and interstitial lung disease (ILD).[4,5]

ILD is an important form of RA-related lung disease.[5,6] In studies with chest computed tomography (CT), its prevalence ranges from 28 to 58%,[6-8] but only 5 to 10% are estimated to be clinically relevant cases.[9,10]

This study aims to evaluate risk factors for ILD in RA patients in follow-up at an outpatient clinic of a tertiary healthcare service, as well as to assess the association of ILD with the use of methotrexate and joint disease activity.

METHODS

This was a retrospective, cross-sectional study that included patients aged ≥ 18 years old, in follow-up for RA at an outpatient clinic of a tertiary healthcare service in Brazil, from March to December 2019, who had undergone pulmonary function tests (PFTs) and chest CTs for any reason.

Patients with overlapping collagen diseases, undergoing radiation therapy with potential for radiation-induced lung injury or lung resection procedures, were excluded.

All patients were diagnosed with RA by a rheumatologist, according to specific diagnostic criteria.[11,12]

Joint disease activity data was collected from the patient's medical records and used as the last measure before

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the CT scan. The following validated instruments were used: the Disease Activity Score-28 for RA (DAS-28) with C-reactive protein (DAS28-CRP), the DAS-28 with erythrocyte sedimentation rate (DAS28-ESR) and the Clinical Disease Activity Index (CDAI). For the analysis, we stratified the patients into two groups: moderate/high and low activity/remission. We chose this stratification system on the grounds that low activity of joint disease or remission are recommended as treatment targets in clinical practice.[13,14]

Respiratory symptoms such as cough, sputum and degree of dyspnea (modified Medical Research Council (mMRC) scale), as well as data from physical examination (clubbing, fine crackles, peripheral oxygen saturation at rest), use of drugs for current RA treatment, previous use of methotrexate at any time (duration in years and maximum dose used), dosing of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP), were evaluated.

The CT images were assessed independently, in random order, by two chest radiologists. Upon divergence in the interpretation of results, a final decision was reached by consensus of both radiologists. Interobserver agreement between radiologists was not calculated. The HRCT findings were categorized as absent, limited or extensive ILD, according to the extent of the involvement in five levels and classification algorithm proposed by Goh et al.[15] CT scans with more than 20% involvement were categorized as extensive ILD. CT scans presenting any abnormality less than 20% involvement were categorized as limited ILD.

Pulmonary function tests (PFTs), such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio, total lung capacity (TLC), residual volume (RV), RV/TLC ratio, diffusing capacity for carbon monoxide (DLCO), and lung diffusion capacity corrected for alveolar ventilation (DLCO/AV) were also evaluated.

This study was approved by the Human Research Ethics Committee of the institution.

Statistical analysis

Data analysis was performed with the Excel® and SPSS Statistics v. 22.0 software.

The quantitative variable's results were described in mean and standard deviation. Categorical variables were described in frequency and percentage. The ROC curve was adjusted to evaluate the existence of cut-off points for age related to ILD (yes or no) (^{3}62 years, p = 0.013, specificity 56.3% and sensitivity 69.7%). For the comparison of the three assessments of the disease extent (absent, limited or extensive) with the quantitative variables, nonparametric Kruskal-Wallis test and post-hoc Dunn test were applied. Comparisons of disease extent assessment (limited or extensive) were made with the Mann-Whitney nonparametric test. As for the categorical variables, the comparison was made with the chi-square test. A multivariate model was adjusted to include sex, fine crackles, age and DLCO as explanatory variables (those presenting with $p < 0.05$ in the univariate analysis), in order to evaluate the control of the joint disease activity, the variables were found to be both statistically significant ($p < 0.05$) and clinically relevant.

Logistic regression models were adjusted for univariate and multivariate analysis of factors associated with ILD. The Wald test was used to assess the statistical significance of the variables and the estimated measure of association was calculated by a odds ratio with 95% confidence intervals. P-values < 0.05 indicated statistical significance.

RESULTS

Among the 1.233 patients treated from March to December 2019, 1.052 were not eligible for this study on account of insufficient data from chest CTs and/or PFTs, lack of RA diagnosis, conflicting or unavailable data (Figure 1). Other 47 patients were excluded from the study due to the following exclusion criteria: presence of another lung disease, presence of overlapping collagen disease, history of radiation therapy with potential for radiation-induced lung injury, or history of lung resection. Thus, 134 patients were included in the present study.

The participants were predominantly female (89.6%), with a mean age of 61 years old. Most patients had no smoking history (53%) and, among smokers, the mean smoking load was 22.8 packs-year. The majority of patients had positive RF (86.2%), while only 18 participants had the anti-CCP result (anti-CCP is not an easily available exam in our public health system) (Table 1).

Almost all patients had a history of prior use of methotrexate or were currently using it at the time of the analysis (93.2%).

Regarding the joint activity scales (DAS28-CRP, DAS28-ESR or CDAI), patients were stratified according to different disease activity levels, displaying discrepancies in these assessment instruments. However, more than 50% of the sample was categorized as in remission or with low activity, regardless of analyzed scale. Furthermore, CDAI was the most used disease activity score in our study, therefore, we used this tool to stratify patients presenting moderate/high disease activity for the univariate analysis.

RA-ILD was present in 49 patients (36.6%), 24.6% were considered as having limited extension disease and 11.9% as having extensive disease. Comparing patients with ILD (RA-ILD) and without ILD, age >= 62 years, smoking history and presence of fine crackles were significantly more prevalent indicators in the RA-ILD group. Although most of the patients had a preserved PFT, DLCO values were remarkably higher among those without ILD (Table 2).

The age of 62 years was used because it was the cut-off point with statistical significance indicated by the ROC curve analysis (p = 0.013) and had 69.7% of

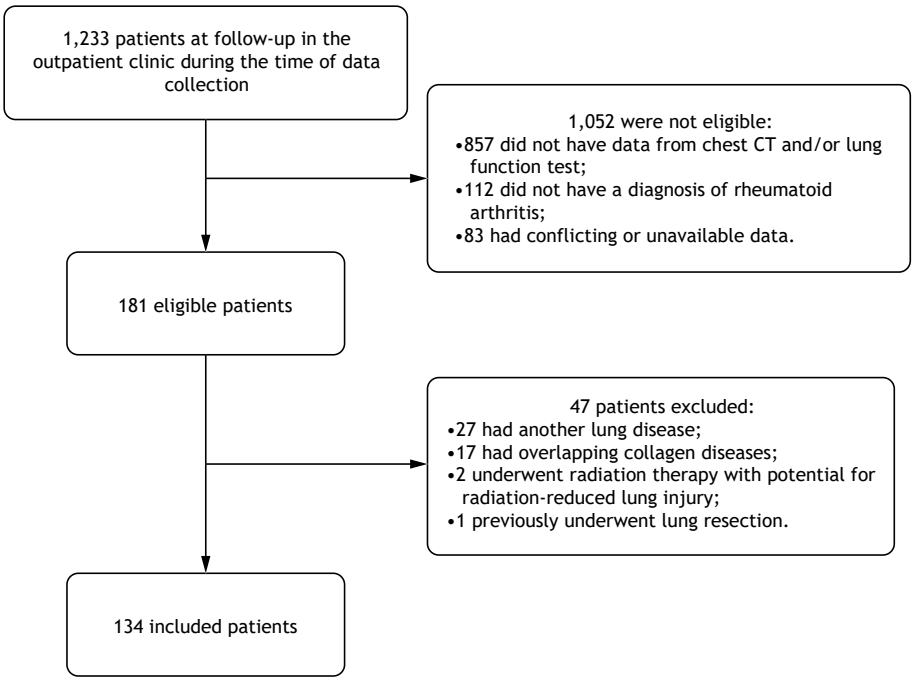

Figure 1. Study design.

sensitivity. The multivariate analysis demonstrated that being aged ≥ 62 years old and presenting moderate/high disease activity (in any of the scores) were independent factors for RA-ILD with an odds ratio of 4.36 and 3.03, respectively (Table 3).

Regarding patients treated with methotrexate (n = 124), there was no association of previous methotrexate treatment and the presence of ILD (p = 0.219). However, when ILD extension was evaluated, 9.7% presented extensive tomographic disease, while 65.3% presented absence of ILD when in use of methotrexate (p = 0.008) (Table 4).

DISCUSSION

The present study indicates that being age ≥ 62 years old, male sex, having a smoking history, and presenting fine crackles are risk factors associated with RA-ILD (presented in 36.6% of the sample). Higher DLCO values are inversely associated with RA-ILD.

The evaluation of risk factors is extremely important for RA-ILD, not only because of its relevant prevalence, but also due to the impact of the diagnosis on both treatment options and mortality.[9,10,16] Although RA is more common among females, being male is considered a risk factor for RA-ILD. This association was found in this study and had already been demonstrated by other authors.[10,16,17]

The presence of RA-related autoantibodies, especially in high titers, has been suggested to be a risk factor for RA-ILD.[2,10,17-19] Kelly et al. demonstrated that high titers of anti-CCP are strongly associated with RA-ILD.[10] In our study, it was found no positive association between positive RF or anti-CCP and RA-ILD; nevertheless, different methods were used for dosing RF, which may have contributed to creating a bias. Moreover, only a small number of patients were tested for anti-CCP, and this could also have influenced the results found herein. That being said, a recently published meta-analysis showed that patients with positive RF or anti-CCP have a higher risk of developing RA-ILD, but the analysis of subgroups by region indicated that even though patients from Asia, Africa and Europe with positive anti-CCP presented a higher risk of ILD-RA, it was not statistically significant for the American population, with two studies from the United States and one study from Mexico included in that analysis.[19] This allows questioning whether the American population has a different pattern.

Although the presence of respiratory symptoms did not present a statistical significance associated with ILD in the studied sample, one third of patients who did not present respiratory symptoms manifested ILD on the chest CT scan. A Spanish cohort study had a similar result, since 33.7% of 90 patients with RA-ILD were asymptomatic.[18] This suggests that the presence of symptoms should not be used alone, isolated Hto determine the presence of ILD in RA patients.

Fine crackles in lung auscultation were associated with the diagnosis of RA-ILD, demonstrating that a

Table 1. Baseline population characteristics.

Clinical-epidemiological characteristics [n = 134]	
Female sex, n (%)	120 (89.6)
Age in years, mean ± standard deviation	61 ± 11
Current or previous smoking history, n (%) [n = 132]	62 (47)
Illness duration in years, mean ± standard deviation	13 ± 9
Positive rheumatoid factor, n (%) [n = 130]	112 (86.2)
Presence of respiratory symptoms, n (%) [n = 133]	106 (79.7)
Joint disease activity DAS28-CRP [n = 105]	
Remission, n (%)	51 (48.6)
Low activity, n (%)	16 (15.2)
Moderate activity, n (%)	31 (29.5)
High activity, n (%)	7 (6.7)
Joint disease activity DAS28-ESR [n = 99]	
Remission, n (%)	28 (28.3)
Low activity, n (%)	22 (22.2)
Moderate activity, n (%)	36 (36.4)
High activity, n (%)	13 (13.1)
Joint disease activity CDAI [n = 115]	
Remission, n (%)	12 (10.4)
Low activity, n (%)	53 (46.1)
Moderate activity, n (%)	34 (29.6)
High activity, n (%)	16 (13.9)
Lung functional characteristics [n = 134]	
Absolute FVC, mean ± standard deviation	2.99 ± 0.99
Relative FVC, mean ± standard deviation	98.2 ± 22
Absolute DLCO, mean ± standard deviation [n = 121]	19.9 ± 5.34
Relative DLCO, mean ± standard deviation [n = 121]	96.4 ± 27.9
Tomographic extension [n = 134]	
Absent, n (%)	85 (63.4)
Limited, n (%)	33 (24.6)
Extensive, n (%)	16 (11.9)

CDAI: Clinical Disease Activity Index; FVC: Forced vital capacity; DAS28-CRP: Disease Activity Score-28 for RA (DAS-28) with C-reactive protein; DAS28-ESR: Disease Activity Score-28 for RA (DAS-28) with erythrocyte sedimentation rate; DLCO: Diffusing capacity for carbon monoxide.

Table 2. Characteristics of patients with rheumatoid arthritis (RA) stratified by presence and absence of interstitial lung disease (ILD).

	N=134	RA-ILD absent	RA-ILD present	p
Age ≥ 62 years old	67	32 (47.8%)	35 (52.2%)	<0.001
Male sex	14	4 (28.6%)	10 (71.4%)	0.008
Previous smoking history	45	22 (48.9%)	23 (51.1%)	0.024
Presence of respiratory symptoms	106	67 (63.2%)	39 (36.8%)	0.738
Presence of fine crackles	26	9 (34.6%)	17 (65.4%)	0.001
Previous treatment with methotrexate	124	81 (65.3%)	43 (34.7%)	0.219
Moderate/high disease activity	50	29 (58%)	21 (42%)	0.075
Positive rheumatoid factor	112	68 (60.7%)	44 (39.3%)	0.172
FVC (%) mean ± standard deviation	134	100.8 ± 19.6	93.7 ± 25.2	0.073
DLCO (%) mean ± standard deviation	121	101.5 ± 26.6	87.6 ± 28.2	0.010

FVC: Forced vital capacity; DLCO: Diffusing capacity for carbon monoxide; RA-ILD: Rheumatoid arthritis-associated interstitial lung disease.

careful lung auscultation should be performed in all RA patients, regardless of their complaints related to their respiratory symptoms. It is a low-cost examination with no contraindications that can contribute to an early diagnosis. A prospective blind study with a sample of 148 patients showed a correlation between bilateral fine

Table 3. Multivariate analysis.

	p	OR	CI95 %
Age ≥ 62 years old	0.005	4.36	1.57 - 12.09
Male sex	0.215	3.29	0.50 - 21.7
Presence of fine crackles	0.774	1.22	0.32 - 4.58
Absolute DLCO	0.235	0.94	0.86 - 1.04
Moderate/high disease activity	0.027	3.03	1.14 - 8.09

DLCO: Diffusing capacity for carbon monoxide.

Table 4. Association of previous treatment with methotrexate with tomographic extension of interstitial lung disease.

		Tomographic extension			p
		Absent	Limited	Extensive	
Previous treatment with methotrexate	No	4 (44.4%)	1 (11.1%)	4 (44.4%)	0.008
	Yes	81 (65.3%)	31 (25%)	12 (9.7%)	

crackles and the presence of fibrotic ILD. This type of abnormality in auscultation was the predictive factor most related to usual interstitial pneumonia (UIP) pattern in chest –CT scans, which is the most frequent tomographic pattern observed in RA-ILD patients.[20] Studies using digital stethoscopes and sound analysis of velcro crackles showed that this new technology has better accuracy if compared with traditional auscultation, presenting a 84 to 90% against a 60 to 70% precision, respectively.[21,22]

In the multivariate analysis, moderate or high joint disease activity were considered independent factors associated with RA-ILD, with an odds ratio of 3.03. This suggests the importance of controlling systemic inflammation for the prevention of RA-ILD development. This was already suggested in a prospective cohort study with 1.419 patients which showed that joint activity in RA is associated with a higher risk of developing ILD.[23] Other studies demonstrate that the CDAI score is also associated with ILD activity.[24,25]

In our study, the mean DLCO was found to be normal in the RA-ILD group, however, it was significantly lower than the group without RA-ILD. Despite the fact that several cut-off points have already been proposed in the literature to facilitate ILD screening, there is no consensus,[21,26,27] and even with a low DLCO cut-off point of 47%, accuracy and sensitivity were low (54.9% and 30.8%, respectively).[21]

The vast majority of patients in the present study were treated with methotrexate at some point; it is noteworthy that 65.3% of these patients were not diagnosed with RA-ILD, and extensive ILD was only present in 9.7% of cases, suggesting a protective factor. Although methotrexate has been historically considered a causal factor of ILD, recent evidence corroborate the findings of our study.[17,28-30]

The results herein should be interpreted considering some limitations. The retrospective nature of the research design is a major limitation of our study. In addition, the study was conducted in a single center. Also, for being a public healthcare profile, some data were incomplete, such as anti-CCP. However, most of the data found is consistent with the literature, a fact that supports this study's relevance.

In conclusion, age and RA disease activity were found to be important risk factors associated with RA-ILD. Methotrexate use was not associated with the development of RA-ILD in the present study.

AUTHOR CONTRIBUTIONS

CRS: investigation, data curation, formal analysis, visualization and writing of the original draft. CC: investigation and formal analysis. MBV: investigation and data curation. DLE and ESP: investigation, formal analysis and writing of the reviewed manuscript. KMS: conceptualization, investigation, formal analysis, visualization and writing of the reviewed manuscript. All authors contributed to the final version of the manuscript.

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