

High-resolution computed tomography of the lung in patients with rheumatoid arthritis

Prevalence of interstitial lung disease involvement and determinants of abnormalities

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Abstract

An international consensus for rheumatoid arthritis (RA) patients at risk of developing interstitial lung disease (ILD) is still lacking. The aims of study were to evaluate: the prevalence of ILD involvement in RA over high-resolution computed tomography (HRCT); the relationships between pulmonary function tests (PFTs), patient-centered measurements, and ILD; and the potential risk factors contributing to RA-ILD patients.

Data regarding the clinical characteristics (age, sex, age at onset of RA), laboratory findings (rheumatoid factor [RF] and anti-citrullinated protein antibodies [ACPA]), respiratory functional assessment (forced vital capacity [FVC] and carbon monoxide diffusion capacity [DLCO]), patient-centred measures of dyspnea (PCMD), Health Assessment Questionnaire—Disability Index (HAQ-DI), and HRCT have collected retrospectively. HRCT abnormalities were evaluated using a conventional visual reader-based score (CoVR) and a computer-aided method (CaM). The relationships between the 2 HRCT scores—PFTs and PCMD—were calculated using Pearson correlation. The area under the receiving-operating characteristic (AUC-ROC) curve was calculated to determine the discriminatory performance of measurements between patients with and without ILD. The multivariate regression model was used to evaluate the association force between ILD and RA characteristics.

In all, 151 patients (45 males and 106 females, mean age 53.4 ± 7.6 years) were included. ILD had been detected in 29 patients out of 151 (19.2%). Usual interstitial pneumonia was the most common HRCT. RA-ILD patients were older, and older at RA onset (both $P < .01$), with a higher HAQ-DI ($P < .05$) than patients without ILD. ACPA positivity and titer were higher in the RA-ILD group ($P = .02$). Extent and severity of ILD, and total CoVR and CaM score closely related to DLCO and PCMD (both $P < .0001$). A reduced DLCO was the most sensitive test for predicting the presence of ILD on HRCT (AUC-ROC 0.811 ± 0.037). Advanced age ($P < .0001$), age at RA onset ($P = .025$), ACPA titer ($P = .004$), and smoking ($P = .008$) were independent explanatory variables of HRCT damage in multivariate analysis.

The RA-ILD is associated with age and older age of RA onset, smoking, and ACPA titer. DLCO seems to be the most sensitive parameter to predict ILD on HRCT, followed by PCMD.

Abbreviations: ACPA = anti-citrullinated protein antibodies, AUC-ROC curve = area under the receiving-operating characteristic curve, BDI = Borg Dyspnea Index, CaM = computer-aided method, CoVR = conventional visual reader-based score, CRP = C-reactive protein, DAD = diffuse alveolar damage, DLCO = carbon monoxide diffusion capacity, DMARDs = disease-modifying anti-rheumatic drugs, EORA = elderly-onset rheumatoid arthritis, ESR = erythrocyte sedimentation rate; FVC = forced vital capacity, HAQ-DI = Health Assessment Questionnaire—Disability Index, HRCT = high-resolution computed tomography, ICC = intraclass correlation coefficient, ILD = interstitial lung disease, IPF = interstitial pulmonary fibrosis, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, PaGH = patient general health status, PCMD = patient-centred measures of dyspnea, PFTs = pulmonary function tests, RA = rheumatoid arthritis, SD = standard deviation, SJC = swollen joint count, TJC = tender joint count, UIP = usual interstitial pneumonia, VAS = visual analog scale, YORA = young-onset rheumatoid arthritis.

Keywords: computer-aided method, high-resolution computed tomography, interstitial lung disease, pulmonary function tests, rheumatoid arthritis

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1. Introduction

Rheumatoid arthritis (RA) is a progressive systemic autoimmune disorder, characterized by joint and extra-articular manifestations, affecting about 0.5% of the Italian adult population.^[1] Lung complications related to RA are the most common extra-articular manifestations of the disease,^[2] including pulmonary nodules, pleural effusion, bronchiectasis, and interstitial pulmonary disease (ILD).^[3] RA patients are also at risk of secondary lung complications due to immunosuppressive therapy, such as drug toxicity or opportunistic infections.^[4]

The prevalence of ILD in RA patients (RA-ILD) varies widely from 1% to 6% in conventional chest radiography studies, and from 5% to 67.3% in high-resolution computed tomography (HRCT) studies.^[5–8] Few studies have identified a higher post mortem incidence of RA-ILD,^[9,10] and a prospective study has shown that RA-ILD is the second leading cause of death in these patients, overcoming the risk of death from malignant tumors.^[11]

Many studies have been published in recent years on the determination of risk factors for the development of RA-ILD,^[12–15] but the results are discordant, and an international consensus has not yet been reached.

High-resolution computed tomography chest imaging provides valuable information on ILD, including the pattern and extent of the disease, the evaluation of disease progression over time, and the evaluation of extra-parenchymal abnormalities.^[16]

Methods for quantifying ILD damage are complex, operator-dependent, and difficult to apply in clinical practice. Computer-aided methods (CaMs) applied to HRCT images allow greater objectivity, sensitivity, and repeatability in the evaluation of quantitative changes in lung characteristics.^[17–19]

In the present study, the following has been investigated: the prevalence of ILD in a cohort of RA patients, measured by chest HRCT; the relationships between patient-centered measurements, pulmonary function tests (PFTs), and ILD; and the potential risk factors that contribute to ILD susceptibility in RA patients.

2. Methods

2.1. Study population

This is a retrospective analysis carried out in RA patients attending the Rheumatology Clinic, Università Politecnica delle Marche, Italy, from January 1, 2014 to June 30, 2018, stored in a dedicated database. All patients had signed a written consent to allow the use of their data for clinical investigation.

Rheumatoid arthritis has been defined according to the classification criteria of the American College of Rheumatology, 2010.^[20] Patients with RA with a history or a suspicion of ILD were included, who underwent rheumatological and pneumological evaluation (dyspnea scale, PFTs, chest HRCT), performed no more than 3 months before the visit. Exclusion criteria included concomitant respiratory infections, pulmonary hypertension, congestive heart failure, or clinically significant pulmonary abnormalities other than ILD identified by chest x-ray or HRCT.

For the purposes of this study, RA patients have been categorized into 2 clinical subsets: elderly-onset RA (EORA) and young-onset RA (YORA), using the age of onset of 60 as the cut-off value.^[21] Current smokers were those who had smoked more than 5 cigarettes a day in the previous 6 months, and nonsmokers had smoked less than 20 packs of cigarettes during their lifetime.^[22] Reference data included age, sex, duration of disease,

concomitant therapy with conventional synthetic or biological disease-modifying anti-rheumatic drugs (csDMARDs or bDMARDs) and glucocorticoids. The data collected are those recorded closest to the HRCT evaluation.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (Comitato Etico Unico Regionale) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

2.2. Clinical and laboratory data

The clinical and laboratory data included the following single items of the activity indices of RA: 28 joint counts for swollen (SJC) and tender (TJC) joints, evaluation of the patient general health status (PaGH), and erythrocyte sedimentation rate (ESR), and the C-reactive protein (CRP) level. These variables were used to calculate Disease Activity Score-28 joint (DAS28, for the purposes of this study we considered DAS28-ESR).^[23] The DAS28 ranges from 0 (totally inactive disease) to 9.4 (very active disease). Functional ability was assessed by the Health Assessment Questionnaire—Disability Index (HAQ-DI), with a range from 0 (no disability) to 3 (severe disability).^[24] The laboratory evaluation was completed considering the serum levels of rheumatoid factor (RF) and of anti-citrullinated protein antibodies (ACPA).

2.3. Patient-centred measures of dyspnea

The following patient-centred measures of dyspnea (PCMD) were included: the modified Borg Dyspnea Index (BDI) and the visual analog scale (VAS) for breathing. The BDI is a numerical scale for evaluating perceived dyspnea on a scale from 0 (no dyspnea) to 10 (maximum dyspnea),^[25] whereas the VAS for breathing is a scale with a range from 0 to 100.

2.4. Pulmonary function tests

The PFTs were performed while the patient was at rest in a seated position. Pulmonary function was measured using a flow-sensing spirometer connected to a computerized lung analyzer (MasterScreen Diffusion, Jaeger GmbH, Höchber, Germany). The forced vital capacity (FVC, % expected) and the diffusion capacity of the single-breath carbon monoxide in the lung (DLCO, % expected, corrected for hemoglobin) were obtained. PFTs were carried out on the basis of published guidelines,^[26] and were expressed as a percentage of the predicted value. At least 3 measurements were made for each variable to ensure repeatability.

2.5. HRCT assessment and visual reader-based disease quantification

The latest HRCT scan of each patient, carried out within 3 months of the clinical evaluation (available in the electronic imaging system of the Department of Radiology of the “Carlo Urbani” Hospital, Jesi [Ancona], Italy) was used for the interpretation. Thin-section volumetric CT examinations were performed using a CT 64 GE light Speed VCT power scanner. The parenchymal abnormalities were examined and evaluated by 2 experienced radiologists (M.C. and A.G.), unaware of the clinical data, using a conventional visual reader-based score

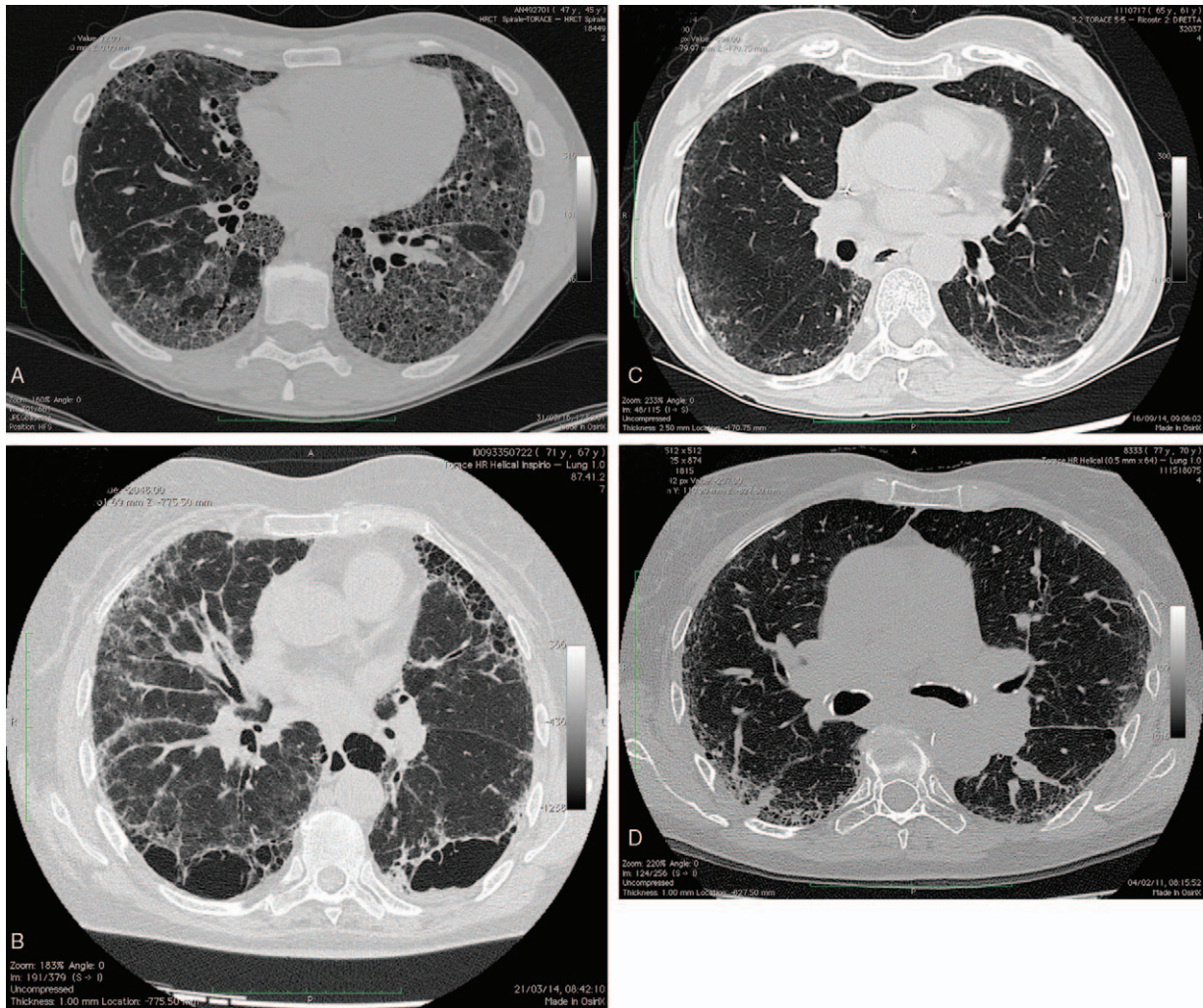


Figure 1. Representative high-resolution computed tomography images from the subjects with rheumatoid arthritis-Interstitial lung disease. (A) A 64-year-old female with fibrotic changes of usual interstitial pneumonia pattern, reticular and ground glass opacity, septal thickening diffusely, and traction bronchiectasis. (B) A 69-year-old male revealing septal thickening diffusely and extensive macrocystic honeycombing. (C) A 65-year-old male with bilateral peripheral ground glass opacity and typical subpleural sparing representing the nonspecific interstitial pneumonia pattern. (D) A 70-year-old female showing evidence of bilateral peripheral reticular and ground glass opacity of the left lower lobe with peripheral consolidations typical of organizing pneumonia.

(CoVR) and the CaM, reaching consensus. Each HRCT examination was evaluated as defined usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD) based on previously published guidelines.^[27] Representative HRCT images of subjects with RA-ILD are shown in Fig. 1.

2.5.1. Conventional visual reader-based score. The CoVR refers to the classification system defined by Warrick et al.^[28] This method categorizes the extent and severity of lung disease, obtaining a total score with a range from 0 to 30 points. The intraclass correlation coefficients (ICCs) for the level of agreement between radiologists on total HRCT scores proved to be good.^[18] Although there is no official consensus, CoVR fibrotic scores, defined according to Warrick et al,^[28] were classified into 2 groups as follows: <7 (normal or mild pulmonary fibrosis) and ≥ 7 (severe pulmonary fibrosis).^[29] A minimum score of 7 on the semiquantitative system was required to consider HRCT abnormalities of ILD, identifying 2 groups: patients with ILD and patients without ILD.

2.5.2. Computer-aided method. The HRCT images were also analyzed by OsiriX MD 7—a DICOM display software (OsiriX MD version 7, 64-bit format) on a Mac Mini (2.8 GHz Intel Core 2 Duo Desktop Computer, 16 GB random access memory; Apple Computer, Cupertino, CA) with Mac OSX 10.12.2 operating system.^[19] Through OsiriX a mask is applied that requires a minimum of intervention by the operator to exclude hilar large blood vessels and bronchi. According to Shin et al,^[30] -700 Hounsfield unit (HU) was selected as the default threshold value for normal lung regions. There was a total agreement between the first and second measurements of CaM scores (95% of agreement limits 0–0, ICC 1).^[18,19]

2.6. Statistical analysis

All data was entered into a Microsoft Excel database developed for the management of all data. The data were analyzed using the MedCalc version 18.6; 64-bit (MedCalc Software, Mariakerke, Belgium). Values in this study were expressed both as mean \pm standard deviation (SD) and median (interquartile range). A

parametric 2-sample *t* test and analysis of variance test were used to compare continuous variables, and the chi-square test was used to compare categorical variables between patients. The relationships among the lung segmentation analysis, the readers, and the PFT results were calculated using univariate regression analysis and Pearson product moment correlation (Pearson “*r*” values). To analyze the predictive potential of patient-centered measures and PTFs for RA-ILD, a receiver-operating characteristic (ROC) curve analysis was conducted. The area under the ROC (AUC-ROC) curve was calculated to quantify the discriminative accuracy. AUC from 0.50 to about 0.70 represent poor accuracy, those from 0.70 and 0.90 are “useful for some purposes,” and higher values represent high accuracy. The nonparametric Wilcoxon signed-rank test was used for calculation and comparison of the AUC-ROCs.

Finally, we performed a multivariate regression analysis adjusted for covariates to identify the potential factors that contributed to ILD in RA patients. HRCT-CaM quantification was taken as dependent variable. Age, sex, disease duration, disease onset (EORA or YORA), smoking habit, titre of RF and ACPA, DAS-28-ESR, and HAQ-DI were included in the model as covariates. The results were expressed as multivariate regression coefficient (*R*) and square regression coefficient corrected (*R*²) for the number of variables entered in the analysis. This enables to calculate the predictivity of each multivariate model according to the number of variables entered in the model itself. Significance was set at *P* < .05.

3. Results

In all, 151 patients were included, 45 (29.8%) males and 106 (70.3%) females, with a mean age of 53.4 ± 7.6 years. The mean \pm SD disease duration was 7.5 ± 3.8 years. There were 110 (72.8%) RF-positive patients and 92 (60.9%) ACPA-positive patients. The mean BMI was 26.9 (range 18.5–44.4). Fifty-five (36.5%) patients were classified as having EORA, whereas 96 (63.5%) patients were classified as having YORA. Also, 145 (96%) patients were treated with at least a DMARD, of which 78 (51.6%) patients were treated with methotrexate and 101 (69.6%) with a combination of methotrexate and a biologic drug, respectively; 21 (13.9%) patients were taking adalimumab, 18 (11.9%) etanercept, 18 (11.9%) abatacept, 16 (10.6%) tocilizumab, 12 (7.9%) certolizumab pegol, 10 (6.6%) infliximab, and 6 (3.9%) golimumab. The most frequently reported concomitant drugs were: systemic corticosteroids in 102 (67.5%) patients, proton pump inhibitor in 72 (47.7%) patients, and nonsteroidal anti-inflammatory drugs in 67 (44.3%) patients.

3.1. RA-ILD prevalence

Twenty-nine (19.2%) patients showed HRCT features indicative of ILD (at the CoVR: mean disease extent = 9.75 ± 2.14 , mean disease severity = 10.93 ± 3.23 , mean total HRCT score = 20.69 ± 5.00). Analysis of the ILD subtypes showed that UIP was found in 18 (62.1%) patients, NSIP in 7 (24.1%) patients, OP in 1 (3.5%) patient, and a combination of NSIP and OP in 3 (10.3%) patients. No patient showed a DAD pattern.

Data from the RA-ILD group and the non-RA-ILD group are summarized in Table 1. Patients with ILD were older (*P* = .04) than those without ILD, and were predominantly in the EORA group (*P* < .03), had a higher ACPA titer (*P* < .001), and a higher percentage of smokers (34.5% compared with 21.3%; *P* = .03).

In addition, patients with ILD had a higher HAQ-DI (1.05 ± 0.39 vs 0.78 ± 0.36 ; *P* < .005), a higher BDI (1.89 ± 0.82 vs 1.74 ± 0.89 ; *P* < .01), and a higher VAS for breathing (36.2 ± 15.44 vs 23.03 ± 13.02 ; *P* < .01) than patients without ILD. We found no statistically significant differences in the evaluation of DAS28-ESR, ESR, CRP, and RF levels.

In the study cohort the mean DLCO was $74.80 \pm 13.53\%$ of the expected and mean FVC was $86.77 \pm 8.35\%$ of the expected. DLCO and FVC were statistically different (*P* = .01) in the 2 patient groups, as were HRCT scores (*P* < .001), both in extension and severity, using CoVR quantification and in extension of fibrosis using CaM quantification. ($21.04 \pm 3.82\%$ vs $8.32 \pm 3.58\%$; *P* < .001). In terms of treatment history, we found no correlation between RA-ILD and drugs.

The EORA patients had a higher percentage of pulmonary fibrosis in the HRCT-CaM assessment (HRCT-CaM 13.7 ± 4.9 vs 9.2 ± 3.7 ; *P* < .001) (Fig. 2A), HAQ-DI (HAQ-DI 0.98 ± 0.38 vs 0.75 ± 0.34 ; *P* < .001) (Fig. 2B), and ESR (44.5 ± 22.9 vs 36.3 ± 20.7 ; *P* = .048) higher than YORA. There were no differences between the EORA and YORA groups in terms of acute-phase proteins and DAS28-ESR scores, although the YORA scores varied more widely. In addition, there were no differences between the groups in FR and ACPA titer.

3.2. Correlation between the HRCT score and clinical and functional data

The mean extension and severity of ILD, the mean total HRCT score, and the mean extension of fibrosis on CaM showed a highly significant negative correlation with DLCO (all at *P* < .001), and positive with BDI and VAS for breathing (all at *P* < .001). There was also a close correlation between HRCT and HAQ-DI results (all at *P* < .001). HRCT CoVR and CaM results showed no significant correlation with FVC (Table 2).

Figure 3 shows the ROC curves of discriminative ability power of PCMD, HAQ-DI, and PFTs to detect RA-ILD. By choosing parameters with maximum diagnostic accuracy, a reduced DLCO was the most sensitive test to predict the presence of ILD on the HRCT scan (AUC-ROC 0.811 ± 0.037), followed by FVC (Fig. 3).

The discriminatory power of BDI and VAS for breathing was moderate, with an AUC of 0.672 (95% confidence interval [CI] 0.556–0.788) and 0.714 (95% CI 0.601–0.827), respectively (difference between areas 0.042, SE 0.072, *P* = .580) (Table 3).

3.3. Potential risk factors for RA-ILD

The results of the multivariate regression analysis indicated that the combination of age (*t* = 4.409, *P* < .0001), ACPA titer (*t* = 2.924, *P* = .004), age at RA onset (*t* = -2.260, *P* = .0253), and smoking status (*t* = 2.660, *P* = .008) explains 60.4% of the variance in the percentage of pulmonary fibrosis by the CaM method. Sex, BMI, disease duration, drugs, FR level, DAS28-ESR, and HAQ-DI were not significantly associated with HRCT damage in this patient population.

4. Discussion

Our study revealed first of all that the prevalence of ILD is very common in RA patients. A prevalence of 19.2% is similar to previously published data.^[6,8,31,32] Different researches report a prevalence ranging from 4% to 68%.^[8,15] This wide range

Table 1
Comparison of characteristics of the interstitial lung disease (ILD) group and the non-ILD group.

| | RA without ILD (122 patients) | | | | RA-ILD (29 patients) | | | | P* | |
|-----------------------------------|-------------------------------|--------|------------|-------------|----------------------|--------|------------|--------------|-------|--|
| | Mean | SD | Median | IQR | Mean | SD | Median | IQR | | |
| Demographic data | | | | | | | | | | |
| Age (y) | 54.66 | 7.80 | 55.00 | 50.00–60.00 | 66.58 | 10.26 | 69.00 | 66.75–73.25 | .04 | |
| Age at RA onset (y) | 45.98 | 7.92 | 46.00 | 44.00–48.00 | 59.44 | 9.4 | 62.00 | 61.00–64.23 | .02 | |
| Disease duration (y) | 7.45 | 3.96 | 7.00 | 5.00–9.00 | 7.48 | 2.83 | 7.00 | 6.00–9.00 | NS | |
| Current smokers | | | 26 (21.3%) | | | | 10 (34.5%) | | .03 | |
| Nonsmokers | | | 96 (78.7%) | | | | 19 (65.5%) | | NS | |
| Clinical variables | | | | | | | | | | |
| Borg score | 1.74 | 0.89 | 2.00 | 1.00–2.00 | 1.89 | 0.82 | 2.00 | 1.00–2.00 | .01 | |
| VAS for breathing | 23.03 | 13.02 | 20.00 | 10.00–30.00 | 36.20 | 15.44 | 30.00 | 30.00–50.00 | .01 | |
| HAQ-DI | 0.78 | 0.36 | 0.87 | 0.50–0.92 | 1.05 | 0.39 | 0.92 | 0.87–1.32 | .02 | |
| DAS28-ESR | 5.66 | 1.06 | 5.70 | 4.97–6.41 | 5.83 | 1.27 | 5.56 | 5.21–6.61 | NS | |
| Acute-phase reactants | | | | | | | | | | |
| ESR (mm/h) | 39.13 | 24.40 | 36.00 | 24.00–52.00 | 35.93 | 23.75 | 28.00 | 21.50–39.00 | NS | |
| CRP (mg/dL) | 15.77 | 27.96 | 8.90 | 3.40–17.20 | 14.94 | 14.40 | 11.00 | 6.25–19.77 | NS | |
| Autoantibodies pattern | | | | | | | | | | |
| RF antibodies positivity (n, %) | | | 88 (72.1) | | | | 22 (75.8) | | NS | |
| ACPA antibodies positivity (n, %) | | | 69 (56.6) | | | | 23 (79.3) | | .01 | |
| RF titer (U/mL) | 123.04 | 197.67 | 42.00 | 9.50–144.00 | 155.62 | 163.67 | 85.00 | 18.00–291.75 | NS | |
| ACPA titer (U/mL) | 56.69 | 114.97 | 7.50 | 2.00–55.00 | 226.65 | 201.26 | 149.00 | 56.00–363.24 | <.001 | |
| Pulmonary function tests | | | | | | | | | | |
| DLCO (% predicted) | 77.30 | 12.77 | 79.65 | 72.70–88.00 | 64.25 | 11.57 | 69.30 | 55.82–72.95 | 0.01 | |
| FVC (% predicted) | 90.78 | 15.32 | 85.75 | 68.00–98.00 | 69.93 | 12.14 | 66.60 | 61.35–79.92 | 0.01 | |
| HRCT CoVR quantification | | | | | | | | | | |
| HRCT extent | 2.62 | 0.65 | 3.00 | 2.00–3.00 | 9.75 | 2.14 | 10.00 | 8.00–11.00 | <.001 | |
| HRCT severity | 2.91 | 0.59 | 3.00 | 3.00–3.00 | 10.93 | 3.23 | 11.00 | 9.75–14.00 | <.001 | |
| HRCT total score | 5.54 | 0.76 | 6.00 | 5.00–6.00 | 20.69 | 5.00 | 22.00 | 18.00–25.00 | <.001 | |
| HRCT CaM quantification | | | | | | | | | | |
| Pulmonary fibrosis (%) | 8.32 | 3.58 | 7.21 | 5.68–10.32 | 21.04 | 3.82 | 20.87 | 17.63–23.19 | <.001 | |

ACPA=anti-citrullinated protein antibodies, CaM=computer-aided method, CoVR=conventional visual reader-based xcore, CRP=C-reactive protein, DAS28=Disease Activity Score of 28 joints, DLCO=diffusion capacity of the lung for carbon monoxide, ESR=erythrocyte sedimentation rate, FEV1=forced expiratory volume in the first second, HAQ-DI=Health Assessment Questionnaire—Disability Index, HRCT=high-resolution computed tomography, ILD=interstitial lung disease, IQR=interquartile range, NS=not significant, RA=rheumatoid arthritis, RF=rheumatoid factor, SD=standard deviation, VAS=visual analog scale.

*P. Student t test; P values less than .05 were considered to indicate statistical significance.

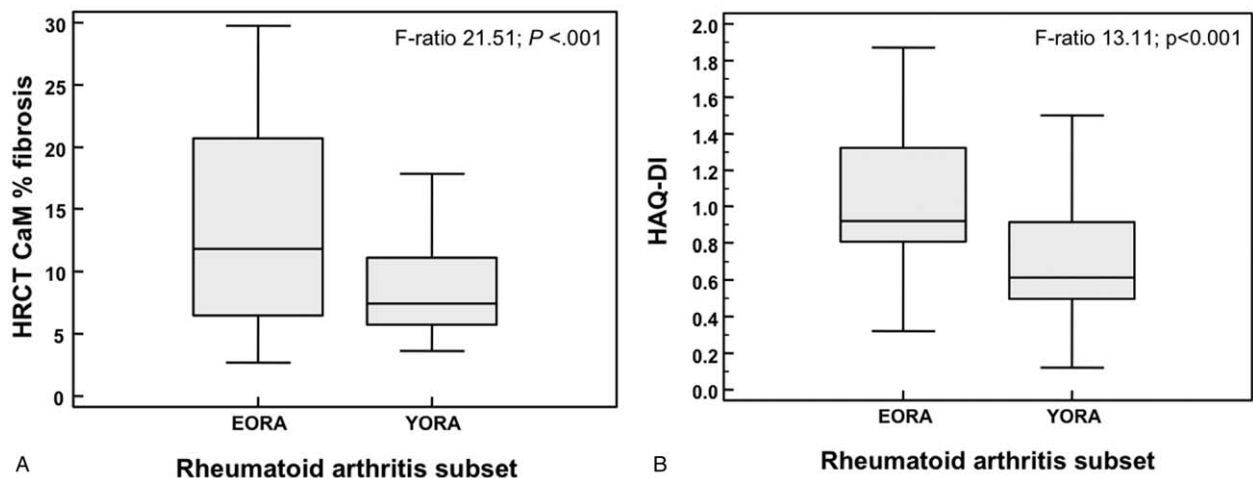


Figure 2. (A) Box-and-Whisker plot of percentage of lung fibrosis evaluated by high-resolution computed tomography (HRCT) computer-aided method (CaM), and (B) Health Assessment Questionnaire—Disability Index (HAQ-DI) values for each clinical subsets, respectively, elderly-onset rheumatoid arthritis (EORA) and young-onset rheumatoid arthritis (YORA). The boxes represent the values from 25th to 75th percentiles. The middle lines inside boxes are the medians (Kruskall-Wallis test).

Table 2

Correlations among high-resolution computed tomography scores, diffusion capacity of the lung for carbon monoxide, forced vital capacity, and patient-centered measures.

| | DLCO (% predicted) | Borg Dyspnea Index | VAS for breathing | HAQ-DI | FVC (% predicted) |
|--------------------------|--------------------|--------------------|-------------------|---------------|-------------------|
| HRCT CoVR quantification | | | | | |
| Extent score (0–15) | −0.552 (<.001) | 0.724 (<.001) | 0.391 (<.001) | 0.321 (<.001) | −0.128 (.116) |
| Severity score (0–15) | −0.520 (<.001) | 0.690 (<.001) | 0.402 (<.001) | 0.317 (<.001) | −0.129 (.113) |
| Total HRCT score (0–30) | −0.546 (<.001) | 0.720 (<.001) | 0.405 (<.001) | 0.325 (<.001) | −0.131 (.107) |
| HRCT CaM quantification | | | | | |
| Percentage of fibrosis | −0.698 (<.001) | 0.891 (<.001) | 0.464 (<.001) | 0.368 (<.001) | −0.138 (.91) |

CaM = computer-aided method, CoVR = conventional visual reader-based score, DLCO = diffusion capacity of the lung for carbon monoxide, DLCO = single breath carbon monoxide diffusing capacity of the lung, FVC = forced vital capacity, FVC = forced vital capacity, HAQ-DI = Health Assessment Questionnaire – Disability Index, HRCT = high-resolution computed tomography, VAS = visual analogue scale.

depends mainly on the methods of detection and the design of the research. A post mortem study showed that ILD is the most common manifestation of lung involvement in RA patients, observed in up to 34% of biopsies.^[17] In our cohort, patients underwent chest HRCT if there was a clinical or instrumental suspicion of ILD, so our results could underestimate the true prevalence of ILD-RA, because subclinical lung involvement was not considered.^[33] Johnson et al^[31] elaborated the results of 2 large cohort studies performed to estimate the prevalence of cardiovascular abnormalities in RA population (Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis study) and no RA-population (Multi-Ethnic Study of Atherosclerosis study): they found a significant correlation between smoking and lung injury with high attenuation on HRCT in both populations, a reduced DLCO in 17%, and a restrictive pattern on PFTs in 8% of the RA population, lower than the results of our study. Therefore, a prospective study in a larger cohort population should be performed to clarify the true prevalence of RA-ILD.

We revealed that the UIP pattern is the most frequent HRCT finding, followed by NSIP and OP. These data corroborate what

previously described literature.^[32,34] Recent data showed that the UIP pattern has the worst prognosis, with a median survival of 8.27 years, similar to that of idiopathic pulmonary fibrosis (IPF), and UIP had the worst response to treatment compared to non-UIP patterns.^[32] Jacob et al^[34] showed that the presence of “honeycombing”—the typical feature of the UIP pattern—is the best predictive parameter of mortality in RA-ILD patients. They also demonstrated that both CoVR and CaM, applied to HRCT images, can predict mortality. These data underline the need to diagnose and characterize RA-ILD as early as possible to define a personalized therapeutic approach and predict mortality.^[35]

Secondly, our study results portray a specific profile of patients with RA at high risk of developing a significant ILD: they are generally over 65 years old and over 65 years of age at RA onset, have been or are smokers, and have a high serum ACPA titer. There were no significant differences in sex, duration and activity of the disease, or in current treatment between patients with RA-ILD and patients without ILD. Other studies identified old age and late onset as risk factors for RA-ILD. Song et al^[36] identified increased age, late onset of disease, male sex, and high RF titer as risk factors for RA-ILD. In another study, an age above 65 years increased the risk of ILD by 4 times.^[37] These results are similar, and the differences recorded may depend on the selection error.

The relationship between tobacco exposure, ACPA positivity, and RA is well-known: smoking demonstrated to increase the risk of ILD,^[38] of the extra-articular manifestations,^[7] and the presence of ACPA in the respiratory tract and serum of smokers appears before arthritis,^[39] emphasizing the role of the lung as the initial site of the pathogenesis of ACPA-positive RA.^[40] Wang and Du^[41] found that older age, being older at the onset of RA,

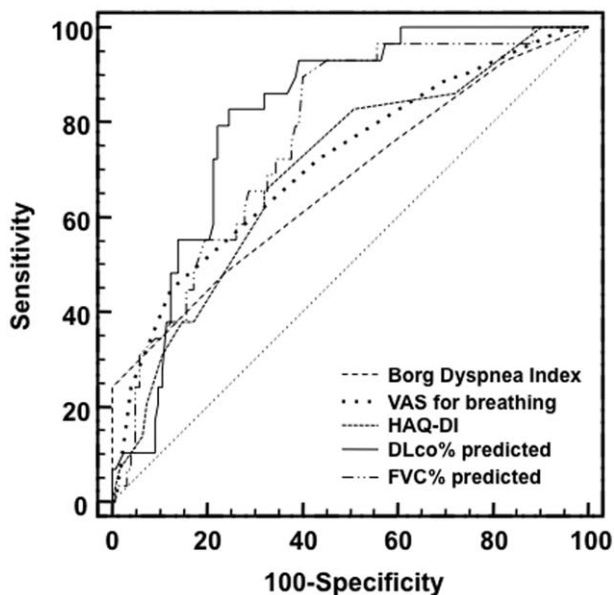


Figure 3. Receiver-operating characteristic curves of patient-centered measures of dyspnea, disability index, and pulmonary function tests to detect rheumatoid arthritis-interstitial lung disease.

Table 3

Discriminatory power of patient-centered measures of dyspnea, Health Assessment Questionnaire—Disability Index, and pulmonary function tests in rheumatoid arthritis-interstitial lung disease.

| | AUC | SE* | 95% CI† |
|--------------------|-------|--------|-------------|
| DLCO (% predicted) | 0.811 | 0.0377 | 0.737–0.885 |
| FVC (% predicted) | 0.777 | 0.0426 | 0.684–0.851 |
| VAS for breathing | 0.714 | 0.0577 | 0.601–0.827 |
| HAQ-DI | 0.699 | 0.0584 | 0.584–0.813 |
| Borg Dyspnea Index | 0.672 | 0.0594 | 0.556–0.788 |

AUC = area under the curve, CI = confidence interval, DLCO = single breath carbon monoxide diffusing capacity of the lung, FVC = forced vital capacity, HAQ-DI = Health Assessment Questionnaire—Disability Index, VAS = visual analogue scale.

* Hanley and McNeil, 1982.

† AUC ± 1.96 SE.

ACPA titer, and smoking habit were all associated independently with a diagnosis of RA-ILD in multivariate analysis. Similar results were derived from our multivariate regression analysis, highlighting the correlation between age, ACPA titer, age at RA onset, smoking, and the CaM score.

As far as sex and ILD are concerned, the data are not exhaustive; in fact, some authors found a positive correlation between male sex and RA-ILD,^[2,36] whereas others did not find such a correlation as in our cohort.^[31,37] This fact could be explained by the increase in the smoking rate in women, influencing the prevalence of RA-ILD in the male group.^[42] As a result, although overall RA mortality appears to be decreasing, RA-ILD mortality appears to be increasing, particularly in women and older age groups.^[43]

Another important clinical aspect is the correlation between RA-ILD and articular disease. Our results revealed that the EORA group did not show a higher disease activity than the YORA group, but patients with RA-ILD showed a higher disability. Pérez-Dórame et al^[44] found in a RA-ILD cohort of 64 patients, a positive correlation between RA disease activity and the HRCT “ground glass score,” using a CoVR score, at the beginning of the study and also after a treatment with high-dose steroids. They found no correlation between disease activity and pulmonary fibrosis score, as our data also confirmed. Bongartz et al^[10] in a larger retrospective study, found a significant correlation between the functional musculoskeletal status and the prevalence of RA-ILD.

Natalini et al^[45] studied the determinants of quality of life in RA-ILD and IPF, showing that the RA-ILD group had a more impaired quality of life than IPF patients, mainly due to joint pain, stiffness, and fatigue. Youssef et al^[46] investigated the value of respiratory symptoms and disease features in predicting RA lung disease, finding that dyspnea was the most frequent symptom (61.1%), followed by cough (52.8%), and that was also the only parameter that could predict a restrictive HRCT pattern. We showed that both HAQ-DI and PMCDs are positively correlated with HRCT scores, in particular, with the CoVR extension and severity score, and with the percentage of fibrosis in CaM quantification. These results underline the importance of assessing respiratory symptoms and quality of life in clinical practice as new elements for determining predictive data for RA-ILD.

Other studies revealed a correlation between PFTs and HRCT damage.^[10,47] Leonel et al^[47] found that a forced expiratory volume in the first second below 81.7 had a sensitivity of 59% and a specificity of 83% to predict HRCT alterations in RA patients, but they did not find such a correlation with DLCO, as we did. Gochoico et al^[15] demonstrated that the predicted percentage of DLCO was statistically lower in RA-ILD than in RA non-ILD. Zamora-Legoff et al^[35] studied the clinical course of RA-ILD in a large single-center cohort. They found that a low value of both DLCO and FVC at the time of ILD diagnosis increases the risk of ILD progression, and higher rates of change of these parameters in the first 6 months increase the risk of severe ILD, requiring supplemental oxygen in 33% of cases within 5 years of diagnosis.

The present study contains some limitations. First, the study is retrospective and the processing of the results comes from the data collected by our database, which suffers from selection errors. Secondly, a larger sample could reach stronger conclusions and a multicenter study with central imaging review could be planned. Finally, we have limited our analysis of

possible causative factors to routine biochemistry for RA patients and their clinical history. Exploratory studies should be carried out to discover new potential markers of ILD in RA patients.

5. Conclusions

Our results offer clinicians some practical points. The need to diagnose RA-ILD before a symptomatic phase becomes a priority, as early treatment in patients with RA can improve quality of life and performance status. To improve the ability to diagnose RA-ILD, a screening tool with a higher sensitivity than those we currently use should be implemented. The introduction of a composite screening method could be considered, including known risk factors (age and age at onset of RA over 65, smoking habit), clinical (HAQ-DI, PCMD), laboratory (ACPA), and instrumental data (DLco) to select patients to be studied with an HRCT scan. In fact, CaM scoring provides clinicians an easy-to-use and repeatable tool for assessing presence and monitoring ILD, making a prognosis and choosing the most appropriate treatment.

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