International
Journal of
**Health
Science**

LUNG INVOLVEMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS: A CROSS-SECTIONAL STUDY

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Abstract: Background: Rheumatoid arthritis (RA) is a chronic inflammatory condition primarily characterized by joint pain and swelling. However, it can also affect various organs, including the heart, nervous system, eyes, and lungs. Pulmonary involvement is a significant contributor to morbidity and mortality in RA patients, encompassing a spectrum of manifestations such as interstitial lung disease (ILD), bronchiectasis, pleural involvement, and more. ILD can progress to pulmonary fibrosis, impacting the overall prognosis of RA. Methods: It is a prospective, analytical, and descriptive cross-sectional study conducted between September 2019 and September 2022 involving RA patients diagnosed according to the 2010 classification criteria of the American College of Rheumatology (ACR) /European Alliance of Associations for Rheumatology (EULAR). Structured interviews collected demographic and clinical data, while laboratory tests, high-resolution computed tomography (HRCT) scans, and pulmonary function tests were performed. Disease activity was assessed using DAS-28 and SDAI. Results: A total of 203 patients were included, predominantly female (88%), with a mean age of 57.14 years. Most patients were non-smokers (74.9%) and exhibited moderate disease activity (35% by DAS-28, 41.1% by SDAI). Nearly half of the sample had antibodies, with 47.5% positive for RF and 48.5% for Anti-CCP. HRCT revealed abnormalities in 89.6% of patients, with ILD present in 17% and pulmonary fibrosis in 6.5%. RF was associated with ILD and small airway involvement, while male gender correlated with emphysema and small airway involvement. Conclusions: Pulmonary involvement, assessed via HRCT, was highly prevalent in RA patients, even those without respiratory symptoms. These findings underscore the importance of early pulmonary evaluation during RA, as well as the need for monitoring and managing pulmonary manifestations, particularly in patients with

specific risk factors such as male gender, advanced age, and positive antibodies.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint pain and swelling. Despite the predominance of joint involvement, RA is a multisystem disease with an autoimmune background, which can affect several organs and systems, such as the heart, the nervous system, the eyes, and the lungs, among others (1,2).

Lung involvement is a significant cause of morbidity and mortality. Manifestations can be varied and sometimes do not result in significant symptoms. However, they can represent different conditions, from interstitial infiltrates, bronchiectasis, and bronchiolitis, pleural involvement, presence of rheumatoid nodules in the lungs, diseases of the vascular bed, pulmonary toxicity due to the medicinal effect of drugs used to treat the condition, and even secondary infectious processes (3).

Interstitial lung disease (ILD) is the most prevalent manifestation, and some cases can progress to pulmonary fibrosis and, consequently, respiratory failure, affecting the prognosis with an autoimmune background, which can affect several organs and systems, such as the heart, the nervous system, the eyes, and sis of the disease. Unfortunately, ILD is underestimated, especially in the early stages of subclinical disease. The epidemiology of ILD in RA is still unknown, and biomarkers for diagnostic and prognostic purposes are lacking. The results of existing scientific studies are not homogeneous and are insufficient to support therapeutic decisions. There is a greater need to publish data clarifying these doubts in managing pulmonary involvement in RA, especially in ILD (3,4).

Given the lack of studies on the subject in our country, with the advantage of having a reference center for diffuse connective tissue diseases, mainly RA, in the Rheumatology service at HUPES, the development of the present study is proposed.

METHODS

STUDY DESIGN

This is a prospective, analytical, and descriptive cross-sectional study in which patients with RA diagnosed according to the 2010 ACR/EULAR classification criteria (5) attended the Rheumatology outpatient clinic of HUPES in Salvador, Bahia, from September 2019 when clinical data collection began until September 2022.

The sample was calculated according to the formula for calculating sample size for a reliable estimate of the population proportion (p) given by:

$$n = \frac{z_{\alpha/2}^2 \cdot p \cdot q}{E^2}$$

Where:

n = Number of individuals in the sample.

Zα/2 = Critical value that corresponds to the desired degree of confidence.

p = Population proportion of individuals that belong to the category we are interested in studying.

q = Population proportion of individuals that do not belong to the category we are interested in studying (q = 1 – p).

E = Margin of error or maximum estimation error. Identifies the maximum difference between the sample and actual population proportions (p).

For "p" and "q" not known, we replace them with and. As these values are unknown, they were replaced by 0.5. For a 95% degree of confidence, the critical value corresponds to 1.96. Maximum estimation error of 5%, i.e., 0.05.

$$\text{So, } n = \frac{1,96 * 0,25}{0,0025} = 196$$

POPULATION SELECTION

All patients underwent a structured interview during the scheduled care visit, including reference data such as age, sex, duration of the disease, use of disease-course modifying drugs (DCMDs), use of corticosteroids, and exposure to smoke (current smokers, ex-smokers, and non-smokers). Current smokers were those who smoked more than five cigarettes per day in the previous six months, and non-smokers smoked less than 20 packs of cigarettes during their lifetime (6,7). These data were collected close to the HRCT assessment. That is, as soon as they were interviewed, the CT scans were scheduled. A complete physical examination was performed, emphasizing the respiratory and musculoskeletal systems. Patients with other overlapping diffuse connective tissue diseases (DCTD) were excluded, except those with secondary sicca syndrome.

Laboratory tests were carried out in the clinical and toxicological analysis laboratory of the pharmacy faculty of the Federal University of Bahia:

a) Erythrocyte sedimentation rate (ESR) using the Wintrobe method. Reference value (RV) : men 0 – 15 mm/1st hour; women 0 – 20 mm/1st hour; we consider <15 mm normal in men; < 20 mm in women; low positive ≥ 15 to < 40 mm in men; low positive ≥ 20 to < 40 mm in women; high positive value ≥ 40 mm.

b) C-reactive protein (CRP) by the nephelometry method. RV: normal < 6 mg/l; low positive > 6 and < 10 mg/l; high positive ≥ 10 mg/l.

c) Research for RF autoantibodies using the nephelometry method. RV < 20 IU/ml (NR negative) ; ≥ 20 IU/ml and < 60 IU/ml positive (high RF) ; ≥ 60 IU/ml strongly elevated (RF in high titers).

d) Search for anti-cyclic citrullinated peptides (anti-CCP) autoantibodies (ACPA) using the ELISA method. RV <20 U/ml (negative anti-CCP) ; ≥20 IU/ml and <60 IU/ml positive (high anti-CCP) ; ≥60 IU/ml strongly elevated (anti-CCP in high titers).

e) Antinuclear factor (ANA) analysis using the indirect immunofluorescence method. Positive titer ≥ 1/80, with nucleus, nucleolus, cytoplasmic, mitotic apparatus and chromosomal metaphase plate patterns.

f) Search for anti-SSA antibodies using the ELISA method. Negative RV <15 U/ml; gray zone 15–25 U/ml; positive >25 U/ml.

g) *Purified protein Derivative* (PPD) or tuberculin test: considered positive when ≥5 mm induration; <5 mm non-reactor; between 5 and 9mm reactor; ≥10 mm strong reactor).

The assessment of disease activity was carried out in the subsequent consultation with the return of laboratory tests, using the DAS 28 tools [(*disease activity score*) (8)] and SDAI [(*simple illness activity index*), (9)]. We calculated DAS 28 with ESR and CRP, considering literature values: remission <2.6; low disease activity ≥2.6 and ≤3.2; moderate disease activity >3.2 and ≤5.1; high disease activity >5.1. The SDAI was considered according to the values referenced in the literature: remission ≤3.3; low disease activity >3.3 and ≤11; moderate disease activity >11 and ≤26; high disease activity >26.

The patients were evaluated at the Pneumology Department of a university hospital, where pulmonary function tests were carried out following the Brazilian Society of Pneumology requirements. HRCT was performed at the Radiology Department of the same university hospital. These tests are usually carried out as part of the care protocol for patients when they are symptomatic from a respiratory point of view. To carry out these

exams in this study, consent was obtained from the Radiology and Pneumology services and authorization from the superintendent of the hospital for all included patients to undergo HRCT and pulmonary function tests multidetector HRCT machine (GE Healthcare) in the supine and prone positions. Non-contrast HRCT was performed during the inspiratory and expiratory apnea phases. Image interpretations were made using visual and automated methods. The visual assessment described the presence of septal lines, reticular lesions, fibrosis, traction bronchiectasis, ground-glass opacities and/or honeycombing. The HRCT reports were given by a radiologist experienced in ILD, belonging to the Radiology Department, who was unaware of the clinical status and demographic data of the patients, and all tomography scans were reviewed by the same pneumologist from the Pneumology Department. The definition of ILD was based on these criteria.

STATISTICAL ANALYSIS

Statistical data analysis was done with the statistical program Statistical Package for Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA, 2018) for Windows. The results were presented using descriptive statistics through absolute and relative distributions (N – %), as well as measures of central tendency (mean or median) and dispersion (standard deviation or interquartile range). The symmetry of continuous distributions was assessed by distributing the variable in a histogram. The primary frequency outcomes had their imprecision described by a 95% confidence interval.

To test the association between clinical, laboratory, and/or tomographic characteristics with the outcomes of ILD, anti-CCP, and RF present and smoking, the variables were compared with the others using Pearson's Chi-square test (if categorical) or Student's T-test (if numerical). For all statistical tests, a p-value <0.05 was considered significant.

Backward selection method Conditional. We chose to use this statistical technique as we sought to test an initial exploratory model. As independent variables, sociodemographic, clinical, laboratory, and tomographic characteristics presented a minimum significance level lower than or equal to 0.1 in the bivariate analysis compared to the outcomes of ILD, anti-CCP, and RF present and smoking.

Hosmer-Lemeshow R2 estimators were considered. The probability of gradually entering variables into the model was 0.05 and 0.10 for removal.

RESULTS

SAMPLE CHARACTERISTICS

A total of 203 patients were included in the analysis. One hundred and seventy-nine (88%, 95%CI, 83 – 91.9) were women; the majority were mixed race (64%; 95%CI, 57.2 – 70.3), and non-smokers (74.9%; 95%CI 68.4 – 80.3) with an average age of 57.14 years (± 11.65). The average duration of illness was 13.54 (± 9.36) years of diagnosis and a median of 8 (interquartile range, 2 – 12) years of follow-up at the service.

Regarding the clinical profile, twenty-two patients (10.8%; 95% CI, 7.2 – 15.8) had respiratory symptoms in the absence of joint symptoms, and thirty-six (17.7%; 95% CI, 13.0 – 23.5) patients had common symptoms concomitant with respiratory symptoms. Cough, dyspnea and chest pain were the respiratory symptoms presented, with cough and dyspnea being the most frequent. Regarding dyspnea, observing the MRC scale (*Medical Research Council*), all patients complaining of dyspnea were in grade 1. Data about the treatment approach is presented in Table 1.

According to the assessment of disease activity based on DAS-28 by serum ESR and CRP level, around 35.1% (95% CI, 28.7 – 41.7) of patients had moderate disease activity (Figure 1 and Figure 2). Finally, evaluating the assessment of disease by SDAI, considering patient opinion, the number of patients with moderate disease activity increased, representing 41.1% (95% CI, 34.5-47.9) of the sample (Figure 3). More information about laboratory tests can be found in Table 2.

PULMONARY FINDINGS IN HRCT

Of the 203 patients in the sample, only 199 could undergo HRCT. Of these 199, 89.6% (95% CI, 86.7 – 94.9) presented some change in the exam. The most common changes were nodules, with 78.4% (95% CI, 72 – 83.9) of cases, followed by opacity in the lung parenchyma, with 15.5% (95% CI, 10.8 – 21.4) (table 3).

The diameter of the most prevalent nodules was less than five millimeters, accounting for 48.2% (95% CI, 41.1 – 55.4). Nodules with calcified characteristics were the most frequently found, representing 37.2% (95% CI, 30.5 – 44.3) of the sample of patients who had pulmonary nodules on HRCT. Regarding interstitial lung findings seen on HRCT, 17% (95% CI, 7.5 – 16.8) had ILD, with usual interstitial pneumoniae (UIP) (4%; 95% CI, 1.7 – 7.8) being slightly lower than non-specific interstitial pneumoniae (NSIP) (5.5%; 95% CI, 2.8 – 9.7) and some patients presented changes on HRCT with images that caused overlap between ILD subtypes. Therefore, they were classified as undefined/incipient subtypes (7.5%; 95%CI, 4.3 – 12.1).

In 13.1% of patients (95% CI, 8.7-18.6), images of pleural involvement, with thickening without other changes, were found. Lower airway involvement in HRCT was seen in 26% (95% CI, 20.2-32.8) of patients. However, small airway involvement was found in 18.6% (95% CI, 13.4 – 24.7). When we grouped them into associates, they were the patients who presented images of bronchiectasis plus bronchiectasis on HRCT.

In this study, we observed that emphysema, in HRCT analysis, was present in 10.5% (95% CI, 6.6 – 15.7). However, in only three patients with ILD, one with UIP presenting centrilobular emphysema, one with NSIP showing centrilobular emphysema associated with the paraseptal and another with undefined ILD presenting paraseptal emphysema. Only one patient with pulmonary fibrosis had emphysema.

Regarding smoking, of the thirty-four (17.1%; 95% CI, 12.1 – 23) patients with ILD, ten (5%; 95% CI, 2.4 – 9%) were smokers and twenty-four (12 %; 95% CI, 7.7 – 17) non-smokers. Patients with centrilobular emphysema, seven (3.5%; 95% CI, 1.4 – 7.1) were non-smokers, one (0.5%; 95% CI, 0.01 – 2.7) was a passive smoker and three (1.5%; 95% CI, 0.3 – 4.3) were smokers. Of the patients with paraseptal emphysema, four (2%; 95% CI, 0.12 – 3.6%) were non-smokers, and three (1.5%; 95% CI, 0.3 – 4.3) were smokers. All three (1.5%; 95% CI, 0.3 – 4.3) patients with associated emphysema were smokers. No patient who described emphysema on HRCT showed restrictive disorder on pulmonary function tests. Only one patient with moderate obstructive disease had emphysema on HRCT.

HRCT found emphysema in twenty-one patients. With pulmonary function tests, only nine patients with the restrictive disorder and three with mixed disease were seen. However, of the 21 patients in whom emphysema was found on HRCT, nineteen did not undergo pulmonary function tests. More information regarding interstitial lung disease findings on HRCT and LTBI prevalence can be found in Table 3.

PULMONARY FUNCTION TESTS IN INTERSTITIAL LUNG DISEASE

Of the thirty-four patients with ILD, we performed pulmonary function tests in twenty-six of them and observed that restrictive disorders were present in nine patients (4.5%; 95% CI, 2.0 – 8.4), obstructive disease in just one patient (0.5%; 95% CI, 0.01 – 2.7) and mixed condition in three patients (1.5%; 95% CI, 0.3 – 4.3). Of the patients with UIP, four did not undergo the examination, two had a moderate restrictive ventilation disorder, one was expected, and one was inconclusive. Of the patients with NSIP, three did not undergo pulmonary function tests, three had restrictive conditions, two were mild, and one was severe, one patient had a moderate obstructive disorder, two patients had regular tests, and two were inconclusive. Patients described as incipient/undefined ILD, one did not perform, four had mild restrictive disorders, three had mixed disorders, three had high resistance results, and four were normal (Table 4). In the total sample, pulmonary function tests were performed on fifty patients, forced vital capacity (FVC) with an average of 81.9 (± 19.8) and carbon monoxide diffusion capacity (DLCO) with an average of 84.9 (± 21.4) (table 5).

Of the fifty-two patients (26.1%; 95% CI, 20.2 – 32.8) with airway involvement on HRCT, only fourteen underwent pulmonary function tests, of which eight (4%; 95% CI, 1.7 – 7.8) with changes, four (2%; 95% CI, 0.5 – 5.0) with restrictive disorders, one (0.5%; 95% CI, 0.3 – 4.3) with obstructive disease and three (1.5%; 95% CI, 0.01 – 2.7) with mixed conditions. Three lung function tests were normal, and three were inconclusive.

INTERSTITIAL LUNG DISEASE PREDICTORS IN PATIENTS WITH RHEUMATOID ARTHRITIS

Patients who use or have previously used biological DCMDs, current use of corticosteroids, elevated inflammatory markers (CRP and ESR), elevated disease activity markers, high titer RF, high titer anti-CCP and smoking were proportionally more frequent among patients with interstitial lung disease (Supplementary Table 1).

A binary logistic regression was performed to verify predictors of ILD and elevated RF (OR = 8.19; 95% CI, 1.06 – 62.91) and symptoms (OR = 3.77; 95% CI, 1.64 – 8.66) were factors associated with the presence of ILD (Table 6).

LOWER AIRWAY INVOLVEMENT PREDICTORS IN PATIENTS WITH RHEUMATOID ARTHRITIS

There was statistical significance between lower airway involvement in males and the presence of RF (Supplementary Table 2). In the multivariate analysis, being male (OR = 2.87; 95% CI, 1.12-7.32) and having a high RF (OR = 2.87; 95% CI, 1.12-7.32) were factors associated with the presence of airway disease (Table 7).

DISCUSSION

RA is one of the most common autoimmune diseases, affecting around 1% of the world population, prevailing two to three times more in females (10,11). This is consistent with the sample studied, which demonstrated that, of 203 patients, 88% were female. The average age of 57.14 ± 11.65 years is also compatible with the literature in which the predominant age range is between 40 and 60. More than half of our patients were of mixed race (64%), followed by black race (30%), following our population, in which there is an intense mix between races.

We found 75% of the sample to be non-smokers. We know that smoking is a risk factor for several diseases, including RA, mainly because it promotes the citrullination of proteins, which, combined with genetic predisposition, produces ACPA, responsible for more significant joint erosion and more severe RA. However, other factors (mentioned below) besides smoking can induce the citrullination of proteins, triggering the immune response with the production of autoantibodies and the emergence of the disease. The fact that this sample is mainly made up of non-smokers corroborates the idea that other environmental factors besides smoking may have been involved in our population (12).

Several other environmental factors have been implicated in the development of RA, such as silicone, other allergens, and microbial agents. Viral peptides function as citrullinated proteins, serving as antigens to ACPA. Viruses such as Epstein Barr, human parvovirus B19, and arboviruses have already been investigated in RA—likewise, bacteria like *Proteus mirabilis*, mycobacteria, mycoplasma etc. Porphyromonas *gingivalis is a* gram-negative anaerobic bacterium intensely involved as an etiological agent of periodontal disease, found very frequently in the initial phase of RA. Through the enzyme peptidyl arginine deiminase, it is speculated that *P. gingivalis* is capable of citrullinating proteins, triggering immunogenicity and the development of circulating ACPA (11,13).

Regarding the clinical profile, around 83% of symptomatic patients were seen, with joint symptoms predominating in 53.7% of the sample and joint symptoms concomitantly with respiratory symptoms in 17.7%. Correlating with the inflammatory activity tests and disease activity indices, we saw that 21.8% of patients had normal ESR, 26.7% had high ESR titers, normal CRP in 59.4% of cases, and 21.8% % in

high securities. Around 30% of patients were in remission assessed by DAS-28 ESR and 47.5% by DAS-28 PCR. These numbers would be directly related to the findings of laboratory tests of inflammation. Only 14% of patients were in remission when assessed by the SDAI. This result can be explained by the fact that this tool uses subjective parameters, such as the impression of the doctor and the patient. Thus, in the present series, most patients had joint pain, and this may not necessarily mean arthritis or active disease but the existence of a mechanical condition due to degenerative sequelae, deformity, or joint erosion.

About the profile of therapeutic behavior, around 71% of patients were using MTX, which is generally consistent with care services and world literature as it is the most prescribed drug in RA. MTX is the anchor drug in the treatment of RA (15). We found 43.3% of biologic DMARD *naïve patients.* Of those who used biologicals, the majority used Anti-TNF. Regarding the use of corticosteroids, less than half of the patients were using them, and the dose used was low, following the usual trend in RA, and even in patients with ILD, the use was low; only one patient with NSIP used a dose of corticosteroids: 20 mg, the highest dose used in the sample. We found no association between drugs and lung disease.

Laboratory data showed that approximately half of the sample was RF and anti-CCP positive, more than 30% with high titer antibodies. RF antibodies recognize the Fc part of IgG, and although it is a non-specific test, it has a high pre-test probability and is, therefore, very useful in the clinic. Other situations may have a positive RF, such as syphilis, tuberculosis, leprosy, visceral leishmaniasis, chronic liver disease, sarcoidosis, SLE and SS. It can even be detected in regular people, especially older people, but generally in low titers, in a low proportion of 5 to 30%, depending on the study type, population and methodology

adopted (16). Anti-CCP antibodies are ACPA, present in 50 to 70% of RA patients, with sensitivity like RF, but more specifically, around 95% specificity (13,16) citrullinated peptide two and third-generation tests (17).

Of the HRCT scans performed, we found changes in 89.6%, drawing attention to the presence of ILD in 17% of patients. In approximately 57%, we describe the company of other findings such as image overlap, atelectasis, parenchymal bands, architectural distortion, tree in budding, honeycombing, air trapping and air cysts that coincide with the tomographic changes described in the literature, in addition to a reticular pattern, interlobular septal thickening, ground glass opacities, mosaic perfusion and traction bronchiectasis (20,21). These other findings, without jointly characterizing a subtype of ILD, are the interstitial lung abnormalities already mentioned in the literature review, described as incidental findings, present in around 20 to 60% of patients with RA and can progress radiologically in more than 50 % of cases, in less than two years (22).

In our series, we observed a considerably significant value of these incidental findings (57%), drawing attention to close care monitoring even in asymptomatic patients since symptoms alone are insufficient to track interstitial changes. The presence of these interstitial lung abnormalities represents a subclinical disease, and we must consider its significance and pay due attention to the progression of the disease so that its extension and worsening can be avoided (23). Therefore, to prevent progression, good clinical follow-up must be carried out, with repeat HRCT and pulmonary function tests, control of the joint disease, avoiding persistence of disease activity, and paying attention to the slightest symptoms. The difficulty lies when we do not know how to treat subclinical disease, especially in asymptomatic patients.

Correlating with pulmonary function tests, we noticed that of patients who presented ILD, 47% had changes in pulmonary function tests, strengthening the understanding of the presence of pulmonary involvement and the need for follow-up of these *patients*.

This raises the question of the need for *screening* for RA patients, especially those with risk factors associated with progression to ILD, such as advanced age, male sex, very active disease, smoking, and high RF and ACPA titers. Even though the association of these variables with ILD has been well established in the literature (24–26), we found only an association between the presence of high RR and symptoms with ILD. In any case, there is a need to ensure effective monitoring of patients with subclinical disease and screening of RA carriers in general.

The prevalence of RA-ILD varies widely from 5 to 60% in HRCT studies and other studies (6,12,26), depending on the population analyzed and the methodology applied. In our series of cases, we verified the presence of ILD in 34/199 patients studied by HRCT (17%), and in 13/199 (6.5%) of the patients, there was fibrosis; all symptomatic patients and nine with respiratory symptoms; of which five also had joint symptoms.

We believe that the prevalence of ILD in our study is underestimated, as the outbreak of the COVID-19 pandemic coincided with the beginning of our data collection, and those patients who were already symptomatic from a pulmonary perspective, fearing COVID-19 might have avoided it. Attend the outpatient clinic. Furthermore, hospitalized and potentially more seriously ill patients were omitted.

A retrospective analysis in Italy (6) found a prevalence of ILD in RA of 19.4% (n=151). On the other hand, a prospective longitudinal and observational study in Spain identified 1.72% of 2729 people with RA, 1.72% had clinically significant ILD, quantifying only patients with

respiratory symptoms (27). However, in this Spanish study, the low prevalence of ILD can be attributed to the inclusion of only those patients with respiratory signs and symptoms and who had abnormal HRCT scans.

In a nine-year retrospective cohort in China, the authors performed HRCT scans on 1,121 RA patients, 923 of whom did not have ILD. During follow-up, 30.12% developed ILD (25), and 9% developed disease progression.

In general, nodules were the most frequently observed changes on HRCT and were present in 78.4% (95% CI, 72 – 83.9) of cases. Most of them were described as residual nodules, residual granulomas, and residual lymph nodes, which leads us to believe that this high frequency of pulmonary nodules in RA patients is more strongly associated with past infections or inactive healed granulomas than the presence of nodules. Lung diseases from other causes. In only three patients, excavated necrobiotic nodules were described on HRCT, compatible with rheumatoid pulmonary nodules. In these patients, TB was ruled out. All of them had had the disease for more than ten years and had a very active joint condition, leading to the belief that there was a greater possibility of extra-articular involvement. Two male patients had RF and high anti-CCP titers; one had subcutaneous nodules. These characteristics (excavated necrobiotic nodules, long-lasting disease, active joint condition, high antibody titers, and subcutaneous nodules) suggest that the pulmonary nodules found are secondary to RA.

With the advent of HRCT, the incidental finding of pulmonary nodules has become very common, described in the literature at around 30% (28). More than twice as many were found in our series compared to literature data. The Fleischner Society (29) guidelines for managing solid nodules are revised recommendations representing the consensus of opinions of an international multidisciplinary group of thoracic radiologists, pulmonologists, surgeons, pathologists, and other experts. These recommendations refer to pulmonary nodules incidentally detected on HRCT in adult patients at least 35 years of age, and some of them are below.

Cancer risk in nodules smaller than 6 mm is less than 1%. If it presents suspicious morphology or is in the upper lobe, the risk increases by 1 to 5%. Early monitoring is unnecessary, as it rarely progresses within 12 months, even though it is malignant. For solitary noncalcified solid nodules 6 to 8 mm in high-risk patients, HRCT of the chest is recommended at 6 to 12 months and again at 18 to 24 months. The intervals can be modified according to individual preferences or risk factors such as smoking, emphysema or other associated comorbidities. Monitor solitary non-calcified solid nodules larger than 8 mm every three months. As they increase in size or change appearance, management should consider invasive and non-invasive measures. Marginal speculation strongly suggests malignancy.

For multiple subsolid nodules smaller than 6 mm, infectious causes must be considered. An opacity bigger than 3 cm is a nodular mass, and the probability of malignancy is greater. Malignant tumors are most often found in the upper lobes. Adenocarcinomas and metastases tend to be seen in the periphery, while squamous cell tumors are more frequent near the hila. Small solid nodules in a perifissural or subpleural location represent intrapulmonary lymph nodes.

In our sample, nodules smaller than 6 mm and calcified nodules prevailed, leading us to believe that benignity prevailed. Interestingly, only two patients with nodules were referred for biopsy, both with non-calcified nodules between 6 and 8 mm, with one patient's results being residual granulomas and the other

being rheumatoid nodules. The latter had a very active disease. In another patient, a solid nodule measuring 7 x 4.8 mm was visualized on HRCT, located on the periphery of the transition of the left lower lobe's superior and posterior basilar segments with tiny eccentric punctate calcification and pleural tail. In control, HRCT, in addition to this nodule, another nodule, semi-solid, 7 x 4 mm, was found to appear in the posterior basilar segment of the left lower lobe. The patient's clinical condition worsened, regardless of the joint disease, culminating in death, the *cause of which* was an intra-abdominal tumor, already metastatic. That is, the pulmonary nodule was most likely a metastasis. In patients with non-calcified nodules, we observed ground-glass images in twelve of them, and due to the pandemic, we sought to correlate them with COVID-19, but only two reported having had COVID-19, neither of which were severe.

In the total number of patients with nodules, the PPD was positive in 19.9%, while in the total number of patients without nodules, the PPD was positive in 16.3%. Of note, PPD positivity in the general Brazilian population varies from 25 to 35%, observed in 27% in a study in Ceará (30) and 33.3% in another carried out in Pernambuco (31). However, in a subgroup of patients with RA or spondylarthritis, candidates for biological therapy, their positivity was 16% (32). Thus, the higher frequency of PPD positivity in the group with pulmonary nodules corroborates the idea that previous infection with *Mycobacterium tuberculosis* could be the cause of such nodules in many patients.

LTBI translates the presence of a persistent immune response to *Mycobacterium tuberculosis* without clinical evidence of active disease. After exposure to the tuberculosis bacillus, the chance of infection is around 30% in healthy people, depending on the degree of exposure, infectivity and the individual's immunological

factors. Around 5% become ill later due to reactivation of latent infection or new exposure to the bacillus. Several factors can increase the risk of tuberculosis reactivation, such as diseases or immunosuppressive treatments (33). In RA, there is a high risk of TB, probably associated with immunosuppression linked to the disease and the use of medications, especially corticosteroids and biological immunomodulators (34,35). In RA patients using Anti-TNF, the relative risk of contracting tuberculosis increases by reducing the phagocytic capacity of macrophages and causing structural disintegration of the granuloma, promoting mycobacterial growth. (32,33)

Reactive PPD results may indicate false positives in individuals infected with non-tuberculous mycobacteria or people previously vaccinated with bacillus Calmette -Guérin (BCG). On the other hand, false negative results may occur in situations of immunosuppression. In RA, there is a decrease in the quantity and function of regulatory T cells (CD4+ and CD25+). As the magnitude of response to PPD occurs through the number of CD4+ T cells, an inability to produce an adequate response to PPD is expected in RA (36). Therefore, we have the option of IGRA, which is a test performed on whole blood and measures the IFN-γ produced by T cells after exposure to purified or synthesized TB antigens, having superiority about PPD with greater specificity and sensitivity in the search for LTBI in RA patients (37). We intend to perform it in our sample. We have already done so in 28 patients, finding positivity in five of them (18%) in addition to four (14%), with results considered indeterminate; all nine of these patients were treated for LTBI.

TB continues to be a public health problem worldwide. In 2020, it was estimated that TB had affected almost ten million people worldwide. In 2021, 68,271 new cases were reported in Brazil, equivalent to an incidence

coefficient of thirty-two cases per one hundred thousand inhabitants (38). Therefore, screening for LTBI is essential, especially in patients undergoing immunosuppressive therapy.

In our study, pleural involvement occurred in 13.1% of patients, characterized by pleural thickening and no pleural effusion or empyema. In the literature, pleural involvement is described in 5% of RA (39), most frequently as a small unilateral pleural effusion, with approximately 3 to 5% symptomatic. In autopsy studies, the frequency of pleural involvement can be observed in up to 70% of patients (2). We did not find any case of pleural effusion in our sample, and we cannot state that the pleural thickening observed was caused by RA. The lower prevalence of pleural effusion in our series is intriguing and unexpected, as, in addition to RA, infectious causes such as TB, which are so common in Brazil, could result in a higher proportion of patients with pleural changes.

When assessed by HRCT, small airway involvement was present in 18.5% of our cases. In a cross-sectional study in northern India (40), which performed lung function tests on patients with RA, one-third had small airway disease (n=50), that is, 32% of the sample. They performed HRCT in those patients with small airway involvement, and in half of them, they observed a mosaic attenuation image. The authors concluded that small airway disease is prevalent even in patients with short-term or low-activity disease. Little is known about the pathogenesis, clinical impact, or treatment strategies for airway disease in RA (41). Few studies in the literature address this subject, and a much smaller number are concerned with exclusively analyzing the involvement of small airways. Most studies focus on ILD because it causes more significant damage. In our sample, the intention was to perform HRCT and pulmonary function tests on all patients. As pulmonary function tests were not completed in most patients, we have limitations in interpreting the results. However, it is worth mentioning that of the fourteen patients who on HRCT showed airway involvement and underwent pulmonary function tests, only three had typical results; that is, more than half had altered lung function tests, highlighting the importance of the exam. Lower airway involvement was associated with high RF levels (p = 0.016).

Likewise, carrying out pulmonary function tests is also a limitation of our study regarding assessing the "emphysema" variable. Of the twenty-one patients with emphysema on HRCT, only two underwent pulmonary function tests, one with a moderate obstructive disorder and the other with increased resistance; that is, we did not find emphysema. Of these twenty-one patients with emphysema observed on HRCT, three had ILD, and two of them had pulmonary fibrosis. One of these patients had NSIP and moderate obstructive disorder, being an elderly patient, a heavy smoker, with RF and anti-CCP present in high titers.

Smoking is described in the literature as a risk factor for ILD (3,24,42) as well as being associated with anti-CCP antibodies by promoting the citrullination of proteins (12,43,44). However, in the present study, we did not find an association between smoking and the presence of anti-CCP. However, we found it with male sex (p = 0.018) and older age (p = 0.002). In isolation, we found a smoker patient with high titers of antibodies, male, older, who was the patient mentioned in the paragraph above, who also had ILD and pulmonary fibrosis.

CONCLUSION

We conclude, therefore, that pulmonary involvement, when assessed by HRCT, in the studied sample had a high prevalence, and it is suggested that patients with RA should have this type of assessment early in the course of the disease, even if they are asymptomatic. Such an initiative has additional value in our environment, associated with carrying out the PPD, as a screening for possible LTBI, since most patients use synthetic or biological medications for their treatment, which predispose to the activation of TB.

LIST OF ABBREVIATIONS

ACPA: Antibodies against citrullinated proteins
ACR: American College of Rheumatology
ANA: Antinuclear Factor
Anti-CCP: Anti–Cyclic Citrullinated Peptide
Anti-TNF: Anti-Tumor Necrosis Factor
BCG: Bacillus Calmette–Guérin
CRP: C-Reactive Protein
DAS-28: Disease Activity Score-28
DCTD: Diffuse Connective Tissue Disease
DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide
ESR: Erythrocyte Sedimentation Rate
FVC: Forced vital capacity
HRCT: High-Resolution Computed Tomography
IL-6: Interleukin-6
ILD: Interstitial lung disease
LTBI: Latent Tuberculosis Bacillus Infection
MRC: Medical Research Council
MTX: Methotrexate
NSIP: Nonspecific Interstitial Pneumonia
PPD: Purified Protein Derivative
RA: Rheumatoid Arthritis
RF: Rheumatoid Factor
SDAI: Simple Disease Activity Index
SLE: Systemic Lupus Erythematosus
SPSS: Statistical Package for Social Sciences
TB: Tuberculosis
TNF: Tumor Necrosis Factor
UIP: Usual interstitial pneumonia

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The project developed for the research carried out in the doctorate was sent to the Research Ethics Committee (CEP) with Human Beings at Professor Edgard Santos University Hospital and started only after approval and consent from the institution. The researchers committed to complying with the ethical aspects of resolution 466/12 of the National Council for Research Involving Human Beings of the Ministry of Health and the principles of good clinical practice in the Declaration of Helsinki.

Initially, it received the opinion from CEP number 3.482.903, CAAE 15556719.7.0000.0049, dated August 2, 2019. However, with the delay in data collection due to the COVID-19 pandemic, this opinion expired, and the project research was submitted again to the CEP and received opinion number 5,423,292, CAAE 58731822.0.0000.0049, on May 23, 2022. Written informed consent was obtained before the inclusion.

CONSENT FOR PUBLICATION

It is not required.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article. The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

COMPETING INTERESTS

None of the authors of this study has any financial interest or conflict with industries or parties.

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TABLES

Variable analyzed	Values
Age in years, average	57.1 (± 11.6) *
Women	179 (88.2%)
Race	
White	12 (5.9%)
Brown	130 (64.0%)
Black	61 (30.0%)
Smoker	51 (25.1%)
Time since RA diagnosis in years, average	13.5 (± 9.3) *
Follow-up time in years, median	8 (2 – 12) **
Symptoms	
Joint symptoms	109 (53.7%)
Respiratory symptoms	22 (10.8%)
Joint and respiratory symptoms	36 (17.7%)
No symptoms	36 (17.7%)
Synthetic DMCD	
Methotrexate	54 (26.6%)
Leflunomide	36 (17.7%)
Methotrexate and Leflunomide	90 (44.3%)
Other associations	1 (0.5%)
Azathioprine	1 (0.5%)
Have used in the past	13 (6.4%)
Never used	8 (3.9%)
Biological DMCD	
Anti-TNF	52 (25.6%)
Anti-CD20	3 (1.5%)
Anti-IL6	10 (4.9%)
Abatacept	31 (15.3%)
JAK kinase inhibitor	17 (8.4%)
Have used in the past	2 (1.0%)
Does not use and has never used	88 (43.3%)
Corticosteroid use	
In use (average dose 6.2mg ± 3.4)	81 (39.9%)
Used in the past	113 (55.7%)
Never used	9 (4.4%)
Previous use of Anti-TNF	94 (46.3%)
Death	12 (5.9%)

Table 1 – Epidemiological and clinical characteristics of patients with Rheumatoid Arthritis evaluated at a specialized outpatient clinic in Salvador in 2022 (n = 203)

*Standard deviation in parentheses. ** Interquartile range in parentheses.

RA: Rheumatoid Arthritis; DMCD: Disease-modifying medications; IL-6: Interleukin 6; JAK: Janus Kinase; TNF: Tumor Necrosis Factor.

Source: data from the authors themselves.

Variable analyzed	Values
DAS-28 CRP	
Remission	96 (47,5%)
Low disease activity	31 (15,3%)
Moderate disease activity	65 (35,2%)
High disease activity	10 (4,9%)
DAS-28 ESR	
Remission	62 (30,7%)
Low disease activity	34 (16,8%)
Moderate disease activity	71 (35,1%)
High disease activity	35 (17,3%)
SDAI	
Remission	29 (14,4%)
Low disease activity	52 (25,7%)
Moderate disease activity	83 (41,1%)
High disease activity	38 (18,8%)
CRP	
Normal	118 (59%)
Low positive	38 (18.8%)
High positive	44 (21.8%)
VHS	
Normal	44 (22%)
Low positive	102 (51%)
High positive	54 (27%)
FR	
Normal	105 (52.5%)
Low positive	22 (10.5%)
High positive	73 (36.5%)
Anti-CCP	
Normal	103 (51.5%)
Low positive	23 (11.5%)
High positive	74 (37.0%)
Anti-SSA positive	11 (5.5%)
ANA positive	30 (15%)
Homogeneous nuclear pattern	20 (10%)
Dotted nuclear pattern	10 (5%)
PPD (n = 151)	
Non-reactor	113/151 (74.8%)
5 – 9 millimeters	22/151 (14.5)
> 9 millimeters	16/151 (10.6%)
Did not take the exam	52/203 (25.6%)

Table 2 – Laboratory and disease activity profile of patients with rheumatoid arthritis evaluated in a specialized outpatient clinic in 2022 (n = 200)

Anti-CCP: antibodies against cyclic citrullinated peptide; Anti-SSA: antibodies against the Ro antigen; DAS-28 CRP: Disease Activity Score-28 for rheumatoid arthritis calculated by serum CRP level; DAS-28 ESR: Disease Activity Score-28 for rheumatoid arthritis calculated by ESR level; ANA: antinuclear factor; RF: rheumatoid factor; PCR: polymerase chain reaction; PPD: Tuberculin test; SDAI: Simplified Disease Activity Index; ESR: erythrocyte sedimentation rate.

Source: data collected by the author.

Variable analyzed	Values
Lung nodules	
< 5 millimeters	96 (48.2%)
5 – 10 millimeters	56 (28.1%)
1.1 – 2.0 centimeters	2 (1.0%)
2.1 – 5.9 centimeters	2 (1.0%)
Absent	43 (21.6%)
Nodular consistency	
Calcified	74 (37.2%)
Not calcified	56 (28.1%)
Both	26 (13.1%)
Absent	42 (21.1%)
Pulmonary fibrosis	13 (6.5%)
Honeycombing	6 (3%)
Bronchiectasis/ Traction bronchiectasis	9 (4.5%)
Reticular pattern	8 (4%)
Interstitial Lung Disease	34 (17%)
Usual interstitial pneumonia	8 (4%)
Non-Specific Interstitial Pneumonia	11 (5.5%)
Undefined / Incipient	15 (7.5%)
Absent	165 (83%)
Pleural involvement	26 (13.1%)
Lower airway involvement	
Bronchiectasis	8 (4.0%)
Bronchioloectasis	11 (5.5%)
Bronchiolitis	8 (4.0%)
Air trapping	4 (2.0%)
Bronchial thickening	11 (5.5%)
Associates	10 (5.0%)
Absent	147 (73.9%)
Emphysema	
Centrilobular	11 (5.5%)
Paraseptal	7 (3.5%)
Associate	3 (1.5%)
Absent	178 (89.4%)
Latent tuberculosis bacillus infection (n=151)	
Treated with Isoniazid	27 (17.9%)
Treated with Rifampicin	2 (1.32%)
Progressed to active TB	1 (0.7%)
History of active TB	11 (7.34%)
Non-reactor	113 (74.8%)
Didn't treated	52 (25.6)

Table 3 – Patterns of change on HRCT in patients with rheumatoid arthritis evaluated in a specialized outpatient clinic in 2022 (n = 199)

HRCT: High-Resolution Computed Tomography; TB: tuberculosis

Source: data collected by the author.

Pulmonary function tests	UIP (4)	NSIP (8)	Incipient (14)
Restrictive disorder	2 (1%)	3 (1.5%)	4 (2%)
Obstructive disorder		1 (0.5%)	
Mixed disorder			3 (1.5%)
Inconclusive	1 (0.5%)	2 (1%)	
Normal	1 (0.5%)	2 (1%)	4 (2%)
High resistance			3 (1.5%)

Table 4 – Pulmonary function tests performed on patients with ILD in a specialized outpatient clinic (n = 26)

UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia

Source: data collected by the author.

ILD	FVC	DLCO
UIP	66.7 ± 12	60.25 ± 13.5
NSIP	79.7 ± 24.1	68 ± 19.7
Incipient	83.3 ± 15.3	89.9 ± 17.9
Normal	84.25 ± 20.4	89.8 ± 19.9

Table 5 – Interstitial lung findings by HRCT in patients with rheumatoid arthritis evaluated in a specialized outpatient clinic in 2022 (n = 76)

ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; FVC: forced vital capacity; DLCO: carbon monoxide diffusion capacity.

Source: data collected by the author.

Variable analyzed	OR (95% CI)	P-value
Lung and joint symptoms present	3.77 (1.64-8.66)	0.002
High Rheumatoid Factor	8.19 (1.06-62.91)	0.043

Table 6 – Multivariate binary logistic regression for ILD (n=203).

Source: data collected by the author.

Variable analyzed	OR (95% CI)	P-value
Male	3.18 (1.31-7.74)	0.011
High RF	2.09 (1.08-4.05)	0.028

Table 7 – Multivariate binary logistic regression for airway involvement (n = 203).

RF: Rheumatoid Factor

Source: data collected by the author.

Variable analyzed	Interstitial lung disease		P-value
	Yes (34)	No (165)	
Women	27 (79.4%)	148 (89.7%)	0.142
Use of synthetic DMARDs	31 (60.9%)	160 (72.2%)	0.139
Use of biological DMARDs	25 (73.5%)	90 (54.5%)	0.065
Corticosteroids			0.931
Is using	14 (41.2%)	65 (39.4%)	
Used in the past	19 (55.9%)	93 (56.4%)	
Never used	1 (2.9%)	7 (4.2%)	
Previous Anti-TNF use	19 (55.9%)	75 (45.5%)	0.346
high titer PCR	15 (44.1%)	66 (40.0%)	0.703
VHS high titles	25 (73.5%)	131 (79.4%)	0.494
DAS-28 PCR, average	2.8 (± 1.2) *	2.8 (± 1.3) *	0.895
DAS-28 VHS, medium	3.6 (± 1.4) *	3.5 (± 1.4) *	0.787

SDAI, average	16.2 (± 11.7) *	15.9 (± 11.3) *	0.883
Elevated rheumatoid factor	25 (73.5%)	69 (41.8%)	0.001
High anti-CCP	20 (58.8%)	77 (46.7%)	0.258
Smoker present	10 (29.4%)	39 (23.6%)	0.514
Associated comorbidities	23 (67.6%)	118 (71.5%)	0.681
Joint and/or respiratory symptoms	33 (97.1%)	131 (79.4%)	0.012

Supplementary Table 1 – Comparison of the characteristics of patients with Rheumatoid Arthritis with interstitial lung disease versus those without interstitial lung disease (n=203).

*Standard deviation in parentheses.

Anti-CCP: antibodies against cyclic citrullinated peptide; Anti-TNF: Anti-tumor necrosis factor antibody; DAS-28 CRP: Disease Activity Score-28 for rheumatoid arthritis calculated by serum CRP level; DAS-28 ESR: Disease Activity Score-28 for rheumatoid arthritis calculated by serum ESR level; DMCD: Disease-modifying medications; PCR: polymerase chain reaction; SDAI: Simplified Disease Activity Index; ESR: erythrocyte sedimentation rate.

Source: data collected by the author.

Variable analyzed	Airway Involvement		P-value
	Yes (52)	No (147)	
Women	36 (76.6%)	109 (92.4%)	0.008
Use of synthetic DMCD	36 (69.2%)	105 (71.4%)	0.764
Use of biological DMCD	30 (57.7%)	85 (57.8%)	0.987
Corticosteroids			0.992
Is using	21 (40.4%)	58 (39.5%)	
Used in the past	29 (55.8%)	83 (56.5%)	
Never used	2 (3.8%)	6 (4.1%)	
Previous use Anti-TNF	23 (44.2%)	71 (48.3%)	0.613
high positive PCR	25 (48.1%)	56 (38.1%)	0.208
high positive VHS	39 (75.0%)	117 (79.6%)	0.489
DAS-28 PCR, average	2.9 (± 1.3) *	2.7 (± 1.3) *	0.612
DAS-28 VHS, medium	3.5 (± 1.3) *	3.5 (± 1.4) *	0.907
SDAI, average	15.3 (± 11.2) *	16.1 (± 11.4) *	0.643
Rheumatoid factor high titers	32 (61.5%)	62 (42.2%)	0.016
Anti-CCP high titers	31 (59.6%)	66 (44.9%)	0.068
Smoker	16 (30.8%)	33 (22.4%)	0.231
Associated comorbidities	42 (80.8%)	99 (67.3%)	0.067

Supplementary Table 2 – Comparison of the characteristics of patients with Rheumatoid Arthritis with lower airway involvement versus those without (n=203).

*Standard deviation in parentheses.

Anti-CCP: antibodies against cyclic citrullinated peptide; Anti-TNF: Anti-Tumor Necrosis Factor antibody; DAS-28 CRP: Disease Activity Score-28 for rheumatoid arthritis calculated by serum CRP level; DAS-28 ESR: Disease Activity Score-28 for rheumatoid arthritis calculated by serum ESR level; DMCD: Disease-modifying medications; PCR: polymerase chain reaction; SDAI: Simplified Disease Activity Index; ESR: erythrocyte sedimentation rate.

Source: data collected by the author.