Rheumatoid arthritis-associated airway disease: longitudinal pulmonary function behavior

Maria Laura Bertozo Sabbag[1], Camila de Assis Molina[1], Márcio Valente Yamada Sawamura[2], Karina Bonfiglioli[3], Ana Cristina Medeiros-Ribeiro[3], Alisson Pugliesi[4], Renato Hideo Nakagawa[5], Fabio Eiji Arimura[6], Rodrigo Abensur Athanazio[6], Ronaldo Adib Kairalla[6], Bruno Guedes Baldi[6], Leticia Kawano-Dourado[6,7]

TO THE EDITOR,

Rheumatoid Arthritis-associated airway disease (RA-AWD) is a commonly overlooked pulmonary manifestation of Rheumatoid Arthritis (RA).[1] Its prevalence varies widely, from 8 to 60%, depending on the source of the cases (hospital-based studies or autopsy) and the criteria used to define RA-AWD, whether based on symptoms, pulmonary function tests (PFTs), or imaging.[1]

The spectrum of manifestations ranges from small (bronchiolar) to large airway disease.[2] Despite its high prevalence and complexity, there are few studies in the literature characterizing RA-AWD, and even fewer evaluating its longitudinal course.[3]

In the present study, we describe the longitudinal behavior of PFTs in patients with RA-AWD. This single-center retrospective study involved subjects aged 18 years or older, diagnosed with RA-AWD at a tertiary pulmonary clinic, that were followed between 2016 and 2017. RA-AWD was defined by the absence of interstitial lung disease (ILD) and the presence of features of airway disease on high-resolution computed tomography (HRCT) of the chest, not explained by other diagnoses, such as asthma or COPD. Since smoking is in the causal pathway of RA and likely in the causal pathway of RA-AWD, it was not used as an exclusion criterion.[2]

In order to be considered eligible, patients were required to have undergone a chest HRCT and PFTs. Baseline PFTs were defined as the earliest PFT within a 6-month interval since the HRCT. Up to four additional PFT results were retrieved from the electronic health records (EHR) for estimating the rate of change in forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio. Clinical data were obtained from the EHR. This project received institutional review board approval from the Clinics Hospital's ethics committee (Process No. 2.825.510).

The earliest available chest HRCT was qualitatively analyzed by two independent readers (LKD and MVYS) for the presence of RA-AWD. Inconsistencies were resolved through consensus (kappa agreement between readers: 0.71).

Imaging findings of RA-AWD were categorized as follows: unequivocal bronchial thickening, mosaic attenuation, centrilobular micronodules, and/or focal or multifocal bronchiectasis.

The annual rate of change in FEV_1, FVC, and the FEV_1/FVC ratio were estimated using a mixed regression model (random slopes and intercepts), including age, sex, and baseline FEV_1, FVC, and FEV_1/FVC (respectively) as covariates. The R Statistical Package was used in the analysis.

Among the 2,495 patients who underwent a follow-up visit at our pulmonary clinic between 2016 and 2017, 96 (3.8%) matched our case definition for RA and pulmonary involvement. Forty-eight out of these 96 (50%) subjects fulfilled the criteria for RA-AWD. The majority of individuals with seropositive RA were females in their sixth decade of life, and the mean disease duration was 15 years. Approximately half of the RA-AWD subjects (48%) had never smoked. No differences were observed between RA-AWD and Rheumatoid Arthritis Interstitial Lung Disease (RA-ILD) regarding previous tuberculosis (TB) contact or treatment for latent TB.[4] Additional clinical variables are shown in Table 1.

The most common HRCT findings among the RA-AWD patients were unequivocal bronchial thickening in 46 (96%), followed by mosaic attenuation in 30 (63%), centrilobular micronodules in 28 (58%), and focal or multifocal bronchiectasis in 23 (48%).

Forty-four patients had at least two PFTs included in the longitudinal analysis. The median interval between the first and last PFTs analyzed was 20 months [IQR: 9.3 – 22.5]. The mean baseline FVC was 79 ± 19% of the predicted value, FEV_1 was 65 ± 22% of the predicted value, and the FEV_1/FVC ratio was 0.65 ± 0.17, characterizing a mild obstructive ventilatory defect (OVD) (Table 1). A statistically significant annual decline in FVC was observed (-1.45% predicted, 95% CI: -2.37 to -0.53), while the FEV_1 remained stable (-0.62% predicted, 95% CI: -1.54 to 0.30), leading

1. Centro Universitário São Camilo, Faculdade de Medicina, São Paulo (SP), Brasil.
2. Divisão de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (SP), Brasil.
3. Divisão de Reumatologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (SP), Brasil.
4. Divisão de Reumatologia, Universidade Estadual de Campinas, São Paulo (SP), Brasil.
5. Divisão de Gerenciamento de Dados e Estatística, Instituto de Pesquisa Hcor, Hospital Hcor, São Paulo (SP), Brasil.
6. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (SP), Brasil.
7. Divisão de Pesquisa Clínica, Instituto de Pesquisa Hcor, Hospital Hcor, São Paulo (SP), Brasil.

Table 1. Baseline characteristics of patients with rheumatoid arthritis-associated airway disease (RA-AWD).

Characteristics	RA-AWD n = 48 (50%)
Age in years, mean (SD)	62 (11)
Females, n. (%)	43 (90%)
RA disease duration in years, mean (SD)	15 (10)
RF positivity, n. (%)	36 (78%)
RF titer, mean in IU/mL (SD)	166 (141)
ACPA positivity, n. (%)	10 (71%) n = 14
ACPA titer (IU/mL)	163 (70)
Ever smokers, n. (%)	25 (52%)
Asthma, n. (%)	6 (15%) n = 39
COPD, n. (%)	8 (20%) n = 39
Sjögren Syndrome, n. (%)	3 (8%) n = 39
Latent TB treatment, n. (%)	5 (10%)
Past history of treated TB, n. (%)	4 (8%)
Environmental exposures, n. (%)	
Avian antigen	14 (61%)
Wood burning	8 (35%)
Mold	8 (35%)
Metal processing industry	1 (4%)
Comorbidities, n. (%)	
Arterial hypertension	19 (58%)
Hypothyroidism	13 (39%)
Ischemic heart disease	8 (24%)
Dyslipidemia	6 (18%)
Diabetes mellitus	6 (18%)
Previous treatments for RA§, n. (%)	
Prednisone	32 (67%)
Methotrexate	30 (63%)
Leflunomide	24 (50%)
Biologic and/or targeted synthetic DMARDs	13 (25%)
Airway HRCT findings, n. (%)§§	
Bronchial wall thickening	46 (96%)
Mosaic attenuation	30 (63%)
Centrilobular micronodules	28 (58%)
Focal or multifocal bronchiectasis	23 (48%)
Baseline Pulmonary Function Test	
FVC, L (SD)	2.25 ± 0.62
FVC, % of predicted	79 ± 19%
FEV_1, L (SD)	1.46 ± 0.53
FEV_1, % of predicted	65 ± 22%
FEV_1/FVC ratio	0.65 ± 0.17

Abbreviations: RA-AWD: rheumatoid arthritis-associated airway disease; SD: standard deviation; RA: rheumatoid arthritis; RF: rheumatoid factor; ACPA: cyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; TB: Tuberculosis; DMARDS: disease-modifying antirheumatic drugs; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; NA: not available; HRCT: high-resolution computed tomography. §Use at any time for longer than 3 months until first chest HRTC. §§Proportion of cases presenting the image finding. One case may present more than one finding.

to a statistically significant increase in the FEV_1/FVC ratio of 0.01 (95% CI: 0.005 to 0.016), suggesting air trapping and/or hyperinflation (Figure 1).

As expected for a sample of RA patients, half of the subjects had been exposed to tobacco. Excluding patients with a smoking history from the analyses would likely bias the results, as smoking is in the direct causal pathway of RA itself.[5] Functionally, one case of mild OVD evolved with FVC reduction and an increase in the FEV_1/FVC ratio, suggesting air trapping/hyperinflation, replicating previous longitudinal findings in RA-AWD.[3] Of note, the estimation of air trapping/hyperinflation by the FEV_1/FVC ratio is considered accurate when compared to the residual volume/total lung capacity ratio.[6] In COPD, air trapping/hyperinflation is associated with an increased risk of

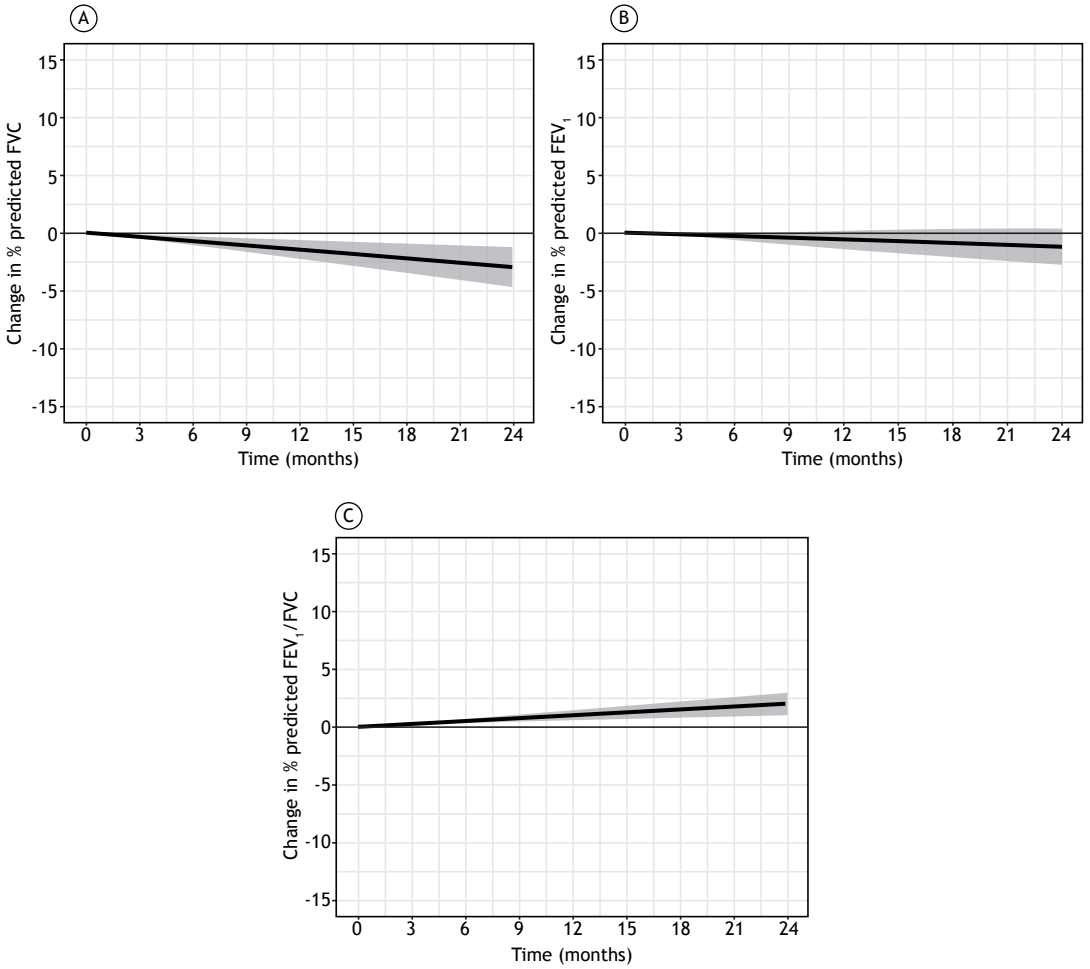

Figure 1. Longitudinal pulmonary function test behavior among rheumatoid arthritis-associated airway disease (RA-AWD) cases. (A) Change in % predicted in forced vital capacity (FVC). (B) Change in % predicted in the forced expiratory volume in one second (FEV1). (C) Change in % predicted FEV1/FVC ratio. The grey shadow represents the 95% confidence interval (95% CI).

disease exacerbation, a higher degree of dyspnea, and a poorer quality of life. While these aspects were not assessed in our study, they should serve as plausible research hypotheses to be investigated in RA-AWD.[7]

The tomographic findings observed in this study are consistent with what has been previously described.[2] Additionally, despite this cohort originating from an endemic region for TB, the proportions of bronchiectasis and bronchial wall thickening (common TB sequelae) found in our sample were similar to previous reports on RA-AWD from non-endemic TB regions.[8,9]

This study had some limitations. Firstly, it was a retrospective single-center study. Nevertheless, our sample characteristics are similar to previous RA-AWD reports in the literature.[1,2,3,9] Secondly, data on HRCT follow-up were unavailable. On the other hand, our study thoroughly characterized the baseline HRCT findings and the longitudinal PFT behaviour in RA-AWD subjects, suggesting air trapping/hyperinflation as an important mechanism of disease progression. Patients self-reported environmental exposure avoidance and smoking cessation; hence, these factors are unlikely to be the causal determinants of our functional longitudinal findings. A past history of tuberculosis treatment was present in only 8% of our sample, and the removal of these patients did not alter the results (data not shown).

In conclusion, in the present cohort, RA-AWD was characterized by small and large airway imaging findings that were associated with an obstructive ventilatory defect. During follow-up, the observed increase in air trapping and/or hyperinflation potentially accounted for the reduction in FVC and the increase in the FEV_1/FVC ratio. Additional studies are warranted to confirm air trapping/hyperinflation as a mechanism of progression in RA-AWD, which, in turn, may impact the choice of interventions to be tested in the management of this condition.

AUTHOR CONTRIBUTIONS

The authors confirmed contribution to the paper as follows: study conception and design MLBS, CAM, MVYS,

KB, RAK, BGB, LKD; data collection MLBS, CAM, FEA, LKD; analysis and interpretation of results MLBS, CAM, AP, RHN, RAA, BGB, LKD; draft manuscript preparation MLBS, CAM, MVYS, KB, ACMR, AP, RHN, FEA, RAA, RAK, BGB, LKD. All authors reviewed the results and approved the final version of the manuscript. Both MLBS and LKD contributed equally.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Matson SM, Demoruelle MK, Castro M. Airway Disease in Rheumatoid Arthritis. Ann Am Thorac Soc. 2022 Mar;19(3):343-52. https://doi.org/10.1513/AnnalsATS.202107-876CME.
2. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1658-65. https://doi.org/10.1164/ajrccm.157.5.9710018.
3. Fuld JP, Johnson MK, Cotton MM, Carter R, Watkin SW, Capell HA, et al. A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis. Chest. 2003;124(4):1224-31. https://doi.org/10.1378/chest.124.4.1224.
4. Sabbag ML, Molina C de Assis, Sawamura M, Bonfiglioli K, Arimura FE, Athanazio RA et al. Characterization of Airway Disease in Rheumatoid Arthritis. Am J Resp Crit Care Med 2019; 199:A1440. Disponível em: <https://observatorio.fm.usp.br/handle/OPI/32693>.
5. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006 Jan;54(1):38-46. https://doi.org/10.1002/art.21575.
6. Alter P, Orszag J, Kellerer C, Kahnert K, Speicher T, Watz H, et al. Prediction of air trapping or pulmonary hyperinflation by forced spirometry in COPD patients: results from COSYCONET. ERJ Open Res. 2020 Jul;6(3):00092-2020; https://doi.org/10.1183/23120541.00092-2020.
7. Kim Y, Kim SH, Rhee CK, Lee JS, Lee CY, Kim DK, et al. Air Trapping and the Risk of COPD Exacerbation: Analysis From Prospective KOCOSS Cohort. Front Med (Lausanne). 2022 Mar;9:835069. https://doi.org/10.3389/fmed.2022.835069.
8. Kronzer VL, Westerlind H, Alfredsson L, Crowson CS, Nyberg F, Tornling G, et al. Respiratory Diseases as Risk Factors for Seropositive and Seronegative Rheumatoid Arthritis and in Relation to Smoking. Arthritis Rheumatol. 2021 Jan;73(1):61-8. https://doi.org/10.1002/art.41491.
9. Vuorela M, Mars NJ, Salonen J, Kauppi MJ. Tuberculosis in people with rheumatic disease in Finland 1995–2007: a nationwide retrospective register study. Rheumatol Adv Pract. 2019 Aug;3(2):rkz020. https://doi.org/10.1093/rap/rkz020.