Baseline Characteristics and Progression of a Spectrum of Interstitial Lung Abnormalities and Disease in Rheumatoid Arthritis

Leticia Kawano-Dourado, MD; Tracy J. Doyle, MD; Karina Bonfiglioli, MD; Márcio V. Y. Sawamura, MD; Renato H. Nakagawa, BS; Fábio E. Arimura, MD; Hye J. Lee, MD; Diana Arrais de Souza Rangel, MD; Cleonice Bueno, BS; Carlos R. R. Carvalho, MD; Maria Laura Sabbag; Camila Molina; Ivan O. Rosas, MD; and Ronaldo A. Kairalla, MD

BACKGROUND: Interstitial lung abnormalities (ILA) and interstitial lung disease (ILD) are seen in up to 60% of individuals with rheumatoid arthritis (RA), some of which will progress to have a significant impact on morbidity and mortality rates. Better characterization of progressive interstitial changes and identification of risk factors that are associated with progression may enable earlier intervention and improved outcomes.

RESEARCH QUESTION: What are baseline characteristics associated with RA-ILD progression?

STUDY DESIGN AND METHODS: We performed a retrospective study in which all clinically indicated CT chest scans in adult individuals with RA from 2014 to 2016 were evaluated for interstitial changes, and the data were further subdivided into ILA and ILD based on clinical record review. Progression was determined visually and subsequently semiquantified.

RESULTS: Those individuals with a spectrum of interstitial changes (64 of 293) were older male smokers and less likely to be receiving biologics/small molecule disease-modifying antirheumatic drugs. Of 44% of the individuals with ILA, 46% had had chest CT scans performed for nonpulmonary indications. Of the 56 individuals with ILA/ILD with sequential CT scans, 38% had evidence of radiologic progression over 4.4 years; 29% of individuals with ILA progressed. Risk factors for progressive ILA/ILD included a subpleural distribution and higher baseline involvement.

INTERPRETATION: Of 293 individuals with RA with clinically indicated CT scans, interstitial changes were observed in 22%, one-half of whom had had a respiratory complaint at the time of imaging; radiologic progression was seen in 38%. Of individuals with progressive ILA, one-half had had baseline CT scans performed for nonpulmonary indications. Subpleural distribution and higher baseline ILA/ILD extent were risk factors associated with progression. Prospective longitudinal studies of RA-ILA are necessary.

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KEY WORDS: interstitial lung disease; pulmonary fibrosis; radiology; rheumatoid arthritis; thoracic

ABBREVIATIONS: ILA = interstitial lung abnormality; ILD = interstitial lung disease; RA = rheumatoid arthritis

AFFILIATIONS: From the Pulmonary Division (Drs Kawano-Dourado, Arimura, Rangel, Carvalho, and Kairalla), the Heart Institute (InCor), the Division of Rheumatology (Dr Bonfiglioli), and the Division of

Radiology (Drs Sawamura and Lee; and Ms Bueno), Hospital das Clínicas HCFMUSP, Medical School, University of São Paulo; the Research Institute (Dr Kawano-Dourado and Mr Nakagawa), Hospital do Coração (HCor); and the Centro Universitário São Camilo-São

Take-home Point

Interstitial lung abnormalities/interstitial lung disease was observed in 22% of patients with rheumatoid arthritis who underwent high resolution CT scan. Risk factors for progression (38%) were subpleural distribution and higher baseline interstitial involvement.

Interstitial lung abnormalities (ILA)¹ in smokers and the general population have been associated with increased respiratory symptoms, functional decrements,² FVC decline, and increased mortality rates.^{3,4} Risk factors for ILA include increasing age, smoking, and the MUC5B promotor polymorphism.⁵ The combination of traction bronchiectasis and honeycombing have been identified recently as a risk factor for radiologic progression of ILA and early death.⁶ Based on these data, it has become apparent that ILA are not benign.⁷ Given the aforementioned studies, a validated method to quantify radiologic progression of ILA is critical.

Rheumatoid arthritis (RA)⁸ is a highly prevalent systemic connective tissue disease that affects

approximately 1% of the population.⁹⁻¹¹ Although overall RA mortality rates are declining, interstitial lung disease (ILD) has become one of the leading causes of death in individuals with RA^{12,13} with an increasing prevalence.⁹⁻¹⁴ ILD in RA has a median survival of 7.8 years¹⁴ and is responsible for 7% to 13% of all RA-associated deaths,⁹ with the usual interstitial pneumonia pattern producing the worst outcomes.^{15,16} Although clinically evident ILD occurs in 2% to 10%,^{13,17,18} ILA is reported to occur in an additional 20% to 60% of individuals with RA and has been associated with reductions in pulmonary function, increased symptoms, and biomarkers associated with idiopathic pulmonary fibrosis outcomes.¹⁹⁻²¹ In addition, ILA in RA has been shown to be radiographically progressive in 57% of cases over a 1.5-year period.²² Improved recognition of progressive ILA will enable improved follow up and earlier treatment, with the goal to positively impact morbidity and mortality rates of established RA-ILD.

The primary aim of this study was to characterize risk factors of ILA and ILD in a cohort of individuals with RA with clinically indicated CT scans and to include quantifying and identifying risk factors for the progression of interstitial changes in RA.

Materials and Methods

Study Design

Individuals who were >18 years old with RA²³ and had a chest CT scan for clinical indications who were evaluated at the Rheumatology Outpatient Clinic of the Hospital das Clinicas of the University of Sao Paulo, Brazil, between 2014 and 2016 were included. Clinical, pulmonary function testing, and laboratory information, including CT scan indications, were collected by medical records review. Institutional review board approval was obtained by Hospital das Clinicas n. 2.133.192.

Qualitative High-Resolution CT Analysis

The earliest available chest CT scan was analyzed visually by three readers for the presence of interstitial abnormalities with a sequential

reading method that was described previously (e-Fig 1).^{1,24} Scans were classified as (1) no interstitial abnormalities, (2) indeterminate (focal alterations with <5% involvement of the lung), or (3) interstitial abnormalities and were further subdivided into (a) subpleural, (b) centrilobular, (c) mixed, and (d) extensive distributions (e-Fig 1).

Classification of ILD or ILA

Individuals were subdivided in two clinical subgroups: (1) ILD indicated individuals with previously diagnosed ILD or the presence of extensive changes that are consistent with a firm radiologic evidence of ILD; (2) ILA indicated individuals with ILA without a prior diagnosis of ILD and more subtle changes on chest CT imaging than those observed in individuals with established ILD.

Imaging Progression

Individuals with ILA/ILD and at least two HRCTs were evaluated for disease progression by two independent observers blinded to clinical information: the first (baseline) and last (follow up) complete volumetric CT images were rated as progression or no progression; disagreement was resolved by consensus.

Semiquantification of Interstitial Abnormalities

Subsequently, a semiquantitative method adapted from Goh et al²⁵ was used to quantify the total disease extent in baseline and follow-up scans (e-Appendix 1). Briefly, interstitial involvement was rated from 0% to 100% by two independent raters in five levels: (1) origin of great vessels; (2) main carina; (3) pulmonary venous confluence; (4) halfway between the third and fifth section; and (5) immediately

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CORRESPONDENCE TO: Leticia Kawano-Dourado, MD, Research Institute-Hcor, Rua Abílio Soares, 250, 12° andar, São Paulo, SP, Brazil 04005-000; e-mail: ldourado@hcor.com.br

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above the right hemi-diaphragm. Total disease extent was reported as the mean of the five levels. Change in the percent of total extent was defined as the difference between baseline and follow-up scans for each subject. Discrepancies of >10% were resolved by consensus. Because the semiquantification of interstitial abnormalities was performed on only five CT slices, it is possible that some CT scans with qualitatively defined ILA (>5% lung involvement) have a semiquantified score of <5% interstitial involvement.

Fibrotic Burden Measurement

Coarseness of reticulation determination was previously described.²⁵ Briefly, the most severe disease in each of the five levels was quantified in the following manner: 0 = ground glass opacities; 1 = fine intralobular fibrosis; 2 = microcystic honeycombing (<4 mm); and 3 = macrocystic honeycombing (>4 mm). Total coarseness

score was the summed score for all five levels (0 to 15) that were adjusted to a five-level score in individuals with no disease in more than one CT section.²⁵ Discrepancies of more than one grade were resolved by consensus.

Statistical Analysis

Univariate analyses were conducted with Fisher exact test and two-tailed *t*-tests or Wilcoxon rank-sum tests, where appropriate. Individuals whose condition was indeterminate for ILA (*n* = 25) were excluded from the analyses. Longitudinal data were analyzed with the nonparametric Wilcoxon paired tests; if lack of symmetry was detected, a pseudomedian was estimated by Hodges-Lehmann estimator with its respective 95% CIs. All analyses were performed using R software (version 3.3.3). Probability values of <.05 were considered statistically significant.

Results

Of 1076 individuals seen in the RA clinic from 2014 to 2016, 300 (28%) had clinically indicated, interpretable chest CT scans (Fig 1). Seven individuals were excluded, five with concurrent illness and two with mycobacterial disease. The remaining 293 CT scans were scored: 204 (70%) had no interstitial abnormalities; 25 (9%) were indeterminate, and 64 (22%) showed ILA/ILD.

Spearman rank correlation coefficient for CT scoring interobserver agreement between the first two readers was 0.91. Of 64 individuals with ILA/ILD, 26 (41%) were classified as ILA; 35 (55%) were classified as ILD, and three (5%) lacked sufficient medical records to establish clinical subgroup. The most common pattern of distribution was subpleural in both ILA (46%) and ILD (69%); extensive disease was observed in 16% (e-Table 1;

Figure 1 – Flow diagram of subject inclusion. HRCT = high-resolution CT; ILA = interstitial lung abnormalities; ILD = interstitial lung disease; RA = rheumatoid arthritis

e-Fig 1). Among individuals with ILD, 15 (43%) had usual interstitial pneumonia or probable usual interstitial pneumonia on CT scan; five (14%) had nonspecific interstitial pneumonia, and 15 (43%) had an unclassifiable pattern.

Chest CT indications were divided into three major groups: chest CT indications related to pulmonary indications (n = 131), chest CT indications not related to pulmonary indications (n = 115), and not identified (n = 44). The most common indications for chest CT scans were chronic respiratory symptoms and/or altered physical examination, which were present in 35% of no ILA cases and 54% of ILA (e-Table 2). Chest CT scans that were performed for these indications uncovered 57% (16/28) of all undiagnosed ILA cases. Of the 115 scans that were performed in individuals without pulmonary indications, 10% (11/115) showed ILA or ILD. The most common indication in individuals with ILD was ILD follow up (94%). Among chest CT indications that were not related to pulmonary indications, ILA was present in 8% (9/115) of these chest CT scans (e-Table 2).

Individuals with the spectrum of ILA/ILD as compared with no ILA were older, male, and ever smokers (Table 1), with a lower exposure to biologics or small molecule disease modifying antirheumatic drugs

(60% vs 36%; $P < .001$). Additional information on disease modifying antirheumatic drugs use can be found in e-Table 3. When we compared ILA and ILD, those individuals with ILA were more likely to be ever smokers (61% vs 26%; $P = .006$), and there was a trend toward a higher percentage of male individuals in the ILD group (37% vs 15%; $P = .06$) (e-Table 4).

Of the 56 individuals (87%) with ILA/ILD with sequential CT scans, mean time between baseline and follow-up CT was 4.4 ± 2.3 years. The visual radiographic assessment classified 21 individuals (38%) as progressors and 35 individuals (62%) as nonprogressors (Fig 1). Spearman rank correlation coefficient for CT scoring interobserver agreement for changes $>10\%$ between the two radiologists was 0.80. Although clinical baseline characteristics of progressors and nonprogressors did not significantly differ, progressors had a significantly higher median baseline ILA/ILD involvement based on the semiquantitative method (11% [interquartile range (IQR), 6 to 24] vs 4% [IQR, 2.5-7.5]; $P = .001$) (Table 2) and a significant increase in ILA/ILD extent (11%-21%; $P = .001$) between baseline and follow-up CT scan compared with nonprogressors (4%-6%; $P = .16$) (Fig 2A). In addition, although coarseness of reticulation increased among both progressors and nonprogressors, the score variation in

TABLE 1 Baseline Characteristics of Individuals With Rheumatoid-Arthritis Stratified by Presence/Absence of the Spectrum of Interstitial Lung Abnormalities and Interstitial Lung Disease

Variables	ILA/ILD (n = 64)	No ILA ^a (n = 204)	P Value
Age, mean $\pm$ SD, y	65.6 $\pm$ 9.9	59.5 $\pm$ 10.9	.001
Female, No. (%)	46 (72)	175 (86)	.023
Ever smoking, No. (%)	29 (45)	60 (30)	.034
Pack.years, mean $\pm$ SD	24.6 $\pm$ 18.8	27.3 $\pm$ 18.1	.523
Disease duration, mean $\pm$ SD, y	11.3 $\pm$ 10.5	13.1 $\pm$ 10.4	.237
DAS28-ESR, mean $\pm$ SD	3.8 $\pm$ 1.8	4.2 $\pm$ 1.6	.116
RF positive, No. (%)	45 (87)	113 (74)	.07
RF, mean $\pm$ SD	216 $\pm$ 122	217 $\pm$ 193	.976
Anti-CCP positive, No. (%)	39 (75)	141 (74)	.88
Anti-CCP, mean $\pm$ SD	334 $\pm$ 464	248 $\pm$ 317	.216
Methotrexate use, No. (%)	57 (89)	194 (95)	.08
Biologics/small molecule DMARD use, ^b No. (%)	23 (36)	123 (60)	< .001

CCP = cyclic citrullinated peptide; DAS28 = disease activity score-28; DMARD = disease modifying anti-rheumatic drugs; ESR = erythrocyte sedimentation rate; ILA = interstitial lung abnormalities; ILD = interstitial lung disease; RF = rheumatoid factor.

^aMissing data (ILA/no ILA): ever smoking (n = 0/n = 7), RF (n = 12/n = 52), CCP (n = 12/n = 14).

^bBiologics/small molecule DMARD use refers to anti-tumor necrosis factor agents (infliximab, etanercept, adalimumab, golimumab, certolizumab), tocilizumab, rituximab, abatacept, and tofacitinib. For details in the prevalence of use of each drug, see e-Table 1.

TABLE 2] Characteristics of Individuals With Rheumatoid Arthritis With a Spectrum of Interstitial Changes, Interstitial Lung Abnormalities, and Interstitial Lung Disease, Stratified Into Progressors vs Nonprogressors by Volumetric CT Analysis

Variables	Progressor ^a (n = 21)	Nonprogressor ^a (n = 35)	P Value
Baseline characteristics			
Age, mean ± SD, y	65 ± 9.4	66 ± 9.9	.71
Female, No. (%)	17 (81)	25 (71)	.40
Ever smoking, No. (%)	10 (48)	14 (40)	.56
Pack years, median [IQR]	23 [13-41]	28 [20-40]	.46
Rheumatoid arthritis duration, median [IQR], y	6.5 [3-21]	7 [2-17]	.51
DAS28-ESR, mean ± SD	3.8 ± 1.6	3.9 ± 1.9	.84
RF			
Positivity, No. (%)	17 (94)	20 (74)	.09
Titer, mean ± SD, international units/mL	235 ± 132	208 ± 107	.45
ACPA			
Positivity, No. (%)	12 (70)	22 (78)	.55
Titer, median [IQR], international units/mL	375 [210-392]	259 [188-394]	.46
Methotrexate use, No. (%)	20 (95)	29 (83)	.19
Biologics/small molecule DMARD use, ^b No. (%)	8 (38)	11 (31)	.59
Classification of interstitial changes			
ILA, No. (%)	6 (29)	15 (43)	.30
ILD, No. (%)	15 (44)	20 (56)	.39
Involvement baseline, median [IQR], %			
Baseline	11 [6-24]	4 [2.5-7.5]	.001
Follow up	21 [15-46]	6 [3-10]	.09
Time between baseline and follow-up CT scans, mean ± SD, y	4.9 ± 2	4.1 ± 2.4	.20
Follow-up: Death, No. (%)	9 (43)	8 (23)	.31

ACPA = anti-citrullinated protein antibodies; IQR = interquartile range. See Table 1 legend for expansion of other abbreviations.

^aMissing data: RF (n = 3/n = 8); ACPA (n = 4/n = 7).

^bBiologics/small molecule DMARD use refers to anti-tumor necrosis factor agents (infliximab, etanercept, adalimumab, golimumab, certolizumab), tocilizumab, rituximab, abatacept, and tofacitinib. For details in the proportion of use of each drug, see e-Table 1.

progressors was greater than in nonprogressors (pseudomedian variation difference, +2; 95% CI, 0-3; $P = .026$) (e-Appendix 1, e-Fig 2A). Longitudinal data for indeterminate scans can be found in the supplement.

Of the 28 cases of ILA, 21 (75%) had at least two CT scans for evaluation of progression; of these 21 individuals, 12 (57%) were diagnosed with ILD during follow up. Of the 35 cases of ILD, 32 had longitudinal follow up. Progressors accounted for 29% of ILA cases and 44% of ILD cases. There were no differences between progressive and nonprogressive ILA (Table 3) or progressive and nonprogressive ILD. One-half the baseline CT scans were performed in progressive ILA were for nonpulmonary indications. The subpleural pattern of ILA on baseline CT was

more likely to be associated with progressive ILA ($P = .06$), whereas the centrilobular and mixed pattern were associated exclusively with nonprogressors. In addition, ILA progressors had a significant increase in ILA extent (5%-15%; $P = .0009$) between baseline and follow-up CT scan as compared with no change among nonprogressors (3%-3%; $P = .54$) (Fig 2B). Progressors with ILA also had a significant increase in coarseness of reticulation (2 [95% CI, 0-4.8] to 6.5 [95% CI, 4.2-9.5]; $P = .035$) as compared with no change among nonprogressors (5 [95% CI, 0.6-5] to 5 [95% CI, 2.9-5]; $P = .14$). (e-Appendix 1, e-Fig 2B).

Approximately one-half of individuals with ILA and ILD had clinical pulmonary function test results available for review. After we excluded two individuals

Figure 2 – A-B, ILA/ILD extent percent of baseline and follow-up CT scan stratified as progressors and nonprogressors based on high-resolution CT analysis. Spectrum of A, ILA/ILD ($n = 56$) and B, ILA ($n = 21$). Note that probability values over the box plots represent the comparison between progressors vs nonprogressors at each point in time. The probability value next to the horizontal arrow represents the comparison between the variation of the ILA/ILD extent seen among nonprogressors vs progressors. See [Figure 1](#) legend for expansion of abbreviations.

with obstructive lung disease, nine of 26 individuals with ILA (35%) had baseline spirometry, and seven of 26 individuals with ILA (26%) had follow-up spirometry, whereas 20 of 35 (57%) and 16 of 35 (46%) individuals with ILD had baseline and follow-up spirometry, respectively. When we compared ILA and ILD, neither

baseline nor follow-up spirometry differed significantly between the groups ([e-Table 5](#)). Although the mean FVC percent declined over time in both ILA and ILD, there was no statistical significance (ILA, 86% [95% CI, 75-90] to 76% [95% CI, 60-91]; $P = .39$; ILD, 85% [95% CI, 68-98] to 76% [95% CI, 59-91]; $P = .16$) ([e-Table 6](#), [e-Fig 3](#)).

TABLE 3] Characteristics of Rheumatoid Arthritis-Associated Interstitial Lung Abnormalities Stratified Into Progressors vs Nonprogressors

Variables	ILA Progressors (n = 6)	ILA Nonprogressors (n = 15)	P Value
Baseline characteristics			
Age, mean $\pm$ SD, y	63 $\pm$ 6.3	64 $\pm$ 7.8	.78
Female, No. (%)	5 (83)	13 (86)	.86
Ever smoking, No. (%)	5 (83)	9 (60)	.32
Pack years, median [IQR]	22 [10-32]	26 [19-37]	.35
Rheumatoid arthritis duration, median [IQR], y	16 [2.5-36]	10 [2-22]	.33
DAS28-ESR, mean $\pm$ SD	3.0 $\pm$ 1.9	3.9 $\pm$ 2.1	.37
RF			
Positive, No. (%)	5 (83)	11 (73)	.67
Titer, median [IQR], international units/mL	128 [76.5-400]	160 [100-256]	.87
ACPA			
Positive, No. (%)	5 (83)	9 (60)	.39
Titer, median [IQR], international units/mL	264 [98-375]	285 [211-596]	.68
Methotrexate use, No. (%)	5 (100)	13 (87)	.37
Biologics/small molecule DMARD use, ^a No. (%)	1 (17)	6 (40)	.32
CT indications, No. (%)			
Pulmonary indications	3 (50)	9 (60)	.68
Nonpulmonary indications/other	3 (50)	6 (40)	1.00
Classification of ILA			
Subpleural pattern of distribution on baseline CT, No. (%)	6 (100)	8 (53)	.06
Centrilobular pattern of distribution on baseline CT, No. (%)	0 (0)	5 (33)	...
Mixed pattern of distribution on baseline CT, No. (%)	0 (0)	2 (14)	...
ILA involvement			
Baseline, median [IQR], international units/mL	5 [3-8]	3 [2-6]	.21
Follow up, median [IQR], international units/mL	15 [7-30]	3 [2-8]	.009
Time between baseline and follow-up CT scans, mean $\pm$ SD, y	4.5 $\pm$ 2.2	3.8 $\pm$ 2.5	.55

See Table 1 and 2 legends for expansion of abbreviations.

^aBiologics/small molecule DMARD use refers to anti-tumor necrosis factor agents (infliximab, etanercept, adalimumab, golimumab, certolizumab), tocilizumab, rituximab, abatacept, and tofacitinib. For details in the prevalence of use of each drug, see e-Table 1.

Discussion

In this single center RA cohort with clinically indicated chest CT scans, 22% of the individuals had a spectrum of interstitial changes, which is comparable with previous studies in which the prevalence of ILA/ILD in RA is estimated to be approximately 20% to 60%.^{13,17,18,26,27} The association between older age, male sex, smoking, and ILA/ILD that was seen in our cohort has also been reported in the literature.^{17,19,20,28} Of those individuals with interstitial changes in our study, 41% were categorized as having undiagnosed ILA. Although chronic respiratory symptoms or altered physical examination were the most common CT indications in those with undiagnosed ILA, among individuals who had a CT chest scan that was not ordered for chronic

respiratory signs/symptoms or ILD follow up, approximately 8% of them (9/115) had ILA, which is less than what is reported in the literature. Among individuals with follow-up CT scans, 44% of the individuals with ILD and 29% of the individuals with ILA progressed radiologically over an average of four years; progressors had a significantly higher baseline ILA/ILD extent. One-half of the individuals with progressive ILA had baseline CT scans performed for nonpulmonary indications, and all of them had a subpleural ILA distribution. Of the 21 individuals with ILA and longitudinal data, 12 (57%) received a diagnosis of ILD during follow up, which supports the idea that there may be a role for screening individuals with RA for ILD in the future, with particular attention to signs and

symptoms of ILD, baseline ILA extent, and ILA distribution. In addition, this study suggests that a modified semiquantitative method for the determination of ILD progression²⁵ can be used to assess ILA progression accurately.

Chronic respiratory symptoms and/or altered physical examinations were the most common indications for chest CT scans in our cohort and identified one-half the ILA cases. This finding is consistent with previous data that demonstrated that bibasilar crackles were significantly more common in RA-ILD than in RA without ILA/ILD (53% vs 9%; $P < .001$)²⁹ and reaffirms the idea that chronic respiratory symptoms and/or altered physical examinations in individuals with RA deserve close attention and further work up. Of equal importance is that, among individuals who had a chest CT scan ordered for indications not related to the possible ILD, approximately 8% of them had ILA, which accounted for approximately one-half of our ILA individuals. This indicates that symptoms alone are not sufficient to screen for mild interstitial changes in RA and supports the idea that there may be a role for screening asymptomatic individuals with RA for ILA. This is an important area of study, given that there are no current recommendations from rheumatologic societies regarding the necessity for or method of screening for ILA in individuals with RA. In addition, improved identification of high risk individuals with clinical and biomolecular risk factors for RA-ILD can further inform such recommendations and be used to design effective screening algorithms.³⁰

Previous studies suggest that individuals with RA with ILA are at an increased risk of experiencing clinically significant disease with its associated morbidity and death, which is a premise that is supported by recent data that demonstrated that ILA in smokers is associated with an increase in all-cause mortality rates.^{4,6} There is an unmet need to better understand the natural history of early stages of pulmonary fibrosis to identify modifiable risk factors and, in turn, develop timely interventions to prevent disease progression.³¹ Our study is one of the first to look at the progression of a spectrum of interstitial abnormalities, which includes mild interstitial involvement. We demonstrated that 29% of individuals (6/21) with ILA and 44% of individuals (15/35) with ILD progressed over 4.4 years. Radiographic risk factors for progression included higher baseline ILA/ILD extent for all interstitial

changes and subpleural distribution for ILA. This further supports that improved understanding of the clinical, physiologic, molecular, and genetic characteristics of progressive RA-ILD is needed.

Chest high-resolution CT scanning is the radiologic standard in the evaluation of ILD and presently the preferred method for the detection of ILA in the research setting.²⁴ Radiologic progression has been demonstrated in both subclinical RA-ILD²² and smokers^{32,33} at two to three years of follow up, with a higher rate of progression to fibrotic ILA,^{6,34} older individuals, and those with the MUC5B promotor polymorphism.⁵ Our group used a semiquantitative visual inspection method to measure ILA changes and showed a good correlation with the visual assessment of progression.²⁴ This suggests that radiographic disease extent and coarseness of reticulation could be effective research tools to measure progression of ILA/ILD in RA and other at-risk individuals.

Our study had some limitations. First, there were small numbers of individuals in each group with missing data that included pulmonary function testing, which is often true of a retrospective study. This may limit the statistical significance and the generalizability of our analysis. Second, it was a single-center study, which could reduce its generalizability. Third, we analyzed only clinically indicated chest CT scans, which introduces a selection bias, potentially overestimating the prevalence of ILA. Last, our cases were derived from the rheumatology clinic, so cases seen only in the pulmonary clinic may have been missed. This may have excluded some of the more severe cases.

This study suggests that a significant number of individuals with RA with and without respiratory signs and symptoms could have interstitial changes and that there is a missed opportunity for earlier diagnosis, given that a high percentage of these individuals will progress over time. In addition, this study is the first to quantify progressive ILA radiologically in a population with RA and to look at radiologic risk factors that are associated with progression, such as a subpleural ILA distribution. Future multicenter prospective studies that will screen for ILA in a population with undiagnosed RA are crucial to estimate the true incidence of ILA and progressive subclinical disease and to identify risk factors that are associated with progressive disease.

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Additional information: The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

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