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Functional Impact of a Spectrum of Interstitial Lung Abnormalities in Rheumatoid Arthritis

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PODCAST

BACKGROUND: Approximately 10% of patients with rheumatoid arthritis (RA) have interstitial lung disease (ILD), and one-third have subclinical ILD on chest CT scan. In this study, we aimed to further characterize functional decrements in a spectrum of RA-associated ILD.

METHODS: All subjects were enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS). The presence of interstitial lung abnormalities (ILAs) on clinically indicated chest CT scans was determined using a previously validated sequential reading method. Univariate and multivariate analyses were used to assess the association between degree of ILAs and physiologic, functional, and demographic variables of interest.

RESULTS: Of 1,145 BRASS subjects, 91 subjects (8%) were included in this study. Twelve had radiologically severe ILAs, 34 had ILAs, and 38 had no ILAs on CT scan. Subjects with radiologically severe ILAs were older ($P = .0037$), had increased respiratory symptoms (cough, $P = .027$; dyspnea, $P = .010$), and more severe RA disease (rheumatoid factor, $P = .018$; total swollen joints, $P = .046$) compared with subjects with no ILAs. Participants also had a trend toward having an increased smoking history ($P = .16$) and having lower FVC % predicted (77% vs 94%, $P = .097$) and diffusion capacity of carbon monoxide % predicted (52% vs 77%, $P = .068$). Similar but attenuated increases in respiratory symptoms, functional decrements, and RA disease severity were observed in subjects with ILAs compared with those with no ILAs.

CONCLUSIONS: We have shown that patients with RA have varying degrees of ILAs that are associated with a spectrum of functional and physiologic decrements. Our findings suggest that improved risk stratification and detection of ILAs will provide a therapeutic window that could improve RA-ILD outcomes. CHEST 2014; 146(1):41-50

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ABBREVIATIONS: 6MWD = 6-min walk distance; BRASS = Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; CCP = cyclic citrullinated peptide; DLCO = diffusion capacity of the lung for carbon monoxide; HRCT = high-resolution CT; ILA = interstitial lung abnormality; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; MDHAQ = Multidimensional Health Assessment Questionnaire; PFT = pulmonary function test; RA = rheumatoid arthritis; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; RF = rheumatoid factor; TNF-α = tumor necrosis factor-α

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Rheumatoid arthritis (RA) is a destructive, systemic, inflammatory disorder[1] that currently affects approximately 3 million adults in the United States, or 1% of the population.[2,3] A major portion of disease burden and excess mortality is due to extraarticular manifestations,[4] such as interstitial lung disease (ILD). Median survival following a diagnosis of RA-associated ILD (RA-ILD) is 2.6 years,[5] and the risk of death for individuals with RA-ILD is three times higher than in patients with RA and without ILD. Although studies have demonstrated that overall mortality rates for RA are declining, death from RA-ILD has increased significantly.[3] Overall, these statistics highlight the need for strategies that improve risk stratification, detection, and timely interventions for patients with RA and ILD.

Approximately 10% of the RA population has ILD,[3] with an additional notably high percentage of subclinical RA-ILD demonstrated on high-resolution CT (HRCT) scans.[6] In one study, 33% of patients with RA without dyspnea or cough had interstitial lung abnormalities (ILAs) on chest CT scans.[7] Importantly, radiologic progression has been observed in 34% to 57% of subjects with subclinical RA-ILD after a mean follow-up of 1.5 to 2 years,[7,8] suggesting that progression of asymptomatic radiologic changes could lead to the development of symptomatic RA-ILD. Taken together, these findings strongly suggest that subclinical RA-ILD is prevalent and that a subset of patients will experience progression of lung disease over time.

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Currently, there is limited understanding surrounding the clinical and physiologic characteristics of ILD in the RA population, and even less is known about individuals with subclinical RA-ILD or the natural history of progressive subclinical disease. In this study, we aimed to further characterize clinical characteristics and functional decrements in patients affected with a spectrum of RA-ILD.

Materials and Methods

Study Design

Protocols for participant enrollment and data collection in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) have been described previously.[9,10] The BRASS registry is a large, single-center, prospective, observational cohort of 1,145 subjects established in 2003. Patients aged ≥ 18 years with a diagnosis of RA[1] were recruited from rheumatology practices. Information was collected on > 1,000 variables including demographics, RA disease activity, and comorbidities. Further details of the BRASS study are available online (www.BRASSstudy.org) and in e-Appendix 1. This project was granted institutional review board approval by the Partners Human Research Committee at the Brigham and Women's Hospital (protocol number 2010-P-002840/1).

HRCT Scanning Analysis

BRASS subjects with chest CT scans performed for clinical indications prior to 2010 were included in this study; the scan performed in closest temporal proximity with a BRASS visit was chosen for review. All CT scans were evaluated for the presence of ILAs (no ILAs, indeterminate, ILAs, radiologically severe ILAs) using a sequential reading method as previously described (e-Appendix 1).[11,12] No pathology was available for definitive diagnosis.

Pulmonary Function Testing

Pulmonary function tests (PFTs) performed for clinical indications and in closest temporal proximity to a BRASS visit were selected. For consistency, prebronchodilator values were used for the analysis as not all patients had a trial of bronchodilators. Reference values were derived from the third National Health and Nutrition Examination Survey in the United States.[13]

6-Min Walk Tests

A subset of BRASS subjects had a standardized 6-min walk test performed in accordance with American Thoracic Society guidelines.[14] These data were included in the BRASS database and included in our analysis.

Respiratory Questionnaires

At 6-month intervals, each patient received a questionnaire in the mail that included a section on respiratory symptoms. The questionnaire in closest proximity to the HRCT scan was used for this study. The question used for the study was "Please fill in the response next to any of the following symptoms that you have experienced in the PAST MONTH: Chest, Lungs, Heart: Coughing. Shortness of breath." A filled-in square was considered a positive response.

Statistical Analysis

Univariate analyses were conducted with Fisher exact tests (for binary and categorical variables), and two-tailed *t* tests or Wilcoxon rank-sum tests (for continuous variables) where appropriate. For multivariate analyses, unadjusted and adjusted linear and logistic regression models were used to assess the strength of the association between RA-ILD and variables of interest. In all models, subjects indeterminate for ILAs (n = 50) were excluded. All analyses were performed using Statistical Analysis Software, version 9.2 (SAS Institute Inc). *P* values < .05 were considered statistically significant.

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Results

Of 1,145 BRASS subjects, 188 subjects (16%) had clinically indicated chest CT scans performed as part of routine care or due to a change in symptoms, such as hypoxia or increased dyspnea (Fig 1). Subjects were excluded if radiologic changes suggesting concurrent illness (ie, pleural effusions or pneumonia) limited the CT scan interpretation (n = 47) (e-Table 1). The remaining 141 subjects were scored for ILAs, as discussed later in this section. Ten individuals (29%) with subclinical ILD and five individuals (13%) with no evidence of ILAs had CT scans done for chronic respiratory symptoms, including cough, shortness of breath, or dyspnea on exertion. Other clinical indications for CT scans included lung nodule follow-up, cancer staging and follow-up, acute infections, and evaluation for possible vascular or cardiac pathology (e-Table 2).

From the 141 RA chest CT scans interpreted, 12 patients (9%) had radiologically severe ILAs, 41 had ILA (29%), and 38 had no evidence of ILAs (26%) (Fig 2). Fifty subjects (35%) had indeterminate CT scans and were excluded from the primary analyses except where indicated. Subjects with ILAs on CT scan who had a documented history of pulmonary fibrosis by their physician (n = 7) were also excluded from the primary analyses. Additional analyses including these seven individuals are given in e-Figure 1 and e-Table 3, which include those with ILAs and a history of pulmonary fibrosis in the radiologically severe ILA group, and in e-Figure 2 and e-Table 4, which include those with ILAs and a history of pulmonary fibrosis in the ILA group.

Characteristics of Subjects With Radiologically Severe ILAs

Characteristics of individuals with radiologically severe ILAs as compared with those without ILAs are presented in Table 1. As expected, individuals with radiologically severe ILAs were older, had higher rheumatoid factor (RF) levels, increased levels of anti-cyclic citrullinated peptide (CCP) antibodies, and greater RA disease severity as measured by the Multi-Dimensional Health Assessment Questionnaire (MDHAQ) score and total swollen joint count. Subjects demonstrated trends toward more likely being male ($P = .082$) and having an increased smoking history ($P = .16$). Subjects with radiologically severe ILAs also had a significantly increased incidence of cough, dyspnea, and a trend toward lower FEV_1 % predicted ($P = .086$), FVC % predicted ($P = .097$), and diffusion capacity of the lung for carbon monoxide (DLCO) % predicted ($P = .068$). A statistically significant decline in FEV_1 % predicted and FVC % predicted was observed with the addition of the seven individuals with ILAs and a history of pulmonary fibrosis (e-Table 3). Multivariable analyses adjusting for age and smoking history demonstrated attenuated but consistent associations in respiratory symptom and functional variables. Of note, there was no difference between use of tumor necrosis factor-α (TNF-α) inhibitors or methotrexate in subjects with and without radiologically severe ILAs (Table 1).

Characteristics of Subjects With ILAs

Characteristics of individuals with ILAs as compared with no ILAs are presented in Table 2. After excluding subjects with RA who had a history of pulmonary fibrosis, those with ILAs were significantly older, had an increased smoking history, and had higher levels of RF and anti-CCP antibodies. Subjects with ILAs also had an increased incidence of cough and dyspnea, as well as significantly lower FEV_1 % predicted and FVC % predicted. Interestingly, the addition of the seven individuals with ILAs and a history of pulmonary fibrosis to the ILA group did not significantly change the results (e-Table 4). Multivariable analyses adjusting for age and smoking history demonstrated attenuated but consistent associations in respiratory symptom and functional variables. As with subjects with radiographically severe ILAs, there was no difference between use of TNF-α inhibitors or methotrexate in subjects with and without ILAs (Table 2).

A comparison of subjects in all study groups, including a combined group of ILAs and radiologically severe ILAs, is presented in Table 3. A comparison that includes subjects with indeterminant CT scan abnormalities is presented in e-Table 5. Interestingly, individuals with indeterminant CT scan abnormalities had an intermediate phenotype for some variables (pack-years of smoking, RF and anti-CCP levels, Disease Activity Score-28-C-reactive protein with three variables and MDHAQ scores, and respiratory symptoms) and were similar to ILAs and radiologically severe ILAs for age and most physiologic and functional variables.

Discussion

Our study demonstrates that patients with RA who also have ILAs or radiologically severe ILAs have a spectrum of disease severity that is associated with smoking, severity of RA, and physiologic and functional decrements of varying degrees. Individuals with ILAs had increased cough and dyspnea, and decreased PFT results and

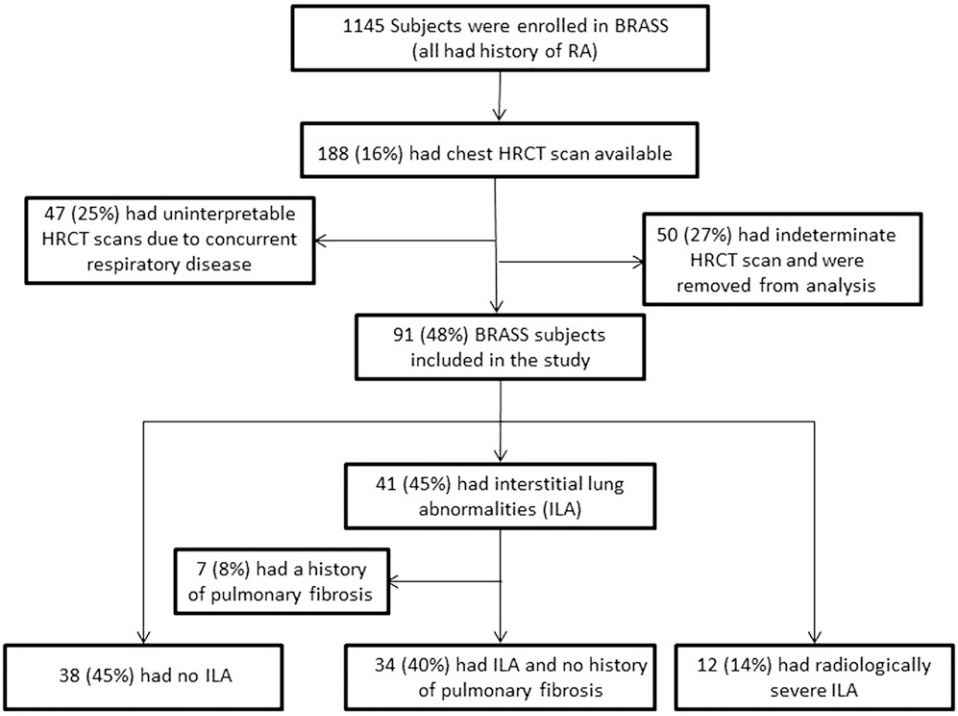

Figure 1 – *A flow diagram of study enrollment divides participants into three groups according to presence and subtype of subclinical ILAs. BRASS = Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; HRCT = high resolution CT; RA = rheumatoid arthritis.*

6-min walk distance (6MWD). Individuals with radiologically severe ILAs had similar but more severe increases in respiratory symptoms, as well as functional decrements of a similar magnitude to ILAs. These results outline the clinical and physiologic characteristics of a spectrum of RA-ILD, and suggest that individuals with ILAs may have more severe functional impairments than previously expected, even when not recognized by either the subject or physician.

The unrecognized increase in respiratory symptoms and functional decrements noted in patients with RA and ILAs in our study suggest that this population may have subclinical RA-ILD; the radiologically severe ILA group represents clinically significant RA-ILD, as all these subjects had CT scans done for follow-up of pulmonary fibrosis and almost all indicated they had a previous diagnosis of pulmonary fibrosis on their baseline BRASS physician questionnaire.

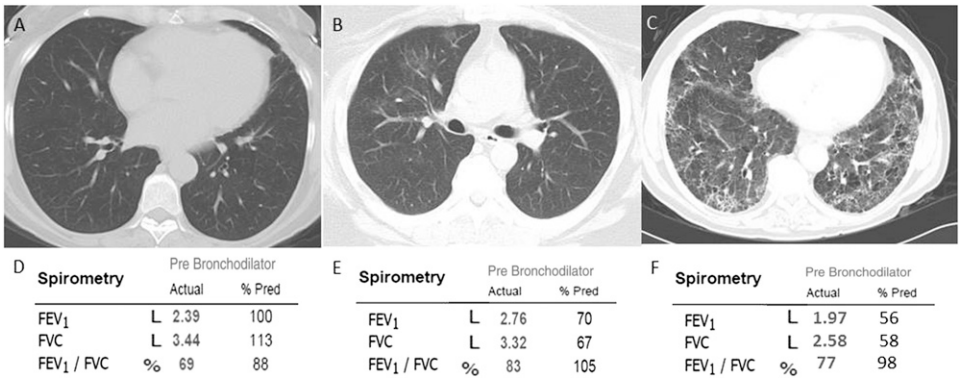

Figure 2 – *A-C, Chest CT images from three representative subjects. D-F, Pulmonary function test results obtained in three representative individuals. A, D, Images from an individual without evidence of ILAs and normal spirometry. B, E, Images from an individual with evidence of ILAs and spirometry suggestive of a mild restrictive ventilatory defect. C, F, Images from an individual with evidence of radiologically severe ILAs and spirometry suggestive of a moderate restrictive ventilatory defect. % Pred = % predicted. See Figure 1 legend for expansion of other abbreviation.*

TABLE 1] Baseline Characteristics of BRASS Subjects Stratified by ILAs, Excluding Subjects Indeterminate for ILAs (n = 50) or Unable to Assess (n = 47)

Variable[a]	No ILAs (n = 38, 76%)	Radiologically Severe ILAs (n = 12, 24%)	*P* Value
Demographic parameters			
Age, y	53 ± 11	65 ± 7	.0037
Female sex	34 (89)	8 (67)	.082
White race	36 (95)	11 (92)	1.00
BMI	28 ± 7	27 ± 4	.92
Pack-y of smoking	9 ± 17	19 ± 22	.16
Ever smoker	15 (39)	7 (58)	.32
Past medical history			
Asthma	2 (5)	0 (0)	1.00
COPD	0 (0)	4 (33)	.0021
Bronchiolitis obliterans	0 (0)	1 (8)	.24
Bronchiectasis	0 (0)	4 (33)	.0021
RA parameters			
RF level	90 ± 165	415 ± 731	.018
Anti-CCP antibody positive	16 (43)	9 (82)	.039
HLA-DR1 shared epitope	0.74 ± 0.75	0.89 ± 0.78	.62
DAS28-CRP3 score	3.52 ± 1.49	4.36 ± 1.96	.23
MDHAQ score	0.59 ± 0.48	0.89 ± 0.45	.041
Total swollen joints	6 ± 7	11 ± 8	.046
Medication use			
TNF-α inhibitor use	23 (61)	10 (83)	.18
Methotrexate use	30 (79)	10 (83)	1.00
Respiratory parameters			
Cough	8 (21)	7 (58)	.027
Dyspnea	8 (21)	8 (67)	.010
Spirometric parameters[b]	n = 14	n = 9	
FEV_1 % predicted	92 ± 18	78 ± 18	.086
FVC % predicted	94 ± 18	77 ± 18	.097
FEV_1/FVC % predicted	94 ± 11	103 ± 10	.086
	n = 8	n = 6	
TLC % predicted	86 ± 16	79 ± 32	.24
	n = 8	n = 7	
D_{LCO} % predicted	77 ± 18	52 ± 24	.068
Exercise capacity	n = 5	n = 3	
6-min walk distance	1,715 ± 206	1,451 ± 281	.40
Systolic BP	118 ± 22	113 ± 16	.89
Heart rate	76 ± 7	81 ± 29	1.00
Resting oxygen saturation	98 ± 2	95 ± 3	.22

Data given as mean ± SD or No. (%). BRASS = Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study; CCP = cyclic citrullinated peptide; DAS28-CRP3 = Disease Activity Score-28-C-reactive protein (three variable); D_{LCO} = diffusion capacity of the lung for carbon monoxide; ILA = interstitial lung abnormality; MDHAQ = Multi-Dimensional Health Assessment Questionnaire; RA = rheumatoid arthritis; RF = rheumatoid factor; TLC = total lung capacity; TNF-α = tumor necrosis factor-α.

[a]Data missing: BMI (n = 2), pack-y of smoking (n = 8), RF level (n = 4), anti-CCP antibody level (n = 2), HLA-DR1 shared epitope (n = 18), DAS28 score (n = 1), MDHAQ score (n = 3), total swollen joints (n = 1).

[b]Prebronchodilator pulmonary function measurements presented.

TABLE 2] Baseline Characteristics of BRASS Subjects Without a History of Pulmonary Fibrosis, Stratified by ILAs, Excluding Subjects Indeterminate for ILAs (n = 50) or Unable to Assess (n = 47)

Variable[a]	No ILAs (n = 38, 53%)	ILAs (n = 34, 47%)	*P* Value
Demographic parameters			
Age, y	53 ± 11	68 ± 10	< .0001
Female sex	34 (89)	27 (79)	.33
White race	36 (95)	29 (88)	.41
BMI	28 ± 7	28 ± 5	.6817
Pack-y of smoking	9 ± 17	23 ± 36	.031
Ever smoker	15 (39)	21 (62)	.098
Past medical history			
Asthma	2 (5)	1 (3)	1.00
COPD	0 (0)	2 (6)	.22
Bronchiolitis obliterans	0 (0)	1 (3)	.47
Bronchiectasis	0 (0)	2 (6)	.22
RA parameters			
RF level	90 ± 165	319 ± 638	.013
Anti-CCP antibody positive	16 (43)	28 (88)	.00049
HLA-DR1 shared epitope	0.74 ± 0.75	0.86 ± 0.83	.65
DAS28-CRP3 score	3.52 ± 1.49	4.10 ± 1.62	.16
MDHAQ score	0.59 ± 0.48	0.82 ± 0.55	.11
Total swollen joints	6 ± 7	7 ± 6	.21
Medication use			
TNF-α inhibitor use	23 (61)	19 (56)	.81
Methotrexate use	30 (79)	5 (15)	.55
Respiratory parameters			
Cough	8 (21)	15 (44)	.045
Dyspnea	8 (21)	16 (47)	.025
Spirometric parameters[b]	n = 14	n = 18	
FEV_1 % predicted	92 ± 18	69 ± 27	.0048
FVC % predicted	94 ± 18	75 ± 21	.0093
FEV_1/FVC % predicted	94 ± 11	87 ± 16	.30
	n = 8	n = 7	
TLC % predicted	86 ± 16	78 ± 15	.34
	n = 8	n = 7	
D_{LCO} % predicted	77 ± 18	69 ± 13	.40
Exercise capacity	n = 5	n = 3	
6-min walk distance	1,715 ± 206	1,382 ± 388	.40
Systolic BP	118 ± 22	117 ± 22	1.00
Heart rate	76 ± 7	74 ± 10	1.00
Resting oxygen saturation	98 ± 2	95 ± 6	.66

Data given as mean ± SD or No. (%). See Table 1 legend for expansion of abbreviations.
[a]Data missing: BMI (n = 2), pack-y of smoking (n = 10), race (n = 1), RF level (n = 5), anti-CCP antibody level (n = 3), HLA-DR1 shared epitope (n = 27), DAS28-CRP3 score (n = 13, MDHAQ score (n = 6), total swollen joints (n = 1).
[b]Prebronchodilator pulmonary function measurements presented.

Our previous research demonstrated that ILAs are frequently associated with physiologic and functional abnormalities in at-risk populations, such as smokers[12,15] and individuals with RA.[7] We have shown that smokers with ILAs, even when unrecognized by the patient or physician, may already exhibit increased respiratory

TABLE 3] Characteristics of BRASS Subjects Stratified by ILAs, Excluding Subjects Indeterminate (n = 50) or Unable to Assess (n = 47)

Variable	No ILAs (n = 38)	ILAs (n = 34)	Radiologically Severe ILAs (n = 12)	ILAs and Radiologically Severe ILAs (n = 46)
Demographic parameters				
Age, y	53 ± 11	68 ± 10[a]	65 ± 7[a]	67 ± 9[a]
Pack-y of smoking[b]	9 ± 17	23 ± 36[a]	19 ± 22	22 ± 33[a]
Respiratory parameters				
Cough	8 (21)	15 (44)[a]	7 (58)[a]	22 (48)[a]
Dyspnea	8 (21)	16 (47)[a]	8 (67)[a]	24 (52)[a]
Spirometric parameters[c]	n = 14	n = 18	n = 9	n = 27
FEV_1 % predicted	92 ± 18	69 ± 27[a]	78 ± 18[d]	72 ± 24[a]
FVC % predicted	94 ± 18	75 ± 21[a]	77 ± 18[d]	76 ± 20[a]
	n = 8	n = 7	n = 6	n = 13
TLC % predicted	86 ± 16	78 ± 15	79 ± 32	78 ± 23
	n = 8	n = 7	n = 7	n = 14
DLCO % predicted	77 ± 18	69 ± 13	52 ± 24[d]	60 ± 21
Exercise capacity	n = 5	n = 3	n = 3	n = 6
6-min walk distance	1,715 ± 206	1,382 ± 388	1,451 ± 281	1,416 ± 305

Data given as mean ± SD or No. (%). See Table 1 legend for expansion of abbreviations.
[a]$P \leq .05$ when compared with No ILA group.
[b]Data missing: pack-years of smoking (n = 12).
[c]Prebronchodilator pulmonary function measurements presented.
[d]$P \leq .10$.

symptoms and have reductions in lung volumes,[12,16,17] DLCO,[7,18-20] and 6MWD.[12,18] We have also demonstrated that individuals with subclinical RA-ILD have impaired gas exchange demonstrated by a lower DLCO % predicted, but PFTs were insensitive methods to detect subclinical RA-ILD.[7] In this article, we demonstrate not only that respiratory symptoms, PFT results, and 6MWD may be abnormal in patients with RA and ILAs, but that some of these decrements are of a similar magnitude to those seen in RA-ILD. Taken together, these findings suggest that some patients with RA and ILAs may already have increased respiratory symptoms, physiologic decrements, and a reduced exercise capacity. This, coupled with the expectation that a subset of these individuals with subclinical disease may progress to established disease,[7] demonstrates a spectrum of RA-ILD and may lead to an improved understanding of the natural history of RA-ILD.

In general, physiologic and functional decrements have not been well characterized in the RA-ILD population, although some small retrospective studies have shown that RA-ILD may be associated with a restrictive deficit and decreased DLCO.[21,22] It has been suggested that RA-ILD may be compared with idiopathic pulmonary fibrosis (IPF), as they have similar radiologic and pathologic findings.[22-27] It has been well established that IPF is more prevalent in older men with a history of smoking, which is similar to the demographics of individuals in our study with RA-ILD. IPF is also associated with increased dyspnea and decreased PFT and 6MWD results, which is consistent with our findings.[28] This study further suggests that ILD in RA has a similar physiologic profile to IPF and, importantly, begins to define the magnitude of the physiologic and functional decrements specifically associated with RA-ILD.

Smoking has been shown to be a risk factor for fibrotic lung diseases in general,[24,29-32] as well as RA-ILD.[7,33] It has also been demonstrated that a significantly higher percentage of subjects with subclinical ILD are current or former smokers.[17,18,34-36] The high prevalence of ILD in smokers with RA suggests that these individuals are now not only at an increased risk of cardiovascular disease and cancer but also the morbidity and mortality that accompanies RA-ILD. Approximately 50% of BRASS subjects are ever smokers, with a higher percentage of those individuals having ILD. In addition, smoking promotes citrullination in the lungs, which leads to generation of CCP antibodies, possibly contributing to the development of lung abnormalities early in the rheumatoid process,[37] especially in

individuals with the HLA-DRB1 shared epitope.[38] Our data demonstrate a significantly higher percentage of anti-CCP antibodies in both ILAs and RA-ILD. This information underlines the importance of smoking cessation as a key component of the management of these individuals. This may be particularly true for those with ILAs, as smoking cessation may help to prevent or slow the progression to RA-ILD.

In addition to anti-CCP antibodies,[39] high-titer RF[40] and severity of joint disease[5] have been associated with a higher incidence of RA-ILD and may be helpful in risk stratifying individuals who should be screened for ILD. Our study supports these findings by demonstrating that increasing levels of RF, MDHAQ scores, and total swollen joint counts are associated with increasing severity of ILD. This also highlights the fact that some patients with RA may not have sufficient joint functionality to develop respiratory symptoms, and, thus, the diagnosis of ILD may be missed. This finding may suggest that there is a subset of patients with RA and with severely limiting joint disease who would benefit from screening for ILD with PFTs or HRCT scans.

Taken together, our findings suggest that there should be a high suspicion of ILD in any patient with RA who has respiratory symptoms or functional decrements, especially if the patient is a smoker with more severe RA. In the future there may be a role for the risk stratification of asymptomatic patients with RA for ILAs,[6] as it may represent the early stages of RA-ILD and could lead to closer monitoring and earlier treatment. Additional, larger, prospective studies are necessary to replicate and expand on these preliminary findings, with particular attention dedicated to the role of earlier identification of ILD in the RA population. Longitudinal studies could help explore the natural history of progressive subclinical disease and how early interventions, such as smoking cessation, will promote secondary prevention of RA-ILD, potentially leading to improved clinical outcomes.

Our study has several limitations. First, it was unclear if individuals in the ILA group who had a previous diagnosis of pulmonary fibrosis (n = 7) were truly representative of subclinical disease or if these individuals had more clinically significant disease. As such, we excluded these individuals from the primary analyses, although additional analyses including these individuals are included in the supplement. Second, there is significant bias in patient selection, as all subjects had clinical indications for CT scans, although many of those indications were unrelated to the diagnosis of ILD (ie, lung nodule or chest pain). Third, within an individual subject, the CT scan, PFT, and 6MWD data may have been separated by considerable variations in time, up to 6.6 years (e-Appendix 1). Since RA-ILD is a progressive disease, it is hard to correlate functional data that are not temporally close to the CT scan. This important limitation should be addressed in subsequent, prospective studies. Fourth, not every subject included in this study who had a CT scan had PFT and 6MWD data available, adding another source of bias and limiting the generalizability of the results. Last, the limited number of subjects with data available for this study hindered our ability to perform multivariate analyses adjusting for such confounders as RA disease severity, comorbidities, and medication-induced lung changes.

Conclusions

In our study, subjects with ILAs and RA-ILD were older, reported an increased smoking history, had increased RA disease severity, and had a spectrum of functional and physiologic decrements. Additional prospective and longitudinal follow-up studies will be important to verify these abnormalities, to evaluate if the decrements present in subclinical disease are progressive, and to determine the best way to screen for RA-ILD in an outpatient clinical setting.

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