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Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD)

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Summary
Background: Rheumatoid arthritis (RA) is a systemic autoimmune disorder with a variety of extra-articular manifestations. The lung is a common target and diffuse parenchymal lung disease can appear as any of the patterns found with idiopathic interstitial pneumonia. Controversy exists as to the prognostic significance of these patterns among patients with RA-ILD.
Methods: We retrospectively identified 48 patients with a diagnosis of RA-ILD confirmed by surgical lung biopsy. The pathology was reviewed by four expert pulmonary pathologists. We examined survival after stratifying on the presence or absence of fibrotic ILD, and contrasted it with a matched idiopathic pulmonary fibrosis (IPF) population. The Cox proportional hazards model was used to identify independent predictors of survival.
Results: The majority of subjects were male smokers with physiologic restriction. A usual interstitial pneumonia (UIP)-pattern was identified in 31% of subjects. Median survival time for the

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entire cohort was 1360 days. Subjects with fibrotic ILD had worse survival than subjects with non-fibrotic ILD (log rank $p = 0.02$). There was no difference in survival between UIP-pattern RA-ILD subjects and IPF controls (log rank $p = 0.94$). Multivariable analysis revealed that age (hazard ratio [HR] = 1.04, $p = 0.01$) and fibrosis (HR = 2.1, $p = 0.02$) were independent predictors of mortality.

Conclusions: Both cellular and fibrosing ILD patterns are common among RA-ILD patients who undergo surgical lung biopsy. These patients have a shortened survival when compared to the general population and all-comers with RA. Age and the presence of a fibrosing interstitial pneumonia predict shortened survival in these patients. Survival in UIP is similar to matched IPF patients.

Introduction

Rheumatoid arthritis (RA) is a common systemic autoimmune disorder characterized by severe inflammatory arthritis. Over two million adults—approximately 1% of the adult population—in the United States have RA. Its incidence ranges from 12 to 70/100,000 patient-years in men and 25—130/100,000 in women. A major portion of RA disease burden, particularly the excess mortality, appears to be due to extra-articular manifestations (exRA).[1,2] The extra-articular manifestations are common (the prevalence of clinically "severe" exRA approaches 40% in some studies[3]) and accumulate over a patient's lifetime at an incidence of 1—3 distinct exRA/100 patient-years.[4]

Although cardiovascular disease is responsible for the majority of RA-related deaths,[5] pulmonary complications are common, directly responsible for 10—20% of deaths[6—8] and increasing in frequency.[9] While pulmonary infection and drug-induced lung disease occur,[10,11] RA can also directly affect the lung with any pulmonary compartment—airways, pulmonary vasculature, pleura, or parenchyma — at risk. Interstitial lung disease (ILD) in RA was first described in 1948 by Ellman and Ball[12] and more systematically evaluated in several subsequent studies.[13—18] The prevalence of RA-ILD varies based on the population studied, how the condition is defined, and the sensitivity of the detection methods.

Yousem and colleagues[19] were the first to report that among RA patients with diffuse parenchymal lung disease, those with a histologic pattern of usual interstitial pneumonia (UIP) in surgical lung biopsy specimens had the worst prognosis. Results from subsequent studies have confirmed their findings[20,21]; however, data on whether patients with RA-related UIP-pattern lung injury have prognoses similar to or better than patients with idiopathic pulmonary fibrosis (IPF) are conflicting.[14,22—28] We sought to determine the effect of histologic pattern in surgical lung biopsy specimens on survival of patients with RA-ILD. We hypothesized that the histopathologic pattern would define prognosis and that subjects with fibrosing lung disease would have the worst prognosis.

Methods

Study population

The databases of the ILD programs at National Jewish Health (NJH) ($N = 22$) and the Mayo Clinic ($N = 34$) were retrospectively queried for subjects with a confirmed diagnosis of RA who had undergone surgical lung biopsy for the further evaluation of diffuse parenchymal lung disease between 1977 and 1999 (56 subjects in total). Approval for this study was obtained through the National Jewish Institutional Review Board (approval number HS-1603) and the Mayo Clinic Institutional Review Board (approval number 1184-00). All subjects were evaluated by a board certified rheumatologist and met the revised criteria for RA set forth by the American College of Rheumatology.[29] Patients without ILD ($n = 1$) or alternate diagnoses, such as pulmonary edema ($n = 1$), infectious pneumonia ($n = 3$), Wegener's granulomatosis ($n = 1$), blastomycosis ($n = 1$) or emphysema ($n = 1$) were excluded. The final cohort consisted of 48 subjects. A matched control population of 11 subjects with a surgical lung biopsy confirmed diagnosis of IPF was obtained from the NJ Health ILD database. Each subject signed an informed consent to have their data and specimens stored in a research database for later use, and the Institutional Review Boards of NJH and the Mayo Clinic approved the protocol.

Pulmonary function assessment

Pulmonary function testing was performed according to American Thoracic Society (ATS) standards and included forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), diffusion capacity for carbon monoxide (DLCO) and total lung capacity (TLC). Values were expressed as a percentage of normal (e.g., FEV_1%, FVC%, DLCO%, and TLC%) predicted from the patient's height, age and gender. Only physiology obtained within two months of the date of diagnosis was included in the analysis.

Pathologic assessment

Surgical lung biopsy specimens were processed in routine fashion, and the original slides were reviewed by four expert pulmonary pathologists (CC, RT, HT, JM) blinded to clinical, radiologic or physiologic findings. A consensus pattern diagnosis was made from the following list of injury patterns based on ATS/ERS criteria[30]: bronchiolitis, diffuse alveolar damage (DAD), desquamative interstitial pneumonia (DIP), lymphoid interstitial pneumonia (LIP), cellular nonspecific interstitial pneumonia (cNSIP), fibrotic nonspecific interstitial pneumonia (fNSIP), organizing pneumonia (OP), unclassifiable fibrosing interstitial lung

disease (uILD) and usual interstitial pneumonia (UIP). For purpose of analysis, patients with fNSIP, uILD or UIP-pattern histology were grouped together under the title "fibrotic" ($N = 23$), and those with bronchiolitis, DAD, DIP, LIP, cNSIP and OP patterns were grouped under the title "non-fibrotic" ($N = 25$).

Statistical methods

Counts or measures of central tendency were determined for baseline characteristics. We used the product-limit method to derive and Kaplan–Meier curves to display survival for the sample as a whole; after stratifying on the presence or absence of fibrotic ILD; and for FVC- and DLCO-matched IPF controls. We used the log-rank test to test for statistically significant differences between survival curves. We performed a side-by-side comparison of the survival curve from our cohort with two from a study by Turesson and colleagues ("RA Cohort" — 412 patients with RA; and "exRA"—169 patients who developed extra-articular manifestations[31]) and "Age Cohort"—age-matched and derived from United States white population life tables. We used Cox proportional-hazards regression to assess the impact of lung fibrosis (i.e., "fibrotic" vs. "non-fibrotic") on survival while controlling for other potentially important predictors. The assumption of proportional hazards for the main effect (i.e., "fibrotic" vs. "non-fibrotic") was confirmed with a log(−log) plot. Bivariate analyses were run on candidate variables; those with $p < 0.15$ were included in the final multivariable model. To develop the most parsimonious model, we used candidate variable selection techniques. We ensured model stability by using stepwise, forward and backward (entry of any variable with a p-value<0.15 and retained any variable with a p-value <0.15) techniques in the "selection=" option in SAS PROC PHREG. We considered $p < 0.05$ to represent statistical significance. All data analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Baseline demographics, histopathologic findings and physiology

Baseline demographics of the cohort stratified on the presence or absence of fibrosis are listed in Table 1. Over half the subjects were male. Most were current or former smokers. A UIP-pattern was identified in 31% of subjects. DIP (6%) and LIP (2%) were rarely identified. The majority of subjects had restrictive physiology and impaired diffusion on pulmonary function studies.

Survival

The overall survival of all patients in the cohort is shown in Fig. 1. Median survival was 1360 days, and there were 40 deaths during this time. Survival for the entire cohort appeared similar to that for historical control subjects with exRA, worse than all-comers with RA[31] and worse than age-matched controls from the general population (the Age Cohort).[31]

Table 1 Baseline demographics. Baseline demographics for patients grouped by the presence or absence of fibrosis on biopsy.

	Fibrotic ILD	Non-fibrotic ILD	Total
N	23	25	48
Age, yr[a]	61 (11.1)	59 (11.1)	60 (11.1)
Gender			
Male	15	12	27
Female	8	13	21
Smoking Status			
Never	6	12	18
Former	11	6	17
Current	4	3	7
Unknown	2	4	6
Pathology (*N*)	fNSIP (4) uILD (4) UIP (15)	Bronchiolitis (6) DAD (6) DIP (3) LIP (1) cNSIP (2) OP (7)	
Physiology			
%FEV_1[a]	65 (23.1)	57 (25.8)	61 (24.2)
%FVC[a]	64 (17.5)	59 (18.5)	61 (17.9)
FEV_1/FVC[a]	76% (16.2)	76% (18)	76 (16.8)
%DLCO[a]	41 (12.6)	55 (13.4)	48 (12.6)
%TLC[a]	68 (10.5)	77 (20.5)	73 (17)

[a] Continuous variables are expressed as mean (standard deviation).

Effect of fibrosis on survival

Subjects with fibrotic RA-ILD had worse survival than subjects with non-fibrotic ILD (Fig. 2, log-rank $p = 0.02$).

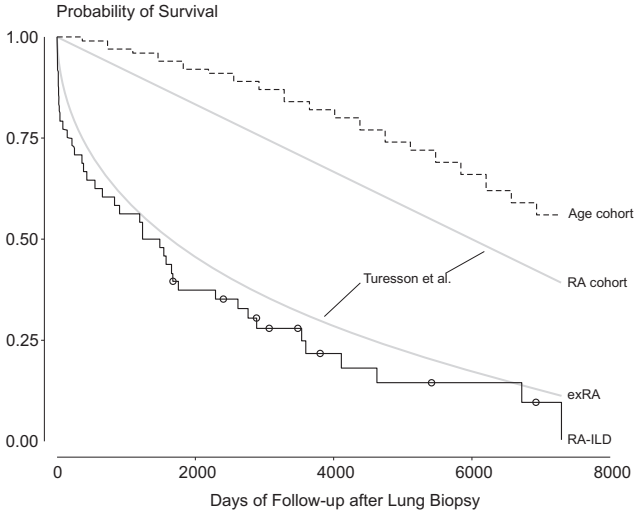

Figure 1 Kaplan Meier curves comparing patients with RA and ILD (RA-ILD), RA with all extra-articular manifestations (exRA), all-comers with RA (RA cohort) and age matched controls (age cohort).

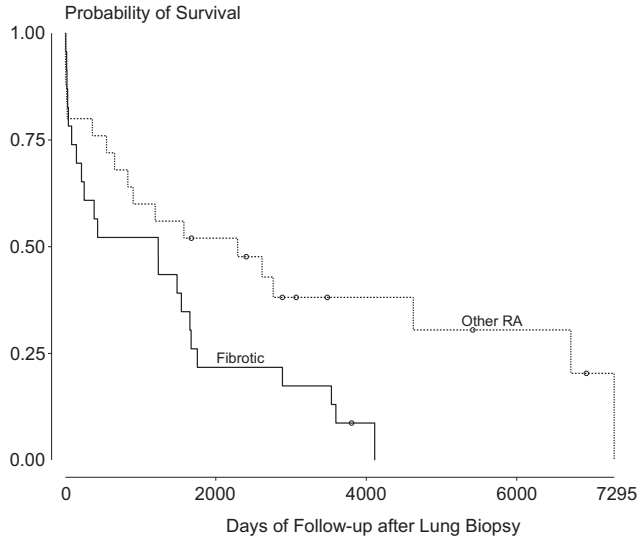

Figure 2 Kaplan Meier curves comparing RA patients with and without fibrotic ILD (log rank $p = 0.02$).

Survival for subjects with RA-UIP (Fig. 3) was similar to that of FVC- and DLCO-matched historical controls with IPF (log-rank $p = 0.94$). Results of the bivariate analyses are displayed in Table 2. In a multivariable model that included potentially influential predictors (as determined by the bivariate analyses) and was the same regardless of the selection technique used, the only two independent predictors of mortality were age and the presence of fibrosis. Thus, even when controlling for age (hazard ratio [HR] = 1.04, $p = 0.01$) the presence of lung fibrosis (HR = 2.1, $p = 0.02$) was an independent predictor of mortality. There was no difference in survival for patients with UIP, fNSIP or uILD (data not shown).

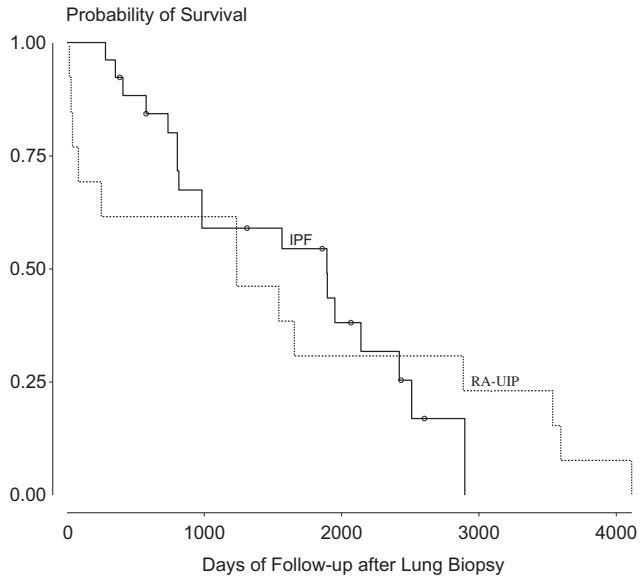

Figure 3 Kaplan Meier curves comparing RA-UIP with FVC- and DLCO matched historical controls with IPF (log rank $p = 0.94$).

Table 2 Potential predictors of survival and results of bivariate analyses.

	Hazard ratio	Confidence interval	*p*-value
TLC	1.0	0.98—1.02	0.9
FVC	0.9	0.98—1.01	0.5
DLCO	0.9	0.98—1.01	0.5
Age	1.04	1.01—1.07	0.01
Gender	1.8	0.92—3.41	0.08
Presence of fibrosis	2.1	1.11—4.26	0.02

Discussion

Histologically confirmed ILD in patients with RA confers a prognosis much worse than that seen in an age-matched healthy control population and worse than for all-comers with RA. The majority of our study group had histologic patterns of injury classifiable by current ATS/ERS consensus guidelines for the idiopathic interstitial pneumonias (IIP).[30] UIP was the most common pattern of interstitial pneumonia, accounting for nearly a third of all biopsies and two thirds of those with established lung fibrosis.

The presence of fibrosis in surgical lung biopsies from patients with RA is associated with shortened survival. In our cohort, patients with fibrotic forms of RA-ILD had a risk of dying two times the risk of RA patients with non-fibrotic lung disease. Baseline pulmonary physiology was not a predictor of survival, but histologic pattern (or more precisely, the presence of fibrosis, regardless of specific injury pattern) was. We included fNSIP in a category of patients that included UIP and uILD for a number of reasons. In patients with idiopathic interstitial pneumonia (IIP), those with fNSIP on surgical lung biopsy have a worse prognosis compared to cNSIP.[32] Also, survival is better for patients with fNSIP compared to those with UIP at 5 years, but this difference decreases at the 10-year mark (10-year survival for fNSIP is 35% compared to 15% for UIP).[33] In our patients, there was no difference in survival in patients with fNSIP when compared to uILD or UIP (data not shown).

We observed no statistically significant difference in survival between subjects with RA-UIP and matched IPF controls. Our results add to the ongoing debate on whether UIP in patients with connective tissue disease (CTD) carries a prognosis different from IPF. Turesson et al. reviewed 424 cases of RA and concluded that most of the excess mortality occurred in patients with extra-articular manifestations (including pleuritis, pulmonary fibrosis and organizing pneumonia).[31] Subjects in our cohort had survival that paralleled survival in subjects with all exRA.

Other investigators have compared the survival of patients with connective tissue disease-related ILD (CTD-ILD) to survival for patients with idiopathic interstitial pneumonia. Hubbard and colleagues performed a survival analysis of patients from the U.K. General Practice Research Database and found that survival among patients with CTD-related fibrosing ILD (80% with RA) was similar to that for IPF—each group had an average survival of less than three years.[26] Lee and co-investigators examined 18 patients with

RA who underwent surgical lung biopsy and observed that a UIP-pattern was most common.[21] Over a median of 50 months of follow-up, the only deaths they observed ($N = 5$) were in the subgroup with UIP-pattern histology. Rajasekaran and colleagues observed better survival among 18 patients with RA-related ILD (either "alveolitis" or fibrosis on HRCT scan) than among controls with IPF (60 mos vs 27 mos, $p = <0.05$).[27] Park and colleagues have conducted the largest study aimed at comparing the clinical features and survival of subjects with CTD-ILD to those among subjects with IIP. They observed longer survival for subjects with CTD-ILD than IIP and, contrary to previous assertions, the effect was not solely because of a higher incidence of NSIP-pattern pathology among those with CTD; rather, it was largely due to significantly better survival in subjects with CTD-UIP than those with IPF.[28] Interestingly, they observed no difference in survival between the subgroup of subjects with RA-UIP and those with IPF. Recently, Song and colleagues identified the presence of RA as the only significant predictor of survival among a cohort consisting of subjects with various CTD and UIP-pattern histology.[34]

There are limitations to this study. Selecting subjects from the two academic referral centers could introduce tertiary referral bias. There also is an inherent selection bias in our subjects with RA-ILD; they represent a subset of RA patients with either severe pulmonary symptoms or atypical features that led to a surgical lung biopsy. Whether the results translate to patients without symptoms and subtle chest imaging abnormalities, or those with symptoms and ILD on chest imaging that have not undergone surgical lung biopsy requires further investigation. The impact of fibrosis on survival may be a more general phenomenon in ILD and not specific to RA-ILD. Indeed, fibrosis has been shown to impact survival in other ILDs.[33,35,36] The small number of subjects limits our ability to detect other differences between the groups that may have impacted survival. Another limitation relates to more precise characterization of the RA phenotype of these subjects. Autoantibody test data were not available on these subjects and this cohort predates the routine use of anti-cyclic citrullinated peptide (anti-CCP) testing. Because it is not yet known whether the presence of rheumatoid factor or anti-CCP antibodies convey and clinical significance in regards to RA-ILD, it would be of interest to know the autoantibody profile of this and subsequent cohorts of RA-ILD. Other variables that were not measured such as 6 min walk distance and pulmonary artery pressures may also have had an impact on survival. Finally, recent data suggests that HRCT findings (a definite UIP pattern with traction bronchiectasis and honeycomb fibrosis) are associated with a worse survival.[37] We were unable to analyze the relationship between HRCT findings and outcome in this cohort. It is possible that this association may be strong enough to obviate the need for biopsy. Further studies are needed to look at the specific pathologic subtypes in relation to clinical course and decline in pulmonary function as well as the association of radiographic findings in comparison with pathologic subtype with outcome. Despite these limitations, this study has merits: it clarifies the usefulness of histologic data in prognostication for patients with RA-ILD and adds to the growing debate on survival differences between idiopathic and CTD-related ILD.

In conclusion, we examined the effect of an underlying pattern of fibrosis on the survival of patients with RA-ILD and found an overall decreased survival in these patients, while those with a UIP histologic pattern had an outcome similar to those with IPF.

Authors contributions

Solomon — data analysis, manuscript writing.

Ryu, Tazelaar, Myers, Tuder, Cool — pathology review.

Swigris, Fischer, Brown — data analysis, manuscript editing.

Conflict of interest statement

There are no conflicts of interest between the authors and any material presented in this manuscript.

The work was performed at National Jewish Health in Denver, Colorado and the Mayo Clinic in Rochester, MN.

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