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Early View

Research letter

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Duration of Rheumatoid Arthritis and the Risk of Developing Interstitial Lung Disease

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To the Editor:

Rheumatoid arthritis (RA) is an autoimmune disease that classically presents as a symmetric inflammatory polyarthritis. Extra-articular manifestations are prevalent, with the lungs being the most common site[1], and interstitial lung disease (ILD) being the most severe form of pulmonary involvement. In some studies, the median survival of patients with RA and a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) is around 3 years (similar to that in idiopathic pulmonary fibrosis [IPF][2,3]); however, in other studies, median survival is greater than 7 years[4,5]. When present, ILD accounts for 10-20% of all deaths in this patient population[6].

There have been many reported risk factors for ILD in patients with RA, including male gender, the severity of RA, and cigarette smoking [7-,9]. High titers of circulating autoantibodies (rheumatoid factor, anti-cyclic citrullinated (CCP) antibodies) may also predict ILD[10,11]. RA-ILD onset has previously been shown to occur in the 6th or 7th decade[12], prompting many to think of ILD as a late occurring phenomenon in RA. In a single-center, retrospective study of 582 subjects with RA, of which only 46 had RA-ILD, every decade increase in age at the time of RA diagnosis was associated with a 41% increased risk of RA-ILD[9]. Though it is occasionally reported in the literature that a longer duration of RA is a risk factor for ILD, there are no supporting data[13-15].

The aim of this retrospective, single center study, was to evaluate duration of rheumatoid arthritis as a risk factor for ILD and to determine whether duration of RA and age correlated with a radiologic pattern of nonspecific interstitial pneumonia (NSIP) or UIP. Our institutional research database was queried for all subjects with a diagnosis of RA-ILD, with radiological UIP or NSIP pattern, between 2000 and 2014 (n=137). Subjects without sufficient data to determine a date of ILD diagnosis were excluded, with final cohort including 121 subjects. The date of ILD diagnosis was defined as the earlier between the first report of ILD on imaging, the first date an outside pulmonologist confirmed a diagnosis of ILD, or the first visit

with an ILD specialist. A “concomitant” diagnosis of RA and ILD is defined as both conditions being diagnosed within a year of each other to account for the time from symptom onset to diagnosis. For initial analysis, all 121 patients in the cohort were included. In assessment of ILD diagnosis concomitant to, or after RA diagnosis, patients with preceding ILD diagnoses were excluded. Each subject’s HRCT scan was independently reviewed by two expert thoracic radiologists (JC and SH) with all disagreements resolved through discussions until consensus was reached. Scans were classified as showing a pattern of UIP (RA-UIP, including both “UIP” and “probable UIP”) or NSIP (RA-NSIP). Pulmonary function tests (PFTs) performed within 6 months of ILD diagnosis were recorded. This cohort has been previously reported on[4].

Statistical analysis was performed use SAS statistical software, Version 9.3 (SAS, Inc.; Cary, NC). For initial analysis, all 121 patients in the cohort were included. In certain analyses, we excluded subjects diagnosed with ILD > one year prior to the diagnosis of RA. We assessed time-to-ILD using the product-limit method, displayed results using Kaplan-Meier curves and compared curves using the log rank test. We used Cox proportional hazards to analyze time-to-ILD while controlling for potentially influential and confounding variables. We did not use selection methods but chose to include in our models clinically relevant potential confounders. We considered $p<0.05$ to represent

statistical significance.

As shown in Figure 1a**,** the mean age at diagnosis of RA-ILD in our study was 63 years and did not differ between UIP and NSIP. Subjects were more likely to be male (51%) and current or former smokers (61%). When divided by HRCT pattern, those with UIP were more likely to have smoked and had higher RF titers than subjects with NSIP. Treatments were similar between the two groups. Compared to subjects with RA-NSIP, those with RA-UIP were diagnosed with RA at an older age (53.5 +/- 16 vs. 45.6 +/- 14 y, p=0.01). After accounting for gender and smoking, this difference remained significant (p=0.001).

The range in age at diagnosis of ILD was similar between RA-UIP and RA-NSIP (Figure 1b). A significant percentage of patients had ILD either predating (10%, N=12) or concomitant with (17%, N=20) the diagnosis of RA. Forty nine percent of subjects developed ILD either before or within 5 years of the RA diagnosis and 67% of subjects developed ILD either before or within 13 years of being diagnosed with RA.

To evaluate the duration of RA prior to the diagnosis of ILD, only those subjects whose ILD diagnosis was "concomitant" with or following the diagnosis of RA were analyzed (N=109, Figure 1c). The mean duration of RA before the diagnosis of ILD was 12.4 years. Compared to NSIP, UIP was diagnosed closer to the onset of RA (10.6 vs. 18.3 years from diagnosis of RA, p=0.025, Figure 1d**).** When controlling for cofounders such as gender and smoking status, this difference remained significant (p=0.011). UIP was the ILD pattern in 84% of patients whose ILD was diagnosed prior to or concomitant with RA. When ILD was diagnosed ≥15 years after RA, patients were more likely to have NSIP than UIP (p=0.039).

The development of ILD is a dreaded consequence of rheumatoid arthritis. Though there are established risk factors there aren't good prediction models to help clinicians determine who with RA will get ILD and when in the course of RA their ILD will develop. Our results add to this field of study by shedding light on the age at time of ILD diagnosis and its relationship to the time of RA diagnosis with respect to radiologic ILD pattern.

Our study has limitations. This is a retrospective assessment of patients evaluated at a tertiary referral center and may not be representative of patients seen in a community pulmonary practice. We rely on the time of clinical diagnosis of RA and ILD and there is clear evidence that both synovitis and interstitial lung abnormalities can be present for months or years prior to a clinical diagnosis of RA or ILD. We did not analyze the impact of RA disease activity which may have impacted the timing, subtype and severity of the ILD diagnosis.

In conclusion, we found that the pattern of ILD in patients with RA depends on the age of RA diagnosis and the duration between the diagnosis of RA and the diagnosis of ILD. ILD diagnosis clusters around the time of RA diagnosis and has a mean age of onset similar to that seen in IPF. We also found that smokers are more likely to develop a UIP-pattern of lung involvement and the majority of subjects who developed ILD prior to RA had a radiologic UIP pattern. We are currently not able to predict who with RA will develop ILD, but the knowledge that ILD clusters around the time of RA diagnosis with a strong predilection for the 7th decade of life can aid clinicians in a timely diagnosis of ILD in those at risk.

Figure 1.

(a.) Baseline characteristics of cohort. (b.) Age at ILD diagnosis in rheumatoid arthritis patients. Histogram demonstrating number of patients at a given age (batched on 5-year intervals) at time of ILD diagnosis in all RA-ILD patients, and divided by HRCT radiologic pattern of UIP and NSIP.

(c.) Kaplan-Meier curve showing the time to development of ILD after the diagnosis of RA in all RA-ILD patients and divided by HRCT radiologic pattern of UIP and NSIP.

(d.) Duration of rheumatoid arthritis at time of ILD diagnosis. Histogram demonstrating number of patients at a given rheumatoid arthritis duration, defined as years from diagnosis of RA, (batched on 5 year intervals) at time of ILD diagnosis in all RA-ILD patients, and divided by HRCT radiologic pattern of UIP and NSIP.

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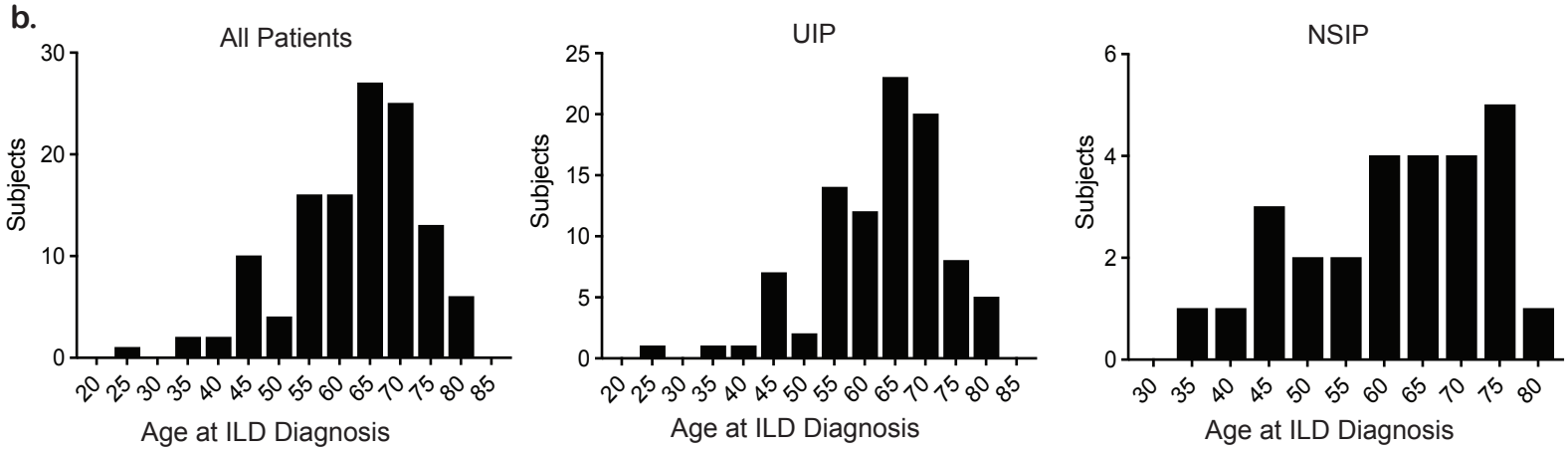
Figure 1.

a.

	Total Cohort	UIP	NSIP	P-value
N	121	94	27	
Male Gender, %	50%	51%	44%	0.663
Age at ILD diagnosis, mean	62.5	62.8	61.7	0.682
Age at RA diagnosis, mean	52	53.5	45.6	0.014*
Current or Former Smoker, %	61%	67%	41%	0.023*
CCP, mean	138.48	138.8	137.3	0.950
RF, mean	654.55	772.9	258.1	0.0023*
Methotrexate use	64%	63%	66%	0.822
Biologic use	66%	64%	74%	0.365
FVC (%), mean	70%	70%	69%	0.864
DLCO (%), mean	49%	50%	47%	0.632

b.



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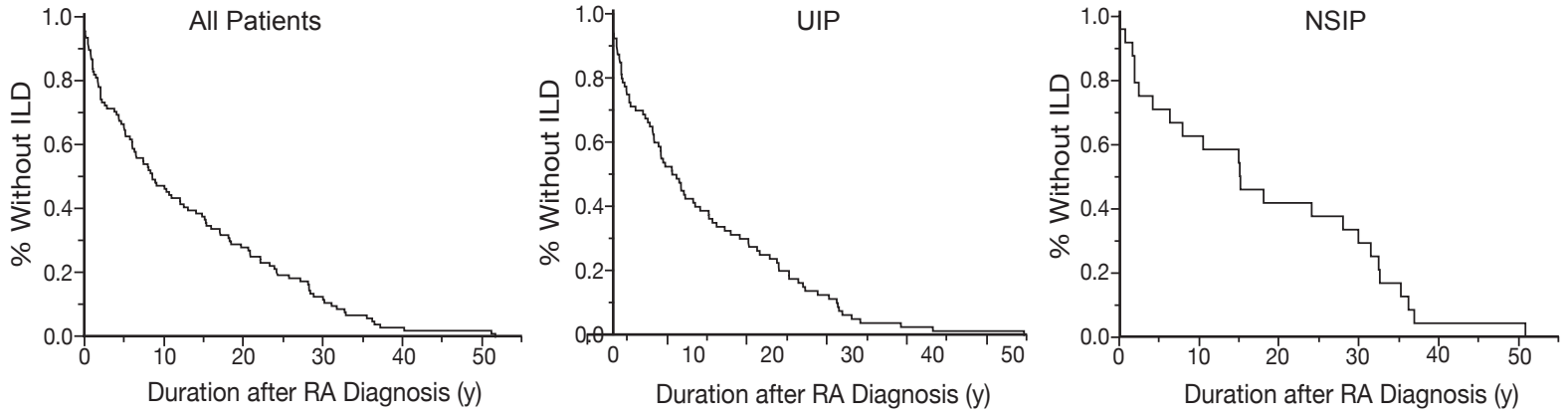

d.