**Usual Interstitial Pneumonia in Rheumatoid Arthritis-Associated Interstitial Lung Disease**

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## ABSTRACT

Interstitial lung disease is a common manifestation of rheumatoid arthritis, yet little is known about factors that influence its prognosis. We sought to determine whether the usual interstitial pneumonia pattern on high-resolution computed tomography (HRCT) has prognostic significance in rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Patients with RA-ILD were retrospectively identified (n=82). The relationship of definite usual interstitial pneumonia pattern on HRCT scanning to survival was determined and compared to a cohort of patients with radiologically-diagnosed idiopathic pulmonary fibrosis (n=51).

A definite usual interstitial pneumonia pattern was seen in 20 of 82 (24%) patients with RA-ILD. These patients had a worse survival compared to those without this pattern (median survival 3.2 versus 6.6 years), and a similar survival to patients with idiopathic pulmonary fibrosis. On multivariate analysis, definite usual interstitial pneumonia pattern on HRCT was associated with worse survival (hazard ratio 2.3). Analysis of specific HRCT features demonstrated that traction bronchiectasis and honeycomb fibrosis were associated with worse survival (hazard ratio 2.6 and 2.1, respectively). Female gender (hazard ratio 0.30) and higher baseline diffusing capacity (hazard ratio 0.96) were associated with better survival.

A definite usual interstitial pneumonia pattern on HRCT has important prognostic implications in rheumatoid arthritis-associated interstitial lung disease.

# INTRODUCTION

Interstitial lung disease (ILD) is a common extra-articular manifestation of rheumatoid arthritis (RA) and is a significant cause of morbidity and mortality in this patient population [1]. Using high-resolution computed tomography (HRCT) scanning, the estimated prevalence of RA-associated ILD (RA-ILD) among patients with RA is 19-56% [2-5]. Despite this considerable prevalence, little is known about the natural history of RA-ILD or features associated with prognosis.

Among patients with idiopathic interstitial pneumonia (IIP), HRCT and histopathologic patterns have been shown to have important prognostic significance [6, 7]. Most notably, the usual interstitial pneumonia (UIP) pattern, the histopathologic and radiologic pattern found in patients with idiopathic pulmonary fibrosis (IPF), is associated with poorer outcomes [7-9]. It remains unknown whether the UIP pattern in patients with RA-ILD has the same prognostic implications for these patients as it does for patients with IPF.

Unlike other forms of connective tissue disease related ILD (e.g. scleroderma, polymyositis, dermatomyositis, Sjögren's syndrome, and undifferentiated connective tissue disease) where the nonspecific interstitial pneumonia (NSIP) pattern predominates [10-18], RA-ILD has a higher proportion of patients with the UIP pattern [19, 20]. Patients with RA-ILD infrequently undergo surgical lung biopsy, making comparative histopathologic studies in RA-ILD challenging and at risk for selection bias.

Data from the IIP population have demonstrated that HRCT can accurately predict the presence of histopathologic UIP pattern in a subset of patients [7, 21, 22], and several studies in RA-ILD

have suggested a similar specificity [19, 20, 23, 24]. High-resolution computed tomography is non-invasive and commonly performed in RA-ILD patients, making it an ideal method for evaluating the prognostic significance of the underlying pattern. We hypothesized that a definite UIP pattern on HRCT in patients with RA (RA-UIP) would predict worse survival compared to non-UIP patterns (RA-nonUIP) and that survival of patients with RA-UIP would mirror the survival found in patients with IPF.

## MATERIALS AND METHODS

### Study Population

Patients with RA-ILD and IPF were identified from the longitudinal cohorts of ILD patients seen at the University of California, San Francisco (UCSF) and the Mayo Clinic Rochester from January 1, 2001 to November 1, 2008. Enrollment into these cohorts included permission to review all medical records. Demographics, clinical features, medication history, and pulmonary function tests on all patients were obtained via medical record chart review. The Institutional Human Subject Review Committee at each institution approved the protocol.

**RA-ILD** - Patients with RA at UCSF and Mayo Clinic were included in this study if they had: (1) a diagnosis of RA based on American College of Rheumatology criteria [25]; (2) evidence of diffuse ILD on HRCT (as defined by the interpreting radiologist), and (3) a HRCT performed within 1 year of ILD diagnosis available for review. Medical records were screened to exclude other likely causes of ILD.

**Idiopathic Pulmonary Fibrosis** - A retrospective cohort of patients with radiologically-diagnosed IPF seen at UCSF was used as a comparison group. Radiologically-diagnosed IPF was defined by the presence of a definite UIP pattern on HRCT in patients who met modified American Thoracic Society/European Respiratory Society (ATS/ERS) consensus diagnostic criteria [6].

*HRCT Analysis*

High-resolution computed tomography scans from subjects with RA-ILD were reviewed independently in a blinded fashion by two thoracic radiologists experienced in the interpretation of diffuse lung disease, with disagreements resolved by consensus. Standard high-resolution protocols were used to obtain images for evaluation. As this was a retrospective study, there was no single protocol that was utilized for all patients. All images were less than 2.0 mm in collimation and were reconstructed using high-resolution algorithms. In most cases, supine, prone and expiratory images were available for review. Each scan was scored as definite UIP or not definite UIP pattern, with the latter group further separated into indeterminate UIP/NSIP, likely NSIP, and other. Determination of definite UIP pattern was based on previously published guidelines [6, 9]. Briefly, scans consistent with definite UIP contained basilar predominant reticulation, traction bronchiectasis and honeycombing, with limited ground-glass abnormality. Predominant bibasilar ground-glass attenuation with limited to no reticulation and absent honeycombing was consistent with likely NSIP. Ground-glass attenuation, consolidation, reticulation, traction bronchiectasis, and honeycombing were scored as absent, mild, or moderate/severe for each HRCT.

*Histopathologic Analysis*

All available lung biopsy specimens were reviewed prospectively at the time of initial enrollment in the parent longitudinal cohort studies by a lung pathologist at each center with experience in the evaluation of diffuse lung disease and were classified using the histopathologic patterns described in the ATS/ERS International Consensus Classification of the IIPs [6] .

### Statistical Analysis

The primary analysis compared RA-UIP (as defined by the presence of a definite UIP pattern on HRCT) with RA-nonUIP (as defined by the absence of a definite UIP pattern on HRCT). Both groups were also compared with radiologically-diagnosed IPF. Descriptive data are presented as mean (standard deviation) unless otherwise noted. Inter-group comparisons were performed using the student's t-test or Wilcoxon rank sum test as appropriate for continuous variables, and the chi-squared test or Fisher's exact test as appropriate for categorical variables. Survival time was defined as time from initial clinic visit to death (as determined by review of clinic records and the Social Security Death Registry) or censoring. Kaplan-Meier curves were generated and compared using the log-rank test. Cox regression was performed to assess the predictive value of HRCT pattern and selected covariates identified a priori on survival time. Any variable with a p-value of <0.1 on bivariate analysis was included in multivariate analysis. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Statistical significance was defined as a p-value of ≤0.05.

## RESULTS

### Patient Population

Ninety-nine patients with RA-ILD were identified, of whom 84 had HRCTs that were available for review and performed within one year of the initial clinic visit (Figure 1). Two of these patients had HRCT patterns categorized as "other" (1 organizing pneumonia, 1 bronchiolitis) and were excluded from additional analyses as they did not have diffuse disease. Of the remaining 82 patients, an HRCT pattern of definite UIP was present in 20 (24%, kappa value 0.54), likely NSIP in 19 (23%), and indeterminate in 43 (52%).

Patient demographics and clinical characteristics of the 82 RA-ILD patients are presented in Table 1. Comparing the RA-UIP, RA-nonUIP and IPF groups, only age and gender differed significantly. When compared directly, there were no significant differences in age, gender, or pulmonary function between the RA-UIP group and either the RA-nonUIP or IPF groups. The RA-UIP group had fewer smokers than the RA-nonUIP group (p = 0.05). Longer RA disease duration was present in the RA-UIP group (p = 0.03). There were no significant differences in demographics or baseline characteristics between patients with RA-ILD and likely NSIP or indeterminate UIP/NSIP pattern on HRCT (data not shown).

### RA-UIP and Survival Time

Overall median follow-up in the RA-ILD cohort was 3.9 years (range 0.3 – 7.5 years). Median follow-up for the RA-UIP group was 3.9 years (0.5 – 7.5 years) and for the RA-nonUIP group was 3.9 years (0.3-7.5 years). Cause of death was available for only a small number of the RA-ILD cohort. Of the 8 known causes of death, 7 were pulmonary in nature and were felt to be at least partially related to the underlying RA-ILD.

The median survival time for all RA-ILD subjects was 5.0 years. RA-UIP had a worse median survival time than RA-nonUIP (3.2 vs 6.6 years, respectively, p = 0.04; Figure 2). Median survival time did not differ between the RA-UIP and IPF groups (p = 0.66). On bivariate analysis, gender, baseline percent predicted forced vital capacity (FVC), baseline percent predicted diffusing capacity for carbon monoxide (DLCO), and a definite UIP pattern on HRCT were associated with survival time in RA-ILD (Table 2). Age, duration of RA, and history of smoking were not predictive. Cox regression modeling demonstrated that a definite UIP pattern on HRCT, female gender, and increased baseline DLCO were associated with survival time (Table 2).

*HRCT Pattern, Radiologic Features, and Survival Time*

Estimated survival times between RA-ILD patients with a definite UIP pattern, likely NSIP pattern, and indeterminate UIP/NSIP pattern on HRCT were compared (Figure 3). RA-ILD patients with a definite UIP pattern had worse survival when compared to those with a likely NSIP pattern (p=0.02). Survival in patients with an indeterminate pattern did not differ statistically from those with a definite UIP pattern or a likely NSIP pattern (p = 0.15 and p=0.19 respectively). On bivariate survival analysis of specific HRCT features in the RA-ILD patients, reticulation, traction bronchiectasis, and honeycombing were significantly associated with worse survival time. Cox regression modeling found the presence and extent of traction bronchiectasis and honeycombing to be significant independent predictors of worse survival time (HR 2.6, p = 0.02 and HR 2.1, p = 0.002, respectively).

*HRCT Pattern and Histopathology*

Eighteen (22%) of the RA-ILD patients had histopathology available; four were transbronchial biopsies, one was an explanted lung, and the remaining thirteen were surgical lung biopsies (Figure 4). The median time from initial HRCT to obtaining a tissue specimen was 80 days (range -903 days to 3606 days). A majority of patients (72%) had tissue obtained within one year of the initial HRCT.

Only one of twenty patients (5%) with a definite UIP pattern on HRCT underwent surgical lung biopsy. This patient, who underwent surgical lung biopsy to help diagnose a focal pulmonary process and not the underlying chronic lung disease, had necrotizing pneumonia without note of an underlying ILD. One other patient with definite UIP pattern on HRCT underwent transbronchial biopsies which were indeterminate. Of the nineteen patients with likely NSIP pattern on HRCT, six (32%) underwent surgical lung biopsies (final histopathology: four UIP, two NSIP), two underwent transbronchial biopsies (final histopathology: one organizing pneumonia, one indeterminate), and one had an explanted lung reviewed (final histopathology: UIP). Finally, seven of 43 patients (16%) with an indeterminate pattern on HRCT had surgical lung biopsies (final histopathology: five UIP, one NSIP) and one had transbronchial biopsies (final histopathology: diffuse alveolar damage).

*Treatment regimen and survival in RA-ILD*

Medication regimens at the initial clinical visit and at last follow-up were reviewed (Figure 5). The majority of patients (80%) were treated with a regimen that included more than one agent. Prednisone was the most common medication used (71%). Methotrexate and an anti-tumor necrosis factor agent (anti-TNF) were the next most commonly used (28% and 27%,

respectively). Methotrexate and anti-TNF therapies were not associated with worse survival (data not shown).

## DISCUSSION

The results of this study demonstrate the prognostic significance of an HRCT pattern of definite UIP in patients with RA-ILD. As is true for patients with IPF compared to patients with other IIPs, patients with RA-UIP have a worse survival than patients with RA-nonUIP. Indeed, there was no detectable difference in survival between patients with RA-UIP and patients with IPF in this study. In further support of these findings, the extent of traction bronchiectasis and honeycomb fibrosis on HRCT were both powerful radiological predictors of survival time in RA-ILD. These data suggest that the identification of the UIP pattern in patients with RA-ILD is clinically relevant, both in defining the stage of disease (RA-UIP with minimal honeycomb fibrosis suggesting earlier disease) and the overall prognosis of the patient with RA-UIP. Similar relationships between the extent of honeycomb fibrosis and survival have been found in patients with IPF [26, 27].

*UIP Pattern and Survival*

Several studies of patients with RA-ILD have suggested a relationship of the UIP pattern to survival [20, 30, 28, 29]. Yousem and colleagues described 40 patients with RA-ILD, 5 of whom had UIP pattern on surgical lung biopsy [28]. Four of the UIP pattern patients died during follow-up, whereas only one of the nonUIP pattern patients died. Hakala and colleagues reported

on 24 patients with RA-ILD [29]. Two patients died; both had honeycombing present on surgical biopsy. Yoshinouchi and colleagues studied 16 patients with RA-ILD; nine had UIP pattern and seven had NSIP pattern. Contrary to other studies, survival in the NSIP group was worse (47% vs 77%) although two of the three NSIP deaths were from non-respiratory causes [20]. Park and colleagues reported on 28 biopsy proven RA-ILD patients as part of a larger connective tissue disease-related ILD cohort [30]. This study found a trend toward worse survival in RA-UIP patients as compared to RA-ILD patients with NSIP pattern (HR 18.95, 95% CI 0.67-513.65, p=0.08) [30]. These data support our findings.

Our data show a longer duration of RA in the RA-UIP cohort, suggesting RA-nonUIP may progress to RA-UIP over time. There are limited data addressing this hypothesis in patients with RA-ILD, and they are discordant. One study of RA-ILD patients found that those with a predominant reticular pattern on HRCT had a longer duration of RA than those with predominant ground-glass on HRCT [31]. However, a subsequent study of RA-ILD found that patients with an HRCT pattern consistent with NSIP had a longer duration of articular symptoms compared those with a HRCT pattern consistent with UIP [5]. It remains unclear if RA-nonUIP and RA-UIP represent a continuum of disease or are separate entities.


### Relationship of HRCT Pattern and Histopathology

Patients with RA-ILD infrequently undergo surgical lung biopsy, making comparative histopathologic studies in RA-ILD challenging and at risk for selection bias. Few of our RA-ILD patients had surgical lung biopsy performed; only two patients with definite UIP on HRCT

underwent histopathological evaluation (one surgical lung biopsy, one transbronchial biopsy). Thus, we cannot comment on the correlation of definite UIP pattern on HRCT and histopathology. However, studies in both RA-ILD and IIP have demonstrated that definite UIP pattern on HRCT is highly specific for UIP on biopsy [19, 21].

Tissue examination was more often sought in patients with a nonUIP HRCT pattern. Our data show that in the absence of a definite UIP radiographic pattern, the histopathologic findings are difficult to predict. In the cases with radiologic NSIP pattern or indeterminate pattern, a UIP pattern is commonly found on histopathologic examination. These results mirror findings in studies of IIP patients [7].

### Impact of Treatment on Survival

We did not find any relationship between the use of anti-TNF agents and survival time in our cohort of RA-ILD patients. There have been several case reports of anti-TNF agent use and acute worsening or death in RA-ILD patients [32-34]. However, a retrospective study utilizing a national registry of over 17,000 RA patients did not find any association between current anti-TNF use (infliximab or etanercept) and hospitalization related to ILD [35].

There are several limitations to our study. First, this is a retrospective study based on patients seen at pulmonary clinics at two tertiary care referral centers. It is likely that the patients seen at our centers represent a population with more advanced or difficult-to-treat disease, thereby introducing a selection bias. Compared to RA-ILD subjects in other recently published studies

[19, 30], our patients had a similar percent predicted FVC (69% vs. 67% in prior studies), but a somewhat lower diffusing capacity at baseline (48% vs 53-63% in prior studies).

Second, we recognize that we have misclassified some histopathological UIP as non-UIP (indeed, this is why we included only radiologically-diagnosed IPF patients as our control group). Given the high degree of specificity of a definite UIP pattern on HRCT for histopathological UIP, it is unlikely that definite UIP cases were misclassified. Thus, the discordance between radiologic and histopathologic pattern has, if anything, biased our results toward the null hypothesis by reducing the mean survival of the nonUIP group.

Finally, we are aware that there are other factors that could have influenced mortality in the RA-ILD group. We were not able to obtain information on extra-articular manifestations of RA (which are known to increase mortality) in our RA-ILD cohort. We are not aware of any data that suggest there is a difference in the prevalence of extra-articular manifestations based on the ILD pattern (i.e. RA-UIP versus RA-nonUIP) or that non-pulmonary deaths are preferentially increased in either group, but these issues should be addressed in subsequent studies.

In conclusion, our study demonstrates that the UIP pattern on HRCT is clinically relevant and suggests that all RA-ILD patients should undergo evaluation of their HRCT pattern. High resolution computed tomography is widely available, reliable in the hands of experienced radiologists, low-cost, and low-risk compared to surgical lung biopsy. Quantification of the extent of radiologic fibrosis lends additional prognostic value. Patients with UIP pattern and extensive fibrosis on HRCT should be counseled on their poor prognosis, and appropriate patients should be considered for lung transplantation. Whether or not RA-UIP is less responsive to immunomodulatory therapy than RA-nonUIP is unknown, and further studies are needed to

answer this question. In patients with indeterminate or likely NSIP pattern on HRCT, it remains unresolved whether or not surgical lung biopsy should be pursued. It is clear that many such cases will demonstrate histopathologic UIP, similar to what is seen in the IIPs. The clinical implications of these radiologically atypical UIP cases should be the focus of future research.

## ACKNOWLEDGEMENTS

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**FIGURE LEGENDS**

**Figure 1. Flowchart showing the HRCT pattern in patients with RA-ILD**

Eighty-four of 99 patients with RA-ILD had HRCTs available within one year of initial presentation and enrollment into a longitudinal cohort. The HRCT pattern distribution was as follows: 20 definite UIP, 19 NSIP, 43 indeterminate, and 2 with an alternate pattern. The two alternate pattern cases (organizing pneumonia [n=1], bronchiolitis [n=1]) were excluded from the study analysis.

Abbreviations: HRCT = high-resolution computed tomography; NSIP=nonspecific interstitial pneumonia; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; UIP = usual interstitial pneumonia
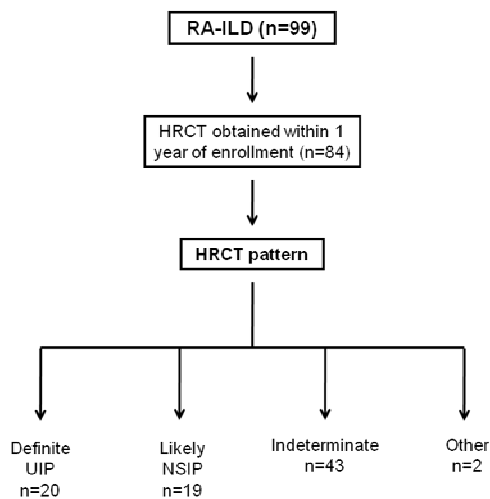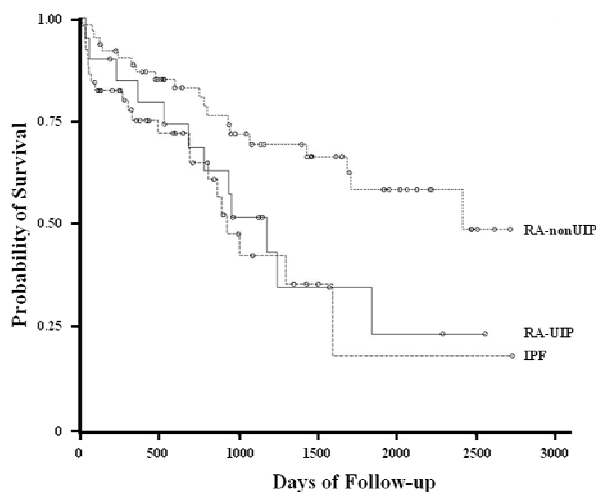


**Figure 2. The Kaplan-Meier survival curve for patients with RA-UIP, RA-nonUIP, and IPF.**

Comparing across all three groups, there were significant differences in survival estimates (p = 0.01). Estimated survival of RA-UIP was significantly worse than RA-nonUIP (median survival of 3.2 v 6.6 years, p = 0.04). Estimated survival of RA-UIP did not differ significantly from IPF (median survival of 3.2 v 2.6 years, p = 0.66).

Abbreviations: IPF = idiopathic pulmonary fibrosis; RA-nonUIP = non-usual interstitial pneumonia pattern in patients with rheumatoid arthritis; RA-UIP = usual interstitial pneumonia pattern in patients with rheumatoid arthritis



**Figure 3. The Kaplan-Meier survival curve for patients with RA-ILD based on the HRCT pattern**

Comparing across the three main HRCT patterns (definite UIP, likely NSIP, and indeterminate UIP/NSIP), there was a trend toward differences in survival estimates (p = 0.06). Estimated survival of definite UIP was significantly worse than likely NSIP (median survival of 3.2 v incalculable p = 0.02). Estimated survival for an indeterminate UIP/NSIP pattern did not differ

statistically from definite UIP or likely NSIP (median survival 6.6 v 3.2 years (p = 0.15) and 6.6 v incalculable (p = 0.19), respectively).
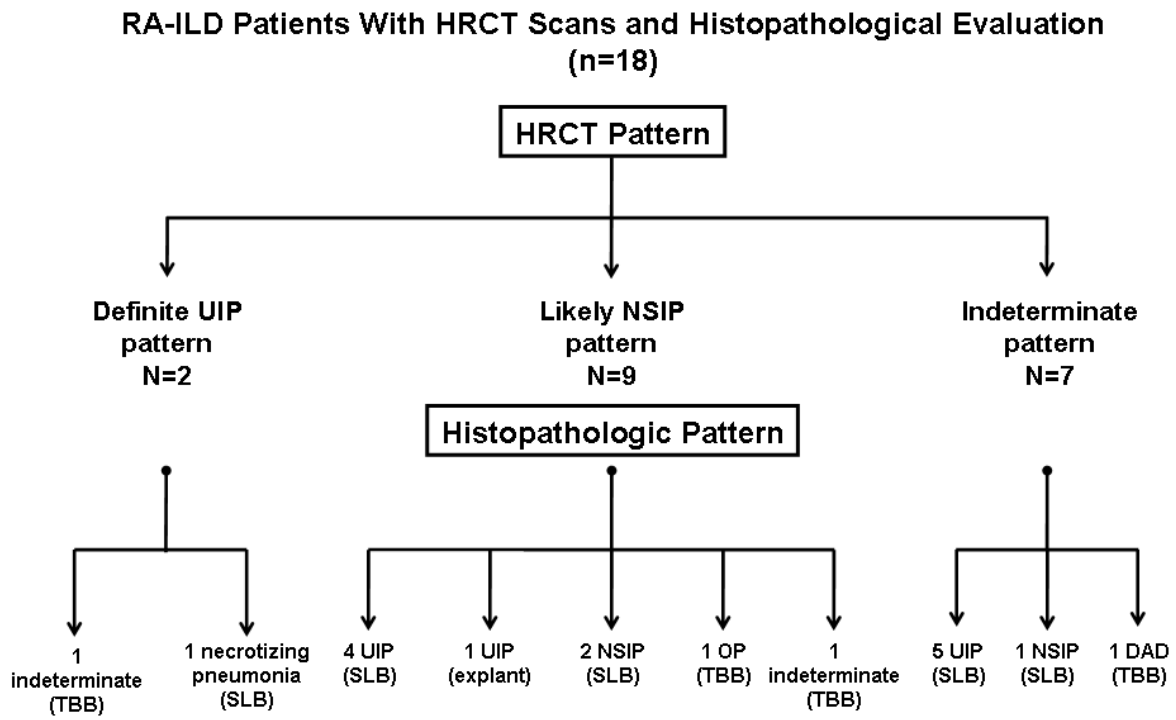
Abbreviations: HRCT = high-resolution computed tomography; NSIP = nonspecific interstitial pneumonia; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; UIP = usual interstitial pneumonia
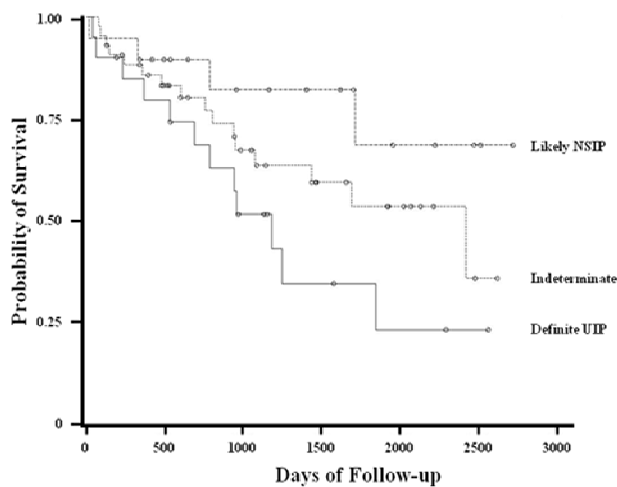


**Figure 4. Flowchart of histopathology and HRCT pattern in patients with RA-ILD**

Histopathology was available for 18 of the RA-ILD patients (2 with HRCT pattern of definite UIP, 9 with HRCT pattern of NSIP, and 7 with an indeterminate HRCT pattern).

Abbreviations: DAD = diffuse alveolar damage; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; UIP = usual interstitial pneumonia; SLB = surgical lung biopsy; TBB = transbronchial biopsy

RA-ILD Patients With HRCT Scans and Histopathological Evaluation (n=18)

HRCT Pattern

Definite UIP pattern N=2

Likely NSIP pattern N=9

Indeterminate pattern N=7

Histopathologic Pattern

1 indeterminate (TBB)

1 necrotizing pneumonia (SLB)

4 UIP (SLB)

1 UIP (explant)

2 NSIP (SLB)

1 OP (TBB)

1 indeterminate (TBB)

5 UIP (SLB)

1 NSIP (SLB)

1 DAD (TBB)

**Figure 5. Medication use in RA-ILD patients**

Medication regimens were reviewed from the time of initial and last follow-up visit. Prednisone was the most common agent prescribed, followed by methotrexate and an anti-TNF agent.

Abbreviations: anti-TNF = anti-tumor necrosis factor agent; MTX = methotrexate, RA-ILD = rheumatoid arthritis-associated interstitial lung disease.
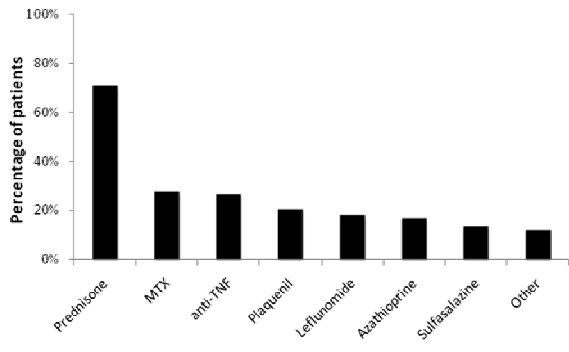
**Table 1.**

**Demographic and Clinical Characteristics**

| VARIABLE | STUDY POPULATIONS | | | p-values | | |
|---|---|---|---|---|---|---|
| | RA-UIP (n=20) | RA-nonUIP (n=62) | IPF (n=51) | Overall | RA-UIP vs. RA-nonUIP | RA-UIP vs. IPF |
| Age, years | 69 ± 6 | 65 ± 10 | 72 ± 9 | 0.001 | 0.15 | 0.08 |
| Male gender, % | 55 | 50 | 75 | 0.03 | 0.70 | 0.11 |
| Duration of RA, years* | 7 (3, 30) | 2 (0, 9) | N/A | N/A | 0.03 | N/A |
| Ever smoker, % | 55 | 77 | 76 | 0.12 | 0.05 | 0.07 |
| FVC, % predicted | 66 ± 25 | 70 ± 20 | 69 ± 21 | 0.72 | 0.39 | 0.63 |
| Diffusing capacity, % predicted | 50 ± 22 | 48 ± 21 | 41 ± 16 | 0.10 | 0.56 | 0.07 |

* Data for RA duration are presented as median (25th, 75th percentile)

Abbreviations: FVC = forced vital capacity; HRCT = high resolution computed tomography; IPF = idiopathic pulmonary fibrosis; N/A = not applicable; NSIP = nonspecific interstitial pneumonia; RA = rheumatoid arthritis; RA-ILD = rheumatoid arthritis associated interstitial lung disease; RA-nonUIP = non-usual interstitial pneumonia pattern in patients with rheumatoid arthritis; RA-UIP = usual interstitial pneumonia pattern in patients with rheumatoid arthritis; UIP = usual interstitial pneumonia

**Table 2.**

**Predictors of Survival Time in Patients with RA-ILD**

| Variable | Bivariate | | Multivariate | |
|---|---|---|---|---|
| | **Hazard ratio *** | **p-value** | **Hazard ratio *** | **p-value** |
| Female gender | 0.55 | 0.10 | 0.30 | 0.008 |
| Baseline FVC, % predicted | 0.98 | 0.01 | -- | -- |
| Baseline diffusing capacity, % predicted | 0.97 | 0.002 | 0.96 | 0.003 |
| HRCT pattern: definite UIP | 2.09 | 0.04 | 2.34 | 0.05 |

* Hazard ratios reflect the relative risk of death associated with the listed variable (or, for continuous variables, a one unit increase in the variable).

Abbreviations: FVC = forced vital capacity; HRCT = high-resolution computed tomography; RA-ILD = rheumatoid arthritis-associated interstitial lung disease; UIP = usual interstitial pneumonia