**Word counts:** Abstract 246/250, Text 3189/2500

Deleted: 2500

**Risk prediction model in rheumatoid arthritis-associated interstitial lung disease**

Ho Cheol Kim[1], Jeong Seok Lee[2], Eun Young Lee[2], You-Jung Ha[3], Eun Jin Chae[4], Minkyu Han[5], Gary Cross[6], Joseph Barnett[7], Jacob Joseph[8,9], Jin Woo Song[1]

[1]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea;
[2]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea;
[3]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, Republic of Korea;
[4]Department of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea;
[5]Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, Republic of Korea;
[6]Department of Radiology, Royal Free Hospital, Royal Free London NHS Foundation Trust, United Kingdom;
[7]Department of Radiology, Royal Brompton Hospital, Royal Brompton and Harefield NHS Foundation Trust, United Kingdom;
[8]Department of Respiratory Medicine, [9]Centre for Medical Image Computing, University College London, United Kingdom

**Corresponding Author:** Jin Woo Song, M.D. PhD

Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-Ro 43-Gil, Songpa-Gu, Seoul 05505, Republic of Korea.
E-mail: jwsongasan@gmail.com

**Running title**: Staging system in patients with RA-ILD

**Summary at a glance**

The risk prediction model for RA-ILD patients using age (≥ 60 years) and imaging parameters (extent of fibrosis at ≥ 20% of the total lung extent, a UIP pattern, and emphysema) were effective in predicting prognosis both in of the derivation and validation cohorts.

**Abstract**

**Background**: Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) has a variable clinical course, and its prognosis is difficult to predict. Moreover, risk prediction models for prognosis remain undefined.

**Methods**: The prediction model was developed using retrospective data from 153 patients with RA-ILD and validated in an independent RA-ILD cohort (n=149). Candidate variables for the prediction models were screened using a multivariate Cox proportional hazard model. Concordance statistics (C statistics) were calculated to assess and compare the predictive ability of each model.

**Results:** In the derivation cohort, the median follow-up period was 54 months, and 38.6% of the subjects exhibited a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) imaging. In multivariate Cox analysis, old age [≥60 years, hazard ratio (HR), 2.063], high fibrosis score (≥20% of the total lung extent; HR, 4.585), a UIP pattern (HR, 1.899), and emphysema (HR, 2.596) on HRCT were significantly poor prognostic factors and included in the final model. The prediction model demonstrated good performance in the prediction of five-year mortality (C-index, 0.780; $P < 0.001$); furthermore, patients at risk were divided into three groups with 1-year mortality rates of 0%, 5.1%, and 24.1%, respectively. Predicted and observed mortality at 1, 2, and 3 years were similar in the derivation cohort, and the prediction model was also effective in predicting prognosis of the validation cohort (C-index, 0.638; $P < 0.001$).

**Conclusions:** Our results suggest that a risk prediction model based on HRCT variables could be useful for patients with RA-ILD.

**Key Words:** interstitial lung diseases; prognosis; rheumatoid arthritis

## Introduction

Clinically evident interstitial lung disease (ILD) occurs in approximately 10% of the patients with rheumatoid arthritis (RA) and is a leading cause of death.[1-3] While connective tissue disease-associated ILD (CTD-ILD) usually has a more favorable course compared with that of idiopathic interstitial pneumonia, the prognosis of RA-ILD is variable and challenging to predict.[4] Previous studies have reported that a usual interstitial pneumonia (UIP) pattern,[5-7] old age,[8] male sex,[9,10] and reduced baseline lung function[7] are associated with mortality in patients with RA-ILD. Recently, some reports have suggested that imaging parameters may be associated with the prognosis of patients with RA-ILD.[11-13] In a study involving 65 patients with RA-ILD, Ito et al. also reported that radiological fibrosis score (sum of the extent of reticulation and honeycombing) was associated with worse survival.[12] Additionally, a recent study demonstrated that RA-ILD patients with emphysema experienced worse outcomes (mean survival, 75.5 vs. 161.7 months; $P < 0.001$) than did those without emphysema.[13] However, in previous studies, the number of patients was small, and the development of multi-dimensional risk prediction models for RA-ILD has not yet been reported.

The Gender-Age-Physiology (GAP) model is a validated risk prediction model for the prognosis of idiopathic pulmonary fibrosis (IPF).[14] Previous studies have suggested that the GAP model would also be useful for predicting RA-ILD-related mortality.[15,16] However, CTD-ILD, including RA, may be accompanied by the involvement of the airway, blood vessel, and pleura.[17] Therefore, the utility of physiological variables, such as lung function, can be limited in the prediction of RA-ILD prognosis. Additionally, the GAP model was not developed considering important prognostic factors for RA-ILD, such as a UIP pattern and emphysema on high-resolution computed tomography

(HRCT).[7,10,13,18] Therefore, this study aimed to investigate predictors of mortality, including HRCT variables, and to develop a multi-dimensional risk prediction model for patients with RA-ILD.

## Materials and Methods

### Study population

The derivation cohort included a total of 153 patients with RA-ILD (biopsy proven cases, n = 33) who were diagnosed from May 1995 to July 2015 at the Asan Medical Center, Seoul, Republic of Korea. The validation cohort comprised 149 patients with RA-ILD, who were diagnosed between July 2000 and September 2017, at the Seoul National University Hospital, Seoul, Republic of Korea. The diagnosis of RA was made by a rheumatologist according to the revised criteria of the American College of Rheumatology/European League Against Rheumatism Collaborative Initiative,[19] and that of ILD was made based on HRCT imaging and/or pathological findings. The study protocol was approved by the Institutional Review Board of Asan Medical Center (approval number: 2017-1661) and Seoul National University Hospital (approval number: 1801-044-931). Given the retrospective nature of the present study and the use of anonymized patient data, requirements for written informed consent were waived.

### Methods

Clinical and survival data of all patients were retrospectively collected from medical records, telephone interviews, and/or the records from the National Health Insurance of Korea. Spirometry, diffusing capacity of the lung for carbon monoxide (DLco), and total lung capacity (TLC) were measured according to the recommendations by the

American Thoracic Society (ATS)/European Respiratory Society (ERS), and the results were expressed as percentages of the normal predicted values.[20,21]

**HRCT evaluation**

Each HRCT scan image was evaluated independently by two specialized radiologists (GC, JB), who were blinded to all clinical information. The extent of ground-glass opacities, reticulation, consolidation, and honeycombing was semi-quantitatively scored on a lobar basis estimated to the nearest 5%. The extent of traction bronchiectasis was scored on a 19-point scale. The most disparate 5% (two standard deviations) of the values and any disagreement between two radiologists were resolved by a third radiologist (JJ). All CT variables were expressed as a percentage of the total lung volume. Fibrosis score was defined as the sum of reticulation and honeycombing scores. Emphysema presence and overall HRCT patterns (categorized as UIP or non-UIP pattern) were confirmed by two radiologists (JJ and EJC). A UIP pattern was defined as subpleural, basal predominance of reticular abnormalities, honeycombing with or without traction bronchiectasis, and absence of inconsistent findings with a UIP pattern such as extensive ground-glass opacities, micro-nodules, discrete cysts, or segmental/lobar consolidations.[22]

**Statistical analysis**

All values for continuous variables are expressed as mean ± standard deviation and those for categorical variables are expressed as percentages (see supplementary information). Candidate variables for prediction models were screened using a multivariate Cox proportional hazard model. For the survival analysis, start date was

date of initial HRCT, and date of vital status ascertainment was December 31, 2017 (derivation cohort), and July 1, 2018 (validation cohort). When performing the survival analysis, we censored the following conditions: (1) survival at certain time point (1, 2, 3, and 5 year), and (2) follow-up loss. The performance of prediction models was compared by calculating their concordance statistics (C statistics), which is conceptually similar to the area under ROC curve (AUC). C statistical data between the prediction models were compared using the method proposed by Kang L et al.[23] The performance of various models was also compared by net reclassification improvement (NRI) and integrated discrimination improvement (IDI).[24] After selecting the final model, each variable was assigned a value from 0 to 2 points (the total points ranged from 0 to 5) based on Cox coefficient values. According to the total points of the variables, a staging system was created by classifying subjects into one of the three groups based on the results of pairwise Fisher's exact test. Internal validation using bootstrap was performed to control the concordance overestimate. Finally, predicted and observed mortality rates were descriptively compared at 1, 2, and 3 years after diagnosis. All *P* values were two-tailed, with the statistical significance set at a *P* value of $< 0.05$. All data were analyzed using SPSS version 20.0 for Windows and R software version 3.5.1.

## Results

### Baseline clinical characteristics

The median follow-up period for the derivation cohort was 54 months [interquartile range (IQR), 37–95 months], the mean age of the subjects was 61.0 years, 57.5% of the cohort consisted of females, and 43.1% were ever-smokers (Table 1). Surgical lung biopsy was performed in 33 (21.6%) patients, and UIP was the most common

histopathological pattern (60.6%), followed by nonspecific interstitial pneumonia (30.3%), and organizing pneumonia (9.1%), respectively. Forty-five (29.4%) patients died within 5 years after diagnosis. Non-survivors were older, had lower lung function, and tended to have a higher GAP stage as opposed to survivors (Table 1). During follow-up, there was no significant difference in treatment between survivors and non-survivors (Table S1 in Supplementary Information).

**HRCT findings**

A UIP pattern was identified on HRCT in 59 patients (38.6%). Non-survivors had higher scores for reticulation, honeycombing, traction bronchiectasis, and fibrosis score compared with survivors (Table 2). Non-survivors also more frequently exhibited UIP pattern and emphysema compared with survivors.

**Risk factors for mortality**

In the univariate Cox analysis, old age, low forced vital capacity (FVC), high consolidation and fibrosis score, emphysema, and UIP pattern on HRCT were significant predictors of 5-year mortality (Table S2 in Supplementary Information). Among them, continuous variables, including age, FVC, consolidation, and fibrosis score were converted into categorical variables based on the optimal cut-off value by ROC analysis. In multivariate analysis, old age (≥60 years), high fibrosis score (≥20%), a UIP pattern, and emphysema were independent predictors of 5-year mortality (Table 3).

**Development of the risk prediction model**

Among various prediction models, the model developed using old age (≥60 years) and HRCT variables (fibrosis score of ≥20%, a UIP pattern, and emphysema) demonstrated the best performance for predicting mortality (C-index: 0.780) and was consequently selected (Table 4). Additionally, this model demonstrated better performance than that demonstrated by the GAP model (C-index, 0.780 vs. 0.623; $P < 0.001$) (Table 4). Based on the coefficient values, the points (range, 0–2) were assigned to each independent predictor of a five-year mortality to obtain the total points (range 0–5) (Table 5). Survival rate decreased as the total points increased ($P < 0.001$) (Figure S1 in Supplementary Information). Based on the total points that demonstrated a similar survival pattern, patients were divided into three groups: stage I (0 point), stage II (1–3 points), and stage III (4-5 points) (Table 5). To reduce the overfitting bias of our model, bootstrap was performed 1000 times. Consequently, the median value of the bootstrap-adjusted concordance was 0.751, and the 2.5–97.5% quartile value was found to be in the range of 0.694–0.809. Survival rates were significantly different at each stage ($P < 0.001$) (Figure 1A). The predicted and observed survival rate at 1–3 years were similar in the derivation cohort (Table S4 in Supplementary Information).

Deleted: S3

**Validation of the risk prediction model**

The median follow-up period in the validation cohort was 42 months (IQR, 17–87 months). The mean age of the subjects was 64.5 years, 40.9% were males and 33.3% were ever-smokers. The validation cohort was older, and exhibited higher lung function, and lower prevalence of emphysema and high fibrosis score (≥20%) than the derivation cohort (Table S5 in Supplementary Information). Similar to the derivation cohort, the risk prediction model was useful for mortality prediction (C-index, 0.638, $P < 0.001$) in

Deleted: S4

the validation cohort, and Kaplan–Meier survival analysis revealed a significant difference in survival at each stage ($P < 0.001$) (Figure 1B).

**Adjustment of the risk prediction model**

To improve the applicability of the risk prediction model in patients with an indeterminate fibrosis score (ranging from 10% to 30%), we investigated the substitution parameter for fibrosis score. In ROC analysis, the optimal cut-off level of FVC for predicting 20% of the fibrosis score was 72% predicted [C-index = 0.775 ($P < 0.001$)], and as shown by quadratic function, 70% predicted of the FVC threshold corresponded to 20% of the fibrosis score threshold (Figure S2 in Supplementary Information). When FVC (< 70%) was substituted for fibrosis score (≥20%) among patients with an indeterminate fibrosis score (C-index: 0.777, $P < 0.001$, Table S6 in Supplementary Information), survival rates were also significantly different at each stage in the derivation cohort (Figure S3 in Supplementary Information).

Deleted: S5

## Discussion

In this study, imaging parameters were superior to physiological parameters as mortality predictors in patients with RA-ILD. The risk prediction model based on imaging parameters was effective in predicting the prognosis of both cohorts. This model demonstrated better performance in predicting the mortality of RA-ILD patients than the existing GAP model.

Our results demonstrated that imaging parameters including a UIP pattern and high fibrosis score were independent prognostic factors for patients with RA-ILD. The results from previous studies also support our findings.[6,7] Among 137 patients with RA-

ILD (including 108 UIP and 29 nonspecific interstitial pneumonia (NSIP) on HRCT), Solomon et al. reported that RA-UIP patients experienced worse survival than did those with RA-NSIP (median 10.18 vs. 13.62 years; $P = 0.02$).[6] Among 82 patients with RA-ILD, Kim et al. also reported that the median survival of RA-UIP patients was not different from that of IPF patients (3.2 vs. 2.6 years; $P = 0.66$), but it was shorter than that of RA-non-UIP patients (3.2 vs. 6.6 years; $P = 0.04$).[7] With regard to the fibrosis score, a recent study involving 65 patients with RA-ILD revealed that a high fibrosis score (≥20% of the total lung extent) on an HRCT scan predicts mortality (HR, 9.019; $P < 0.05$);[12] this result and that of the study on systemic sclerosis-associated ILD (SSc-ILD)[25] was compatible with the findings of our study, in that the optimal cut-off value of fibrosis score was 20% of the total lung extent.

In our study, emphysema was associated with poor prognosis of patients with RA-ILD. Patients with CTD may have combined pulmonary fibrosis and emphysema (CPFE).[26] Although smoking is the main cause of emphysema,[27,28] there is growing evidence that autoimmune pathways may contribute to the development of emphysema, especially among RA patients.[29,30] A recent study supports this hypothesis; Jacob et al. reported that among 245 patients with RA-ILD, emphysema was common (approximately 27%) in never-smokers and was independently associated with mortality both in never-smokers (HR 2.30, $P = 0.04$) and smokers (HR 2.16, $P = 0.047$).[13] Although emphysema has recently been reported to make no prognostic difference in IPF,[31,32] it may be an important prognostic factor for patients with RA-ILD.

Although the GAP model was developed and validated to predict mortality in patients with IPF,[14,33] some studies have suggested that the GAP model could be applied for estimating the prognosis of patients with RA-ILD.[15,16] Morisset et al. reported that in

309 patients with RA-ILD, the C-index of GAP model for mortality risk prediction was 0.746, and the discriminative ability of the prediction model remained unchanged by adding UIP pattern on HRCT scan.[15] Nurmi et al. revealed that among 59 patients with RA-ILD, the GAP score (HR 1.56, $P = 0.004$) or ILD GAP score (HR 1.51, $P = 0.026$) were significant predictors for mortality in a univariate analysis;[16] however, both scores had no statistical significance in mortality prediction after adjustment for age. These conflicting results suggest that the GAP model may not be the optimal model for predicting the prognosis of RA-ILD, probably owing to the limited role of lung function and different demographic features (younger age and female predominance) in this group.[7,34] The GAP model also did not consider the important prognostic factors for RA-ILD, such as a UIP pattern and emphysema on HRCT.[7,10,13,18] Our results support the following hypothesis: the CT-based prediction model demonstrated better performance in predicting the mortality of patients with RA-ILD than did the GAP model. Recently, Jacob et al. reported that a radiology-based prediction model, which was a combination of the scleroderma and Fleischner systems, identified 23% of RA-ILD cohort with an IPF-like progressive fibrotic phenotype (C-statistic, 0.71).[35] However, we developed a risk prediction model specific for patients with RA-ILD, and validated the model in a separate RA-ILD cohort.

There were several limitations in current study, among which were its retrospective design and the fact that it was conducted in a single tertiary referral center. In addition, the development and validation of the model were both conducted in Korean patients and this may limit the generalizability of our study results. However, the demographic features and lung function of our patients were comparable with those reported in other studies.[6,18] Second, the treatment was not considered in our model. However, no treatments have

been proven yet for RA-ILD, and in this study, treatment with a steroid and/or cytotoxic agent was not associated with survival. Third, in our model, it may be challenging for clinicians to estimate 20% of the fibrosis score, especially among RA-ILD patients with a fibrosis score between 10% and 30%. However, our adjusted model using FVC instead of fibrosis score- showed compatible results with the original model. A previous study also revealed that 70% predicted of FVC threshold can be used instead of 20% of the disease extent threshold, especially for patients with a marginal disease extent (between 10% to 30%).[25] Finally, the performance of the staging system appeared to be lower in the validation cohort than in the derivation cohort. This was probably owing to a milder disease status of the validation cohort; however, the staging system remained effective in separating patients with different prognoses. Despite these limitations, our study is the first to develop a risk prediction model specifically for the mortality of patients with RA-ILD.

## Conclusion

In conclusion, our results suggest that a CT-based risk prediction model may be useful for predicting the prognosis of patients with RA-ILD. However, further prospective studies involving larger sample sizes and different ethnic populations are warranted to validate our results.

**Disclosure statement**

Conflict of interests: Dr. Joseph Jacob received consultancy fees from Boehringer Ingelheim and lecture fees from Roche, unrelated to the current work. Dr. Joseph Jacob

was also supported by Wellcome Trust Clinical Research Career Development Fellowship 209553/Z/17/Z. Other authors have nothing to declare.

**Funding information**

This study was supported by a grant from the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Science and Technology (NRF-2019R1A2C2008541)

**Author contributions**

Conceptualization: J.W.S.; Data curation: J.W.S.; Formal analysis: H.C.K., J.W.S. Funding acquisition: J.W.S.; Investigation: H.C.K., J.S.L., E.Y.L, Y.H., E.J.C., M.H., G.C., J.B., J.J. J.W.S.; Methodology: J.W.S.; Project administration: J.W.S.; Resources: E.Y.L, Y.H., J.W.S. ;Software: E.J.C, M.H., G.C., J.B., J.J.; Supervision: H.C.K., J.S.L., E.Y.L, Y.H., J.W.S.; Validation: J.S.L, E.Y.L, Y.H.; Visualization: H.C.K., J.S.L., J.W.S.; Writing – original draft: H.C.K., J.W.S.; Writing – review & editing: H.C.K., J.S.L., E.Y.L, Y.H., E.J.C., J.W.S.

**Abbreviation list**

ATS, American Thoracic Society; AUC , area under receiver operating characteristic curve; BMI, body mass index; C statistics, Concordance statistics; CCP, cyclic citrullinated peptide; CI, confidence interval; CPFE, combined pulmonary fibrosis and emphysema; CTD-ILD, connective tissue disease-associated interstitial lung disease; DLco, diffusing capacity of the lung for carbon monoxide;ERS, European Respiratory Society; FS, fibrosis score; GAP, Gender-Age-Physiology; GGO, ground-glass opacity;

HR, hazard ratio; HRCT, high-resolution computed tomography; IDI, integrated discrimination improvement; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; NRI, reclassification improvement; NSIP, nonspecific interstitial pneumonia; RA, rheumatoid arthritis; RA-ILD, Rheumatoid arthritis-associated interstitial lung disease; RF, rheumatoid factor; ROC, receiver operating characteristic; SSc-ILD**,** systemic sclerosis-associated interstitial lung disease; TLC, total lung capacity; UIP, usual interstitial pneumonia

**References**


1 Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, Murphy J, Cohen M, Raghu G, Brown KK. Rheumatoid arthritis-interstitial lung disease-associated mortality. *Am. J. Respir. Crit. Care Med.* 2011; **183**: 372-8.

2 O'Dwyer DN, Armstrong ME, Cooke G, Dodd JD, Veale DJ, Donnelly SC. Rheumatoid Arthritis (RA) associated interstitial lung disease (ILD). *Eur. J. Intern. Med.* 2013; **24**: 597-603.

3 Antin-Ozerkis D, Evans J, Rubinowitz A, Homer RJ, Matthay RA. Pulmonary manifestations of rheumatoid arthritis. *Clin. Chest Med.* 2010; **31**: 451-78.

4 Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, Colby TV. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. *Am. J. Respir. Crit. Care Med.* 2007; **175**: 705-11.

5 Tsuchiya Y, Takayanagi N, Sugiura H, Miyahara Y, Tokunaga D, Kawabata Y, Sugita Y. Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome. *Eur. Respir. J.* 2011; **37**: 1411-7.

6 Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER,

Fischer A, Frankel SK, Hobbs SB, Huie TJ, Ketzer J *et al.* Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur. Respir. J.* 2016; **47**: 588-96.

7 Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, Lee JS, King TE, Jr., Collard HR. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur. Respir. J.* 2010; **35**: 1322-8.

8 Dixon WG, Hyrich KL, Watson KD, Lunt M, Symmons DP. Influence of anti-TNF therapy on mortality in patients with rheumatoid arthritis-associated interstitial lung disease: results from the British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.* 2010; **69**: 1086-91.

9 Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. *Scand. J. Rheumatol.* 2007; **36**: 172-8.

10 Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, Dawson J, Sathi N, Ahmad Y, Koduri G *et al.* Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics--a large multicentre UK study. *Rheumatology (Oxford)*. 2014; **53**: 1676-82.

11 Nurmi HM, Kettunen HP, Suoranta SK, Purokivi MK, Karkkainen MS, Selander TA, Kaarteenaho RL. Several high-resolution computed tomography findings associate with survival and clinical features in rheumatoid arthritis-associated interstitial lung disease. *Respir. Med.* 2018; **134**: 24-30.

12 Ito Y, Arita M, Kumagai S, Takei R, Noyama M, Tokioka F, Nishimura K, Koyama T, Tachibana H, Ishida T. Radiological fibrosis score is strongly associated with worse survival in rheumatoid arthritis-related interstitial lung

disease. *Mod. Rheumatol.* 2018 doi 10.1080/14397595.2018.1442170: 1-7.

13 Jacob J, Song JW, Yoon HY, Cross G, Barnett J, Woo WL, Adams F, Kokosi M, Devaraj A, Renzoni E *et al.* Prevalence and effects of emphysema in never-smokers with rheumatoid arthritis interstitial lung disease. *EBioMedicine*. 2018; **28**: 303-10.

14 Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, Poletti V, Buccioli M, Elicker BM, Jones KD *et al.* A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann. Intern. Med.* 2012; **156**: 684-91.

15 Morisset J, Vittinghoff E, Lee BY, Tonelli R, Hu X, Elicker BM, Ryu JH, Jones KD, Cerri S, Manfredi A *et al.* The performance of the GAP model in patients with rheumatoid arthritis associated interstitial lung disease. *Respir. Med.* 2017; **127**: 51-6.

16 Nurmi HM, Purokivi MK, Karkkainen MS, Kettunen HP, Selander TA, Kaarteenaho RL. Are risk predicting models useful for estimating survival of patients with rheumatoid arthritis-associated interstitial lung disease? *BMC Pulm. Med.* 2017; **17**: 16.

17 Gutsche M, Rosen GD, Swigris JJ. Connective tissue disease-associated interstitial lung disease: A review. *Curr Respir Care Rep*. 2012; **1**: 224-32.

18 Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. *Respirology*. 2014; **19**: 493-500.

19 Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD *et al.* 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European

League Against Rheumatism collaborative initiative. *Ann. Rheum. Dis.* 2010; **69**: 1580-8.

20 Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R, Enright P, van der Grinten CP *et al.* Standardisation of the measurement of lung volumes. *Eur. Respir. J.* 2005; **26**: 511-22.

21 Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P *et al.* Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur. Respir. J.* 2005; **26**: 720-35.

22 Assayag D, Elicker BM, Urbania TH, Colby TV, Kang BH, Ryu JH, King TE, Collard HR, Kim DS, Lee JS. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. *Radiology*. 2014; **270**: 583-8.

23 Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. *Stat. Med.* 2015; **34**: 685-703.

24 Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat. Med.* 2008; **27**: 157-72; discussion 207-12.

25 Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj A *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am. J. Respir. Crit. Care Med.* 2008; **177**: 1248-54.

26 Cottin V, Cordier JF. Combined pulmonary fibrosis and emphysema in

connective tissue disease. *Curr. Opin. Pulm. Med.* 2012; **18**: 418-27.

27 Cottin V, Nunes H, Mouthon L, Gamondes D, Lazor R, Hachulla E, Revel D, Valeyre D, Cordier JF. Combined pulmonary fibrosis and emphysema syndrome in connective tissue disease. *Arthritis Rheum.* 2011; **63**: 295-304.

28 Antoniou KM, Walsh SL, Hansell DM, Rubens MR, Marten K, Tennant R, Hansel T, Desai SR, Siafakas NM, du Bois RM *et al.* Smoking-related emphysema is associated with idiopathic pulmonary fibrosis and rheumatoid lung. *Respirology*. 2013; **18**: 1191-6.

29 Zhang C, Yan MY, Lu P, Chen P, Yang M, Ye XW, Xu M, Yang ZH, Zhang XY. Hypomethylation of perforin regulatory elements in CD4+ T cells from rat spleens contributes to the development of autoimmune emphysema. *Respirology*. 2014; **19**: 376-81.

30 Yang DH, Tu CC, Wang SC, Wei CC, Cheng YW. Circulating anti-cyclic citrullinated peptide antibody in patients with rheumatoid arthritis and chronic obstructive pulmonary disease. *Rheumatol. Int.* 2014; **34**: 971-7.

31 Ryerson CJ, Hartman T, Elicker BM, Ley B, Lee JS, Abbritti M, Jones KD, King TE, Jr., Ryu J, Collard HR. Clinical features and outcomes in combined pulmonary fibrosis and emphysema in idiopathic pulmonary fibrosis. *Chest*. 2013; **144**: 234-40.

32 Jacob J, Bartholmai BJ, Rajagopalan S, Kokosi M, Maher TM, Nair A, Karwoski R, Renzoni E, Walsh SLF, Hansell DM *et al.* Functional and prognostic effects when emphysema complicates idiopathic pulmonary fibrosis. *Eur. Respir. J.* 2017; **50**: 1700379

33 Kim ES, Choi SM, Lee J, Park YS, Lee CH, Yim JJ, Yoo CG, Kim YW, Han SK,

Deleted: .

Lee SM. Validation of the GAP score in Korean patients with idiopathic pulmonary fibrosis. *Chest*. 2015; **147**: 430-7.

34 Su R, Bennett M, Jacobs S, Hunter T, Bailey C, Krishnan E, Rosen G, Chung L. An analysis of connective tissue disease-associated interstitial lung disease at a US Tertiary Care Center: better survival in patients with systemic sclerosis. *J. Rheumatol.* 2011; **38**: 693-701.

35 Jacob J, Hirani N, van Moorsel CHM, Rajagopalan S, Murchison JT, van Es HW, Bartholmai BJ, van Beek FT, Struik MHL, Stewart GA *et al.* Predicting outcomes in rheumatoid arthritis related interstitial lung disease. *Eur. Respir. J.* 2019; **53** (1): 1800869.

Deleted: .

**Table 1.** Comparison of baseline characteristics between non-survivor and survivor patients with rheumatoid arthritis-associated interstitial lung disease

| | Total | Non-survivors | Survivors | *P* value |
|---|---|---|---|---|
| Patients, number | 153 | 45 | 108 | |
| Age, years | 61.0 ± 10.2 | 65.2 ± 9.0 | 59.3 ± 10.2 | 0.001 |
| Female sex | 88 (57.5) | 22 (48.9) | 66 (61.1) | 0.163 |
| Ever-smokers | 66 (43.1) | 23 (51.1) | 43 (39.8) | 0.199 |
| BMI, $kg/m^2$ | 23.5 ± 3.0 | 23.2 ± 3.3 | 23.6 ± 2.8 | 0.464 |
| *RA duration, months | 60 (17-126) | 60 (21-108) | 59 (15-141) | 0.695 |
| RF positivity (n = 148) | 116 (78.4) | 37 (86.0) | 79 (75.2) | 0.147 |
| Anti-CCP positivity (n = 137) | 106 (77.4) | 34 (82.9) | 72 (75.0) | 0.310 |
| C-reactive protein | 2.5 ± 4.4 | 3.1 ± 4.5 | 2.3 ± 4.4 | 0.309 |
| Pulmonary function test | | | | |
| FVC, % predicted | 75.6 ± 18.6 | 68.8 ± 20.1 | 78.4 ± 17.3 | 0.003 |
| DLco, % predicted (n = 146) | 61.1 ± 19.5 | 53.5 ± 20.4 | 64.3 ± 18.2 | 0.002 |
| TLC, % predicted (n = 141) | 77.0 ± 16.4 | 71.7± 17.0 | 79.3 ± 15.6 | 0.010 |
| GAP stage (n = 146) | | | | 0.051 |
| 1 | 110 (75.3) | 27 (62.8) | 83 (80.6) | |
| 2 | 33 (22.6) | 14 (32.6) | 19 (18.4) | |
| 3 | 3 (2.1) | 2 (4.7) | 1 (1.0) | |

Data are presented as mean ± standard deviation, median (interquartile range), or number (%), unless otherwise indicated.

*Duration was only evaluated in patients who were diagnosed with RA first.

476 BMI: body mass index; RA: rheumatoid arthritis; RF: rheumatoid factor; CCP: cyclic
477 citrullinated peptide; FVC: forced vital capacity; DLco: diffusing capacity of the lung
478 for carbon monoxide; TLC: total lung capacity; GAP: gender–age–physiology
479

480 **Table 2.** Comparison of high-resolution computed tomography findings between non-
481 survivor and survivor patients with rheumatoid arthritis-associated interstitial lung
482 disease

| Characteristic | Total | Non-survivors | Survivors | *P* value |
|---|---|---|---|---|
| Patients, number | 153 | 45 | 108 | |
| Reticulation, % | 19.3 ± 12.0 | 26.4 ± 13.5 | 16.4 ± 10.0 | <0.001 |
| Honeycombing, % | 2.7 ± 4.6 | 5.4 ± 6.3 | 1.6 ± 3.2 | <0.001 |
| GGO, % | 2.5 ± 4.1 | 3.0 ± 5.2 | 2.3 ± 3.5 | 0.331 |
| Consolidation, % | 0.4 ± 1.0 | 0.6 ± 1.2 | 0.3 ± 0.9 | 0.127 |
| Traction bronchiectasis, point | 7.5 ± 3.8 | 9.3 ± 3.9 | 6.7 ± 3.5 | <0.001 |
| *Fibrosis score, % | 22.1 ± 14.3 | 31.8 ± 15.7 | 18.0 ± 11.6 | <0.001 |
| UIP pattern | 59 (38.6) | 27 (60.0) | 32 (29.6) | <0.001 |
| Emphysema | 74 (48.4) | 32 (71.1) | 42 (38.9) | <0.001 |

483 Data are presented as mean ± standard deviation or number (%), unless otherwise
484 indicated.
485 *Fibrosis score was defined as the sum of reticulation and honeycombing score.
486 GGO: ground-glass opacity; UIP: usual interstitial pneumonia
487
488

**Table 3.** Risk factors for mortality in patients with rheumatoid arthritis-associated interstitial lung disease assessed using a multivariate Cox proportional hazards model

| Variable | HR | 95% CI | *P* value | Cox coefficient value |
|---|---|---|---|---|
| Age ≥ 60 years | 2.063 | 1.009–4.218 | 0.047 | 0.724 |
| Fibrosis score ≥ 20% | 4.585 | 2.309–9.104 | <0.001 | 1.523 |
| UIP pattern | 1.899 | 1.002–3.599 | 0.049 | 0.641 |
| Emphysema | 2.596 | 1.342–5.022 | 0.005 | 0.954 |

HR: hazard ratio; CI: confidence interval; UIP: usual interstitial pneumonia

**Table 4.** Comparison of performance of the risk prediction models for mortality in patients with rheumatoid arthritis-associated interstitial lung disease

| Model | C-index | 95% CI | *P* value | NRI | 95% CI | *P* value | IDI | 95% CI | *P* value |
|---|---|---|---|---|---|---|---|---|---|
| (1) FS ≥ 20 % | 0.688 | 0.614–0.762 | Ref. | | | | | | |
| (2) FS ≥ 20 % + UIP | 0.747 | 0.665–0.829 | <0.001* | 0.300 | 0.092–0.480 | 0.020* | 0.077 | 0.009–0.200 | 0.013* |
| (3) FS ≥ 20 % + UIP + Emphysema | 0.769 | 0.685–0.853 | 0.276** | 0.331 | 0.017–0.507 | 0.047** | 0.054 | −0.001–0.135 | 0.066** |
| (4) FS ≥ 20 % + UIP + Emphysema + Age ≥ 60 years | 0.780 | 0.694–0.866 | 0.344† | 0.331 | −0.194–0.478 | 0.146† | 0.023 | −0.006–0.090 | 0.179† |
| FS ≥ 20 % + UIP+ Emphysema +Age ≥ 60 years | 0.780 | 0.694–0.866 | Ref. | | | | | | |
| GAP stage | 0.623 | 0.531–0.708 | <0.001 | | | | | | |

CI: confidence interval; NRI: net reclassification improvement; IDI: integrated discrimination improvement; FS: fibrosis score; UIP: usua interstitial pneumonia; GAP: gender–age–physiology; Ref: Reference

**P* value between group (1) and group (2), ***P* value between group (2) and group (3), and †*P* value between group (3) and group (4)

**Table 5.** Points assigned for each variable and the staging system

| Variable | Classification | Points |
|---|---|---|
| Age ≥ 60 years | Yes | 1 |
| | No | 0 |
| Fibrosis score ≥ 20% | Yes | 2 |
| | No | 0 |
| UIP pattern | Yes | 1 |
| | No | 0 |
| Emphysema | Yes | 1 |
| | No | 0 |
| | Staging system | |
| Stage | I | 0 |
| | II | 1-3 |
| | III | 4-5 |

UIP: usual interstitial pneumonia

**Figure legends**

**Figure 1.** Comparison of the survival curves using Kaplan–Meier analysis according to each stage. (A) Derivation cohort and (B) validation cohort.