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Development of a prediction model for progression of rheumatoid arthritis-associated interstitial lung disease using serologic and clinical factors: The prospective KORAIL cohort

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ABSTRACT

Objective: To develop a prediction model for rheumatoid arthritis-associated interstitial lung disease (RA-ILD) progression.
Methods: We investigated predictors of RA-ILD progression in the Korean RA-ILD (KORAIL) cohort, a prospective study that enrolled patients with RA meeting ACR/EULAR criteria and ILD on chest computed tomography (CT) scans and followed for 3 years. Pulmonary function tests (PFTs) and chest CT scans were conducted annually. RA-ILD progression was defined as both physiological and radiological worsening, adapted from the 2023 ATS/ERS/JRS/ALAT definition of progressive pulmonary fibrosis. Baseline factors included clinical factors and biomarkers (autoantibodies, inflammatory markers, and pulmonary damage markers).
Results: We analyzed 138 RA-ILD patients (mean age 66.4 years, 30.4 % male, 60.1 % usual interstitial pneumonia [UIP] pattern). During a median follow-up of 2.9 years, 34.8 % ($n = 48$) had RA-ILD progression. Baseline associations with progression included: UIP pattern, ILD extent >10 %, DLCO %pred., anti-cyclic citrullinated peptide (anti-CCP), Krebs von den Lungen-6 (KL-6), and human surfactant protein D. We developed prediction models using UIP pattern, ILD extent, DLCO % pred., and anti-CCP titer with or without serum KL-6 levels. The models had areas under the curve (AUCs) of 0.73 and 0.75, respectively. The high-risk group had a positive predictive value for progression of 85.7 %, while the low-risk group had a negative predictive value of 94.7 %.
Conclusion: In this prospective cohort, UIP pattern, ILD extent, lower DLCO, RA disease activity, anti-CCP levels, and pulmonary damage biomarkers were associated with RA-ILD progression. We developed prediction models that may be clinically useful to risk stratify once externally validated.

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Introduction

Interstitial lung disease (ILD) is a serious extra-articular manifestation of rheumatoid arthritis (RA). Previous studies indicate that clinically apparent ILD occurs in approximately 10 % of patients, leading to a mortality rate up to three times as high as that of RA patients without ILD [1,2]. Demographic factors, such as older age, male sex and smoking history, have been recognized as prognostic indicators associated with mortality in patients with RA-ILD [3–6]. Regarding ILD factors, reduced forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLco), along with the usual interstitial pneumonia (UIP) pattern, have been associated with poorer prognosis [3,4,7,8]. Recent prospective cohort studies reported that RA disease activity, as represented by higher disease activity score 28 (DAS28), was also a significant risk factor for mortality in RA patients with ILD [9,10].

Of note, antifibrotic agents have shown potential in slowing disease progression in RA-ILD [11–13]. Nintedanib has been demonstrated to slow lung function decline in progressive fibrosing ILD, including RA-ILD [11,12]. Similarly, pirfenidone also showed a reduction in FVC decline in RA-ILD, although it did not meet the primary outcome in clinical trials [13]. However, the course of RA-ILD is highly heterogenous-while a subset of patients experiences progressive deterioration, others remain stable or even show improvement in pulmonary function [14,15]. Unlike other systemic autoinflammatory rheumatic disease-associated ILDs (SARD-ILDs), in which ILD management is more structured, treatment strategies for RA primarily focus on controlling arthritis rather than ILD. Furthermore, no established guidelines currently are available for ILD surveillance or treatment in RA, making it challenging to determine the optimal approach for managing these patients.

Given this variability, predicting which patients will experience progression, allowing the clinical importance of early intervention, remains challenging. Therefore, identifying patients who may benefit from additional ILD targeted treatment by evaluating individual risk factors is essential. In this study, we aimed to identify risk factors for RA-ILD progression using the recent PPF definition with modification and to develop a prediction model for RA-ILD progression. Through this study, we aim to improve our understanding of RA-specific drivers of ILD progression and establish a foundation for more personalized therapeutic approaches.

Methods

Study design and participants

We performed a prospective cohort study using data from the Korean RA-ILD (KORAIL) study. KORAIL is a multicenter prospective, longitudinal observational cohort from six tertiary hospitals in Korea. We enrolled participants 18 years or older who were diagnosed with RA based on the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria for RA [16] and ILD based on chest CT scan. Enrollment occurred from January 2015 to July 2018, and the last follow-up of the last subject was October 2020. Participants were followed annually for three years (four total study visits, including baseline). Serum samples were collected at each visit. All participants gave informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki and Good Clinical Practice and approved by the ethics committee of each institution (IRB numbers are indicated in Supplementary Table 1). Additional details about the cohort design and methodology were previously provided [14,17,18]. Patients and the public were not involved in the design of this study.

Outcome: RA-ILD progression

Progression was defined using PPF criteria published by the 2022 ATS/ERS/JRS/ALAT clinical practice guidelines with modifications [19]. Among the three domains of PPF criteria, we considered RA-ILD progression when participants met the criteria of both pulmonary physiology and radiographical domains after study enrollment. Specifically, the pulmonary physiology domain was defined as a 5 % or more absolute decline in forced vital capacity (FVC) % predicted or 10 % or more in diffusing capacity of the lungs for carbon monoxide (DLCO) % predicted within one year of observation. Participants met radiological domain criteria if the extent or severity of pulmonary lesions increased or there was newly developed reticular opacity (RO), honeycombing (HC), or ground glass opacities (GGOs) with concurrent traction bronchiectasis/bronchiolectasis (TBE) on their chest computed tomography (CT) scan compared to baseline. The respiratory symptoms domain was not applicable in the current study, as data on respiratory symptoms were not collected. Since follow-up occurred annually, all outcomes occurred at or after the 1-year follow-up (2nd visit).

RA and ILD clinical factors

At each visit, we assessed RA disease activity using disease activity score using 28 joints (DAS28), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and health-associated questionnaire-disability index (HAQ-DI). Pulmonary assessment included pulmonary function tests (PFTs), including forced expiratory volume in 1 s (FEV_1), FVC, and DLCO, in addition to chest CT and chest x-ray. Information on prescription medications, including RA treatment, and demographic information, including smoking status, were also collected at each visit.

Visual chest CT scoring

Participants underwent chest CT scans at end-inspiration of 1 to 2 mm section at each visit. Two independent experienced chest radiologists reviewed those chest CT scans without the knowledge of clinical information and scored visually. On visual scoring, the visual quantitative scoring system of Scleroderma Lung Study was utilized with modifications [20]. Briefly, we divided the lung field into six zones (upper, middle, and lower for right and left), and each lesion was scored in every zone. We then evaluated lung lesions, including GGOs, RO, TBE, HC, and emphysema, using a semi-quantitative scale as follows: no involvement scored as 0, 1–25 % involvement scored as 1 point, 26–50 % involvement scored as 2 points, 51–75 % involvement scored as 3 points, and 76–100 % involvement scored as 4 points. The mean scores from each domain of the entire lung were employed as predictors in statistical analysis. We also assessed the extent of ILD across the entire lung field using a quantitative scale: $\leq$10 %, >10 % to <30 %, and $\geq$30 %.

Biomarkers

We evaluated several candidate serum biomarkers at baseline based on previous our study [17,18]. Peptides with post-translational modifications and their corresponding autoantibodies play a role in RA pathogenesis and RA-associated lung disease [21,22]. Among these, we selected anti-cyclic citrullinated peptide (anti-CCP), anti-citrullinated enolase peptide (anti-CEP) for measurement, as they are widely used in routine clinical practice and readily available. In addition, pulmonary damage biomarkers, including Krebs von den Lungen-6 (KL-6), surfactant protein D (hSP-D), matrix metallopeptidase 7 (MMP7), have been reported to be associated with ILD, including IPF and SARD-ILD [23–27]. Inflammatory markers, such asinterleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor (TNF) serve as key cytokines that reflect inflammatory pathways in RA and other SARDs [28].

Candidate biomarkers were assessed using serum samples obtained at study entry. Samples were preserved at −80 °C. We quantified levels of anti-CCP and anti-CEP using enzyme-linked immunosorbent assay (ELISA, EUROIMMUN Medizinische Labordiagnostika AG, Lübeck, Germany; catalog numbers EA 1505–9601 G EA 151b-9601 G,

respectively). We measured serum KL-6 levels by latex-enhanced immunoturbidimetric assay (the Nanopia KL-6 assay, Sekisui Medical, Tokyo, Japan) while other pulmonary damage biomarkers (hSP-D and MMP7) by MSD's R-Plex assay platform (catalog numbers K1519XR-2 and K1510KR-2). Cytokine levels (IL-1β, IL-6, and TNF) were assessed using the MSD multi-spot assay system (Meso Scale Discovery, Gaithersburg).

Statistical analysis

For baseline characteristics, we reported mean with standard deviation (SD) for normally distributed predictors, median with interquartile ranges (IQR) for predictors that were not normally distributed and counts with percentage for binary predictors. Missing data in biomarkers and DLCO % pred. was imputed 100 times using Multiple Imputation by Chained Equations (MICE). For statistical analysis, we calculated the mean across imputed values by each participant. Biomarkers were log-transformed and standardized, including pulmonary damage biomarkers (KL-6, hSP-D, and MMP7) and cytokines (IL-1β, IL-6, and TNF).

We developed and validated the prediction models following the guidelines outlined in the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement [29]. Cox proportional hazards regression analysis was performed to estimate hazard ratios (HRs) for RA-ILD progression within each domain, adjusting for age and sex. Study follow-up was computed from baseline until the earliest date of meeting progression criteria or the last observed study visit, whichever occurred first. Additionally, Cox regression models stratified by UIP and non-UIP patterns were performed as part of a sensitivity analysis.

Five models were constructed to predict ILD progression based on significant predictors from each category. We selected predictors with p-values $\leq$0.05 within each domain and applied them to the prediction model. Since no demographic predictors reached the p-value threshold of 0.05, age and sex were included in the demographic model (Model 1). We modeled RA-specific factors, ILD-specific factors, and serum biomarkers individually (Model 2–4) as follows: DAS28-ESR category for RA category (Model 2), ILD pattern (definite/probable UIP versus others), ILD extent ($\geq$ 10 % versus $<$ 10 % involvement), and DLCO % pred. for ILD category (Model 3), and anti-CCP, KL-6, and hSP-D levels for biomarker category (Model 4). We also compared a composite model with predictors from all categories (Model 5). To evaluate the predictive accuracy of models, we constructed receiver operator characteristic (ROC) curves and calculated the area under the curve (AUC). For internal validation, we performed 1000 bootstrap replications for each model to estimate the AUCs and 95 % confidence intervals (CI) to adjust for optimism, given the lack of an external dataset.

For the establishment of the final prediction model, we determined the weights of each predictor using estimates from Cox regression analysis. We iteratively tested various thresholds, optimizing them based on sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to identify the most clinically applicable cut-off values. Stratified cumulative incidence functions were examined to assess the effectiveness of the risk stratification criteria.

All analyses were performed using R (version 4.4.1). Two-sided p-values $<$0.05 were considered statistically significant.

Results

Study sample and baseline characteristics

We analyzed 138 participants with available follow-up data to determine RA-ILD progression (Supplementary Figure 1). During a median follow-up of 2.9 years (IQR 2.6, 3.4), 48 (35 %) participants had RA-ILD progression by the modified PPF definition. Among the 138 participants, 12 patients passed away. In the progression group, five participants died, all after experiencing the event (i.e., ILD progression). In the non-progression group, seven participants died, all after censoring (i.e., following their last visit).

The mean age of 138 participants was 66.4 (SD 8.2) years, 30 % were male, and 25 % were ever smokers (Table 1). The median duration of RA was 6.1 years (IQR 1.0, 10.5), and nearly all participants (99 %) had seropositive RA. Sixty-six percent of participants had moderate or high disease activity by DAS28-ESR; the mean DAS28-ESR score was 3.9 (SD 1.5). The median ILD duration and interval between RA and ILD diagnosis were 1.6 years (IQR 0.1, 4.9) and 1.5 years (IQR 0.2, 7.0), respectively. Sixty percent of participants had definite/probable UIP patterns on chest CT scans. Sixty-three percent of participants had ILD extent with 10 % or less. The mean fibrosis score, which sums up the RO, TBE, and HC scores from visual CT scoring, was 10.4 (SD 7.2).

Model development: predictors of RA-ILD progression

Results of age- and sex-adjusted models for RA-ILD progression are shown in Table 2. Regarding RA characteristics, participants with low and moderate DAS28-ESR had an increased hazard of progression compared to those in remission, adjusting for age and sex (hazard ratio [HR] 2.82, 95 %CI 1.00, 7.94, $p = 0.0497$ for low disease activity; HR 2.45, 95 %CI 1.00, 6.02, $p = 0.0501$ for moderate disease activity).

Participants with definite/probable UIP had increased progression hazards compared to those without UIP (HR 2.72, 95 %CI 1.38, 5.39). Participants with an ILD extent of$>$ 10 % had increased hazards for progression than those with an ILD extent of $\leq$10 % (HR 3.51, 95 %CI 1.96, 6.31). Increasing RO, TBE, and HC scores, as well as the combined fibrosis scores, were associated with increased hazards of progression. Among PFT predictors, lower DLCO was associated with increased progression hazards (HR 0.67 per SD, 95 %CI 0.49, 0.91, $p = 0.01$).

Considering biomarkers, higher anti-CCP levels were associated with increased hazards of progression (HR 1.33 per unit, 95 %CI 1.02, 1.72). Higher levels of serum pulmonary damage biomarkers, including KL-6 and hSP-D, were also associated with higher hazards of progression (HR 1.41 per SD, 95 %CI1.07, 1.84 for KL-6; HR 1.51 per SD, 95 %CI 1.11, 2.04 for hSP-D) while MMP7 levels were not associated. Inflammatory biomarkers, including ESR, CRP, and cytokines, were not significantly associated with progression.

Parameter calibration

Among the above-described 5 models, the combined model (Model 5) showed the highest AUC (0.77 [95 %CI 0.69, 0.85]), followed by the model that included ILD-specific factors with age and sex (Model 3, AUC 0.72 [95 %CI 0.63, 0.81]). Optimism-corrected AUC showed similar, albeit slightly attenuated results– the highest corrected AUC for the combined model (Model 5, corrected AUC, 0.73 [95 %CI 0.65, 0.80]) followed by the ILD category model (Model 3, corrected AUC, 0.71 [95 %CI 0.61, 0.79]). Fig. 1 and Supplementary Table 2 indicate the apparent and optimism-corrected AUC results.

Model specification

To establish the model with the highest AUC, we started with an ILD-specific factors model incorporating anti-CCP, one of the most measured biomarkers (Model 6). These included ILD patterns (definite/probable UIP vs. others), ILD extent ($>$10 % vs. $\leq$10 %), DLCO % predicted ($<$55 % vs. $\geq$55 %), and anti-CCP levels ($\geq$40 $\times$ the upper limit of normal [ULN] vs. $<$40 $\times$ ULN). Next, we added pulmonary damage biomarkers one at a time to evaluate their contribution to improving AUC (Models 7 and 8). Pulmonary damage biomarkers were further dichotomized into the highest quartile versus the lower three quartiles. Between these two models, the model with serum KL-6 (Model 7) was selected for the second model as it showed the highest AUC.

The final prediction models, both without and with KL-6, along with the weights of each predictor, are presented in Table 3 and

Table 1
Baseline characteristics of patients with RA-ILD, overall and by progression status during follow-up in the KORAIL cohort ($n = 138$).

	Total ($n = 138$)	Progression ($n = 48$)	No progression ($n = 90$)
Demographic data			
Age, years	66.4 (8.2)	66.5 (8.1)	66.5 (8.3)
Male sex, n (%)	42 (30.4 %)	15 (31.3 %)	27 (30.0 %)
Smoking, ever, n (%)	35 (25.4 %)	11 (22.9 %)	24 (26.7 %)
BMI, kg/m^2	23.9 (3.2)	24.2 (3.2)	23.8 (3.2)
RA characteristics			
RA duration, years, median (IQR)	6.1 (1.0, 10.5)	5.5 (0.8, 9.9)	6.3 (1.2, 13.1)
RF positive, n (%)	122 (88.4 %)	43 (89.6 %)	79 (87.8 %)
Anti-CCP positive, n (%)	131 (94.9 %)	45 (93.8 %)	86 (95.6 %)
Tender joint count	3.3 (4.8)	2.8 (3.6)	3.6 (5.3)
Swollen joint count	2.7 (3.4)	2.5 (3.2)	2.7 (3.6)
Patient global assessment	35.2 (26.3)	35.9 (26.0)	34.9 (26.7)
DAS28-ESR score	3.9 (1.5)	4.0 (1.3)	3.9 (1.5)
DAS28-ESR categories, n (%)			
Remission	28 (20.3 %)	6 (12.5 %)	22 (24.4 %)
Low	19 (13.8 %)	9 (18.8 %)	10 (11.1 %)
Moderate	61 (44.2 %)	25 (52.1 %)	36 (40.0 %)
High	30 (21.7 %)	8 (16.7 %)	22 (24.4 %)
HAQ score	0.70 (0.78)	0.66 (0.71)	0.72 (0.82)
RA medications, n (%)			
Glucocorticoid use	121 (87.7 %)	39 (81.3 %)	82 (91.1 %)
Methotrexate use	73 (52.9 %)	23 (47.9 %)	50 (55.6 %)
ILD characteristics			
ILD duration, years, median (IQR)	1.6 (0.1, 4.9)	1.2 (0.1, 4.2)	1.9 (0.2, 5.0)
Interval between RA and ILD diagnosis, years, median (IQR)	1.5 (0.2, 7.0)	1.0 (0.1, 6.2)	2.3 (0.3, 8.3)
ILD pattern, n (%)			
Definite/probable UIP	83 (60.1 %)	37 (77.1 %)	46 (51.1 %)
Non-UIP	55 (39.9 %)	11 (22.9 %)	44 (48.9 %)
ILD extent >10 %, n (%)	51 (37.0 %)	28 (58.3 %)	23 (25.6 %)
Fibrosis score, total*	10.4 (7.2)	13.8 (7.4)	8.6 (6.5)
Ground glass opacity	1.1 (2.1)	1.3 (2.3)	1.0 (1.9)
Reticular opacity	5.0 (2.8)	6.0 (2.2)	4.5 (2.9)
Traction bronchiectasis/ bronchiolectasis	3.6 (3.0)	5.1 (3.0)	2.8 (2.7)
Honeycombing	1.8 (2.5)	2.7 (3.3)	1.3 (1.7)
Emphysema	0.8 (2.7)	1.1 (3.9)	0.7 (1.9)
FEV_1% pred.	92.1 (21.0)	89.8 (18.5)	93.3 (22.3)
FVC% pred.	84.6 (16.7)	81.8 (16.0)	86.0 (17.0)
DLCO% pred.	71.3 (19.8)	66.4 (20.7)	73.9 (18.9)
Biomarkers			
Autoantibodies			
Anti-CCP, RU/mL	208.6 (41.7, 461.5)	271.2 (57.2, 578.0)	161.4 (37.0, 385.7)
Very high titer (≥40x ULN)	73 (52.9 %)	31 (64.6 %)	42 (46.7 %)
Anti-CEP, RU/mL	33.3 (5.7, 90.0)	45.3 (10.8, 91.2)	25.5 (4.8, 83.4)
Pulmonary damage biomarkers, median (IQR)			
KL-6, U/mL	425.1 (326.2, 733.3)	627.6 (373.9, 957.0)	406.3 (291.4, 610.7)
hSP-D, pg/mL	7306 (4294, 12,602)	9523 (6516,13,292)	6148 (3903, 10,964)
MMP7, pg/mL	6243 (4770, 9057)	8043 (5742, 10,313)	5686 (4380, 7639)
Inflammatory biomarkers			
ESR, mm/hr	39.3 (26.4)	39.9 (25.4)	38.9 (27.0)
CRP, mg/L	8.8 (13.8)	9.8 (15.7)	8.2 (12.7)
IL-1β, pg/mL	0.11 (0.05, 0.27)	0.11 (0.05, 0.24)	0.11 (0.05, 0.28)
IL-6, pg/mL	1.64 (0.83, 3.88)	1.51 (0.75, 4.16)	1.65 (0.90, 3.78)
TNF, pg/mL	1.29 (0.73, 2.21)	1.27 (0.74, 2.18)	1.35 (0.74, 2.23)

BMI, body mass index; CCP, cyclic citrullinated peptide; CEP, citrullinated α-enolase peptide; CI, confidence interval; CRP, c-reactive protein; CT chest tomography; DAS, disease activity score; DLCO % pred., predicted % diffusing capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FEV1 % pred., predicted % forced expiratory volume; FVC % pred., predicted % forced vital capacity;; HAQ, health associated questionnaire; hSP-D, human surfactant protein-D; IL-1β, interleukin-1β; IL-6, interleukin-6; ILD, interstitial lung disease; IQR, interquartile range; KL-6, Krebs von den Lungen-6; MMP7, matrix metalloprotein 7; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis associated interstitial lung disease; RF, rheumatoid factor; SD, standard deviation; TNF, tumor necrosis factor α; UIP, usual interstitial pneumonia.

Supplementary Table 3. Supplementary Table 4 provides the median and interquartile ranges of total scores from the prediction models, with and without KL-6.

Model performance and defining risk categories

We then determined the cut-off values for each prediction model, stratified by the risk of progression, as shown in Table 4 and Fig. 2. For the prediction model without a pulmonary damage biomarker, a cut-off value of ≥3 yielded a sensitivity of 95.8 % and an NPV of 90.5 % but a specificity of 21.1 % and a PPV of 39.3 %. A higher cut-off value of ≥13.5 provided a sensitivity of 22.9 % and an NPV of 69.9 %, with a specificity of 95.6 % and a PPV of 73.3 %. Accordingly, scores below 3 were categorized as low-risk, and scores ≥13.5 as high-risk. In the prediction model with a pulmonary damage biomarker KL-6, a cut-off value of ≥4 resulted in a sensitivity of 97.9 % and an NPV of 94.7 %, with a specificity of 20.0 % and a PPV of 39.5 %. A cut-off of ≥25.5 showed a sensitivity of 25.0 %, an NPV of 71.0 %, a specificity of 97.8 %, and a PPV of 85.7 %. Therefore, we classified scores below 4 as low-risk and those ≥25.5 as high-risk. The associations of these categories with progression were evaluated through the cumulative incidence curves shown in Fig. 2, illustrating distinct progression incidences among the risk groups during the follow-up period. For the prediction model without KL-6, the HR for progression was 4.4 (95 %CI 1.1, 18.3) for the moderate-risk group and 13.7 (95 %CI 3.0, 62.3) for the high-risk group (reference low-risk group). For the prediction model with KL-6, the HR for progression was 7.6 (95 %CI 1.0, 55.2) for the moderate-risk group and 33.8 (95 %CI 4.4, 261.9) for the high-risk group, compared to the low-risk group.

Sensitivity analysis

We also stratified the analysis by UIP and non-UIP patterns (Supplementary Tables 5 and 6). Results for the UIP analysis were similar to the main analysis. Among the participants with non-UIP, scores of GGOs from visual scoring (HR 1.32, 95 %CI 1.07, 1.62) and CRP levels (HR 2.16, 95 %CI 1.13, 4.13 per unit) were novel associations with RA-ILD

Table 2
Multivariable hazard ratios for RA-ILD progression, adjusted for age and sex.

	Hazard Ratio (95 % CI)	P
Demographic data		
Age (per year)	1.01 (0.98, 1.05)	0.58
Male sex (vs. female sex)	1.18 (0.64, 2.18)	0.59
Smoking, ever (vs. never)	0.71 (0.27, 1.82)	0.47
BMI (per kg/m^2)	1.02 (0.93, 1.12)	0.60
RA characteristics		
RA duration (per year)	0.96 (0.92, 1.00)	0.07
RF positive (vs. negative)	1.00 (0.39, 2.54)	1.00
Tender joint count (per joint)	0.98 (0.92, 1.05)	0.55
Swollen joint count (per joint)	1.00 (0.92, 1.08)	0.99
Patient global assessment (per unit)	1.00 (0.99, 1.01)	0.70
DAS28-ESR score (per unit)	1.04 (0.86, 1.27)	0.67
DAS28-ESR (categories)		
Remission	Ref	
Low	**2.82 (1.00, 7.94)**	**0.0497**
Moderate	2.45 (1.00, 6.02)	0.0501
High	1.47 (0.51, 4.26)	0.48
HAQ score (per unit)	0.91 (0.61, 1.36)	0.64
RA medications		
Glucocorticoid use (vs. no use)	0.54 (0.26, 1.12)	0.10
Methotrexate use (vs. no use)	0.83 (0.47, 1.48)	0.53
ILD characteristics		
ILD duration (per year)	0.96 (0.87, 1.06)	0.40
Interval between RA and ILD diagnosis (per year)	0.96 (0.91, 1.01)	0.09
ILD pattern		
Definite/probable UIP	**2.72 (1.38, 5.39)**	**0.004**
Non-UIP	Ref	
ILD extent > 10 % (vs. or less)	**3.51 (1.96, 6.31)**	**<0.001**
Fibrosis score, total (per unit)*	**1.09 (1.05, 1.13)**	**<0.001**
Ground glass opacity	1.08 (0.96, 1.22)	0.20
Reticular opacity	**1.21 (1.09, 1.35)**	**<0.001**
Traction bronchiectasis/bronchiolectasis	**1.22 (1.12, 1.33)**	**<0.001**
Honeycombing	**1.16 (1.07, 1.27)**	**0.001**
Emphysema	1.04 (0.94, 1.17)	0.44
FEV_1% pred. (per SD)	0.85 (0.64, 1.15)	0.29
FVC% pred. (per SD)	0.78 (0.59, 1.05)	0.10
DLCO% pred. (per SD)	**0.67 (0.49, 0.91)**	**0.01**
Biomarkers (per SD)		
Autoantibodies		
Anti-CCP (RU/ml)		
Continuous variable per SD	**1.35 (1.04, 1.75)**	**0.02**
Very high titer (≥40x ULN)	1.81 (0.99, 3.29)	0.054
vAnti-CEP (RU/ml)	0.95 (0.71, 1.26)	0.70
Pulmonary damage biomarkers**		
KL-6 (U/ml)	**1.41 (1.07, 1.84)**	**0.01**
hSP-D (pg/ml)	**1.51 (1.11, 2.04)**	**0.01**
MMP7 (pg/ml)	1.28 (0.87, 1.87)	0.20
Inflammatory biomarkers		
ESR (mm/hr)	1.13 (0.84, 1.52)	0.42
CRP (mg/L)	1.19 (0.91, 1.55)	0.21
IL-1β (pg/mL) **	1.02 (0.75, 1.38)	0.89
IL-6 (pg/mL) **	1.08 (0.81, 1.43)	0.61
TNF (pg/mL) **	1.17 (0.89, 1.55)	0.27

Bolded values are statistically significant.

* Fibrosis score was the sum scores of reticular opacities, traction bronchiectasis/bronchiolectasis, and honeycombing.

** Log transformed values were used

BMI, body mass index; CCP, cyclic citrullinated peptide; CEP, citrullinated α-enolase peptide; CI, confidence interval; CRP, c-reactive protein; CT chest tomography; DAS, disease activity score; DLCO % pred., predicted % diffusing capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FEV1 % pred., predicted % forced expiratory volume; FVC % pred., predicted % forced vital capacity;; HAQ, health associated questionnaire; hSP-D, human surfactant protein-D; IL-1β, interleukin-1β; IL-6, interleukin-6; ILD, interstitial lung disease; IQR, interquartile range; KL-6, Krebs von den Lungen-6; MMP7, matrix metalloprotein 7; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis associated interstitial lung disease; RF, rheumatoid factor; SD, standard deviation; TNF, tumor necrosis factor α; UIP, usual interstitial pneumonia.

progression compared to the main analysis.

Discussion

This study analyzed data from a prospective longitudinal observational cohort of RA-ILD patients to identify clinical predictors of RA-ILD progression, utilizing the recent PPF definition with modification. Key predictors included ILD pattern, ILD extent, DLCO % predicted, anti-CCP, and pulmonary damage biomarkers such as KL-6 and hSP-D. Importantly, anti-CCP and RA disease activity were identified as novel RA-specific factors associated with progression. Using these predictors, we developed models to stratify RA-ILD progression risk. A model based on clinical data (excluding KL-6) effectively identified individuals at both high and low risk for progression. Incorporating KL-6 further improved the model's predictive performance. These findings offer a framework for RA-ILD risk stratification and establish a foundation for future external validation studies.

Although definitions of PPF (progressive pulmonary fibrosis) have varied across studies, the proportion of patients with progressive fibrosing ILD—referred to as PPF—has been reported to range from 18.9 % to 47.5 % in real-world cohort studies involving patients with fibrotic ILD [30]. Older age, male sex, lower FVC% predicted at baseline, lower DLCO % predicted, gastroesophageal reflux disease, and baseline KL-6 > 1000 U/mL have been reported to be risk factors for PPF in non-IPF fibrotic ILD [31,32]. In many of these studies, RA-ILD is included only as a small subset of SARD-ILD, with some studies reporting that only 4.2 % of SARD-ILD cases are identified as RA-ILD [33]. However, there may be different risk factors for PPF among RA-ILD compared to those among other SARD-ILD populations [34–36]. A retrospective single-center study conducted in China identified several factors associated with RA-ILD progression, including high RA disease activity as measured by DAS28-ESR, a higher HAQ-DI score, a history of smoking, definite UIP pattern, elevated fibrosis scores, and reduced use of cyclophosphamide [34]. Another single-center retrospective cohort study from China reported high-titer anti-CCP antibody and DLCO % pred. <45 % were associated with 4- and 8-fold higher odds for ILD progression, adjusting for age, smoking history, and HRCT characteristics [35]. Multicenter study from Italy showed that RF titers, DLCO, and UIP patterns were associated with a fibrosing progressive phenotype in RA-ILD [36]. Overall, distinct factors of PPF among RA-ILD populations are emerging, including the presence of UIP pattern [34,36], high RA disease activity [34], and high RF titers [36]. Thus, our findings of factors associated with RA-ILD progression extend these previous observations.

In the current study, several ILD characteristics, including pattern, extent, and lung function, were associated with RA-ILD progression. Unlike other SARD-ILDs, the UIP pattern predominates in RA-ILD and is a well-established risk factor for mortality, comparable to IPF [7,37,38]. This study also identified the UIP pattern as a significant risk factor. We also confirmed the prognostic importance of ILD extent despite applying a lower threshold (>10 % vs. ≤10 %) that was not a primary focus in previous studies [31,39]. However, it is notable that RA-ILD progression was observed in 35 % of our cohort, even in many patients whose baseline ILD extent was 10 % or less. A reduced DLCO has been consistently identified as a key determinant associated with elevated risk of mortality and disease progression, as demonstrated in the current study [9,31,37].

We found that higher anti-CCP levels were associated with progression of RA-ILD. As SARD-ILDs, including RA-ILD, autoantibodies have been reported to be associated with poor prognosis among other SARD-ILDs although the specific autoantibodies differ across the specific disease. For example, anti-melanoma differentiation-associated gene (anti-MDA5) is known to be associated with poor prognosis [40–42]. In SSc-ILD, anti-topoisomerase antibody positivity was associated with progression in the SENSCIS trial [43]. Yet, given the distinctive role of citrullination in RA, anti-CCP autoantibodies in RA hold more substantial implications compared to other autoantibodies in SARD other than

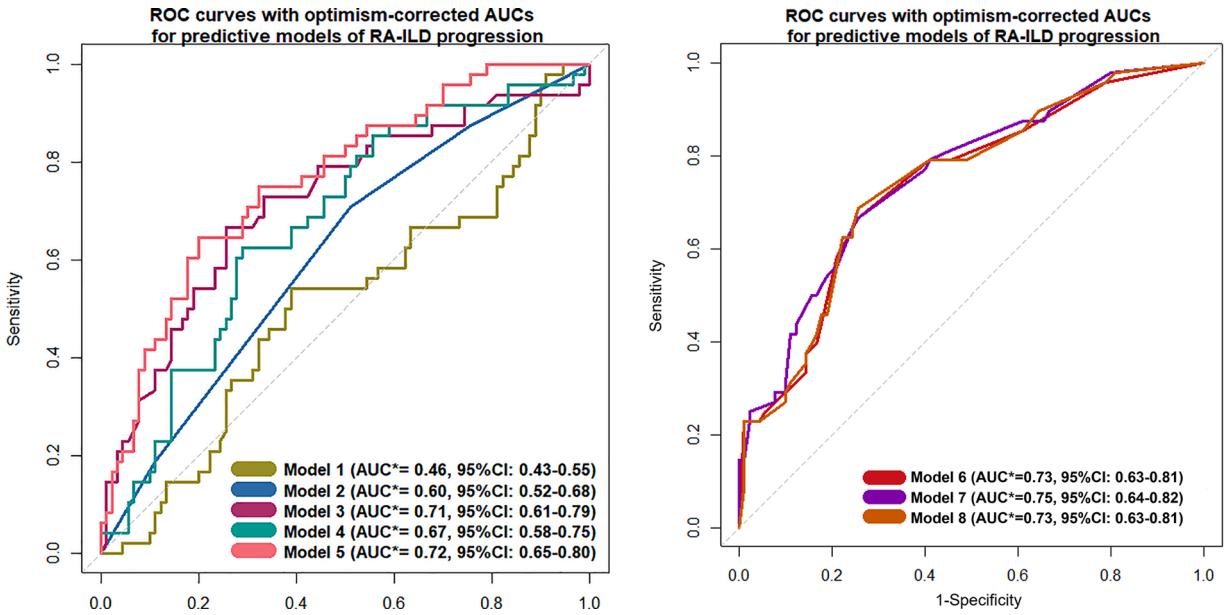

Fig. 1. Areas under the receiver operating characteristics curves for RA-ILD progression by baseline demographic, RA factors, ILD factors, and biomarkers.
A. Comparative Performance of predictors by categories, Model descriptions:, Model 1: Age, sex, Model 2: DAS28-ESR category, Model 3: ILD pattern**, ILD extent*** and DLCO % pred., Model 4: Anti-CCP, KL-6†, and hSP-D†, Model 5: All of the above, B. Comparative performance of prediction moModel descriptions‡:, Model 6: ILD pattern, ILD extent and DLCO % pred, Anti-CCP, Model 7: ILD pattern, ILD extent and DLCO % pred, Anti-CCP + KL-6, Model 8: ILD pattern, ILD extent and DLCO % pred, Anti-CCP + hSP-D, *Optimism corrected AUC, **Definite/probable UIP versus others, ***Less than 10 % involvement versus 10 % or more involvement, †Log transformed values were used, ‡To construct a parsimonious and clinically applicable model, all predictors were configured as binary variables as follows: ILD pattern, definite/probable UIP versus others; ILD extent, > 10 % versus ≤ 10 % involvement; DLCO % pred., <55 % versus ≥55 %; anti-CCP, ≥x40UNL versus <x40 UNL; KL-6, ≥730 U/ml versus <730 U/ml; hSP-D, ≥12,602 pg/ml versus <12,602 pg/ml; MMP7, ≥9057pg/ml versus <9057pg/ml, AUC, area under the curve; CCP, cyclic citrullinated peptide; CT, computed tomography; DAS28, disease activity score28; DLCO % pred., predicted % diffuse capacity of the lung for carbon dioxide; ESR, erythrocyte sedimentation rate; hSP-D, human surfactant protein D; ILD, interstitial lung disease; KL-6, Kreb von den Lungen-6; MMP7, matrix metalloprotein 7; ROC, receiver operating characteristic; ULN, upper limit of normal; UIP, usual interstitial pneumonia

Table 3
KORAIL prediction models for rheumatoid arthritis-associated interstitial lung disease progression.

Predictors	Score	Without KL-6 Weights	With KL-6 Weights
Anti-CCP		3	4
Very high titer (≥40x ULN)	1		
Not very high titer (<40x ULN)	0		
ILD extent		5	7
>10 % involvement	1		
≤10 % involvement	0		
ILD pattern		4	8
Definite/probable UIP	1		
Non-UIP	0		
DLCO% pred.		4.5	7.5
<55 %	1		
≥55 %	0		
Serum KL-6		–	6
≥730 U/mLl	1		
<730 U/mLl	0		

CCP, cyclic citrullinated peptide; DLCO % pred., predicted % diffuse capacity of the lung for carbon dioxide; ILD, interstitial lung disease; KL-6, Kreb von den Lungen-6; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia; ULN, upper limit of normal.

Table 4
Performance characteristics of the KORAIL RA-ILD progression risk score by thresholds of predicted probability.

Without pulmonary damage biomarker (KL-6)				
Cut-off	Sensitivity	Specificity	PPV	NPV
<3 (low risk)	95.8 %	21.1 %	39.3 %	90.5 %
≥13.5 (high risk)	22.9 %	95.6 %	73.3 %	69.9 %
With pulmonary damage biomarker (KL-6)				
Cut-off	Sensitivity	Specificity	PPV	NPV
<4 (low risk)	97.9 %	20.0 %	39.5 %	94.7 %
≥25.5 (high risk)	25.0 %	97.8 %	85.7 %	71.0 %

ILD, interstitial lung disease; KL-6, Kreb von den Lungen-6; NPV, negative predictive value; PPV, positive predictive value; RA, rheumatoid arthritis.

RA. Citrullination, a post-transcriptional modification, predominantly occurs when proteins are exposed to external stressors [44,45]. In the context of RA, individuals with genetic predispositions, such as the presence of the shared epitope [46,47], are more prone to developing autoantibodies against citrullinated peptides, which have been identified as risk factors for ILD in RA patients. Given prior studies showing a burden of citrullinated peptides in the lungs [48–50], these autoantibodies may damage the lungs even after ILD develops. This finding highlights a distinction between RA-ILD and IPF. While the course and nature of RA-ILD have long been considered similar to IPF [7,51], particularly when compared to other SARD-ILDs, our findings imply that autoantibody burden facilitate not only to trigger development of lung disease [52,53] but also exacerbate lung disease. This may suggest that the mechanisms underlying RA-ILD progression differ from those in IPF. Further research is needed to clarify the specific mechanisms involved and to assess whether reducing the autoantibody burden can lead to improved outcomes in RA-ILD.

Among non-IPF fibrotic ILDs, people with SARD-ILD typically have more favorable outcomes [31,54], though their clinical courses remain highly variable even after the onset of PPF [14,15,55]. This variability, combined with the frequent need for polypharmacy in RA-ILD patients and the lack of clear guidelines on when to discontinue RA and ILD therapies, highlights the importance of identifying not only those at high risk of progression but also those at low risk. In our study, we developed

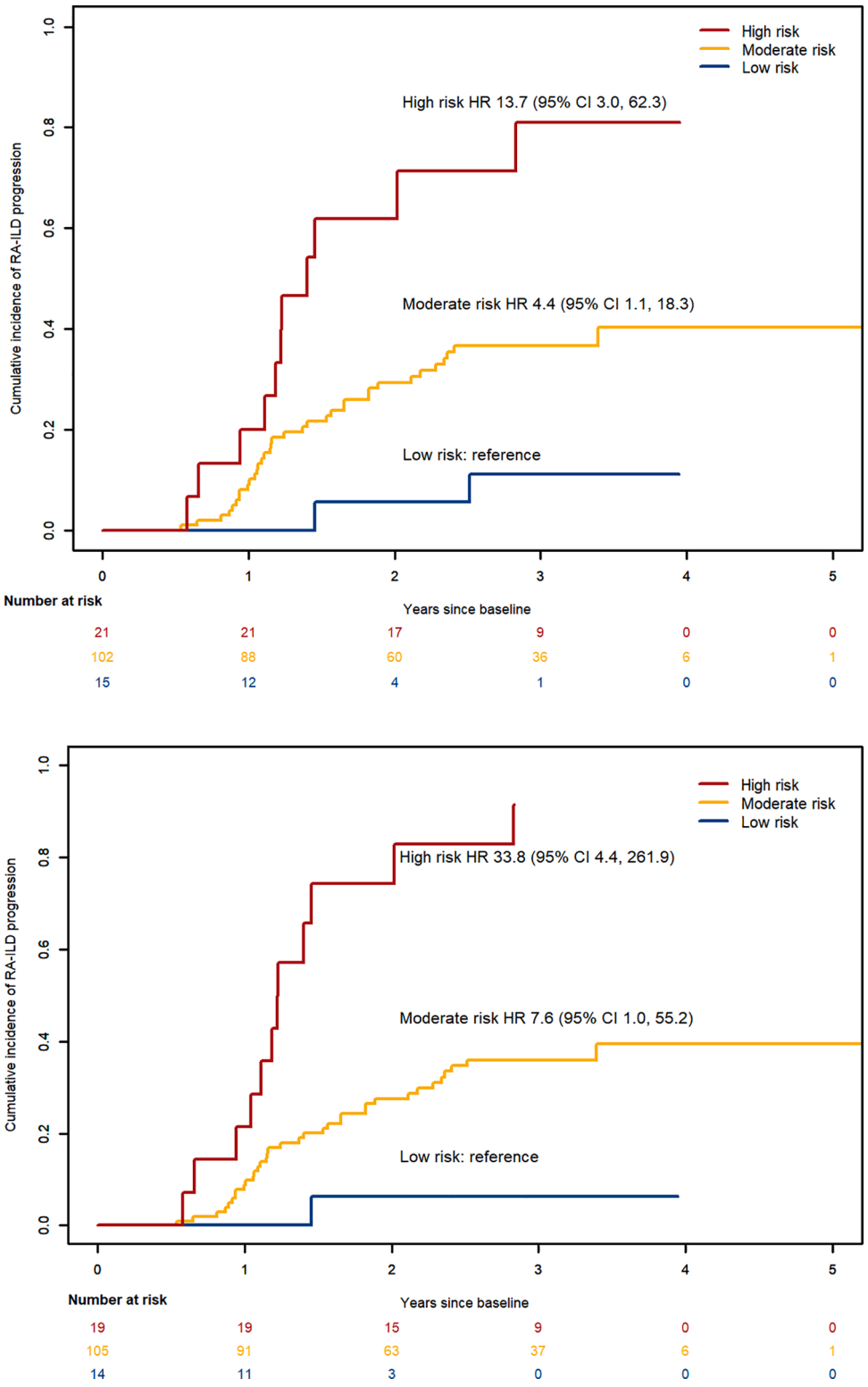

Fig. 2. Cumulative incidence of RA-ILD progression stratified by KORAIL prediction model.
A. Prediction model without KL-6, Total Score =3(AntiCCP≥ × 40 ULN)+ 4(Definite/probable UIP) +4.5(DLCO % pred.<55 %) +5(ILD extent>10 %), Low risk: score <3, Moderate risk: score ≥3 to <13.5, High risk: score ≥13.5, B. Prediction model with KL-6, Total Score =4(AntiCCP≥ × 40 ULN)+6(Serum KL6≥730U/ml)+ 7(ILD extent>10 %)+7.5(DLCO % pred.<55 %)+ 8(Definite/probable UIP), Low risk: score <4, Moderate risk: score ≥4 to <25.5, High risk: score ≥25.5, CCP, cyclic citrullinated peptide; DLCO % pred., predicted % diffuse capacity of the lung for carbon dioxide; ILD, interstitial lung disease; RA, rheumatoid arthritis; KL-6, Kreb von den Lungen-6; ULN, upper limit of normal; UIP, usual interstitial pneumonia

a predictive scoring system that efficiently stratified participants into low-, moderate-, and high-risk categories. In the low-risk group, only 4.2 % had RA-ILD progression, while only 4.4 % of patients classified as high-risk remained progression-free over a median observation period of 2.9 years. Implementing this predictive model could help in tailoring patient management strategies. High-risk patients may benefit from more frequent monitoring to enable timely intervention, while low-risk patients could potentially reduce the frequency of detailed follow-ups, such as chest CT scans, thereby decreasing healthcare costs. Further studies are warranted to assess the generalizability of this scoring system to other patient cohorts and to evaluate its potential for guiding anti-fibrotic treatment.

The strengths of our study include the inclusion of RA patients who met established classification criteria, ensuring a well-defined and clinically relevant cohort. ILD was systematically assessed using chest CT within a nationwide multicenter framework, while annual study visits allowed for the collection of comprehensive and detailed data on both RA and ILD characteristics. This approach included repeated CT scans and PFTs, enabling robust longitudinal monitoring of ILD progression. Consequently, we were able to apply the recently developed PPF criteria to RA-ILD, offering valuable insights into the dynamic nature of disease progression and advancing efforts to refine risk stratification in this patient population.

This study has several limitations. First, the KORAIL cohort predominantly includes patients with mild ILD and is limited to a Korean population, with nearly all participants having seropositive RA and a lower proportion of ever-smokers. As a result, the findings may not be generalizable to other populations, particularly those with end-stage ILD. Second, certain factors that could have provided additional insights, such as pulmonary symptoms and oxygen saturation, were not assessed. Regarding RA-specific treatments, while we analyzed the use of RA medications, none were found to be associated with progression. It is notable that rituximab is the second-line biologic used after TNF failure in Korea, and antifibrotics were not clinically available during the study period. Moreover, considering the results of this study, achieving RA remission may potentially play a more critical role in preventing ILD progression than the choice of specific medications. Lastly, the relatively small sample size and the loss to follow-up of some participants may have introduced bias and reduced the statistical power of the study. Furthermore, the absence of an external validation cohort required us to rely on internal validation, limiting the generalizability of our findings. Future studies with larger cohorts and external validation are necessary to confirm the proposed prediction model.

In conclusion, we identified key risk factors for RA-ILD progression, as defined by the recent PPF criteria with modification, including ILD pattern, extent of lung involvement, DLCO % predicted, anti-CCP titer, disease activity, and pulmonary damage biomarkers such as KL-6 and hSP-D. Furthermore, based on these factors, we developed a prediction model for RA-ILD progression based on predictors. The implementation of this model may facilitate the timely initiation of appropriate treatment by shortening the time required to fulfill the PPF criteria.

Ethical approval

This study was approved by the Institutional Review Board of each participating center (Supplementary Table 1).

Authors contributions

SHC, EYL and JAS had access to the study data, developed the figures and tables, and vouched for the data and analyses. SHC and JAS performed statistical analyses and contributed to data quality control, data analysis, and interpretation of the data. SHC, YBP, YJH, JSL, JWK, JWH, SWC, SWL, EHK, YAL, JYC, and EYL contributed to data collection. MUK and CHP contributed to data analysis. QZ, SF, GCM and MLP contributed data analysis, interpretation of the data, and drafting of the manuscript. EYL and JAS directed the work, designed the data collection methods, obtained funding, contributed to data collection, data analysis, and interpretation of the data and had final responsibility for the decision to submit for publication. All authors contributed intellectual content during the draft and revision of the work and approved the final version to be published.

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Data sharing statement

Data are available upon reasonable request and with appropriate institutional review board approval.

CRediT authorship contribution statement

Sung Hae Chang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Misti L. Paudel:** Writing – review & editing, Software, Methodology, Formal analysis. **Gregory C. McDermott:** Writing – review & editing, Methodology. **Qianru Zhang:** Writing – review & editing, Methodology. **Sho Fukui:** Writing – review & editing, Methodology, Formal analysis. **Minuk Kim:** Writing – review & editing, Visualization, Investigation, Data curation. **You-Jung Ha:** Writing – review & editing, Investigation, Data curation. **Jeong Seok Lee:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Sung Won Lee:** Writing – review & editing, Investigation. **Chan Ho Park:** Writing – review & editing, Investigation, Data curation. **Ji-Won Kim:** Writing – review & editing, Investigation, Data curation. **Jang Woo Ha:** Writing – review & editing, Investigation, Data curation. **Sang Wan Chung:** Writing – review & editing, Investigation, Data curation. **Eun Ha Kang:** Writing – review & editing, Supervision, Investigation, Data curation. **Yeon-Ah Lee:** Writing – review & editing, Supervision, Investigation, Data curation. **Yong-Beom Park:** Writing – review & editing, Supervision, Investigation, Data curation. **Jung-Yoon Choe:** Writing – review & editing, Supervision, Investigation, Data curation. **Eun Young Lee:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Jeffrey A. Sparks:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Eun Young Lee reports financial support was provided by National Research Foundation of Korea. Misti L. Paudel reports statistical analysis was provided by National Institutes of Health. Eun Young Lee reports a relationship with Abbvie, Samsung Bioepis, Novatis Korea, Boehringer Ingelheim Korea, Janssen Korea that includes: speaking and lecture fees.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152729.

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