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The value of biomarkers as predictors of outcome in patients with rheumatoid arthritis-associated usual interstitial pneumonia

Young Seok Lee[1], Ho Cheol Kim[2], Bo Young Lee[2], Chang Keun Lee[3], Mi-Young Kim[4], Se Jin Jang[5], Hye Sun Lee[6], Jieun Moon[6], Thomas V. Colby[7], Dong Soon Kim[2]

[1]Division of Respiratory and Critical Care Medicine, Department of Internal Medicine, Korea University Medical Center, Guro Hospital, Seoul; [2]Department of Pulmonary and Critical Care Medicine and [3]Department of Rheumatology; [4]Department of Radiology and Institute of Radiology; [5]Department of Pathology, Asan Medical Center, University of Ulsan, College of Medicine; [6]Biostatistics Collaboration Unit, Yonsei University College of Medicine, Seoul, South Korea, and [7]Department of Laboratory Medicine and Pathology, Mayo Clinic Scottsdale, AZ, USA

Abstract. *Background:* Because of the highly variable clinical course of rheumatoid arthritis-associated usual interstitial pneumonia (RA-UIP), the prediction of patient prognosis is important. *Objective:* The aim of this study was to investigate the role of blood biomarkers as prognostic predictors in the patients with RA-UIP. *Methods:* The blood levels of biomarkers (Krebs von den Lungen-6 [KL-6], surfactant protein-A [SP-A], matrix metalloproteinase-7 [MMP-7], interleukin-6 [IL-6], and interleukin-32 [IL-32]) were retrospectively compared with the clinical courses of 62 patients with RA-UIP. *Results:* The median follow-up period was 33.4 months. RA-UIP progressed in 15 patients (45.2%) during one year of follow-up. We found that KL-6 and IL-6 were significant predictors of short-term (1 year) prognosis. Multivariate logistic regression analysis showed that the odds ratio (OR) for KL-6 was 1.001 (95% confidence interval [CI]: 1.000–1.003, $p = 0.077$) and that the OR for IL-6 was 1.040 (95% CI: 1.002–1.080, $p = 0.039$) for short-term disease progression. The addition of KL-6 and IL-6 to the clinical parameters (concordance index [C-index]: 0.958, $p = 0.053$) predicted short-term disease progression better than the clinical parameter alone (C-index: 0.853). In addition, patients with high levels of KL-6 (≥933 U/mL) had shorter survival than those with low levels of KL-6 (<933 U/mL) (median survival: 51 vs. 96 months, $p = 0.019$). *Conclusions:* The results of this retrospective study suggested that KL-6 and IL-6 could be used as predictors of short-term disease progression. In addition, high levels of KL-6 could be used as a predictor of mortality. Additional studies involving a larger patient cohort are warranted. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 216-223)*

Key words: biomarkers, rheumatoid arthritis, interstitial lung disease, prognosis, KL-6, IL-6

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Correspondence: Dong Soon Kim, M.D., Ph.D.
Emeritus Professor, Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan, College of Medicine, Asanbyungwon-gil, Songpa-gu, Seoul, 138-736, South Korea
Tel. 82-2-404-5071
Fax 82-2-544-2918
E-mail: dskim615@gmail.com

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects 1-2% of the general population (1, 2). Interstitial pneumonia (IP) has been observed in approximately 5-10% of patients with RA depending on the diagnostic method, and RA-associated IP (RA-IP) is the second most common cause of death among patients with RA

following cardiovascular disease (1, 2). Although more effective therapies for RA have decreased RA-associated mortality rates, the burden of RA-IP in RA-associated mortality has increased due to a lack of effective therapies for RA-IP (2, 3). Furthermore, the mean age of death among patients with RA-IP was lower than that of patients without RA-IP, suggesting that IP may lead to early mortality in patients with RA (2, 3).

In contrast to other connective tissue diseases (CTDs), the usual interstitial pneumonia (UIP) pattern is more frequently observed with RA-IP, and the prognosis of RA-UIP is worse than that of other CTD-related UIP (4-7). However, the disease course of individual patients is highly variable, even among patients with UIP patterns; some patients may have stable disease for many years despite the presence of honeycombing on high resolution computed tomography (HRCT), whereas other patients may progress slowly to respiratory failure and death (3, 7-10). Although the pathology of RA-UIP was determined to be the same as that of idiopathic pulmonary fibrosis (IPF), the prognosis of RA-UIP was shown to be better (8, 10). Previously, the levels of matrix metalloproteinase-7 (MMP-7), surfactant protein-A (SP-A), and Krebs von den Lungen-6 (KL-6) were reported to be blood biomarkers that could be used to predict the prognosis of patients with IPF (11, 12). However, the role of blood biomarkers in patients with RA-UIP is unclear. In patients with RA-UIP, it is clinically important to predict prognosis at the time of diagnosis because it can be highly variable and it is still not known whether corticosteroid therapy with or without immunosuppressive agents, which is commonly administered to RA-UIP patients, is effective or harmful.

The aim of this study was to investigate the role of blood biomarkers as prognostic predictors (e.g. of disease progression and mortality) in patients with RA-UIP.

Methods

Study population

This study was a retrospective study of 62 patients who were diagnosed with RA-UIP between 2005 and 2012 at Asan Medical Center, a tertiary referral hospital in Seoul, Korea. The patients were diagnosed with RA by a rheumatologist, and the diagnosis was made according to the revised criteria of the American College of Rheumatology. The UIP pattern was diagnosed by surgical lung biopsy in 25 patients and by the typical UIP pattern on HRCT in 37 patients. The UIP pattern on HRCT has recently been reported to be highly specific for pathologic UIP, in RA-IP patients, similar to the specificity for IPF (13). The diagnoses for all patients were confirmed though a multidisciplinary discussion between the radiologist, pathologist, and pulmonologist, and were made according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus Classification for idiopathic IP (14, 15). Patients who had other coexisting CTDs and drug-induced ILD (e.g. methotrexate- induced ILD) were excluded after multidisciplinary discussion. Only patients who were followed for more than one year after sampling were included in the study. The Institutional Review Board of Asan Medical Center in Korea (No: 2013-0433) approved the study, and written informed consent for the use of blood samples for clinical research was obtained from all patients.

Although this was a retrospective study, all of the data including a detailed systematic history, a physical examination, serologic tests, lung function tests, and HRCT, were prospectively collected at the time of the initial evaluation and during follow-up, according to the clinical study protocols for ILD. The survival status of each patient was obtained from medical records, telephone interviews, and/or the records of the National Health Insurance of Korea. Lung function was measured according to the ATS recommendations. The results were expressed as percentages of the normal predicted values (16-18). The HRCTs were reviewed by a thoracic radiologist with more than 15 years of experience in ILD and who was blinded to the clinical information. The biopsy slides were reviewed independently by two lung pathologists (TVC and SJJ) who were also blinded to the clinical information, and a consensus histopathological diagnosis was achieved.

Definitions

The disease course was classified as improved, stable, or progressive. Improvement or progression was defined as a 10% or greater change in the forced

vital capacity (FVC) and/or a 15% or greater decrease in the diffusing capacity of the lungs for carbon monoxide (DL_{CO}), with or without aggravation of dyspnea and the HRCT findings (15). In addition, the occurrence of acute exacerbations during follow-up and/or death caused by RA-IP was considered disease progression. Acute exacerbation was defined by the following criteria proposed by Collard et al.: 1) unexplained worsening or development of dyspnea within 30 days; 2) new bilateral ground-glass abnormalities and/or consolidation on HRCT; and 3) no evidence of pulmonary infection, pulmonary embolism, left-sided heart failure, or other identifiable causes of acute lung injury (19). Patients who did not satisfy the criteria for disease progression or improvement were considered to have stable disease. Because a given therapy could have influenced the disease course, the disease course was evaluated until therapy was initiated. The disease course was analyzed during the year after the time of sample collection to investigate the relationship between biomarkers and the natural course of the disease without treatment.

Measurement of blood biomarker levels

Blood was collected by using routine procedures and plasma was stored at -70°C. The levels of KL-6 (Eidia Co. Ltd., Tokyo, Japan), SP-A (BioVendor Laboratory Medicine,Inc., Brno, Czech Republic), MMP-7 (R&D Systems, Minneapolis, MN, USA), IL-6 (R&D Systems, Minneapolis, MN, USA), and IL-32(Cusabio, Inc., China) were measured using commercially available enzyme-linked immunosorbent assay kits. All assays were performed in duplicate, and the mean values were used for data analysis.

Comparison between the blood biomarkers and clinical information

The relationship between the clinical courses and the levels of the following blood biomarkers was analyzed: KL-6, SP-A and MMP-7, which are well-known biomarkers for pulmonary fibrosis; IL-6 and IL-32, which are biomarkers for RA (11, 12, 20-24). The biomarker levels at the time of sampling were first evaluated as predictors of patient prognosis (both mortality and disease progression), and were then compared with the acute exacerbation state (12).

Statistical analysis

Fisher's exact tests were used to analyze categorical data and Mann-Whitney U tests were used to analyze continuous data. Correlation analyses using Spearman's rank correlation coefficients were performed to evaluate the relationship between pulmonary function tests and biomarker levels. The biomarker levels were analyzed by using receiver operating characteristic (ROC) curves to determine the cut-off levels that resulted in the optimal diagnostic accuracy for each marker. Survival was evaluated using a Kaplan-Meier approach and log-rank tests. Logistic regression analysis and Cox proportional hazard analysis using backward elimination were used to identify independent risk factors for disease progression and mortality. Variables with few correlations among the other variables and p-values less than 0.1 in the univariate analysis were entered into the multivariate analyses. The results are summarized as the adjusted odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (CIs). The discriminatory capability of the models was evaluated using the C statistic with a concordance index (C-index), which is conceptually similar to the area under the ROC curve (AUC) in a logistic model. A comparison of the AUCs between biomarker levels combined with the clinical parameters, and the clinical parameters alone was performed by using the Hanley & McNeil method. We considered p values that were less than 0.05 to be statistically significant. All statistical analyses were performed using MedCalc version 14.12.0 (MedCalc Software, Ostend, Belgium) and SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the subjects

The mean patient age was 64 years and 32 patients (51.6%) were male. The median follow-up period was 33.4 months and RA-UIP progressed in 15 patients (45.2%) during one year. Because all patients had a prior diagnosis of RA, most were receiving medication for RA treatment such as low-dose prednisolone (n = 59) or methotrexate (n = 28). In the progression group, the patients with RA-UIP

were older and more likely to be male. Patients with disease progression had higher levels of C reactive protein and reduced lung function compared to those with stable disease. The baseline clinical features are shown in Table 1.

The correlation between biomarker levels and disease course in patients with rheumatoid arthritis-associated usual interstitial pneumonia

The individual biomarker levels for all subjects are shown in Table 2. One patient was lost to follow-up and was therefore excluded from the analysis. During one year, 15 patients experienced disease progression. In the patients with progressive disease, the levels of KL-6 was significantly higher (p = 0.006) and IL-6 tended to be higher (p = 0.086) compared to those who had stable disease (Table 3). The optimal cut-off level for KL-6 to distinguish disease progression was 1377 U/mL (sensitivity: 60.0%, specificity: 93.5%) and the optimal cut-off level for IL-6 was 45 pg/mL (sensitivity: 46.2%, specificity: 92.1%) (Table 2). Multivariate logistic analysis using backward elimination revealed that FVC (OR, 0.898; 95% CI, 0.826-0.975; p = 0.011), IL-6 (OR, 1.040; 95% CI, 1.002-1.080; p = 0.039), and KL-6 (OR, 1.001; 95% CI, 1.000-1.003; p = 0.077) were meaningful predictors of short-term prognosis (Table 3). During long-term follow-up (≥2 years), no biomarkers were identified that could predict disease progression.

Performance characteristics of different combinations of parameters for the prediction of disease progression using C statistics

To investigate whether biomarkers were more valuable for predicting patient prognosis than clinical parameters alone (e.g., FVC), the C-index for different combinations of clinical parameters and biomarkers was analyzed. The addition of KL-6 and IL-6 to the clinical parameters (C-index; 0.958) predicted short-term disease progression (1 year) better than the clinical parameters alone (C-index; 0.853) (p = 0.053) (Table 4). The model using the cut-off values of the biomarkers and the clinical parameter (FVC< 80%, KL-6≥ 1377 U/mL, and IL-6≥ 45 pg/mL) showed a sensitivity of 26.7%, specificity of 100%, positive predicted value of 100%, and negative predicted value (80.7%) for predicting short-term disease progression (1 year).

Table 1. Baseline characteristics in patients with rheumatoid arthritis associated usual interstitial pneumonia according disease progression during 1 year

Variables	Total (N=62)	Stable (N=46)	Progression (N=15)	p value
Age (years)*	64±9	63±9	66±9	0.279
Male	32 (51.6)	23 (50)	9 (60)	0.562
Nonsmoker	32 (51.6)	24 (52.2)	7 (46.7)	0.772
Rheumatoid arthritis				
ESR*	50±32	41±26	74±34	0.001
CRP*	2.5±4.1	1.3±2.2	5.7±6.1	0.013
RA Treatment				
Prednisolone	59 (95.2)	43 (93.5)	15 (100)	0.569
Methotrexate	28 (45.2)	22 (47.8)	6 (40)	0.767
Etanercept	4 (6.5)	4 (8.7)	15 (100)	0.564
Leflunomide	9 (14.5)	8 (17.4)	1 (6.7)	0.430
PFT (% predicted value)*				
FVC	80±20	86±18	61±17	<0.001
DLco	66±23	74±20	43±17	<0.001
TLC	80±15	84±13	66±13	<0.001
6 min walk (distance)*	424±131	455±116	324±141	0.003
PaO_2/FiO_2 ratio*	436±205	441±203	421±224	0.750

ESR, erythrocyte sedimentation rate; CPR, C reactive protein; PFT, pulmonary function test; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity
*The data are presented as means±standard deviation. Other variables are presented as numbers (percent).

Table 2. The level of blood biomarkers in patients with RA-UIP according to disease progression during 1 year

Biomarkers	Total (N=61)	Stable (N=46)	Progression (N=15)	P value
KL-6, U/mL	823 (543-1191)	773 (497-1043)	1508 (694-2147)	0.006
SP-A, ng/mL	55 (37-80)	55 (32-78)	64 (41-100)	0.580
MMP-7, ng/mL	8 (6-9)	7 (5-9)	8 (5-11)	0.339
IL-6, pg/mL	12 (5-31)	11 (4-24)	26 (6-87)	0.086
IL-32, pg/mL	542(252-969)	556 (337-1093)	339 (157-668)	0.141

RA-UIP, rheumatoid arthritis-usual interstitial pneumonia; KL-6, Krebs von den Lungen 6 antigen; SP-A, surfactant protein-A; MMP-7, matrix metalloproteinase-7; IL-6, Interleukin-6; IL-32, Interleukin-32

Table 3. Risk factors for disease progression at 1 year in patients with RA-UIP using logistic regression analysis

Risk factors	Odds ratio	95% CI	P value
Univariate analysis (N=61)			
Age	1.039	0.970-1.113	0.276
Male	1.500	0.459-4.900	0.502
Non-smoker	0.802	0.250-2.578	0.711
CRP	1.411	1.108-1.796	0.005
FVC (% predicted value)	0.923	0.882-0.966	0.001
DLco (% predicted value)	0.919	0.879-0.962	<0.001
TLC (% predicted value)	0.903	0.852-0.957	0.001
6 min walk (distance)	0.992	0.987-0.998	0.009
PaO_2/FiO_2 ratio	1.000	0.997-1.002	0.745
KL-6 (U/mL)	1.001	1.000-1.002	0.008
SP-A (ng/mL)	1.004	0.994-1.014	0.418
MMP-7 (ng/mL)	1.099	0.885-1.365	0.394
IL-6 (pg/mL)	1.021	1.000-1.042	0.046
IL-32 (pg/mL)	0.999	0.997-1.001	0.218
Multivariate analysis (N=61)*			
FVC (% predicted value)	0.898	0.826-0.975	0.011
IL-6 (pg/mL)	1.040	1.002-1.080	0.039
KL-6 (U/mL)	1.001	1.000-1.003	0.077

RA-UIP, rheumatoid arthritis-usual interstitial pneumonia; CPR, C reactive protein; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; KL-6, Krebs von den Lungen 6 antigen; SP-A, surfactant protein-A; MMP-7, matrix metalloproteinase-7; IL-6, Interleukin-6; IL-32, Interleukin-32
* CRP, DLco % predicted, and TLC % predicted were excluded in multivariate analysis due to close correlation among variables (CRP-IL 6: r=0.555, p<0.001; DLco % predicted-6 min walk distance: r=0.548, p<0.001; FVC % predicted: r=0.604, p<0.001; TLC % predicted-FVC % predicted: r=0.844, p<0.001). Multivariate logistic regression analysis using backward elimination was performed to predict the disease progression after adjusting for four variables (6 min walk, FVC, IL-6, and KL-6) that were statistically significant in the univariate analysis.

Table 4. Performance characteristics of different combination of parameters for prediction of disease progression in patients with RA-UIP

Models	C-index	95% CI	P value†
Disease progression (N=61)			
Clinical variable*	0.853	0.724-0.937	reference
Clinical variable + KL-6 + IL-6	0.958	0.860-0.995	0.053

RA-UIP, rheumatoid arthritis-usual interstitial pneumonia; KL-6, Krebs von den Lungen 6 antigen; IL-6, Interleukin-6
*Clinical variable included FVC (% predicted value).
†The comparison of AUC is tested by the Hanley&McNeil method.

Prognostic biomarkers for predicting survival

In our study, 30 (48.4%) patients died during follow up and the main causes of death were disease progression (40%), respiratory infection (20%), or unknown cause due to a loss to follow-up (40%). The cumulative mortality rate was 37% at 3 years and 51% at 5 years. The optimal cut-off level for KL-6 to predict mortality was 933 U/mL (sensitivity: 56.7%, specificity: 75.0%). On univariate analysis, high lev-

els of KL-6 (≥933 U/mL) along with six other variables (age, C reactive protein [CRP], FVC, DLco, total lung capacity [TLC], 6 min walk [distance]) were significantly related to mortality. Multivariate Cox proportional hazard analysis using backward elimination indicated that age (HR, 1.073; 95% CI, 1.008-1.143; p = 0.028), 6 min walk (distance) (HR, 0.994; 95% CI, 0.990-0.997; p = 0.001) and high levels of KL-6 (HR, 3.035; 95% CI, 1.168-7.885, p = 0.023) were statistically significant independent predictors (Table 5). Kaplan-Meier analysis revealed that the survival period of patients with high levels of KL-6 (≥933 U/mL) was significantly shorter compared to those with low levels (<933 U/mL) (median survival: 51 vs. 96 months, p = 0.019) (Figure 1).

Biomarker levels at the time of acute exacerbation in patients with rheumatoid arthritis-associated usual interstitial pneumonia

KL-6 levels were significantly higher in patients with acute exacerbation compared to those without acute exacerbation (Table 6). The optimal cut off level for KL-6 to discern an acute exacerbation was 1483 U/mL (sensitivity: 100%, specificity: 88.9%). The IL-6 levels also showed a trend toward association with acute exacerbation (p=0.068).

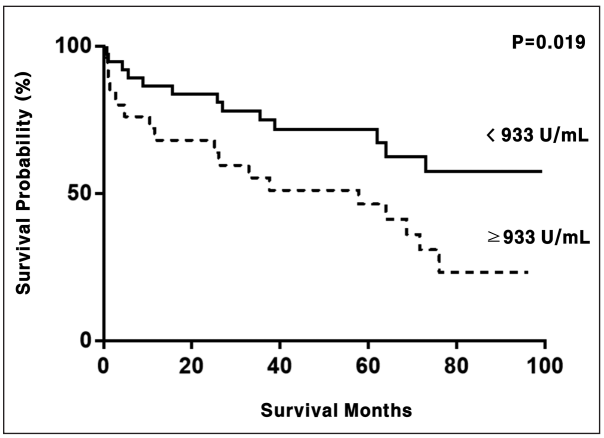

Fig. 1. The survival curve using the Kaplan Meier method, according to high KL-6 (≥933) and low KL-6 (<933) (Log rank test, p=0.019)

Discussion

This study showed that blood biomarkers seem to be useful predictors of outcome among patients with RA-UIP. We found that KL-6 was a significant predictor of short-term (1 year) disease progression and survival. On multivariate analysis, a high level of IL-6 was a significant risk factor for short term disease progression. In addition, C statistics showed that the addition of biomarkers (KL-6 and IL-6) to

Table 5. Risk factors for mortality in patients with RA-UIP using Cox proportional hazard analysis

Risk factors	Hazard ratio	95% CI	P value
Univariate analysis (N=62)			
Age	1.066	1.020-1.114	0.004
Male	1.410	0.684-2.908	0.352
Non-smoker	0.823	0.399-1.697	0.597
CRP	1.218	1.111-1.336	<0.001
FVC (% predicted value)	0.970	0.950-0.991	0.004
DLco (% predicted value)	0.951	0.931-0.971	<0.001
TLC (% predicted value)	0.962	0.937-0.988	0.004
6 min walk (distance)	0.994	0.991-0.997	<0.001
PaO_2/FiO_2 ratio	1.001	0.999-1.002	0.479
KL-6 (≥933 U/mL)	2.314	1.122-4.773	0.023
Multivariate analysis (N=62) *			
Age	1.073	1.008-1.143	0.028
6 min walk (distance)	0.994	0.990-0.997	0.001
KL-6 (≥933 U/mL)	3.035	1.168-7.885	0.023

UIP, usual interstitial pneumonia; CPR, C reactive protein; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; KL-6, Krebs von den Lungen 6 antigen; SP-A, surfactant protein-A; MMP-7, matrix metalloproteinase-7; IL-6, Interleukin-6; IL-32, Interleukin-32

* DLco % predicted, and TLC % predicted were excluded in multivariate analysis due to close correlation among variables (DLco % predicted-FVC % predicted: r=0.604, p<0.001; TLC % predicted-FVC % predicted: r=0.844, p<0.001). Multivariate logistic regression analysis using backward elimination was performed to predict mortality after adjusting for five variables (age, CRP, 6 min walk, FVC, KL-6 (≥933 U/mL)) that were statistically significant in the univariate analysis.

Table 6. The level of blood biomarkers at the time of acute exacerbation in patients with RA-UIP

Biomarkers	Acute exacerbation		P value
	Yes (N=7)	No (N=55)	
KL-6, U/mL	2147 (1713-2553)	794 (546-1088)	<0.001
SP-A, ng/mL	84 (49-163)	62 (50-88)	0.265
MMP-7, ng/mL	6 (3-11)	8 (6-9)	0.580
IL-6, pg/mL	53 (8-201)	11 (4-26)	0.068
IL-32, pg/mL	414 (171-828)	552 (330-1166)	0.461

the clinical parameter (FVC) seems to improve the predictive ability compared with FVC alone. We also found that KL-6 was a possible biomarker for detecting acute exacerbation state.

There have been many reports on the roles of blood biomarkers in patients with IPF (11, 12, 20, 21, 25). Among CTD-related ILDs, scleroderma has been the most widely studied. Yanaba et al. and Hant et al. both reported that the KL-6 and SP-D levels were higher in patients with ILD (26, 27). According to these studies, SP-D was a more sensitive marker, but KL-6 was more specific. Several other studies also reported increased levels of KL-6 in patients with scleroderma (28, 29).

In addition to scleroderma, increased levels of KL-6 have been reported in patients with other types of CTD, like polymyositis/dermatomyositis-related ILD (30, 31). However there were only three reports regarding RA-ILD. Oka et al. screened 274 biomarkers in the pooled sera from patients with CTD and found increased IL-6 levels in RA-IP patients with acute exacerbation, in addition to various changes in several different cytokines (32). However, the number of patients was small (n=25) and included patients with drug- induced ILD (n=16). Recently, Gottenberg et al. reported that IL-6 and IL-21 were associated with B cell activation and radiographic progression in patients with early RA (22). The levels of KL-6 were not measured in either study. A study in which KL-6 levels were measured reported mere increase of KL-6 levels in the patients with RA-IP compared to RA only, but the role of KL-6 as a marker of disease progression or mortality was not studied (33). Our study has shown that in patients with RA-IP, several biomarkers (KL-6 and IL-6) may predict the prognosis (e.g. disease progression and mortality) and detect the acute exacerbation state.

We hypothesized that the pathogenesis and progression of RA-UIP may be related not only to pulmonary fibrosis but also to RA itself. Therefore, we selected KL-6, SP-A, and MMP-7 as markers of pulmonary fibrosis, and IL-6 and IL-32 as markers of RA. Our data showed that in RA-UIP patients, both process of pulmonary fibrosis (KL-6) and RA (IL-6) are important in terms of short-term disease progression. Additionally, mortality may be related more to the fibrotic process in the lungs, similar to IPF. In other words, short-term outcome (disease progression) was affected by both RA itself and pulmonary fibrosis, and long-term outcome (mortality) may be related to the nature of UIP. This finding is not contradictory, because the underlying pathogenesis of RA-UIP might reflect the combined nature of both RA and UIP. Our study provided evidence that measurement of KL-6 and IL-6 levels at the time of diagnosis could help to predict disease progression and mortality. In addition, the model using biomarker cut-off values and the FVC model (FVC<80%, KL-6≥1377 U/mL, and IL-6≥45 pg/mL) had high specificity (100%) and a high positive predictive value (100%). Further prospective studies with larger numbers of subjects are required.

The present study had several limitations. The major limitation is the retrospective design performed in one tertiary medical center. However, because RA-IP, especially RA-UIP, is a rare disease, our study is important for providing the evidence for the possibility of biomarkers' role in the prediction of prognosis. An additional limitation was that we included patients with definite UIP patterns on HRCT without surgical lung biopsies, which could be a potential cause of misclassification. However, a strong correlation between definite UIP patterns on HRCT and histopathologic UIP was confirmed in RA-UIP patients to a similar extent as IPF by multi-institutional studies (13). We measured only five arbitrarily selected biomarkers at a single time-point. It could definitely be helpful to study more biomarkers in serial samples. Finally, the total number of patients in our study (n = 62) was relatively small, but it was large enough to reveal the role of biomarkers in RA-UIP. Despite these limitations, our study represents the first attempt to compare the values of different blood biomarkers as predictors of prognosis in well-characterized patients with RA-UIP.

In conclusion, our retrospective study provided the evidence that the level of blood biomarkers, KL-6 and IL-6 may be helpful to predict short-term

disease progression and mortality and that RA-UIP reflects the combined nature of both RA and UIP. Additional studies of a larger patient cohort are warranted.

Author contribution:
(1) Conception and design of the study: Lee YS, Kim DS
(2) Data generation (When applicable): Lee YS, Kim HC, Lee BY, Lee CK, Kim MY, Jang SJ, Colby TV, Kim DS
(3) Analysis and Interpretation of the data: Lee YS, Kim HC, Lee BY, Lee CK, Kim MY, Jang SJ, Lee HS, Moon J, Colby TV, Kim DS
(4) Preparation or critical revision of the manuscript: Lee YS, Kim HC, Lee BY, Lee CK, Kim MY, Jang SJ, Lee HS, Moon J, Colby TV, Kim DS

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