의학석사 학위논문

Comparison of the clinical characteristics of rheumatoid arthritis patients with and without interstitial lung disease

간질성 폐질환을 동반한 류마티스 관절염 환자와 간질성 폐질환을 동반하지 않은 류마티스 관절염 환자의 임상적 특성의 비교에 관한 연구

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ABSTRACT

Comparison of the clinical characteristics of rheumatoid arthritis patients with and without interstitial lung disease

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Introduction: The clinical importance of rheumatoid arthritis-associated interstitial lung disease has been increased because the usual interstitial pneumonia (UIP) is the most common subtype of interstitial lung disease (ILD) on high-resolution computed tomography (HRCT) in rheumatoid arthritis (RA)and has poor survival rate compared to other forms of ILD related to connective tissue disease. The clinical characteristics and laboratory data of RA patients with and without ILD were compared in order to clarify the risk factors for ILD in RA patients. Furthermore, risk factors of mortality in the RA patients with ILD group were analyzed.

Methods: A total of 77 RA patients with ILD and 231 age/sex-,

and disease duration-matched RA patients without ILD who were followed from 1991 to 2011 at Seoul National University Hospital were enrolled in this study. Epidemiologic, clinical, and laboratory information including rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) were obtained through medical chart review. The erythrocyte sedimentation rates (ESR), C-reactive protein (CRP) levels, presence of erosion on joint X-rays, and mean corticosteroid doses were examined in order to compare RA outcomes between the RA patients with and without ILD. Cox proportional hazard models were used to estimate the risk of mortality in the RA patients with ILD.

Results: In the RA with ILD group, the titers of the RF and the anti-CCP were significantly higher compared with those in the RA without ILD group ($p = 0.001$ for both). The RA patients with ILD had higher frequency of a history of tuberculosis or nontuberculous mycobacteria (NTM) ($p = 0.022$). In addition, the RA with ILD group exhibited higher levels of CRP at the time of RA diagnosis ($p = 0.014$) and higher ESR ($p = 0.022$) and CRP levels ($p < 0.001$) throughout the 10-year follow-up period. These patients received higher mean daily dose of corticosteroid ($p < 0.001$). In the subgroup analysis of RA

patients with ILD, 28 (36.4%) patients died with the mean follow-up duration of 8.7 years. Male patients, high RF titers and UIP subtype on HRCT had significantly worse survival, and those with nonspecific interstitial pneumonia (NSIP) on HRCT had better survival. In the multivariate analysis, a UIP subtype on HRCT and older age at the time of ILD diagnosis were significantly associated with mortality of RA with ILD.

Conclusions: The RA patients with ILD had higher RF and anti-CCP titers and baseline CRP levels compared with those without ILD. A UIP subtype on HRCT and older age at the time of the diagnosis of ILD were significantly associated with mortality of RA with ILD.

Keywords: Rheumatoid arthritis, Interstitial lung disease

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LIST OF ABBREVIATIONS

ILD = interstitial lung disease, RA = rheumatoid arthritis, UIP = usual interstitial pneumonia, HRCT = high-resolution computed tomography, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, NTM = nontuberculous mycobacteria, DMARDs = disease-modifying antirheumatic drugs, MTX = methotrexate, TNF = tumor necrosis factor, FVC = forced vital capacity DLCO = diffusing capacity of carbon monoxide, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, DPB = diffuse panbronchiolitis, LIP = lymphocytic interstitial pneumonia, DIP = desquamative interstitial pneumonia, ACPA = anti-citrullinated protein antibody, IL-6 = interleukin-6

INTRODUCTION

Rheumatoid arthritis-associated interstitial lung disease was reported to increase substantial morbidity and mortality in affected patients (1). However, the presence of interstitial lung disease (ILD) has been largely ignored in the management of rheumatoid arthritis (RA) because the symptoms of ILD are subclinical in most patients (2). Recent studies have indicated that ILD may be a feature of early RA and its prevalence increases with age (3). The usual interstitial pneumonia (UIP) is the most common subtype of ILD on high-resolution computed tomography (HRCT) in RA and an increased risk of mortality has been reported to be associated with the UIP subtype in RA compared to patients with other forms of ILD related to connective tissue disease. In addition, their survival rate is similar to idiopathic pulmonary fibrosis, which is the most devastating ILD (1, 4, 5). These studies recommended a multidisciplinary approach in the management of ILD in RA patients. Most knowledge about determinants of the

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progression and prognosis of patients with ILD related to connective tissue disease from studies of the natural history of patients with systemic sclerosis associated ILD. It remains to be investigated, whether these data are applicable to other forms of ILD related to connective tissue disease (6).

The management of RA patients is complicated by the several drugs with potential lung toxicity in the presence of ILD. Although there is limited evidence at present, these agents should be used with caution in RA patients with ILD (7, 8).

In the present study, the clinical characteristics of RA patients with and without ILD were compared in order to clarify the risk factors for ILD in these patients. Finally, risk factors of mortality were analyzed in the RA with ILD group.

METHODS

Patients

Seventy seven patients with RA with ILD who received longitudinal clinical care at Seoul National University Hospital from January 1991 to December 2011 were enrolled. The diagnosis of RA was based on the 1987 revised classification criteria of the American College of Rheumatology (9). ILD was diagnosed according to the criteria of the American Thoracic Society, which included consistent clinical features and pulmonary function tests, radiographic evidence of interstitial disease, and/or lung histopathology that was consistent with this diagnosis (10). As a reference group, age/sex-, and disease duration-matched 231 RA patients without ILD who received medical care during the same period were randomly selected from the medical record archive at a ratio of 1 to 3. This study was approved by the Institutional Review Board of Seoul National University Hospital.

Outcome measurements

Medical records of the selected patients were reviewed. The epidemiologic, clinical, and laboratory data were examined. Rheumatoid factor (RF) was measured by immunoturbidemetric assay (reference range < 15 IU/ml) and anti-cyclic citrullinated peptide (anti-CCP) was measured by chemiluminescent microparticle immunoassay (reference range < 5.0 IU/ml). Data on the levels of erythrocyte sedimentation rate (ESR, reference range < 20 mm/hr) and C-reactive protein (CRP, reference range < 0.5 mg/dL) were collected annually since the time of RA diagnosis. The presence of erosion on joint X-rays and the mean daily corticosteroid dose were examined as measures of RA outcome over the 10-year follow-up after the diagnosis of RA in the two groups. In order to identify the risk factors of mortality in the RA with ILD group, survival data were obtained from the Ministry of Security and Public Administration.

Statistical analysis

Student's t-test for continuous variables and chi-square or Fisher's exact test for categorical variables were used to compare the patients with and without ILD. The results were reported as mean ± standard deviation.

Cox proportional hazard models were used to identify the risk factors of mortality in the RA-ILD group. The results were expressed as hazard ratios with 95% confidence intervals. Survival was analyzed with the Kaplan-Meier method and compared with the log-rank test. Two-sided p values less than 0.05 were considered statistically significant. All of the analyses were performed with IBM SPSS statistics software, version 21 (IBM Corporation, Armonk, NY, USA)

RESULTS

Comparison of the clinical characteristics between the RA patients with and without ILD

The study cohort was comprised of 77 RA patients with ILD and 231 age/sex-, and disease duration-matched RA patients without ILD.

The proportions of ex-smokers, current smokers and their pack years were not significantly different in the two groups. A history of tuberculosis or nontuberculous mycobacteria (NTM) was more frequently found in RA patients with ILD (Table 1).

RF and anti-CCP positivity did not significantly differ. However, RA patients with ILD had higher RF (mean ± SD, 521.1 ± 828.3 vs. 249.3 ± 332.4, p = 0.001) and anti-CCP titers (242.8 ± 234.4 vs. 125.3 ± 144.3, p = 0.001) than those of RA control group. The baseline ESR did not differ significantly between the RA patients with and without ILD (59.9 ± 37.3 mm/hr vs. 44.9 ± 35.1 mm/hr, respectively). However, the baseline CRP levels in

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the RA with ILD group (29.5 ± 35.3 mg/L) were significantly higher than those of RA patients without ILD group (19.1 ± 29.5, p = 0.014). The percentages of RA patients with erosive change a baseline did not significantly differ between the two groups (Table 1).

The medications, including disease-modifying antirheumatic drugs (DMARDs) and biologic agents were significantly different in the two groups, and this difference might have been due to lung toxicity. More than two-thirds of RA patients without ILD received methotrexate (MTX) (176, 76.2%), while only one-third (30, 39.0%, p < 0.001) of the RA patients with ILD received with MTX. The proportions of patients receiving sulfasalazine (63.2% vs. 32.0%, p < 0.001) and rituximab (2.6% vs. 0%, p < 0.001) were significantly higher in RA with ILD compared to without ILD. Usage of leflunomide, hydroxychloroquine, tacrolimus, and tumor necrosis factor (TNF) inhibitors were similar in the two groups (Table 1). The RA with ILD group (6.7 ± 7.6 mg/day) received higher mean daily dose of corticosteroid compared with

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the RA control group (3.6 ± 2.4 mg/day) ($p < 0.001$) (Table 1).

The mean ESR (47.9 ± 25.5 mm/hr vs. 31.7 ± 21.9 mm/hr, $p = 0.022$) and CRP levels (21.2 ± 23.8 mg/L vs. 11.2 ± 15.4 mg/L, $p < 0.001$) in the RA with ILD group over the 10-year follow up period were significantly higher than those in the RA control group (Figure 1). RA patient with ILD had higher inflammatory burdens over the disease course.

Table 1. Clinical characteristics of RA patients with and without ILD

	RA with ILD (n = 77)	**RA without ILD (n = 231)**	**p value**
Age	56.6 ± 13.1	57.1 ± 11.7	0.731[a]
Female	58 (75.3%)	174 (75.3%)	1.000[b]
Disease duration (years)	11.5 ± 8.5	10.8 ± 6.9	0.458[a]
Smoking			
Ex-smoker	10/68 (14.7)	18/152 (11.8)	0.162[b]
Current smoker	4/68 (5.9)	7/152 (4.6)	0.367[c]
Pack-years	28.4 ± 19.8	33.7 ± 15.4	0.445[a]
History of Tbc or NTM	12 (15.6)	16 (6.9)	**0.022[b]**
Serology			
RF positivity	56/76 (73.7)	160/227 (70.5)	0.838[b]
RF titer	521.1 ± 828.3	249.3 ± 332.4	**0.001[a]**
anti-CCP positivity	33/43 (76.7)	95/142 (66.9)	0.335[b]
anti-CCP titer	242.8 ± 234.4	125.3 ± 144.3	**0.001[a]**
Baseline ESR, mm/hr	59.9 ± 37.3	44.9 ± 35.1	0.193[a]
Baseline CRP, mg/L	29.5 ± 35.3	19.1 ± 29.5	**0.014[a]**
Presence of erosion on joint X-rays at baseline	77 (33.3%)	15 (19.5%)	0.125[b]
Medication			
Methotrexate	30 (39.0)	176 (76.2)	**<0.001[b]**

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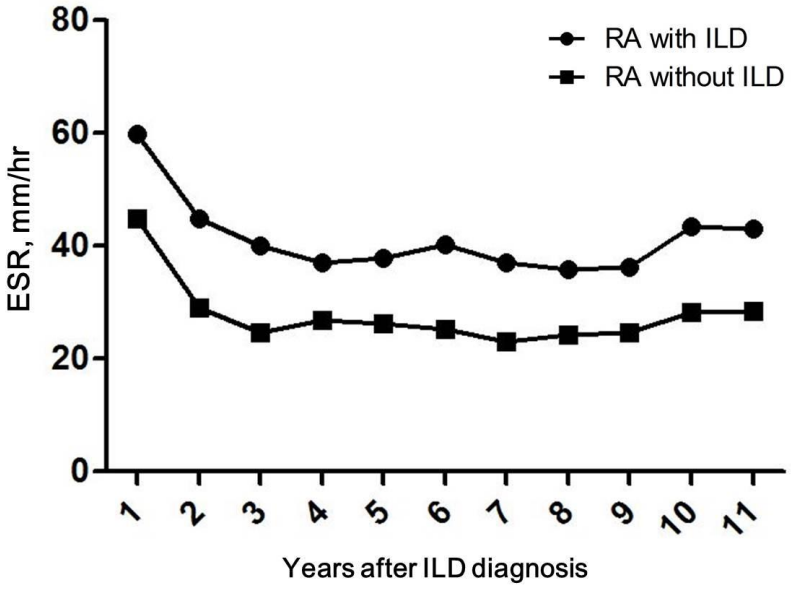
Leflunomide	22 (28.6)	60 (26.1)	0.670[b]
Hydroxychloroquine	46 (59.7)	147 (63.6)	0.540[b]
Sulfasalazine	48 (63.2)	73 (32.0)	**<0.001[b]**
Tacrolimus	2 (2.6)	6 (2.6)	0.991[c]
TNF inhibitor	4 (5.2)	12 (5.2)	1.000[c]
Rituximab	2 (2.6)	0 (0)	**<0.001[c]**
Mean corticosteroid dose, mg/day	6.7 ± 7.6	3.6 ± 2.4	**<0.001[a]**

The data were expressed as mean ± standard deviation or number (percentage). RA = rheumatoid arthritis, ILD = interstitial lung disease Tbc = tuberculosis, NTM = nontuberculous mycobacteria, RF = rheumatoid factor, anti-CCP= anti-cyclic citrullinated peptide, ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, TNF = tumor necrosis factor; [a]student's t-test, [b]chi-square test; [c]Fisher's exact test

Figure 1. Serial changes in ESR and CRP levels in RA patients with ILD compared to those without ILD over the 10-year follow-up

The mean ESR (47.9 ± 25.5 mm/hr vs. 31.7 ± 21.9 mm/hr, p = 0.022) (A) and CRP levels (21.2 ± 23.8 mg/L vs. 11.2 ± 15.4 mg/L, p < 0.001) (B) in the RA with ILD group over the 10-year follow up period were significantly higher than those in the RA control group.

(A)



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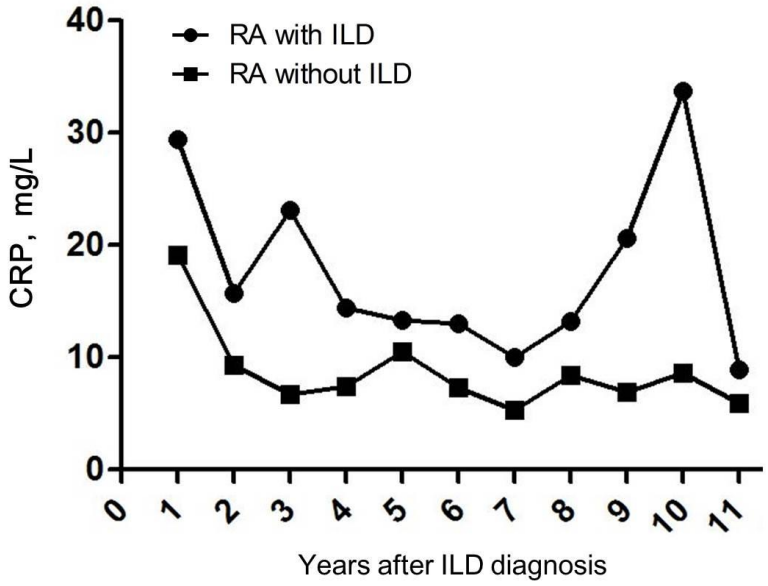

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, RA = rheumatoid arthritis ILD = interstitial lung disease; [a]student's t-test, [b]chi-square test

Subgroup analysis of the RA with ILD group

Demographic characteristics

Seventy seven patients with RA with ILD (58 females, 75.3%) were analyzed. The age at the time of ILD diagnosis was 59.0 ± 13.3 years, and the follow-up duration since the diagnosis of ILD was 8.7 ± 4.9 years. The number of patients who had articular disease that predated the ILD or was synchronous was 57 (74.0%). They had a normal forced vital capacity (FVC) (2.34 ± 0.72 L, 81.2 ± 19.7%) and a mildly decreased diffusing capacity of carbon monoxide (DLCO) (14.06 ± 25.95, 68.0 ± 20.3%) at baseline. High-resolution computed tomography (HRCT) showed that 32 (41.6%) patients had the UIP subtype, 17 (22.1%) had the nonspecific interstitial pneumonia (NSIP) subtype, and 13 (16.9%) had the organizing pneumonia (OP) subtype. Sixteen patients underwent lung biopsies, and the distribution was similar to those suggested by the HRCT subtypes (Table 2).

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Risk factors of mortality in RA with ILD in univariate analysis

Of the 77 RA patients with ILD, 28 (36.4%) patients died. We divided RA patients with ILD into two groups according to the survival for further evaluation of risk factors of mortality. Females had significantly better survival than males ($p = 0.025$), and a high titer of RF was associated with poor survival in RA with ILD group ($p = 0.001$). Patients with the UIP subtype on HRCT had a significantly poor survival ($p < 0.001$), whereas patients with the NSIP subtype had a better survival ($p = 0.004$, by chi-square test). There were no significant differences in baseline lung function, histopathology on the lung biopsies or medication (Table 2).

Table 2. Demographic characteristics and risk factors of mortality of the RA patients with ILD in univariate analysis

	RA with ILD (n=77)	Death (n=28)	Alive (n=49)	P value
Age at the time of ILD diagnosis	59.0 ± 13.3	64. 1 ± 10.4	56.3 ± 11.7	0.314[a]
Female	58 (75.3)	17 (60.7%)	41 (83.7%)	0.025[b]
Smoking				
Ex-smoker	10/68 (14.7)	6/27 (22.2)	4/41 (9.7)	0.096[c]
Current smoker	4 (5.9)	2/27 (7.4)	2/41 (4.9)	0.560[c]
Pack-years	28.4 ± 19.8	21.4 ± 12.1	42.5 ± 26.3	0.154[a]
Serology				
RF positivity	5/76 (73.7)	23/28 (82.1)	34/48 (70.8)	0.161[b]
RF titer	521.1 ± 828.3	774.5 ± 1112.9	345.2 ± 506.4	0.001[a]
anti-CCP positivity	33/43 (76.7)	9/13 (69.2)	24/30 (80.0)	0.151[b]
anti-CCP titer	242.8 ± 234.4	189.4 ± 224.5	263.4 ± 239.1	0.368[a]
Medication				
Methotrexate	30 (39.0)	8 (28.6)	22 (45.8)	0.138[b]
Leflunomide	22 (28.6)	7 (25.0)	15 (31.3)	0.562[b]
Hydroxychloroquine	46 (59.7)	17 (60.7)	29 (60.4)	0.980[b]
Sulfasalazine	48 (63.2)	16 (57.1)	32 (66.7)	0.406[b]

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Tacrolimus	2 (2.6)	1 (3.6)	1 (2.1)	0.696[c]
TNF inhibitor	4 (5.2)	1 (3.6)	3 (6.3)	0.614[c]
Rituximab	2 (2.6)	1 (3.6)	1 (2.1)	0.696[c]
Baseline lung function				
FVC, L	2.34 ± 0.72	2.32 ± 0.78	2.35 ± 0.69	0.304[c]
Predicted, %	81.2 ± 19.7	80.0 ± 19.9	81.9 ± 19.9	0.739[c]
DLCO	14.06 ± 25.95	10.15 ± 3.13	16.23 ± 32.20	0.249[c]
Predicted, %	68.0 ± 20.3	64.5 ± 21.6	70.1 ± 19.5	0.600[c]
Subtypes on HRCT				
NSIP	17 (22.1)	1 (3.6)	16 (32.7)	**0.004**[c]
OP	13 (16.9)	5 (17.9)	8 (16.3)	0.808[b]
UIP	32 (41.6)	19 (67.9)	13 (26.5)	**<0.001**[b]
DPB	2 (2.6)	0 (0.0)	2 (4.1)	0.287[c]
LIP	2 (2.6)	0 (0.0)	2 (4.1)	0.287[c]
DIP	1 (1.3)	1 (3.6)	0 (0)	0.175[c]
Histopathology on lung biopsy	N = 16	N = 4	N = 12	
NSIP	4 (25.0)	0 (0.0)	4 (30.0)	0.205[c]
OP	2 (12.5)	1 (25.0)	1 (8.3)	0.457[c]
UIP	7 (43.8)	2 (50.0)	5 (41.7)	0.952[c]
DPB	1 (6.3)	0 (0.0)	1 (8.3)	0.523[c]
LIP	1 (63.)	0 (0.0)	1 (8.3)	0.523[c]
DIP	1 (6.3)	1 (25.0)	0 (0.0)	0.130[c]

The data were expressed as mean ± standard deviation or number (percentage). RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide, TNF = tumor necrosis factor, FVC = forced vital capacity, DLCO = diffusing capacity of carbon monoxide, HRCT = high-resolution computed tomography, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, UIP = usual interstitial pneumonia, DPB = diffuse panbronchiolitis, LIP = lymphocytic interstitial pneumonia, DIP = desquamative interstitial pneumonia; [a]student's t-test, [b]chi-square test, [c]Fisher's exact test

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Multivariate Cox regression modeling was performed to evaluate the risk factors of mortality while adjusting for confounding variables (Table 3). The factors that were independently associated with fatal outcome included the presence of UIP on HRCT (HR 7.498, 95% CI 2.301–24.434, p = 0.001) and older age at the time of ILD diagnosis (HR 1.196, 95% CI 1.109–1.291, p < 0 .001).

In the Kaplan-Meier survival curves that were stratified by the category of HRCT subtype (Figure 2A), patients with UIP on HRCT had poor survival than those without UIP (p = 0.05, log-rank test). Similarly, as shown in Figure 2B, patients who were older (≥65 years) at the time of ILD diagnosis had poor survival than those who were younger (< 65 years) (p < 0.001, log-rank test)

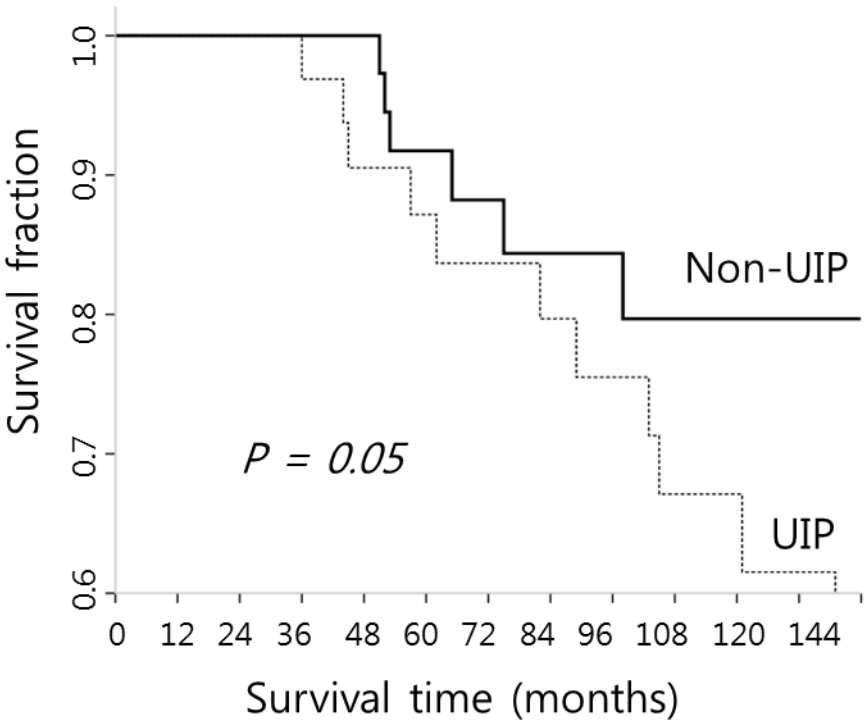
Table 3. Risk factors of mortality in the multivariate model

	Hazard ratio	95% CI	p value
Age at the time of ILD diagnosis	1.196	1.109–1.291	**<0.001**
Male	1.200	0.306–4.710	0.794
Smoking history	0.919	0.259–3.266	0.896
RF positivity	0.641	0.196–2.090	0.460
anti-CCP positivity	1.144	0.466–2.080	0.770
Baseline FVC	0.909	0.385–2.148	0.828
Baseline DLCO	1.003	0.954–1.055	0.895
UIP on HRCT	7.498	2.301–24.434	**0.001**

The hazard ratios for mortality were estimated with the Cox proportional hazard model after adjusting for the confounding factors. 95% CI = 95% confidence interval, ILD = interstitial lung disease, RF = rheumatoid factor, anti-CCP = anti-cyclic citrullinated peptide, FVC = forced vital capacity, DLCO = diffusing capacity of carbon monoxide UIP = usual interstitial pneumonia, HRCT = high-resolution computed tomography

Figure 2. (A) Kaplan-Meier curves of the survival of patients with or without UIP on HRCT (B) Kaplan-Meier curves of the survival of patients stratified by age at the time of ILD diagnosis (≥65 years vs. <65 years). Significantly poor survivals were observed in RA patients with UIP (A) and older age (≥65 years) (B) ($p = 0.05$ and $p < 0.001$, respectively, log-rank test).

(A)



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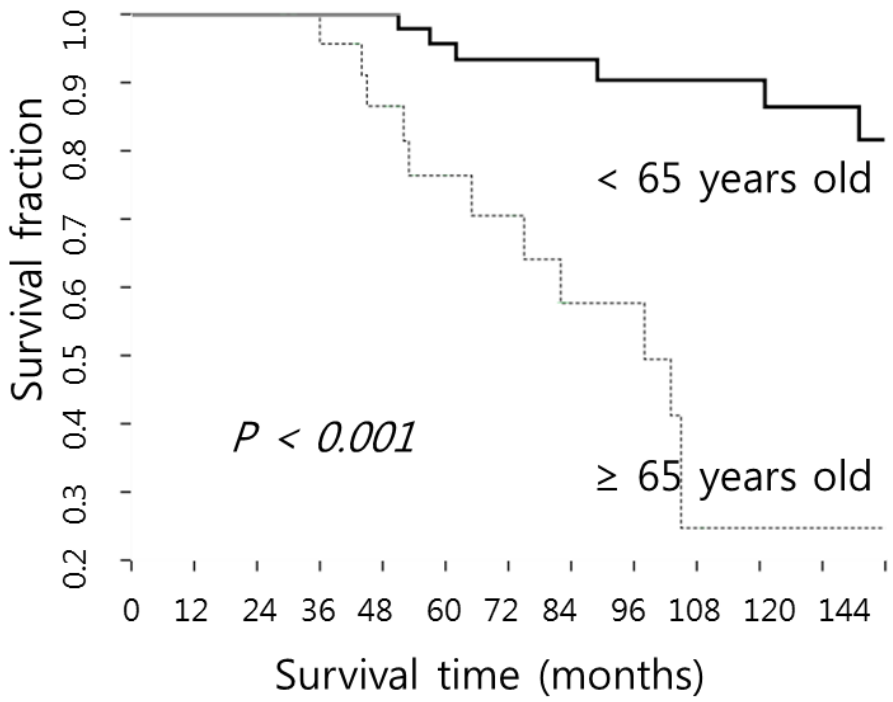

RA = rheumatoid arthritis, UIP = usual interstitial pneumonia, HRCT = high-resolution computed tomography, ILD = interstitial lung disease

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DISCUSSION

Compared to RA patients without ILD, patients with ILD had higher titers of RF and anti-CCP and more frequent history of tuberculosis or NTM infection. In addition, the RA patients with ILD had higher CRP levels at the time of RA diagnosis and higher mean ESR and CRP levels, which were annually collected. They had higher inflammatory burdens during the disease course. And these patients received higher mean daily dose of corticosteroid.

RF was reported to be present in high titers in RA patients with ILD (3). It was also reported that ACPA positivity correlates with the presence of ILD in RA, and higher titers of ACPA may be associated with more severe ILD (11, 12). The current results supported the previous report, but the RF and anti-CCP positivity were similar between RA patients with and without ILD.

The incidence of pulmonary tuberculosis is increased in patients with ILD (13). In this study, patients with history of tuberculosis or NTM was more frequently found in RA

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patients with ILD. It is possible that a patient with a history of pulmonary tuberculosis may have poor lung function and have more chances for ILD to be detected during the follow-up for the tuberculosis.

While the ESR and CRP levels correlated with the disease activity of RA, their roles in the evaluation of lung disease are unclear (14). A previous study has shown that baseline ESR values were increased in RA patients with ILD (15). The present study showed that the baseline CRP levels in RA patients with ILD were higher compared with the age/sex-, and disease duration-matched RA patients without ILD. Baseline CRP levels have been suggested to be predictive of long-term ILD progression in patients with systemic sclerosis associated ILD (16). CRP is a general marker of inflammation and involved in the innate immune response to systemic inflammation that is downstream from interleukin-6 (IL-6) and interleukin-1β (17). IL-6 levels moderately correlated with high sensitivity CRP levels (18). Future study is

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needed to examine whether IL-6 or other proinflammatory cytokines have additional predictive significance beyond the CRP levels for development of ILD in RA.

It has not been reported whether articular disease activity correlates with indices of lung disease. It is controversial whether the limited usage of of MTX and other DMARDs contributing to lung toxicity causes poor outcomes in terms of the RA. A recent study reported that disease activity scores in 28 joints (DAS28) was lower in patients with RA and severe ILD than in those without ILD at RA presentation (19). Some of this data conflicted with our study that RA patients with ILD had significantly higher baseline CRP levels. In the present study we did not include swollen joint count, tender joint count, and patient global assessment representing for arthritis outcome.

RA patients with ILD had received less frequently with MTX and more frequently with sulfasalazine than those without ILD. These results may be due to potential lung

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toxicity of MTX. And in subgroup analysis in RA patients with ILD, any medications including MTX were not significantly different between dead and alive groups. These results suggest that MTX may not significantly affect long term survival of ILD in RA. Therefore MTX may be used carefully in RA patients with ILD.

Deborah et al. reviewed that the significant predictors of mortality in RA patients with ILD were older age, male gender, lower DLCO, the increased extent of fibrosis, and the presence of the UIP subtype (20). Our study showed that patients who were male and who had a UIP subtype on HRCT had a significantly poor survival and that NSIP on HRCT had better survival. These results are concordant with the findings of recent reports (5, 21). Older age at the time of the diagnosis of ILD was a significantly associated with mortality in RA patients with ILD. This finding was consistent with the results of previous studies that suggested that lower performance status and older age were predictors of mortality in RA

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patients with ILD group (21, 22). In addition, our results revealed that the higher titer of RF was also associated with mortality in RA patients with ILD.

No correlation of survival with smoking status, baseline lung function was found in this RA with ILD patient population. Previous study reported that those factors are predictors of the progression of ILD in systemic sclerosis associated ILD (23, 24). We could not further analyze due to lack of regular follow-up data of lung function.

The present study had some limitations. First, data on the number of swollen and tender joints and patient global assessment, which is a representative of RA disease activity, could not be analyzed due to the retrospective study design. However, ESR and CRP levels were assessed, and these variables are known to be associated with disease activity over time. Secondly, the patients in this study did not have regular pulmonary function test follow-up. Third, this study utilized a relatively small number of patients at a single center.

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In conclusion, RA patients with ILD had higher RF and anti-CCP titers and baseline CRP levels compared with those without ILD. A UIP subtype on HRCT and older age at the time of the ILD diagnosis were significantly associated with mortality of RA patients with ILD. A larger prospective study is needed to confirm the present findings.

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국문 초록

서론: 류마티스 관절염에 동반된 간질성 폐질환에 대한 임상적인 중요성이 증가하고 있는데, 이는 류마티스 관절염을 동반한 간질성 폐질환에서 가장 많이 관찰되는 상용 간질성 폐렴을 보이는 환자의 생존률이 다른 결체 조직 질환에 동반된 간질성 폐질환에 비해 비해 낮은 것으로 보고 되었기 때문이다. 이에 본 연구는 류마티스 관절염 환자에서 간질성 폐질환 발생의 위험요인을 알아보고, 간질성 폐질환을 동반한 류마티스 관절염과 간질성 폐질환을 동반하지 않은 류마티스 관절염 환자의 관절염의 예후를 비교하였다. 또한 간질성 폐질환을 동반한 류마티스 관절염에서 사망의 위험 인자를 조사하였다.

방법: 1991 년부터 2011 년까지 서울대학교병원에서 류마티스 관절염 간질성 폐질환을 진단받은 총 77 명의 환자와 나이, 성별, 질병 이환 기간을 일치시킨 류마티스 관절염 환자 (대조군)가 1:3 의 비율로 본 연구에 등록되었다. 의무 기록 리뷰를 통해 역학적, 임상적, 검사 정보를 획득하였다. 관절염의 예후에 대하여 류마티스 인자, 항 CCP 항체, 적혈구 침강 속도, C 반응 단백, 단순 방사선 촬영에서 골 미란의 동반 여부 그리고 평균 스테로이드 용량을 두 군에서 비교하였다. 류마티스 관절염 간질성 폐질환 환자에서 생존분석을 위해 카플란 마이어 곡선과 콕스 비례 위험 모형을 이용하였다.

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결과: 간질성 폐질환을 동반한 류마티스 관절염 환자는 대조군에 비하여 류마티스 인자와 항 CCP 항체의 역가가 통계적으로 유의하게 높았으며, 비정형 결핵 및 결핵의 병력 역시 많았다. 또한 류마티스 관절염 진단 시 C 반응 단백, 10 년의 추적 기간 동안 매년 측정한 적혈구 침강 속도와 C 반응 단백의 평균값 그리고 평균 스테로이드 사용량은 간질성 폐질환을 동반한 환자에서 통계적으로 유의하게 높았다. 류마티스 관절염 간질성 폐질환 환자그룹의 추가 분석에서 28 명 (36.4%)이 사망하였다. 남성, 높은 류마티스 인자 역가, 고해상도 흉부 전산화 촬영에서 전형적인 상용 간질성 폐렴이 관찰된 환자가 예후가 나빴으며, 반대로 비특이성 간질성 폐렴을 가진 환자는 예후가 좋았다. 다변량 분석에서 전형적인 상용 간질성 폐렴을 갖은 환자 및 간질성 폐질환 진단 나이가 많을수록 사망률이 높았다.

결론: 류마티스 관절염 간질성 폐질환 환자는 간질성 폐질환을 갖지 않은 류마티스 관절염 환자에 비하여 류마티스 인자와 항 CCP 역가가 통계적으로 유의하게 높았다. 또한 고해상도 흉부 전산화 촬영에서 전형적인 상용 간질성 폐렴이 관찰된 환자와 간질성 폐질환 진단 나이가 많을수록 사망률이 높았다. 이를 확인하기 위해 추가적으로 대규모, 전향적 연구가 필요하다고 사료된다.

주요어 : 류마티스 관절염, 간질성 폐질환

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