THERAPEUTIC ADVANCES in
Respiratory Disease

Original Research

Protective effect of methotrexate on lung function and mortality in rheumatoid arthritis–related interstitial lung disease: a retrospective cohort study

Ther Adv Respir Dis

2022, Vol. 16: 1–12

DOI: 10.1177/17534666221135314

Kangjoon Kim, Ala Woo, Youngmok Park, Seung Hyun Yong, Su Hwan Lee, Sang Hoon Lee, Ah Young Leem, Song Yee Kim, Kyung Soo Chung, Eun Young Kim, Ji Ye Jung, Young Ae Kang, Young Sam Kim and Moo Suk Park

Abstract

Background: Studies on the risk and protective factors for lung function decline and mortality in rheumatoid arthritis–related interstitial lung disease (RA-ILD) are limited.

Objectives: We aimed to investigate clinical factors and medication uses associated with lung function decline and mortality in RA-ILD.

Methods: This retrospective cohort study examined the medical records of patients with RA-ILD who visited Severance Hospital between January 2006 and December 2019. We selected 170 patients with RA-ILD who had undergone at least one spirometry test and chest computed tomography scan. An absolute decline of ⩾10% in the functional vital capacity (FVC) was defined as significant decline in pulmonary function. Data for analysis were retrieved from electronic medical records.

Results: Ninety patients (52.9%) were female; the mean age was 64.0 ± 10.2 years. Multivariate logistic regression showed that a high erythrocyte sediment rate level at baseline [odds ratio (OR) = 3.056; 95% confidence interval (CI) = 1.183–7.890] and methotrexate (MTX) use (OR = 0.269; 95% CI = 0.094–0.769) were risk and protective factors for lung function decline, respectively. Multivariate Cox regression analysis indicated that age ⩾65 years (OR = 2.723; 95% CI = 1.142–6.491), radiologic pattern of usual interstitial pneumonia (UIP) or probable UIP (OR = 3.948; 95% CI = 1.522–10.242), baseline functional vital capacity (FVC) % predicted (OR = 0.971; 95% CI = 0.948–0.994), and MTX use (OR = 0.284; 95% CI = 0.091–0.880) were predictive of mortality.

Conclusion: We identified risk and protective factors for lung function decline and mortality in patients with RA-ILD. MTX use was associated with favorable outcome in terms of both lung function and mortality in our cohort.

Keywords: interstitial lung disease, methotrexate, mortality, pulmonary function, rheumatoid arthritis

Received: 3 July 2022; revised manuscript accepted: 11 October 2022.

Correspondence to:
Moo Suk Park
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1, Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea.
PMS70@yuhs.ac

Kangjoon Kim
Ala Woo
Youngmok Park
Seung Hyun Yong
Su Hwan Lee
Sang Hoon Lee
Ah Young Leem
Song Yee Kim
Kyung Soo Chung
Eun Young Kim
Ji Ye Jung
Young Ae Kang
Young Sam Kim
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterized by destructive joint disease as well as extra-articular manifestations. The disease affects 0.5–1% of the worldwide population,[1] and interstitial lung disease (ILD) is one of the most common extra-articular complications of RA.[2] In patients with RA, the reported risk of developing ILD is 6–15%.[3–6] Studies have demonstrated that older age, male sex, smoking, and increased rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibody

titers are predictors of rheumatoid arthritis–related interstitial lung disease (RA-ILD).[7,8]

Pulmonary function is the most sensitive parameter for monitoring the clinical course and predicting patient outcomes in cases of idiopathic pulmonary fibrosis, which is the most common subtype of idiopathic interstitial pneumonia.[9] RA-ILD also may result in progressive decline in pulmonary function, and the change in pulmonary function is related to significant morbidity and mortality.[2] Therefore, identifying and managing protective and risk factors related to the decline in pulmonary function is important for improving clinical outcomes in patients with RA-ILD.

Studies on risk and protective factors for lung function decline and mortality in RA-ILD are limited, however.[10,11] Therefore, we aimed to investigate the clinical factors and medications associated with lung function decline and mortality in patients with RA-ILD.

Materials and methods

Patients

This retrospective study examined patients with RA who visited Severance Hospital, a university-affiliated tertiary referral hospital in South Korea, between January 2006 and December 2019.

The diagnosis of RA in this study was based on the 1987 American College of Rheumatology (ACR) or 2010 ACR–European League Against Rheumatism classification criteria for RA.[12,13] Patients with other concomitant connective tissue diseases (i.e. systemic sclerosis, dermatomyositis/polymyositis, mixed connective tissue disease, systemic lupus erythematosus, and Sjogren's syndrome) were excluded. Of the 3664 consecutive RA patients without other concomitant systemic connective tissue diseases, 882 underwent high-resolution computed tomography (HRCT) of the chest during the period between January 2006 and December 2019, and 202 were revealed to have radiologic findings consistent with ILD. Of these patients, 170 whose medical records included the results of at least one pulmonary function test were enrolled (Figure 1). The onset time of RA-ILD was defined as the time in which first documentation of ILD was made on HRCT.

This study was approved by the Ethics Review Committee of Severance Hospital (IRB no. 4-2021-0227), and the need to obtain informed consent was waived by the committee because of the retrospective nature of this study.

Data collection

We collected the following patient data from the electronic medical records: demographics, smoking history, date of RA and RA-ILD diagnosis, results of pulmonary function test, history of medication use, survival status, last visit date, and date of death. The follow-up data were collected between 1 January 2006 and 31 March 2021. Lung transplantation during follow-up was considered as death ($n = 3$).

The anti-CCP titer was measured using a second generation DIASTAT® enzyme-linked immunosorbent assay (Axis-Shield Diagnostics, Dundee, UK), which was performed according to the manufacturer's instructions. The immunoglobulin M (IgM)-RF level was measured using a chemiluminescent immunoassay (QUANTA Flash; Inova Diagnostics, San Diego, CA, USA) in the same laboratory. Unequivocal readings of ⩾5 units (U) for the anti-CCP antibody tests and of ⩾15 IU/ml for the IgM-RF tests were considered positive according to manufacturer's instructions. The C-reactive protein level was measured by nephelometry (Cobas C702 modular analyzer; Roche Diagnostics GmbH, Mannheim, Germany). The erythrocyte sediment rate (ESR) was measured using the modified Westergren method. The laboratory test result retrieved closest to the time of RA diagnosis was selected for statistical analysis.

The definition of disease-modifying antirheumatic drugs (DMARDs) was based on the recent treatment guideline for RA published by the ACR.[14] Oral glucocorticoid and immunosuppressant use was also examined. The history of medical treatment was examined for the period between the initial date on which RA diagnosis was made and final follow-up date. Valid medical treatment was defined as continuation of the specific medical treatment for ⩾12 weeks.

Spirometry and HRCT

Spirometry was performed using VMAX 22 (SensorMedics, Anaheim, CA, USA) according to the American Thoracic Society Standards/European Respiratory Society Guidelines.[15]

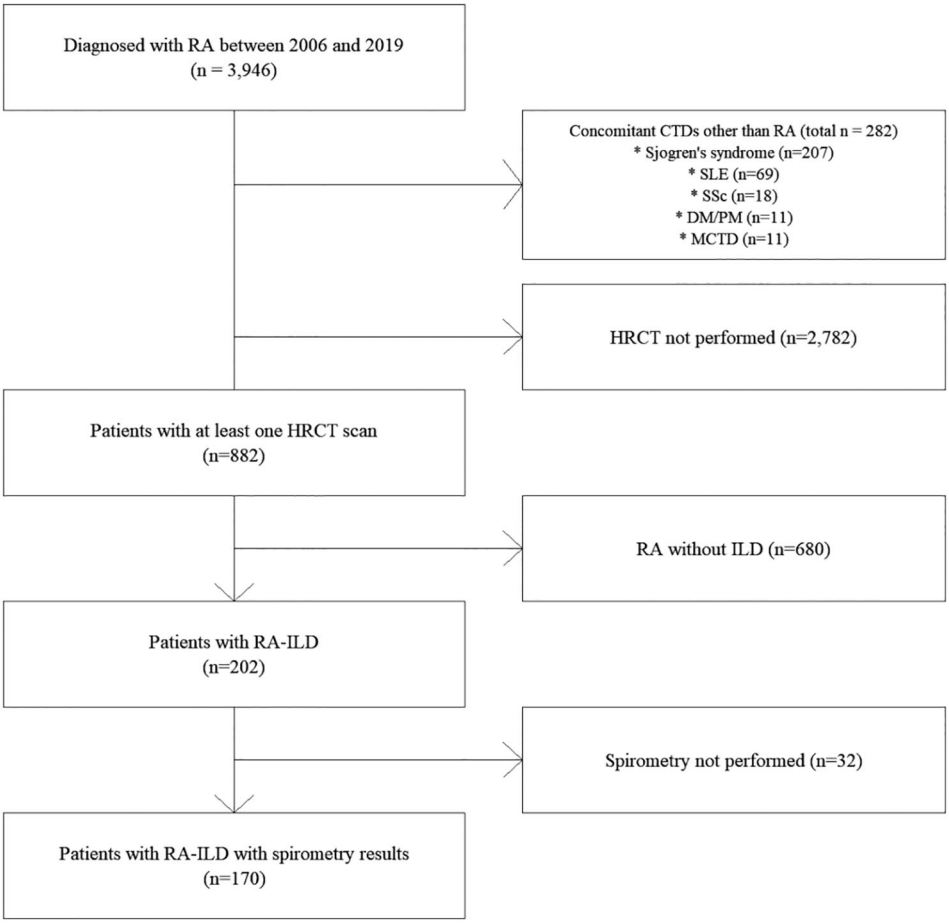

Figure 1. Flow chart of study enrollment.
CTD, connective tissue disease; DM, dermatomyositis; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

Spirometry results are expressed as percentage predicted values of the functional vital capacity (FVC) and were abstracted between 6 months prior to ILD diagnosis and the final follow-up date before the data cut-off (31 March 2021). Baseline FVC values were defined as the spirometry measurements retrieved closest to the time of ILD diagnosis. Changes in FVC were calculated by subtracting the first percentage predicted value from the final value.

HRCT images were obtained using a 64-detector computed tomography (CT) scanner (Discovery CT750 HD; GE Healthcare, Chicago, IL, USA; Somatom Sensation 64, Siemens Healthineers, Erlangen, Germany) and a second-generation dual-source scanner (Somatom Definition Flash, Siemens Healthineers). All scans were performed from the level of the supraclavicular fossae to the adrenal glands under inspiratory breath hold with the following scanning parameters: tube voltage of 120 kVp, average tube current of 300 mA, average pitch of 0.9, and volume CT dose index of $<$6.0 mGy. After scanning, axial images were reconstructed at a slice thickness of 1 mm and slice increment of 1 mm with a medium-smooth convolution kernel.

HRCT images were evaluated by two expert thoracic radiologists, and the radiological patterns on the HRCT images were identified. The HRCT patterns were classified in relation to usual interstitial pneumonia (UIP): definite UIP, probable UIP, indeterminate for UIP, and alternative diagnosis.[16] When an alternative diagnosis was made, the specific radiologic pattern was reported by the radiologists.

Statistical analysis

An absolute FVC decline of 10% was defined as a significant change in lung function, according to a previous study.[17]

Descriptive variables are expressed as mean values, standard deviations, and proportions. These variables were compared using Fisher's exact test or *t* tests. Logistic regression analysis was performed to identify risk factors related to FVC decline and mortality. The ESR cut-off value for logistic regression analysis was determined by a receiver operating characteristic (ROC) curve. The Youden index was calculated based on the sensitivity and specificity of each diagnostic cut-off point in the ROC curve, and the point with the highest Youden index was selected as the optimal cut-off point. The Kaplan–Meier analysis and the log-rank test, as well as the Cox proportional hazards regression analysis, were performed to evaluate the overall survival (OS) rate and identify clinical risk factors related to mortality. Survival duration was calculated from the date of RA-ILD diagnosis.

p values of <0.05 were considered significant for all analyses. Data analysis was performed using SPSS version 26 (IBM, Armonk, NY, USA).

Results

Characteristics of the cohort

A total of 170 patients were included in our cohort. Ninety patients (52.9%) were female, and the mean age at the time of ILD diagnosis was 64.0 ± 10.2 years. Seventy-eight patients (45.9%) were ever-smokers, 152 of 165 patients (92.1%) who were tested for anti-CCP antibody showed positivity at baseline, 67 (39.4%) had radiologic patterns of UIP at baseline, and the mean FVC % predicted was 84.8 ± 18.6 at baseline. Seventy-nine patients (46.5%) were treated with methotrexate (MTX) and 146 (85.9%) were treated with oral glucocorticoids. The detailed characteristics for the cohort are presented in Table 1.

Risk factors for FVC decline

Twenty-seven of 125 patients (21.6%) who underwent ≥ 2 spirometry measurements exhibited significant lung function decline (absolute FVC decline of $\geq 10\%$). Multivariate logistic regression analysis adjusted for age and sulfasalazine history revealed that a high ESR at baseline (≥ 81.5 mm/h) [odds ratio (OR) = 3.056, 95% confidence interval (CI) = 1.183–7.890, $p = 0.021$) and MTX use (OR = 0.269, 95% CI = 0.094–0.769, $p = 0.014$) were risk and protective factors for lung function decline, respectively (Table 2).

Survival analysis

Among the 170 participants, 29 (17.1%) died during the follow-up period. According to the Kaplan–Meier analysis, the mean OS of the cohort was 11.5 years (95% CI = 10.3–12.8 years).

The mean OS of the patients with radiologic patterns of UIP or probable UIP was 9.6 years (95% CI = 7.7–11.5), which was significantly lower than the mean OS of those with other patterns (12.4 years, 95% CI = 11.3–13.5) [log-rank test, $p = 0.001$, Figure 2(a)]. The mean OS of MTX users was 14.4 years (95% CI = 13.3–15.4), which was significantly higher than the mean OS of non-users (8.7 years, 95% CI = 7.2–10.2) [log-rank test, $p < 0.001$, Figure 2(b)].

Multivariate Cox regression analysis adjusted for sex and smoking history revealed that an age of ≥ 65 years (OR = 2.723, 95% CI = 1.142–6.491), radiologic pattern of UIP or probable UIP (OR = 3.948, 95% CI = 1.522–10.242, $p = 0.005$), baseline FVC % predicted (OR = 0.971, 95% CI = 0.948–0.994), and MTX use (OR = 0.284, 95% CI = 0.091–0.880) were predictive of mortality (Table 3).

Discussion

The aim of this study was to investigate the risk and protective factors associated with lung function decline and mortality in patients with RA-ILD. We defined a significant decline as an absolute decline in FVC of $\geq 10\%$, referring to a previously proposed association between lung function change and mortality in RA-ILD.[17] Significant decline in lung function was observed in approximately 20% of the investigated participants. Furthermore, a high ESR at baseline, defined as the measure acquired closest to the time of RA diagnosis, was identified as a risk factor for RA-ILD. The ESR tends to correlate with disease activity in RA,[18] and an elevated ESR in patients with early RA is predictive of greater radiographic joint damage in old age despite treatment with conventional DMARDs.[19] Therefore, a

Table 1. Clinical characteristics.

Variable	Participants ($n = 170$)
Clinical characteristics	
Sex, female	90 (52.9)
Age, years	64.0 ± 10.2
Ever-smoker	78 (45.9)
Anti-CCP positivity, *n* positive/*n* tested	152/165 (92.1)
RF positivity, *n* positive/*n* tested	152/166 (91.6)
CRP, mg/dl	17.3 ± 27.4
ESR, mm/h	64.8 ± 34.7
Baseline FVC, % predicted	84.8 ± 18.6
FVC decline of ⩾10%, *n* declined/*n* with ⩾2 measurements	27/125 (21.6)
Duration of follow-up, years	4.3 ± 3.5
Radiologic pattern	
UIP	67 (39.4)
Probable UIP	30 (17.6)
Indeterminate for UIP	37 (21.8)
NSIP	15 (8.8)
OP	20 (11.8)
RB-ILD	1 (0.6)
Medication history	
DMARDs	
MTX	79 (46.5)
HCQ	76 (44.7)
LEF	62 (36.5)
SSZ	45 (26.5)
Tocilizumab	20 (11.8)
TNF-alpha inhibitors	17 (10.0)
Adalimumab	8 (4.7)
Infliximab	6 (3.5)
Golimumab	3 (1.8)
Etanercept	3 (1.8)

(Continued)

Table 1. (Continued)

Variable	Participants ($n = 170$)
JAK inhibitor	11 (6.5)
Baricitinib	7 (4.1)
Tofacitinib	4 (2.4)
Abatacept	4 (2.4)
Rituximab	4 (2.4)
Oral glucocorticoids	146 (85.9)
Immunosuppressants	
Tacrolimus	56 (32.9)
Azathioprine	2 (1.2)
Mycophenolate mofetil	2 (1.2)
Treatment duration of most prescribed DMARDs	
MTX	
Total, days	1713 ± 1123
Postdiagnosis of RA-ILD, days	1168 ± 967
HCQ	
Total, days	1086 ± 995
Postdiagnosis of RA-ILD, days	1004 ± 906
LEF	
Total, days	1297 ± 1078
Postdiagnosis of RA-ILD, days	911 ± 767
SSZ	
Total, days	760 ± 357
Postdiagnosis of RA-ILD, days	762 ± 353
Tocilizumab	
Total, days	927 ± 850
Postdiagnosis of RA-ILD, days	796 ± 704

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HCQ, hydroxychloroquine; JAK, janus kinase; LEF, leflunomide; MTX, methotrexate; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RA-ILD, rheumatoid arthritis–associated interstitial lung disease; RB-ILD, respiratory bronchiolitis–interstitial lung disease; RF, rheumatoid factor; SSZ, sulfasalazine; TNF, tumor necrosis factor; UIP, usual interstitial pneumonia.
Categorical data are presented as numbers (%) unless otherwise stated and were tested using Fisher's exact test; continuous data are presented as the mean value ± standard deviation and were tested using *t* tests.

Table 2. Logistic regression analysis for risk and protective factors associated with forced vital capacity decline of ⩾10% among 125 participants who underwent ⩾2 spirometry measurements.

Covariates	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Sex, female	1.185 (0.499–2.814)	0.700		
Aged ⩾65 years	1.322 (0.563–3.103)	0.522	1.732 (0.675–4.446)	0.253
UIP or probable UIP	0.938 (0.397–2.211)	0.883		
Ever-smoker	0.844 (0.355–2.003)	0.700		
Anti-CCP positive	1.923 (0.226–16.370)	0.550		
RF positive	0.615 (0.148–2.560)	0.504		
CRP, mg/dl	1.009 (0.991–1.028)	0.316		
High ESR (⩾81.5 mm/h)[a]	2.863 (1.183–6.932)	0.020	3.056 (1.183–7.890)	0.021
Baseline FVC, % predicted	0.999 (0.977–1.022)	0.927		
MTX use	0.274 (0.102–0.738)	0.010	0.269 (0.094–0.769)	0.014
HCQ use	1.122 (0.478–2.631)	0.792		
LEF use	0.890 (0.369–2.145)	0.795		
SSZ use	2.692 (1.125–6.445)	0.026	2.407 (0.936–6.189)	0.068
TNF-alpha inhibitor use	1.236 (0.310–4.924)	0.764		
Tocilizumab use	1.486 (0.479–4.614)	0.493		
Oral glucocorticoids use	1.580 (0.329–7.604)	0.568		
Tacrolimus use	1.748 (0.738–4.138)	0.204		

CCP, cyclic citrullinated peptide; CI, confidence interval; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; RF, rheumatoid factor; SSZ, sulfasalazine; TNF, tumor necrosis factor; UIP, usual interstitial pneumonia.
[a]The cut-off value was determined using the highest Youden index in receiver operating characteristic analysis.

high ESR at baseline may indicate high disease activity and may correlate with the decline in lung function due to the lung involvement of RA. A previous study investigating joint and lung involvement in patients with RA-ILD reported a good correlation between the ESR and the ground glass score of HRCT images of the lungs.[20]

Another notable point is that the use of MTX was a protective factor for both lung function decline and mortality in our cohort. MTX has long been suspected to be a causative agent in lung disease, including fibrotic ILD,[21–23] and many clinicians are reluctant to prescribe MTX in patients with RA-ILD. Recent studies, however, suggested that MTX is not associated with developing ILD in RA patients, and rather reduces the risk of developing RA-ILD and delays its onset. Kiely *et al.*[24] investigated 2701 RA patients with up to 25-year follow-up, and they found no adverse association between RA-ILD and MTX use. Extended analysis from that study also showed that MTX exposure was associated with a reduced risk (OR = 0.48, $p = 0.004$) of developing ILD and longer time to ILD diagnosis (OR = 0.41, $p = 0.004$). Juge *et al.*[25] performed a case–control study in 410 patients with RA-ILD and 673 patients with RA without ILD. In that study, adjusted OR for ILD development was 0.43 (95% CI = 0.26–0.69; $p = 0.0006$) in MTX ever users, and ILD

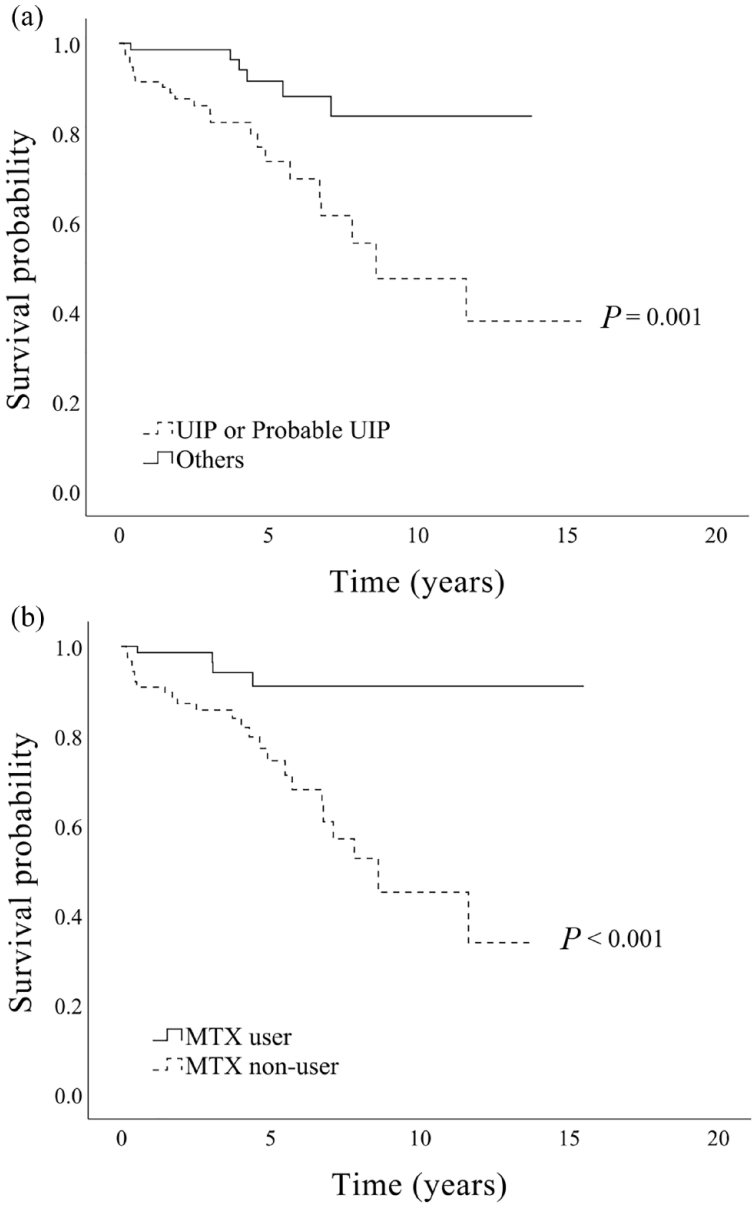

Figure 2. Kaplan–Meier curves displaying the estimated probability of survival for the different groups of patients.
MTX, methotrexate; UIP, usual interstitial pneumonia.

detection was significantly delayed in MTX ever users compared with never users (11.4 ± 10.4 years and 4.0 ± 7.4 years, respectively; $p < 0.001$). Furthermore, a retrospective observational study conducted by Rojas-Serrano *et al.*[26] revealed that treatment with MTX was associated with favorable survival in patients with RA-ILD.

In this study, among the 79 patients who received MTX treatment, 55 patients (69.6%) received MTX before diagnosis of RA-ILD, and 33 of them maintained MTX for more than 12 weeks after diagnosis of RA-ILD. In our supplemental analysis, benefits of MTX treatment observed in patients who received MTX *after* diagnosis of RA-ILD for more than 12 weeks, but the benefit was not observed if the treatment was defined as 12 weeks of MTX use *before* the diagnosis of RA-ILD (Supplemental Tables S1 and S2). Together with the results of previous studies, our current findings suggest that MTX provides protective effects against RA-ILD, particularly with regard to pulmonary function and mortality, and that its benefits may persist when the treatment is provided after the onset of RA-ILD. A prospective study with a larger cohort is warranted to confirm the benefits of MTX in RA-ILD.

In contrast to MTX use, older age (⩾65 years), lower baseline FVC, and radiologic patterns of UIP or probable UIP were associated with an increase in the relative risk of death in our cohort. Although lung function decline did not significantly differ between the different radiologic pattern groups, the OS rate did. This may be explained by the fact that acute disease progression in RA-ILD occurs primarily in those with UIP patterns.[7,27] In a study of a large cohort of 93 subjects with connective tissue disease–associated ILD, the 1-year incidence of acute progression was 3.3% (four subjects), and three of these four patients had RA with biopsy-confirmed UIP.[28]

On the other hand, sulfasalazine use was associated with decline of pulmonary function in univariate analysis, although the association was not statistically significant after multivariate adjustment. There was no significant difference in clinical characteristics of participants according to sulfasalazine use in this study (Supplemental Table S3), which may imply that confounder effect was less of an issue. On the other hand, there are previous studies that suggested lesser efficacy of sulfasalazine compared with other DMARDs. Hider *et al.*[29] investigated to compare the outcome in patients with inflammatory polyarthritis treated with MTX or sulfasalazine as the first DMARD. In that study, the proportion of erosive disease at 5 years was lower in MTX group compared with sulfasalazine group (OR = 0.3; 95% CI = 0.1–0.8). Scott *et al.*[30] evaluated the efficacy and safety of leflunomide and sulfasalazine in RA, and the ACR20% and ACR50% response at 24 months with leflunomide was significantly

Table 3. Cox regression analysis of mortality.

Covariates	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Female	0.300 (0.136–0.662)	0.003	0.525 (0.199–1.383)	0.193
Aged ⩾65 years	1.555 (0.741–3.263)	0.243	2.723 (1.142–6.491)	0.024
UIP or probable UIP	4.021 (1.629–9.925)	0.003	3.948 (1.522–10.242)	0.005
Ever-smoker	3.537 (1.561–8.015)	0.002	2.210 (0.819–5.961)	0.117
Baseline FVC, % predicted	0.966 (0.946–0.988)	0.002	0.971 (0.948–0.994)	0.012
MTX use	0.169 (0.059–0.486)	0.001	0.284 (0.091–0.880)	0.029
HCQ use	0.548 (0.254–1.181)	0.125		
LEF use	0.656 (0.303–1.421)	0.285		
SSZ use	0.641 (0.260–1.578)	0.333		
TNF-alpha inhibitor use	0.554 (0.131–2.349)	0.554		
Tocilizumab use	0.209 (0.028–1.544)	0.125		
Oral glucocorticoids use	0.614 (0.211–1.788)	0.371		
Tacrolimus use	0.826 (0.375–1.817)	0.634		

CCP, cyclic citrullinated peptide; CI, confidence interval; FVC, forced vital capacity; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; OR, odds ratio; RF, rheumatoid factor; SSZ, sulfasalazine; TNF, tumor necrosis factor; UIP, usual interstitial pneumonia.

greater than with sulfasalazine. In that sense, we suspect that there is a possibility that sulfasalazine has a lesser efficacy in preserving pulmonary function in patients with RA-ILD, and further research may be warranted to explore this hypothesis.

While the median survival of RA-ILD patients was reportedly 3.0–10.4 years in previous studies,[31,32] this study showed mean survival duration of 11.5 years which is longer than the survival from the previous reports. As our cohort showed generally better baseline pulmonary function than those of previous studies,[32] we may assume that this study cohort includes more patients who diagnosed ILD in early stage. Recent study suggests that delayed diagnosis of RA-ILD associated with an increased mortality,[33] and, thus, diagnosing RA-ILD in early stage might have resulted in lower mortality in our cohort.

There are some limitations to this study. First, to investigate incidence and clinical factors associated with the decline in lung function, selection of a subgroup of 125 participants with ⩾2 spirometry measurements was inevitable, but this may have resulted in some selection bias. Second, we could not adopt recent definitions of progressive fibrosing phenotype of ILD in this study, because missing data hindered reliable application of the recent definitions. Instead, we used the classic clinical endpoint of FVC decline ⩾10% to evaluate decline of pulmonary function. Third, this was a retrospective cohort study, and association between good prognosis and MTX use may be the result of confounders (e.g. mild patients were preferred to treat with MTX), although the association were still valid after adjustments for age, radiologic pattern, and baseline pulmonary function in this study. Further study with prospective design is warranted to determine beneficial effect of MTX in patients with RA-ILD.

Conclusion

We identified risk and protective factors for lung function decline and mortality in patients with

RA-ILD. MTX use was associated with favorable outcome in terms of both lung function and mortality, while older age, lower baseline FVC, and radiologic patterns of UIP or probable UIP were associated with unfavorable outcome. Further study with a larger sample and prospective design is warranted to investigate beneficial effect of MTX against RA-ILD.

Declarations

Ethics approval

This study was approved by the Ethics Review Committee of Severance Hospital (IRB no. 4-2021-0227), and the need to obtain informed consent was waived by the committee because of the retrospective nature of this study.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Kangjoon Kim: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

Ala Woo: Data curation; Writing – review & editing.

Youngmok Park: Data curation; Writing – review & editing.

Seung Hyun Yong: Data curation; Writing – review & editing.

Su Hwan Lee: Data curation; Writing – review & editing.

Sang Hoon Lee: Data curation; Writing – review & editing.

Ah Young Leem: Data curation; Writing – review & editing.

Song Yee Kim: Data curation; Writing – review & editing.

Kyung Soo Chung: Data curation; Writing – review & editing.

Eun Young Kim: Data curation; Writing – review & editing.

Ji Ye Jung: Data curation; Writing – review & editing.

Young Ae Kang: Data curation; Writing – review & editing.

Young Sam Kim: Data curation; Writing – review & editing.

Moo Suk Park: Conceptualization; Data curation; Methodology; Supervision; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

ORCID iDs

Kangjoon Kim https://orcid.org/0000-0002-9285-6222

Ji Ye Jung https://orcid.org/0000-0003-1589-4142

Supplemental material

Supplemental material for this article is available online.

References

1. Gabriel SE. The epidemiology of rheumatoid arthritis. *Rheum Dis Clin North Am* 2001; 27: 269–281.
2. Zamora-Legoff JA, Krause ML, Crowson CS, *et al.* Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. *Arthritis Rheumatol* 2017; 69: 542–549.
3. Turesson C, O'Fallon WM, Crowson CS, *et al.* Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. *Ann Rheum Dis* 2003; 62: 722–727.

4. Turesson C and Jacobsson LT. Epidemiology of extra-articular manifestations in rheumatoid arthritis. *Scand J Rheumatol* 2004; 33: 65–72.
5. Doyle TJ, Patel AS, Hatabu H, *et al.* Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. *Am J Respir Crit Care Med* 2015; 191: 1403–1412.
6. Kim J-W, Lee H, Hwang JH, *et al.* Factors associated with airway disease and interstitial lung disease in rheumatoid arthritis. *JRD* 2016; 23: 101–108.
7. Dawson JK, Fewins HE, Desmond J, *et al.* Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 517–521.
8. Sathi N, Urwin T, Desmond S, *et al.* Patients with limited rheumatoid arthritis-related interstitial lung disease have a better prognosis than those with extensive disease. *Rheumatology (Oxford)* 2011; 50: 620.
9. Ley B, Collard HR, King TE, *et al.* Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.
10. Mena-Vázquez N, Rojas-Gimenez M, Romero-Barco CM, *et al.* Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. *J Clin Med* 2021; 10: 874.
11. Mena-Vázquez N, Godoy-Navarrete FJ, Manrique-Arija S, *et al.* Non-anti-TNF biologic agents are associated with slower worsening of interstitial lung disease secondary to rheumatoid arthritis. *Clin Rheumatol* 2021; 40: 133–142.
12. Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315–324.
13. Villeneuve E, Nam J and Emery P. 2010 ACR-EULAR classification criteria for rheumatoid arthritis. *Rev Bras Reumatol* 2010; 50: 481–483.
14. Fraenkel L, Bathon JM, England BR, *et al.* 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res Hoboken* 2021; 73: 924–939.
15. Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
16. Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
17. Solomon JJ, Chung JH, Cosgrove GP, *et al.* Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2016; 47: 588–596.
18. Nam J, Villeneuve E and Emery P. The role of biomarkers in the management of patients with rheumatoid arthritis. *Curr Rheumatol Rep* 2009; 11: 371–377.
19. Lindqvist E, Eberhardt K, Bendtzen K, *et al.* Prognostic laboratory markers of joint damage in rheumatoid arthritis. *Ann Rheum Dis* 2005; 64: 196–201.
20. Paulin F, Mercado JF, Fernandez ME, *et al.* Correlation between lung and joint involvement in patients with rheumatoid arthritis and interstitial lung disease: a cross-sectional study. *Rev Invest Clin* 2018; 70: 76–81.
21. Kaplan RL and Waite DH. Progressive interstitial lung disease from prolonged methotrexate therapy. *Arch Dermatol* 1978; 114: 1800–1802.
22. Phillips TJ, Jones DH and Baker H. Pulmonary complications following methotrexate therapy. *J Am Acad Dermatol* 1987; 16: 373–375.
23. Carson CW, Cannon GW, Egger MJ, *et al.* Pulmonary disease during the treatment of rheumatoid arthritis with low dose pulse methotrexate. *Semin Arthritis Rheum* 1987; 16: 186–195.
24. Kiely P, Busby AD, Nikiphorou E, *et al.* Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. *BMJ Open* 2019; 9: e028466.
25. Juge PA, Lee JS, Lau J, *et al.* Methotrexate and rheumatoid arthritis associated interstitial lung disease. *Eur Respir J* 2021; 57: 2000337.
26. Rojas-Serrano J, Herrera-Bringas D, Perez-Roman DI, *et al.* Rheumatoid arthritis-related interstitial lung disease (RA-ILD): methotrexate and the severity of lung disease are associated to prognosis. *Clin Rheumatol* 2017; 36: 1493–1500.
27. Akira M, Sakatani M and Hara H. Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses. *J Comput Assist Tomogr* 1999; 23: 941–948.
28. Park IN, Kim DS, Shim TS, *et al.* Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest* 2007; 132: 214–220.

29. Hider SL, Silman A, Bunn D, *et al.* Comparing the long-term clinical outcome of treatment with methotrexate or sulfasalazine prescribed as the first disease-modifying antirheumatic drug in patients with inflammatory polyarthritis. *Ann Rheum Dis* 2006; 65: 1449–1455.

30. Scott DL, Smolen JS, Kalden JR, *et al.* Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind, placebo controlled trial versus sulfasalazine. *Ann Rheum Dis* 2001; 60: 913–923.

31. Chen RX, Zhao LD, Xiao XY, *et al.* Distinctive clinical characteristics and outcome of ILD-onset rheumatoid arthritis and ACPA-positive ILD: a longitudinal cohort of 282 cases. *Clin Rev Allergy Immunol* 2021; 60: 46–54.

32. Assayag D, Lubin M, Lee JS, *et al.* Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. *Respirology* 2014; 19: 493–500.

33. Cano-Jimenez E, Vazquez Rodriguez T, Martin-Robles I, *et al.* Diagnostic delay of associated interstitial lung disease increases mortality in rheumatoid arthritis. *Sci Rep* 2021; 11: 9184.