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Factors associated with interstitial lung disease in patients with rheumatoid arthritis

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Abstract

Aim: Interstitial lung disease (ILD) is a significant extra-articular manifestation of rheumatoid arthritis (RA). The prevalence and risk factors for ILD in RA exhibit considerable variation. This study aimed to determine the prevalence and factors associated with ILD in Thai patients with RA.

Methods: This cross-sectional study enrolled 290 RA patients from the Siriraj Rheumatoid Arthritis Registry between March and December 2022. Patient characteristics, disease activity and functional status were documented. Chest radiography (CXR) was employed for ILD screening, and suspected cases were further evaluated using high-resolution computed tomography (HRCT) and pulmonary function tests. Two radiologists independently analyzed CXR and HRCT images, with any discrepancies resolved by a pulmonologist.

Results: Among the 290 patients, the majority were female (89.7%) with mean age (SD) of 58.8 (11.5) years, and the median disease duration was 10 years (range 6–17 years). Patients exhibited low disease activity [mean Disease Activity Score 28-erythrocyte sedimentation rate score (SD) 2.69 (0.90)] and mild functional impairment [median Health Assessment Questionnaire score (range) 0.25 (0–0.63)]. Thirteen patients (4.5%) were diagnosed with ILD via HRCT (RA-ILD), with nonspecific interstitial pneumonia being the predominant ILD pattern (69.2%). Pulmonary function tests showed normal results in most patients, with only 15.5% presenting restrictive ventilatory defects. Age ($P = 0.04$), breathlessness ($P < 0.001$), crackles ($P < 0.001$), and functional impairment ($P = 0.02$) exhibited significant associations with RA-ILD.

Conclusions: ILD is relatively infrequent in Thai patients with RA. However, older age, breathlessness, crackles, and functional impairment should prompt investigations for ILD in RA patients.

Keywords

Interstitial lung disease, prevalence, rheumatoid arthritis, risk factors

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects an estimated 0.46% of the global population [1], with a prevalence of approximately 0.09% to 0.13% in the Thai population [2]. The disease is characterized by persistent inflammation of the synovium, primarily affecting diarthrodial joints. If left untreated, RA can result in joint deformity, functional disability, and increased mortality. It can also cause inflammation in extra-articular structures such as the eye, cardiovascular, and respiratory systems.

Among these manifestations, interstitial lung disease (ILD) is one of the most commonly observed complications [3]. Although many patients with ILD do not exhibit symptoms, the disease can significantly impact their quality of life. Furthermore, ILD is a leading cause of death in patients with RA, alongside cardiovascular disease, infection, and malignancy [4, 5]. The reported prevalence of ILD in patients with RA varies widely, ranging from 1.8% to 67%, with an average of 24.9% [6].

Typically, ILD develops as a late manifestation of RA, often occurring approximately 5 years after the RA diagnosis. High-resolution computed tomography (HRCT) commonly reveals nonspecific interstitial pneumonitis (NSIP) and usual interstitial pneumonitis as the prevailing patterns of ILD [7, 8].

The clinical course of ILD varies, ranging from asymptomatic and indolent cases to rapidly progressive and life-threatening conditions in a minority of patients. Previous studies have found that male sex, longer RA disease duration, advanced age, smoking, positive serology, and greater RA severity contribute to an increased risk of ILD [4, 9–13]. Additionally, treatment modalities for RA have been associated with ILD progression. These include conventional disease-modifying antirheumatic drugs such as methotrexate [14] and leflunomide [15], and biologic disease-modifying antirheumatic drugs.

Given the wide range of reported prevalence rates and risk factors for ILD in the RA population, this study aimed to ascertain the prevalence of ILD and identify associated factors in Thai patients with RA.

Materials and methods

Study population

This cross-sectional study was conducted from March 2022 to December 2022. We consecutively recruited outpatients diagnosed with RA from the Siriraj Rheumatoid Arthritis Registry. The Registry was established in 2011 by the Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand with a total of 544 patients enrolled in this registry.

All patients included in the study were aged 18 years or older. They fulfilled either the 1987 American College of Rheumatology criteria [16] or the 2010 American College of Rheumatology and European League Against Rheumatism classification criteria for RA [17]. The patients were regularly followed up at the outpatient rheumatology clinic of Siriraj Hospital.

Patients were excluded if they were pregnant, had active arthritis or severe joint deformities at lower extremities, had an active respiratory infection at enrollment, had overlapping autoimmune diseases except for Sjogren's syndrome, or had previously been diagnosed with ILD from specific causes.

This study adhered to the ethical principles of the Declaration of Helsinki (1964) and its subsequent provisions. Furthermore, it followed the guidelines outlined in the Guideline for Good Clinical Practice International Conference on Harmonization Tripartite Guideline (January 1997). The study protocol received authorization from the Scientific Ethics Committee, Siriraj Institutional Review Board (approval no. Si177/2022). Prior to enrollment, informed consent was obtained from all participants.

Data collection

At the enrollment date, the disease status of RA was assessed. Demographics, comorbidities, disease duration, and serological markers such as rheumatoid factor (RF) and anticitrullinated peptide antibodies (ACPA) were collected. Additionally, radiographs of the hands and feet, as well as treatment information, were recorded. Disease activity was measured using the Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate (DAS28-ESR) scoring system [18], which involved a physical examination of peripheral joints by a rheumatologist. The examination involved determining the count of swollen and tender joints (28 joints in each category).

To further evaluate disease activity, patient global assessment of disease activity and blood tests for inflammatory markers, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), were performed. The patient global assessment is rated on a numerical scale from 0 (none) to 10 (very severe). ESR was measured using an automated ESR analyzer (Ves-matic Easy; Diesse Diagnostic Senese Spa, Milano, Italy; reference range, 0–20 mm/h). CRP was measured using the particle-enhanced immunoturbidimetric method (reference < 5 mg/L). The DAS28-ESR scoring system was used to assess disease activity. In cases where CRP was assessed instead of ESR, the DAS28-CRP score was calculated and converted to the equivalent DAS28-ESR score using the formula DAS28-ESR = DAS28-CRP + 0.2 [19].

Patients were categorized into different disease activity groups based on their DAS28-ESR values. The thresholds for these groups were as follows: remission (DAS28-ESR score less than 2.6), low disease activity (DAS28-ESR score of 2.6 to less than 3.2), moderate disease activity (DAS28-ESR score of 3.2 to 5.1), and high disease activity (DAS28-ESR score greater than 5.1).

The functional status of patients was evaluated using the Thai version of the Health Assessment Questionnaire (HAQ), which consists of eight domains that assess an individual's ability to perform daily activities [20, 21]. The HAQ total score ranges from 0 (indicating no difficulty) to 3 (indicating disability). Patients were categorized into different disability groups based on their HAQ scores: near normal (less than 0.5), mild (0.5 to less than 1.1), moderate (1.1 to less than 1.6), and severe (1.6 to 2.1).

Quality of life was assessed using the Thai version of the EQ-5D-5L, which encompasses five domains: morbidity, self-care, usual activity, pain/discomfort, and anxiety or depression [22]. The final EQ-5D-5L score ranges from 0 to 1, representing death and perfect health, respectively.

For the ILD assessments, several evaluations were conducted in all participants. Initially, a thorough history was taken to assess symptoms such as breathlessness, dry cough, and exertional dyspnea. Additionally, chest auscultation was performed to detect crackles. Subsequently, a six-minute walk test and a chest radiograph (CXR) were conducted.

CXR served as a primary screening tool to identify potential ILD abnormalities. Specifically, the radiograph was examined for interstitial or alveolar opacities that predominantly appeared in the basal lungs, as well as any signs of decreased lung volume. If the CXR raised suspicion of ILD, further investigations were pursued: HRCT and pulmonary function tests (PFTs).

HRCT of the entire chest was conducted using a 64-slice multidetector CT scanner, following a standard protocol with a tube potential of 120 kV and a reference tube current-time product of 40 mAs or 100 mAs. The care dose was also applied during the procedure. The HRCT data were reconstructed with filtered back projection using a slice thickness of 1.25 mm and an increment of 0.8 mm.

PFTs, including spirometry, total lung capacity, residual volume, diffusing capacity for carbon monoxide (DLCO), alveolar volume, and the six-minute walk test, were conducted per the guidelines provided by the American Thoracic Society and the European Respiratory Society [23].

Both the CXR and HRCT images of all participants were meticulously reviewed by two chest radiologists (SW and KB). In the event of discrepancies, a pulmonologist (SD) performed a consensus read. The patient identifications and profiles were kept blind from all readers. Inclusion in the ILD group (RA-ILD) was based on the presence of relevant terms in the HRCT reports, such as "interstitial lung disease," "usual interstitial pneumonia," and "nonspecific interstitial pneumonia".

Sample size calculation

The sample size calculation was derived from a previous study on the Asian population, which reported a 25% prevalence of ILD in patients with RA [12]. The calculation was performed to estimate the proportion of one group with 80% statistical power and a CI of 95%. To achieve statistically significant results with a margin of error of 5%, a minimum sample size of 290 participants was determined.

Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics, version 20 (IBM Corp, Armonk, NY, USA). Categorical variables are shown as frequencies. In the case of continuous variables, values are reported as either the mean ± SD or the median with interquartile range (IQR), depending on whether the variables followed a normal or nonnormal distribution, respectively.

Univariate binary logistic regression analysis was employed to compare the individual variables of the RA-ILD and RA-non ILD groups. The differences in normally distributed variables were assessed using Student's two-tailed *t* test, while the Mann-Whitney *U* test was utilized for nonnormally distributed variables. For categorical variables, either the Pearson chi-square test or Fisher's exact test was applied, as appropriate. A *P* value of less than 0.05 was considered statistically significant in all analyses.

Results

A total of 290 patients were recruited for this study, as summarized in Table 1. The participants had a mean age (SD) of 58.80 (11.54) years, with 89.7% being female. Among the patients, a minority were smokers (7.6%). Most patients were seropositive for RF (75.3%) and ACPA (71.7%). The median disease duration (range) was 10 (6–17) years. In terms of disease activity, patients exhibited low disease activity with a mean DAS28-ESR score (SD) of 2.69 (0.90). The functional impairment was mild, as indicated by a median HAQ score (range) of 0.25 (0–0.63).

The patients reported a mean EQ-5D-5L (SD) score of 0.91 (0.11), reflecting good quality of life. Furthermore, the mean global health (SD) score was 82.99 (13.61), indicating a positive perception of overall health. The mean six-minute walk distance (SD) was 356.66 (83.67) meters, demonstrating reasonable physical endurance.

In terms of treatment, the majority of the 290 patients received conventional disease-modifying antirheumatic drugs, with 87% being treated with methotrexate, 47% with antimalarials, and 28% with leflunomide. Corticosteroid treatment was administered to only 11% of patients.

Based on the CXR findings, ILD was suspected in 24 of the 290 patients (8.3%), with an agreement rate between two chest radiologists of 84%. All 24 patients underwent HRCT and PFTs; ILD was diagnosed in 13 cases (4.5%).

Of the remaining 11 patients in the RA-non ILD group, 5 exhibited bronchiectasis, and 2 exhibited bronchiolitis. These conditions were deemed related to RA. Another 2 of the 11 patients in the RA-non ILD group displayed bronchiectasis that was associated with previous pulmonary tuberculosis infections.

It is worth noting that 2 out of the initial 24 patients did not demonstrate any evidence of pulmonary disease in the HRCT scans and had normal PFT results.

Characteristics of ILD related to RA

Signs and symptoms

Within the RA-ILD group, 12 out of the 13 patients exhibited at least one pulmonary manifestation. These manifestations were crackles (84.6%), breathlessness (38.5%), dry cough (7.7%), and exertional desaturation (7.7%). Only one patient was asymptomatic, with normal pulmonary examination and PFT results; however, HRCT subsequently revealed evidence of an NSIP pattern.

Table 1. Demographic and baseline characteristics of 290 patients

Characteristics	*N* = 290
Age (year), mean (SD)	58.8 (11.54)
Female, *n* (%)	260 (89.7)
Ever smoking, *n* (%)	22 (7.6)
Disease duration (year), median (IQR)	10 (6–17)
RF, *n* (%)	216/287* (75.3)
ACPA, *n* (%)	172/240* (71.7)
Radiographic hands or feet erosion, *n* (%)	160/273* (58.6)
PGA score (0–10), median (IQR)	1 (0–3)
DAS28-ESR score (0–9), mean (SD)	2.69 (0.90)
HAQ score (0–3), median (IQR)	0.25 (0–0.63)
EQ-5D-5L score, mean (SD)	0.91 (0.11)
Global health score (0–10), mean (SD)	82.99 (13.61)
6MWD, meter, mean (SD)	356.66 (83.67)
Medications	
Methotrexate, *n* (%)	251 (86.6)
Antimalarial, *n* (%)	135 (46.6)
Leflunomide, *n* (%)	81 (27.9)
Sulfasalazine, *n* (%)	78 (26.9)
Azathioprine, *n* (%)	4 (1.4)
Cyclosporin, *n* (%)	4 (1.4)
bDMARDs, *n* (%)	18 (6.2)
tsDMARDs, *n* (%)	4 (1.4)
Prednisolone, *n* (%)	34 (11.7)
Pulmonary manifestations	
Breathlessness, *n* (%)	8 (2.8)
Dry cough, *n* (%)	3 (1)
Basal crackles, *n* (%)	17 (5.9)
Exertional desaturation, *n* (%)	5 (1.7)

ACPA: anticitrullinated peptide antibodies; bDMARDs: biologic disease modifying antirheumatic drugs, e.g., adalimumab, etanercept, golimumab, infliximab, rituximab, tocilizumab; DAS28-ESR: Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; PGA: patient global assessment; RF: rheumatoid factor; tsDMARDs: targeted synthetic disease modifying anti-rheumatic drugs, e.g., tofacitinib, baricitinib; 6MWD: six-minute walk distance; IQR: interquartile range; ESR: erythrocyte sedimentation rate. * Some patients did not perform serology testing for RF or ACPA and hand/feet radiography

CXR

Among the 13 patients with RA-ILD, all exhibited at least one abnormal finding on their CXR. These abnormalities were interstitial infiltration (92.3%) and alveolar infiltration (7.7%). Interstitial opacities were observed bilaterally in 92% of cases, predominantly in the lower lung zones, while diffuse lung lesions were present in 8% of cases. One patient showed bilateral alveolar opacities located in the basilar area.

Chest HRCT

Among the 13 patients with RA-ILD, different patterns were observed on HRCT. The most prevalent pattern was NSIP, found in 69.2% of cases. This was followed by usual interstitial pneumonia in 15.4% of cases and NSIP with organizing pneumonia in another 15.4%.

In addition to the ILD findings, other notable abnormalities were observed. Air trapping was present in 76.9% of patients, while bronchiectasis was present in 53.8%. Nodules were detected in 23.1% of cases, and esophageal dilatation and main pulmonary artery enlargement were observed in 23.1% and 15.4% of patients, respectively.

PFTs

Among the RA-ILD patients, the majority (10 out of 13, or 77%) exhibited normal PFT results. This was determined based on the mean values for various parameters. They were forced vital capacity %predicted (SD), 87.18% (21.19%); total lung capacity %predicted (SD), 89.41% (9.8%); DLCO %predicted (SD), 71.29% (25.59%); and DLCO/alveolar volume %predicted (SD), 74.18% (20.11%).

Only 2 of the 13 RA-ILD patients displayed a restrictive ventilatory defect, with one presenting NSIP and the other showing usual interstitial pneumonitis. Additionally, one patient exhibited an obstructive ventilatory defect (NSIP with bronchiectasis).

Factors associated with RA-ILD

Patients with RA-ILD exhibited several distinguishing characteristics compared to RA-non ILD patients. Notably, RA-ILD patients were significantly older, with a mean age (SD) of 65.38 (10.18) years vs. 58.49 (11.52) years ($P < 0.04$). Furthermore, RA-ILD patients experienced greater functional impairment, as evidenced by a higher median HAQ score [IQR = 0.88 (0–1.13) vs. 0.25 (0–0.63); $P = 0.04$].

Regarding the RA disease status, the frequencies of rheumatoid factor positivity, anticyclic citrullinated peptide positivity, inflammatory markers (ESR and CRP), and disease activity were comparable between the two groups. No significant differences were observed in the distribution of sex and the proportion of smokers in the RA-ILD and RA-non ILD groups. However, the six-minute walk distance was notably lower for RA-ILD patients (Table 2).

Our univariate binary logistic regression analysis identified several factors associated with ILD. These were age, breathlessness, crackles, and functional status. The RA-ILD patients were significantly older [relative risk (RR) = 1.06; 95% CI: 1.01–1.12; $P = 0.04$] than the RA-non ILD patients. Furthermore, RA-ILD patients experienced a significantly higher prevalence of breathlessness (RR = 57.08; 95% CI: 11.59–281.23; $P < 0.001$), crackles (RR = 248.42; 95% CI: 44.93–1373.60; $P < 0.001$), and functional impairment (RR = 3.05; 95% CI: 1.25–7.45; $P = 0.02$; Table 3).

Discussion

RA can manifest with various pulmonary complications, including ILD, pleural involvement, airway diseases, and pulmonary vascular disease. The prevalence of these manifestations varies depending on the specific type of pulmonary involvement. ILD is recognized as a severe extra-articular complication of RA due to its high morbidity and mortality rates [24].

The reported prevalence of RA-ILD varies across different studies. In our study, the prevalence of ILD in RA aligns with findings from previous studies conducted in Germany (2%) [25], the USA (9%) [9], Korea (2%) [4], and Malaysia (7%) [26]. However, our study's prevalence rate is notably lower than the values reported in studies from China (15–43%) [11–13].

The discrepancy in the prevalence reported by the studies may be attributed to variations in their screening and diagnostic methods employed. As with the Korean and American studies mentioned above, we utilized CXR as the primary screening tool before performing HRCT for cases with abnormal CXR findings. However, the German population study employed multiple procedures: PFTs, CXR, HRCT, and bronchoscopy. On the other hand, the Chinese studies predominantly relied on HRCT as the primary screening tool. The higher prevalence observed in Chinese patients could be attributed to the greater sensitivity of HRCT as a diagnostic tool [27].

Nevertheless, despite employing HRCT as a screening tool, the Malaysian investigation reported a relatively low prevalence of RA-ILD, as with our findings. The Malaysian study's observation suggests that in addition to diagnostic methods, factors such as ethnicity, geography, and environmental influences may impact the development of ILD in RA.

Table 2. Comparison of RA-ILD and RA-non ILD group characteristics

Characteristics	RA-ILD (*N* = 13)	RA-non ILD (*N* = 277)	*P*
Age, year, mean (SD)	65.38 (10.18)	58.49 (11.52)	0.04
Female, *n* (%)	12 (92.3)	248 (89.5)	1.00
Ever smoking, *n* (%)	1 (7.7)	21 (7.6)	1.00
Disease duration (year), median (IQR)	12 (8–19)	10 (6–16)	0.46
RF, *n* (%)	12 (92.3)	204 (73.6)	0.20
ACPA, *n* (%)	7 (53.8)	165 (59.6)	1.00
Radiographic hands or feet erosion, *n* (%)	8 (61.5)	152 (54.9)	0.77
PGA score, median (IQR)	0 (0–3)	1 (0–3)	0.23
DAS28-ESR score, mean (SD)	2.74 (0.67)	2.69 (0.91)	0.86
HAQ score, median (IQR)	0.88 (0–1.13)	0.25 (0–0.63)	0.04
EQ-5D-5L score, mean (SD)	0.84 (0.18)	0.92 (0.11)	0.14
Global health score, mean (SD)	82.31 (14.81)	83.01 (13.58)	0.85
6MWD, meter, mean (SD)	319.71 (70.67)	358.40 (83.94)	0.10
Medications			
MTX, *n* (%)	11 (84.6)	240 (86.6)	0.69
Antimalarial, *n* (%)	6 (46.2)	129 (46.6)	0.97
LEF, *n* (%)	4 (30.8)	77 (27.8)	0.76
SSZ, *n* (%)	3 (23.1)	75 (27.1)	1.00
AZA, *n* (%)	1 (7.7)	3 (1.1)	0.17
Cyclosporin, *n* (%)	0 (0)	4 (1.4)	1.00
bDMARDs, *n* (%)	0 (0)	18 (6.5)	1.00
tsDMARDs, *n* (%)	0 (0)	4 (1.4)	1.00
Prednisolone, *n* (%)	2 (15.4)	32 (11.6)	0.65
Pulmonary manifestations			
Breathlessness, *n* (%)	5 (38.5)	3 (1.1)	< 0.001
Dry cough, *n* (%)	1 (7.7)	2 (0.7)	0.13
Basal crackles, *n* (%)	11 (84.6)	6 (2.2)	< 0.001
Exertional desaturation, *n* (%)	1 (7.7)	4 (1.4)	0.20

ACPA: anticitrullinated peptide antibodies; AZA: azathioprine; bDMARDs: biologic disease modifying antirheumatic drugs, e.g., adalimumab, etanercept, golimumab, infliximab, rituximab, tocilizumab; CSA: cyclosporin A; DAS28-ESR: Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; LEF: leflunomide; MTX: methotrexate; PGA: patient global assessment; RF: rheumatoid factor; SSZ: sulfasalazine; tsDMARDs: targeted synthetic disease modifying anti-rheumatic drugs, e.g., tofacitinib, baricitinib; 6MWD: six-minute walk distance; IQR: interquartile range; ESR: erythrocyte sedimentation rate; ILD: interstitial lung disease; RA: rheumatoid arthritis

Table 3. Univariate binary logistic regression analysis of RA-ILD and RA-non ILD

Factors	RR	95% CI	*P*
Age, year, mean (SD)	1.06	1.01–1.12	0.04
Smoking, *n* (%)	1.02	0.13–8.20	0.99
Disease duration, median (IQR)	1.02	0.96–1.09	0.46
DAS28-ESR score, mean (SD)	1.06	0.58–1.93	0.86
HAQ score, median (IQR)	3.05	1.25–7.45	0.02
Breathlessness, *n* (%)	57.08	11.59–281.23	< 0.001
Basal crackles, *n* (%)	248.42	44.93–1,373.60	< 0.001

DAS28-ESR: Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; IQR: interquartile range; ESR: erythrocyte sedimentation rate; ILD: interstitial lung disease; RA: rheumatoid arthritis; RR: relative risk

Another significant factor influencing the high prevalence of RA-ILD in several studies is smoking, which has been strongly associated with RA-ILD [11, 13]. One study reporting a prevalence of 24.9% for RA-ILD had a substantial proportion of smokers, who represented 20.7% of the population [12].

The classification and identification of HRCT patterns in RA-ILD vary across studies, and several patterns have been described in the literature. The most commonly observed pattern in RA-ILD is the usual interstitial pneumonitis pattern, with reported frequencies ranging from 40% to 62% of cases [28–30]. The NSIP pattern ranks second most common (11–32% of cases) [29]. Previous studies have indicated that the usual interstitial pneumonitis pattern is more frequent in cases with a longer duration of RA. However, our study and several other investigations involving patients with longstanding RA (over 5 years of disease duration) found NSIP to be the predominant ILD pattern in RA, with frequencies ranging from 29% to 59% of cases [11, 26, 31]. Discrepancy in the most common pattern of ILD in RA among studies may be partly attributed to other risk factors for ILD including smoking. It has been reported that UIP is overrepresented in ever smokers as compared with nonsmokers [32], whereas NSIP in RA is more common in nonsmokers [33]. In this study, there was only one patient in RA-ILD was ever smoker leading to a lower proportion of UIP, when compared with other studies.

Consistent with previous studies, our findings indicate that older age is associated with a higher prevalence of ILD in patients with RA [11, 31]. The presence of breathlessness and crackles in RA-ILD observed in our study can be attributed to the underlying lung pathology characteristic of ILD patients. In line with the univariate analysis conducted in a study from Korea [4], our study revealed a significant association between poor functional status, indicated by high HAQ scores, and the presence of ILD. However, this association did not reach statistical significance in the subsequent multivariate analysis conducted in the Korean study. Our study did not perform a multivariate analysis.

Our study did not identify significant associations between ILD and factors such as disease duration, disease activity, serology positivity, or smoking. This may be attributed to the unexpectedly small number of patients with RA-ILD included in our study, which could have limited our ability to detect such associations.

This study was conducted in one of the largest tertiary hospitals in Thailand that specializes in managing RA-ILD patients. However, several limitations must be acknowledged. First, an unexpectedly small number of RA patients with ILD were included, potentially impacting the study's findings. Consequently, it was deemed inappropriate to perform multivariate analysis to identify independent factors associated with ILD in RA. Future research with a larger cohort is warranted to obtain more accurate results and identify comprehensive risk factors associated with ILD in this population. Second, CXR, which has low sensitivity for diagnosing ILD, was utilized as the screening tool. As a result, our study may have underestimated the true prevalence of RA-ILD. However, it is noteworthy that only half of our patients suspected to have ILD based on CXR were subsequently confirmed to have ILD on HRCT. This suggests that our study may not have significantly underestimated the prevalence of ILD. Third, most patients in this study had low disease activity or remission, therefore the prevalence of ILD may be lower than other patients with higher disease activity. Last, this study encountered a high rate of false-positive interpretations of CXR due to other lung pathologies in our study population, such as bronchiectasis and bronchiolitis related to RA, as well as tuberculosis-related lesions. Additionally, two patients who were ultimately found to have no evidence of pulmonary disease on HRCT were initially reported as having ILD based on CXR findings. These false-positive chest X-ray interstitial opacities may have resulted from various factors, such as suboptimal patient positioning, overlapping anatomical structures, and normal anatomical variations. Employing lateral views in addition to posterior-anterior views for CXR may help mitigate the limitations associated with the latter.

There are currently no international guidelines that recommend a standard method for screening ILD in patients with RA. Due to the low prevalence of clinically significant RA-ILD and practical limitations to perform HRCT in every RA patient in real-world settings, we recommend routinely assessing symptoms and signs, along with performing CXR. If there are any suspicious findings, such as respiratory symptoms, signs, or abnormal CXR results suggestive of ILD, further evaluations with HRCT and PFTs should be performed. This approach aligns with the current recommendation from a Delphi-based consensus statement [34].

In conclusion, our study reveals that ILD is relatively infrequent in Thai RA patients. The predominant interstitial pneumonia pattern identified in this population is NSIP. Consequently, screening for ILD should be conducted in RA patients who are advanced in age, exhibit symptoms of breathlessness, manifest crackles upon examination, or display functional impairment.

Abbreviations

ACPA: anticitrullinated peptide antibodies

CRP: C-reactive protein

CXR: chest radiography

DAS28-ESR: Disease Activity Score in 28 joints using Erythrocyte Sedimentation Rate

ESR: erythrocyte sedimentation rate

HAQ: Health Assessment Questionnaire

HRCT: high-resolution computed tomography

ILD: interstitial lung disease

IQR: interquartile range

NSIP: nonspecific interstitial pneumonitis

PFTs: pulmonary function tests

RA: rheumatoid arthritis

RF: rheumatoid factor

RR: relative risk

Declarations

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Author contributions

BSU: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. SD: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. SW: Investigation, Writing—review & editing. KB: Investigation, Writing—review & editing. WK: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Supervision. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

This study adhered to the ethical principles of the Declaration of Helsinki (1964) and its subsequent provisions, and it was approved by the Institutional Review Board of Siriraj Hospital, Mahidol University (approval no. Si177/2022).

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The data are available from the corresponding author upon reasonable request.

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Not applicable.

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