Journal homepage https://jsmc.univsul.edu.iq
Journal of Sulaimani Medical College
ISSN:2223-148X

Original Article

Association of Pulmonary Fibrosis with Methotrexate in Rheumatoid Arthritis Patients

Soma Qadir Hassan[1*], Niaz Jwad Albarzinji[1]
[1]: Department of Internal Medicine, Rheumatology Institute, Hawler Medical University, Erbil, Kurdistan Region of Iraq

Article Info.

Article History
Received:24/7/2025
Revised: 4/10/2025
Accepted14/11/2025
Published online
21/12/2025

Key words:
Autoimmune condition, Inflammation, Methotrexate, Pulmonary Fibrosis, Rheumatoid Arthritis

Abstract

Background: Rheumatoid arthritis (RA) is a systemic autoimmune disease that primarily affects the joints and can involve extra-articular organs, including the lungs. Methotrexate (MTX), commonly used in RA treatment, has been associated with lung complications, though its role in the development of PF remains unclear.

Objective: The current study investigates the association between methotrexate use and pulmonary fibrosis in RA patients. Given the cross-sectional design, the findings should be considered exploratory and hypothesis-generating.

Patients and Methods: A cross-sectional study was conducted from October 2024 to March 2025 at the outpatient rheumatology clinic of Rizgary General Teaching Hospital, Erbil, Iraq. A total of 86 RA patients were enrolled, with inclusion criteria of RA diagnosis for at least one year and MTX or other DMARD use. Pulmonary assessments were performed with high-resolution computed tomography (HRCT) scans.

Results: Pulmonary fibrosis (PF) was present in 14.0% (12/86) of patients. Methotrexate (MTX) use was more frequent in PF vs. non-PF patients (91.7% vs. 62.2%; P = 0.045), though the mean duration of MTX use was similar (2.38 ± 2.68 years; 95% CI: 0.73–4.09 vs. 2.21 ± 2.88 years; 95% CI: 1.27–2.97; P = 0.673). Although MTX use was more common in PF, the adjusted association was not statistically significant (aOR 7.60, 95% CI 0.89-64.65; p=0.063). Other covariates were not significant: age (63.67 ± 9.98; 95% CI: 50.53–68.47 vs. 55.89 ± 12.65; 95% CI: 54.05–59.75; aOR = 1.00; P = 0.991), female sex (66.7% vs. 93.2%; aOR = 0.37; 95% CI: 0.05–2.54; P = 0.310), and disease duration >5 years (75.0% vs. 43.2%; aOR = 2.34; 95% CI: 0.56–9.72; P = 0.243). Inflammatory markers were higher in PF patients: ESR (36.92 ± 10.62 mm/h; 95% CI: 26.38–41.42 vs. 30.19 ± 18.20; 95% CI: 26.35–36.31; P = 0.044) and CRP (15.29 ± 12.78 mg/L; 95% CI: 4.92–16.13 vs. 10.09 ± 11.45; 95% CI: 7.20–13.05; P = 0.041).

Conclusion: Pulmonary fibrosis was more frequent in older RA patients with longer disease duration and higher inflammation. Methotrexate use showed higher odds of PF, but without statistical significance. These exploratory findings highlight the need for larger longitudinal studies to confirm causality.

DOI: 10.17656/jsmc.10502
Corresponding author: Soma Qadir Hassan somahakkari@gmail.com

1. Introduction Rheumatoid Arthritis (RA) is a significant systemic inflammatory disorder,

primarily recognized for its progressive and symmetrical erosion of cartilage and bone within the joints, a process frequently associated with the production of autoantibodies. This autoimmune condition affects 1% of the population globally in developed countries, is of uncertain origin, and leads to debilitating joint deformities and polyarthritis (1, 2). Although RA can emerge at any point in life, its onset is most common during the 40s, and it demonstrates a notable predilection for women; the incidence of it in females is about threefold higher than in males (3). The exact causes underlying RA's etiology are still not completely known; however, an interplay between an autoimmune and an inflammatory response, which acts in conjunction with diverse environmental factors, has been implicated in both the incidence and development of the disease (4). Unfortunately, the RA is not only related to the joints, but it also plays a crucial role in a systemic disease and can involve many extra-articular organs, including the heart, skin, eyes, and particularly the lungs. The above extra-articular involvement happens in about 17.8–40.9% of the RA population, and may greatly affect the prognosis of these patients (5, 6). Pulmonary involvement is one of them and is particularly prevalent, present in an impressive 60–80% of RA patients (7). In spite that CVD is the most common cause of death in this at-risk population, it is also a significant contributor to 10-20% of all deaths due to pulmonary complications (8).

One of the most important lung involvements of RA is interstitial lung disease (ILD), which may progress to irreversible pulmonary fibrosis (PF). Characterized by the appearance of fibrosis and inflammation of the lung parenchyma, ILD is associated with substantial morbidity and mortality (9-11). RA-ILD occurs as a result of different risk factors, for instance, aging, male sex, smoking, and markers of serology, for example, RF and anti-CCP antibodies (12). At a clinical level, ILD is characterized by a gradual onset of shortness of breath, cough, hypoxia, and decreased lung function with, usually, a presence of bilateral diffuse infiltrates on imaging tests. This eventually results in restricted patient mobility and poor quality of life (13). The lung is progressively scarred and stiffened, and the capacity to deliver oxygen is irreversibly lost, resulting in marked breathlessness and ultimately death (14).

To manage the underlying disease, disease-modifying antirheumatic drugs (DMARDs) serve as the cornerstone of RA therapy. These agents are crucial for controlling synovitis, preventing or reducing joint damage, and preserving joint integrity and function (15). Among the conventional synthetic DMARDs, methotrexate (MTX) is universally regarded as the “anchor drug” for RA treatment (16). Its effectiveness in reducing disease activity, morbidity, and mortality has led to its widespread use, with up to 70% of RA patients receiving this medication (17-19).

Despite its therapeutic benefits, a long-standing debate surrounds the potential association between MTX and lung disease, particularly chronic fibrotic ILD (20). While acute or subacute hypersensitivity pneumonitis is a recognized, albeit rare, complication of MTX [28], the current data did not conclude a relationship between cause-and-effect among the drug and chronic fibrotic RA-ILD in patients. Recent research has cast doubt on this association, with some studies suggesting that MTX may even have a protective effect against the development of RA-ILD (21, 22).

In light of this clinical investigation, this investigation is designed to study the association between pulmonary fibrosis and pharmacotherapy with methotrexate and other DMARDs in rheumatoid arthritis patients. By exploring the intricate association between RA therapies and lung health, this research aims to provide a clearer understanding of the role that MTX plays in the development of pulmonary fibrosis within the RA patient population.

Patients and Methods

Study Design and Setting

This cross-sectional study was conducted from October 2024 to March 2025 on 86 RA patients at an outpatient rheumatology clinic in Rizgary General Teaching Hospital in Erbil, Kurdistan Region, Iraq.

Inclusion Criteria

Male and female adult patients ≥18 years of age with a diagnosis of RA according to the American College of Rheumatology criteria (23). All patients had been treated with methotrexate or an alternative DMARD for at least one year, and consented to participate in the registry, which entailed performing High-Resolution Computed Tomography (HRCT) scans.

Exclusion Criteria

Patients with pre-existing respiratory diseases other than those attributable to rheumatoid arthritis, or other autoimmune diseases and chronic inflammatory diseases that may confound the results (e.g., SLE, Scleroderma) were not included. Other exclusion criteria were a history of smoking or other relevant environmental/occupational lung exposures (such as asbestos, wood dust, coal dust), past exposure to radiation therapy, or the use of medications known to affect the lung (including amiodarone, nitrofurantoin, bleomycin). Also, patients with prior viral infection, such as COVID-19, Epstein-Barr virus, and Cytomegalovirus.

Sample Size Justification

The sample (n=86) comprised all eligible clinic attendees during the study period; no a priori power calculation was performed. Accordingly, the study was designed as exploratory and hypothesis-generating. The limited number of PF events (n=12) results in wide CIs and reduced precision.

Data Collection

Demographic data included age, sex, smoking history, and RA duration. Clinical data included RA activity, current treatment, and serology (RF, anti-CCP). Breathing-related symptoms chest tightness, cough, and dyspnea, were recorded. Data on DMARDs prescribed, the type, dose, and duration of treatment were collected. RF and anti-CCP antibodies were noted. Also, Breathing-related symptoms include such as chest tightness, cough, and shortness of breath, were reported

Pulmonary Assessments

PF was defined on HRCT according to ATS/ERS criteria (reticulation, traction bronchiectasis, and/or honeycombing in basal and subpleural regions). These criteria include the presence of characteristic radiologic patterns such as reticular opacities, traction bronchiectasis, and honeycombing, predominantly in the subpleural and basal regions of the lungs. These patterns are key indicators of fibrosis and are essential for the radiologic diagnosis of PF.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 26. The normality of continuous variables was assessed with the Shapiro-Wilk test. Data are presented as means ± standard deviations (SD) for continuous variables and as frequencies and percentages for categorical variables. Sociodemographic and clinical characteristics were compared between RA patients with pulmonary fibrosis (RA-PF) and those without (RA-non-PF). Independent sample t-tests were used for normally distributed variables (e.g., age, DAS28, CRP, number of large joints), while non-normally distributed variables (e.g., ESR, number of small joints) were analyzed using the Mann–Whitney U test. The Chi-square (χ^2) test was employed to compare categorical variables, including demographics (gender, marital status, residency, family history),

serologic markers (RF, anti-CCP), medication exposure, and radiographic features. A two-tailed p-value ≤ 0.05 was considered statistically significant.

Ethical Consideration

Ethical approval was obtained from the Ethics Committee of the College of Medicine, Erbil University, Erbil, Kurdistan Region, Iraq (Approval No: 47; Date: 28/8/2024).

Results

Sociodemographic and anthropometric features of RA patients with and without pulmonary fibrosis

Overall, 86 participants (patients) with RA were included in the current research. The age (mean ± SD) was 56.98 ± 12.56 years (95% CI: 54.59–59.96). Patients with pulmonary fibrosis (RA-PF) had a significantly higher mean age (63.67 ± 9.98 years; 95% CI: 50.53–68.47) compared to those without fibrosis (RA-non-PF) (55.89 ± 12.65 years; 95% CI: 54.05–59.75; P = 0.046).

The majority of participants in this study are women (89.5%), with females comprising 66.7% of the RA-PF group and 93.2% of the RA-non-PF group. This difference in gender distribution was statistically significant (P = 0.019, Fisher's exact test). Marital status showed similar patterns across groups, with 94.2% of participants married, including 100.0% of RA-PF and 93.2% of RA-non-PF patients (P = 0.353).

Residency outside city areas was reported by 51.2% of all patients, including 58.3% in the RA-PF group and 50.0% in the RA-non-PF group (P = 0.592).

Employment status varied, with 47.7% of participants unemployed, 31.4% employed, and 20.9% homemakers. Among RA-PF patients, 41.7% were employed, and 33.3% were unemployed, while in RA-non-PF, 29.7% were employed and 50.0% unemployed (P = 0.554).

The overall mean body mass index (BMI) was 31.05 ± 5.79 kg/m² (95% CI: 29.80–32.31). There was no statistically significant difference between the RA-PF (30.35 ± 5.40 kg/m²; 95% CI: 27.51–34.36) and RA-non-PF (31.17 ± 5.87 kg/m²; 95% CI: 26.69–32.46) groups (P = 0.609). All data are summarized in Table 1.

Table 1. Sociodemographic Characteristics of RA Patients With and Without Pulmonary Fibrosis.

Sociodemographic and Anthropometric	RA without PF 74 (86.0%)	RA with PF 12 (14.0%)	Total 86 (100.0%)	P value
Age				
Mean ± SD	55.89 ± 12.65	63.67 ± 9.98	56.98 ± 12.56	0.046 *
95 % CI	54.05 – 59.75	50.53 – 68.47	54.59 – 59.96	
Gender				
Female	69 (93.2%)	8 (66.7%)	77 (89.5%)	0.019 *
Male	5 (6.8%)	4 (33.3%)	9 (10.5%)	
Marital state				
Single	5 (6.8%)	0 (0.0%)	5 (5.8%)	0.353 ns
Married	69 (93.2%)	12 (100.0%)	81 (94.2%)	
Residency				
Inside city	37 (50.0%)	5 (41.7%)	42 (48.8%)	0.592 ns
Outside city	37 (50.0%)	7 (58.3%)	44 (51.2%)	
Occupation				
Employed	22 (29.7%)	5 (41.7%)	27 (31.4%)	0.554 ns
Unemployed	37 (50.0%)	4 (33.3%)	41 (47.7%)	
Housewife	15 (20.3%)	3 (25.0%)	18 (20.9%)	
BMI				
Mean ± SD	31.17 ± 5.87	30.35 ± 5.40	31.05 ± 5.79	0.609 ns

95 % CI	26.69 – 32.46	27.51 – 34.36	29.80 – 32.31	

Patient groups are defined as RA without PF (RA patients without Pulmonary Fibrosis), RA with PF (RA patients with Pulmonary Fibrosis), and All RA. Data are presented with 'n' for sample size, '%' for percentage, and 'SD' for standard deviation. Statistical significance (P < 0.05) is marked with an asterisk (*), while 'ns' indicates non-significance. Age was analyzed using an independent sample t-test, BMI with the Mann-Whitney U test, and categorical variables via the Chi-square test (Except for gender using Fisher's exact test).

Clinical characteristics and inflammatory profile of RA patients stratified by pulmonary fibrosis status

As shown in Table 2, 44.2% of participants in the current study had a positive family history of RA, with comparable proportions observed in the RA-PF (50.0%) and RA-non-PF (43.2%) groups (P = 0.662). Regarding disease duration, 52.3% of patients had RA for less than 5 years, while 47.7% had disease duration exceeding 5 years. A significantly higher proportion of RA-PF patients fell in the >5-year category (75.0%) compared to RA-non-PF (43.2%; P = 0.041).

Seropositivity for RF was noted in 58.1% of the total population, with similar frequencies between RA-PF (50.0%) and RA-non-PF (59.5%) groups (P = 0.538). Anti-cyclic citrullinated peptide (anti-CCP) antibodies were present in 64.0% of patients, with positivity in 58.3% of RA-PF and 64.9% of RA-non-PF patients (P = 0.662).

The mean Disease Activity Score (DAS28) was 4.55 ± 1.52 overall. RA-PF patients had a slightly higher mean score (4.88 ± 1.47; 95% CI: 3.15–5.07) than those without fibrosis (4.50 ± 1.53; 95% CI: 4.14–4.92), though not statistically significant (P = 0.426).

Inflammatory markers showed statistically significant differences between groups. The mean erythrocyte sedimentation rate (ESR) was higher in the RA-PF group (36.92 ± 10.62 mm/h; 95% CI: 26.38–41.42) than in RA-non-PF (30.19 ± 18.20 mm/h; 95% CI: 26.35–36.31; P = 0.044). Similarly, mean C-reactive protein (CRP) levels were elevated in RA-PF patients (15.29 ± 12.78 mg/L; 95% CI: 4.92–16.13) compared to RA-non-PF (10.09 ± 11.45 mg/L; 95% CI: 7.20–13.05; P = 0.041).

Mean joint involvement was greater in RA-PF patients for both large joints (3.58 ± 2.50; 95% CI: 1.23–4.37 vs. 2.75 ± 2.56; 95% CI: 1.97–3.24; P = 0.299) and small joints (9.50 ± 8.03; 95% CI: 1.11–11.29 vs. 6.61 ± 6.88; 95% CI: 5.24–8.93; P = 0.181), though these differences were not statistically significant.

Table 2. Clinical Characteristics and Inflammatory Profile of RA Patients Stratified by Pulmonary Fibrosis Status.

Clinical Characteristics	RA without PF 74 (86.0%)	RA with PF 12 (14.0%)	Total 86 (100.0%)	P value
RA Family history				
No	42 (56.8%)	6 (50.0%)	48 (55.8%)	0.662 ns
Yes	32 (43.2%)	6 (50.0%)	38 (44.2%)	
RA Durations (year)				
<5 years	42 (56.8%)	3 (25.0%)	45 (52.3%)	0.041 *
>5 years	32 (43.2%)	9 (75.0%)	31 (47.7%)	
RF				
Negative	30 (40.5%)	6 (50.0%)	36 (41.9%)	0.538 ns
Positive	44 (59.5%)	6 (50.0%)	50 (58.1%)	
Anti CCP				
Negative	26 (35.1%)	5 (41.7%)	31 (36.0%)	0.662 ns
Positive	48 (64.9%)	7 (58.3%)	55 (64.0%)	
DAS 28				

Mean ± SD	4.50 ±1.53	4.88 ± 1.47	4.55 ± 1.52	0.426 ns
95% CI	4.14 – 4.92	3.15 – 5.07		
ESR				
Mean ± SD	30.19 ± 18.20	36.92 ± 10.62	31.13 ± 17.45	0.044 *
95% CI	26.35 – 36.31	26.38 – 41.42		
CRP				
Mean ± SD	10.09 ±11.45	15.29 ± 12.78	10.82 ± 11.71	0.041 *
95% CI	7.20 – 13.05	4.92 – 16.13		
No. large joint involved				
Mean ± SD	2.75 ± 2.56	3.58 ± 2.50	2.87 ± 2.55	0.299 ns
95% CI	1.97 – 3.24	1.23 – 4.37		
No. small joints involved				
Mean ± SD	6.61 ± 6.88	9.5 ± 8.03	7.02 ± 7.08	0.181 ns
95% CI	5.24 – 8.93	1.11 – 11.29		

Patient groups are defined as RA without PF (RA patients without Pulmonary Fibrosis), RA with PF (RA patients with Pulmonary Fibrosis), and All RA (Total RA patients). Data are presented with 'n' for sample size, '%' for percentage, and 'SD' for standard deviation. Statistical significance ($P < 0.05$) is marked with an asterisk (*), while 'ns' indicates non-significance. RF (Rheumatoid factor), CRP (C-reactive protein), ESR (Erythrocyte sedimentation rate), DAS (Disease Activity Score), anti-CCP (anti–cyclic citrullinated peptide), DAS 28, CRP, number of large joints were analyzed using an independent sample t-test, ESR, number of small joints with the Mann-Whitney U test, and categorical variables via the Chi-square test.

Treatment history and medication exposure among RA patients with and without pulmonary fibrosis

As shown in Table 3, a significantly higher proportion of patients in the RA-PF group (91.7%) used methotrexate (MTX) compared to the RA-non-PF group (62.2%; P = 0.045). The mean duration of methotrexate use was similar between the groups, at 2.38 ± 2.68 years (95% CI: 0.73–4.09) in RA-PF and 2.21 ± 2.88 years (95% CI: 1.27–2.97) in RA-non-PF patients (P = 0.673).

Leflunomide therapy was reported in 38.4% of patients, with comparable usage between the RA-PF (33.3%) and RA-non-PF (39.2%) groups (P = 0.699). The average duration of leflunomide use was 2.88 ± 3.65 years (95% CI: 2.49–5.62) among RA-PF patients and 3.75 ± 5.11 years (95% CI: 1.78–5.68) among RA-non-PF patients (P = 0.782).

Hydroxychloroquine was administered to 16.3% of the total sample, including 8.3% of RA-PF and 17.6% of RA-non-PF patients (P = 0.422). The mean duration of use was slightly shorter in the RA-PF group (2.0 years; data insufficient for CI) compared to RA-non-PF patients (2.85 ± 3.54 years; 95% CI: 0.71–4.99), though the difference was not significant (P = 0.616).

Biologic therapies were used by 11.6% of participants. Use was more frequent among RA-PF patients (16.7%) than RA-non-PF patients (10.8%), though this difference was not statistically significant (P = 0.557). The mean duration of biologic therapy was 3.50 ± 3.54 years in the RA-PF group and 2.51 ± 3.57 years in the RA-non-PF group. The corresponding 95% CIs were wide (RA-PF: 23.41–27.41; RA-non-PF: –0.62–7.37), reflecting limited sample size, and no significant difference was detected (P = 0.419).

Table 3. Treatment History and Medication Exposure Among RA Patients with and Without Pulmonary Fibrosis.

Treatment History and Medication Exposure	RA without PF 74 (86.0%)	RA with PF 12 (14.0%)	Total 86 (100.0%)	P value
Methotrexate ever use				

No	28 (37.8%)	1 (8.3%)	29 (33.7%)	0.045 *
Yes	46 (62.2%)	11 (91.7%)	57 (66.3%)	
Duration used (years) Mean ± SD	2.21 ± 2.88	2.38 ± 2.68	2.23 ± 2.83	0.673 ns
95 % CI	1.27 – 2.97	0.73 – 4.09	1.44 – 2.91	
Leflunomide ever use				
No	45 (60.8%)	8 (66.7%)	53 (61.6%)	0.699 ns
Yes	29 (39.2%)	4 (33.3%)	33 (38.4%)	
Duration used (years) Mean ± SD	3.75 ± 5.11	2.88 ± 3.65	3.65 ± 4.91	0.782 ns
95 % CI	1.78 – 5.68	2.49 – 5.62	1.90 – 5.39	
Hydroxychloroquine ever use				
No	61 (82.4%)	11 (91.7%)	72 (83.7%)	0.422 ns
Yes	13 (17.6%)	1 (8.3%)	14 (16.3%)	
Duration used (years) Mean ± SD	2.85 ± 3.54	2.0 ± -	2.79 ± 3.41	0.616 ns
95 % CI	0.71 – 4.99	-	0.82 – 4.76	
Biologic therapy use				
No	66 (89.2%)	10 (83.3%)	76 (88.4%)	0.557 ns
Yes	8 (10.8%)	2 (16.7%)	10 (11.6%)	
Duration of use (years) Mean ± SD	2.51 ±3.57	3.50 ± 3.54	2.73 ± 3.37	0.419 ns
95 % CI	–0.62 - 7.37	23.41 - 27.41	–1.36 - 7.36	

Patient groups are defined as RA without PF (RA patients without Pulmonary Fibrosis), RA with PF (RA patients with Pulmonary Fibrosis), and All RA (Total RA patients). Data are presented with 'n' for sample size, '%' for percentage, and 'SD' for standard deviation. The numerical data were analyzed using the Mann-Whitney U test, and categorical variables via the Chi-square test.

Multivariable Logistic Regression of Risk Factors for Pulmonary Fibrosis in Rheumatoid Arthritis Patients

In the multivariable logistic regression analysis, methotrexate use was associated with a markedly increased—but statistically non-significant—risk of pulmonary fibrosis (adjusted OR = 7.6, 95% CI 0.894-64.646; p = 0.063). Age, modeled as a continuous variable, showed no meaningful association with pulmonary fibrosis (adjusted OR = 1.00, 95% CI 0.95–1.053; p = 0.991). Female sex demonstrated a protective but imprecise effect (adjusted OR = 0.367, 95% CI 0.053–2.536; p = 0.310). Disease duration greater than five years appeared to confer increased odds of pulmonary fibrosis, though this association also did not achieve statistical significance (adjusted OR = 2.337, 95% CI 0.562–9.722; p = 0.243). (Table 4).

Table 4. Multivariable Logistic Regression of Risk Factors for Pulmonary Fibrosis in Rheumatoid Arthritis Patients.

Variable	Adjusted OR	95% CI (low)	95% CI (high)	P value
Methotrexate use (yes vs no)	7.6	0.894	64.646	0.063
Age (per year)	1	0.95	1.053	0.991
Gender (Female vs male)	0.367	0.053	2.536	0.31
Disease duration (>5yaers vs ≤ 5 years)	2.337	0.562	9.722	0.243

Radiological Findings and Interstitial Patterns in RA Patients

As shown in Figure 1, the bar chart representation demonstrated that pulmonary fibrosis (PF) was identified in 14.0% of patients in the study (12 out of 86), while the remaining 86.0% showed no fibrotic changes.

Ground-glass opacities were reported in 15.1% of patients (13 out of 86), whereas 84.9% did not exhibit this radiological feature. Similarly, nodular patterns were observed in 14.0% of participants, with 86.0% showing no nodular involvement. These frequencies reflect the distribution of key interstitial changes among patients with RA included in the present analysis.

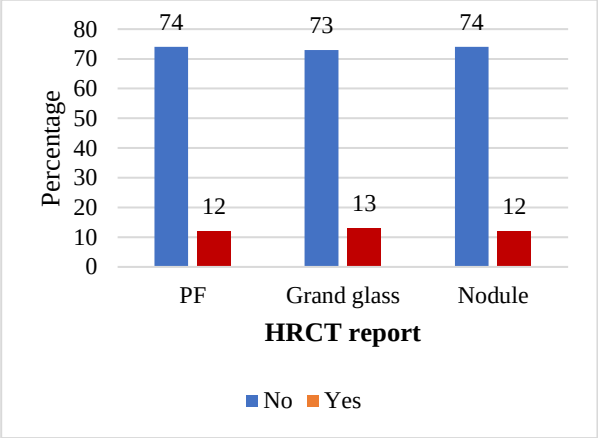

Figure 1. Radiological findings in RA patients. PF was defined by ATS/ERS HRCT criteria. Bars show as percentage. The most frequent HRCT pattern consistent with pulmonary fibrosis (14%) was reticulation and traction bronchiectasis. Ground-glass opacities (15.1%) and nodular patterns (14%) were also observed but were not used alone to define fibrosis.

Discussion

RA frequently involves extra-articular organs, with interstitial lung disease (ILD) recognized as one of the most dangerous problems. Among the ILD subtypes, pulmonary fibrosis (PF) stands out as a major contributor to increased morbidity and mortality, especially in those patients suffering from longstanding disease and seropositivity for rheumatoid factor or anti-cyclic citrullinated peptide (anti-CCP) antibodies (24, 25).

Methotrexate (MTX) is a cornerstone of RA treatment, some studies report no strong association, while others advise caution in patients with underlying or subclinical lung disease (26). This study examined the association between pulmonary fibrosis and methotrexate (MTX) use in RA, aiming to identify prevalence, risk factors, and treatment-related patterns of lung involvement.

In our study of 86 patients diagnosed with rheumatoid arthritis (RA), we observed a 14.0% prevalence of pulmonary fibrosis (PF). This finding aligns with previous research, including a multicenter Italian cross-sectional study by Manfredi et al. (2024), which reported a 38.8% prevalence of progressive pulmonary fibrosis among 156 RA-ILD patients, emphasizing the association with usual interstitial pneumonia patterns (27). Also, Shaw et al. (2015) noted that pulmonary involvement is common in RA, affecting 60-80% of individuals, and can progress to irreversible PF (28). Studies using HRCT have shown the prevalence of RA-ILD, which can progress to PF, to range from 10% to 60% in RA patients, with some HRCT-based studies showing subclinical ILD in up to 50% of patients (29, 30).

Our findings highlight key sociodemographic, clinical, and treatment-related differences between RA patients with and without pulmonary fibrosis, with older age emerging as one of the most notable factors associated with PF. This observation is consistent with a substantial body of literature that consistently identifies advanced age as a prominent risk factor for the development of RA-ILD. For instance, Sparks et al. (2019) conducted a prospective cohort study and found that older age significantly predicted incident clinically apparent RA-ILD, with a hazard ratio of 1.04 per year of age (95% CI 1.02-1.06) (31). Similarly, Casal et al. (2014) reported in their study of 1,000 RA patients that increasing age was a significant risk factor for RA-ILD prevalence and mortality, with a mean age of 66 years in their RA-ILD cohort and a 10-year

survival rate of 39% for those with RA-ILD (32).

In this study, women made up the majority of RA patients, but pulmonary fibrosis was relatively more frequent in men, supporting previous evidence that males with RA are disproportionately affected by pulmonary complications. Sokka et al. (2009), in their cross-national QUEST-RA study, observed that male patients had a higher frequency of extra-articular manifestations, including ILD, despite lower overall RA prevalence (33). Similarly, Assayag et al. (2014) highlighted male sex as a significant risk factor for RA-associated interstitial lung disease (RA-ILD), underscoring a gender-specific susceptibility to fibrotic pulmonary manifestations (24).

Our findings revealed that, patients with pulmonary fibrosis tended to have longer RA duration, suggesting that prolonged disease may contribute to pulmonary involvement, which was consistent with the study of Yuhei Ito et al., which demonstrated that **longer RA disease duration was significantly associated with greater radiological severity of interstitial lung disease (ILD)** in patients with RA (34). Similarly, Zhang et al. (2023) reported in their meta-analysis that longer RA duration was a significant risk factor for ILD (OR 1.05, 95% CI 1.02-1.08). Chronic inflammation and persistent immune activation over time could lead to cumulative lung damage and subsequent fibrosis (35). Interestingly, while seropositivity for RF and anti-CCP antibodies is are known risk factor for RA-ILD, as highlighted by Sparks et al. (2019), who found anti-CCP antibodies to be associated with ILD in RA patients, with a prevalence of 30% in their ILD cohort. (31).

Our analysis of inflammatory markers (ESR and CRP) was higher in RA patients with pulmonary fibrosis, underscoring the role of systemic inflammation in the development of RA-associated lung disease. A study by Jeong Seok Lee et al. explored longitudinal changes in RA-associated interstitial lung disease (RA-ILD) using quantitative high-resolution computed tomography (HRCT) scores. They found that higher HRCT-derived quantitative ILD (QILD) scores reflecting the extent of ground-glass opacities, fibrosis, and honeycombing were significantly correlated with reduced pulmonary function (notably DLCO%) and elevated serum levels of Krebs von den Lungen-6, an inflammatory biomarker (36).

Crucially, our study investigated the Methotrexate use was more common among RA patients with pulmonary fibrosis. However, this association did not reach statistical significance, and CIs were wide, indicating imprecision; thus, these findings should be interpreted cautiously. Dawson et al. (2021), in their systematic review of 29 studies encompassing over 2,000 RA patients, reported that higher-quality studies did not support a causal relationship between MTX and fibrotic interstitial lung disease (ILD), and even proposed a possible protective effect in RA-ILD progression (37). Our observational findings may reflect confounding by indication: patients with longer or more active RA are more likely to receive MTX and are also more susceptible to lung involvement. The wide CIs and nonsignificant aORs underscore imprecision and limit causal inference.

Our data showed no difference in the mean duration of methotrexate use between patients with and without pulmonary fibrosis, which further complicates a direct causal interpretation. This aligns with a growing body of recent evidence that challenges the long-held suspicion of MTX as a primary causative agent for chronic fibrotic RA-ILD. Many contemporary studies, including meta-analyses by Conway et al. (2014) (who found no increased risk of ILD with MTX use in randomized controlled trials, with a pooled relative risk of 0.99, 95% CI 0.77-1.28) (38).

Conclusions

In this cross-sectional sample, MTX use

showed higher odds of PF without statistical significance. The results are exploratory and should not be taken as evidence of a causal effect. While methotrexate remains central in RA management, careful pulmonary monitoring is advised. Future longitudinal studies with larger populations are needed to determine causality and clarify the true impact of methotrexate on lung outcomes.

Recommendations

Clinicians should exercise caution when prescribing methotrexate (MTX) for RA patients with long-standing disease or high inflammatory activity, and ensure routine pulmonary surveillance through regular imaging (X-ray or HRCT when indicated) and systematic monitoring for respiratory symptoms. Future large, longitudinal, multicenter studies are needed to validate these findings, clarify causal pathways, and assess dose–response relationships. Ultimately, treatment decisions should be individualized, taking into account disease duration, systemic inflammation, and patient comorbidities to optimize RA management while minimizing pulmonary risk.

Limitations

The present study is limited in its ability to make causal inferences because of its cross-sectional design. There could have been selection bias, since only those who were willing participated. Potential selection and residual bias of confounding in terms of environmental exposures and concomitant diseases were not completely controlled. Furthermore, the sensitivity of HRCT to diagnose PF can intrinsically lead to differences. Lastly, because no formal power calculation was conducted and event counts were low, the study may be underpowered to detect modest associations.

Conflict of interest

The authors declare that there is no conflict of interest related to this work

Funding

No funding was received for this study

References

1. Atzeni F, Boiardi L, Salli S, Benucci M, Sarzi-Puttini P. Lung involvement and drug-induced lung disease in patients with rheumatoid arthritis. Expert Rev Clin Immunol. (2013);9(7):649-57. https://doi.org/10.1586/1744666X.2013.811173.
2. Shaw M, Collins BF, Ho LA, Raghu G. Rheumatoid arthritis-associated lung disease. Eur Respir Rev. (2015);24(135):1-16. https://doi.org/10.1183/09059180.00008014.
3. Al-Rubaye AF, Kadhim MJ, Hameed IH. Rheumatoid arthritis: History, stages, epidemiology, pathogenesis, diagnosis and treatment. International Journal of Toxicological and Pharmacological Research. (2017);9(2):145-55.
4. Alivernini S, Firestein GS, Mcinnes IB. The pathogenesis of rheumatoid arthritis. Immunity. (2022);55(12):2255-70. https://doi.org/10.1016/j.immuni.2022.11.009.
5. Valentini V, Valentini E, La Paglia G, Bonifacio A, Gerli R. Extra-articular rheumatoid arthritis. Reumatismo. (2018);70(4):212-24. https://doi.org/10.4081/reumatismo.2018.1106.
6. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, et al. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. Autoimmun Rev. (2021);20(2):102735. https://doi.org/10.1016/j.autrev.2020.102735.
7. Kanat F, Levendoglu F, Teke T. Radiological and functional assessment of pulmonary involvement in the rheumatoid arthritis patients. Rheumatol Int. (2007);27(5):459-66. https://doi.org/10.1007/s00296-006-0234-0.
8. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. Rheum Dis Clin North Am. (2015);41(2):225-36. https://doi.org/10.1016/j.rdc.2014.12.004.
9. Kalchiem-Dekel O, Galvin JR, Burke AP, Atamas SP, Todd NW. Interstitial lung disease and pulmonary fibrosis: A practical approach for general medicine physicians with focus on the medical history. J Clin Med. (2018);7(12):476. https://doi.org/10.3390/jcm7120476.
10. Juge PA, Lee JS, Lau J, Kawano-Dourado L, Rojas Serrano J, Sebastiani M, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. Eur Respir J. (2021);57(2). https://doi.org/10.1183/13993003.00337-2020.
11. Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: Manifestations and current

concepts in pathogenesis and management. Eur Respir Rev. (2021);30(160). https://doi.org/10.1183/16000617.0011-2021.
12. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: A prospective cohort study. Arthritis Rheumatol. (2019);71(9):1472-82. https://doi.org/10.1002/art.40904.
13. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official american thoracic society/european respiratory society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. (2013);188(6):733-48. https://doi.org/10.1164/rccm.201308-1483ST.
14. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. (2006);174(7):810-6. https://doi.org/10.1164/rccm.200602-163OC.
15. Schoels M, Knevel R, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: Results of a systematic literature search. Ann Rheum Dis. (2010);69(4):638-43. https://doi.org/10.1136/ard.2009.123976.
16. Pincus T, Yazici Y, Sokka T, Aletaha D, Smolen J. Methotrexate as the" anchor drug" for the treatment of early rheumatoid arthritis. Clinical and experimental rheumatology. (2003);21(5; SUPP 31):179-85.
17. Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate in rheumatoid arthritis: Optimizing therapy among different formulations. Current and emerging paradigms. Clinical therapeutics. (2014);36(3):427-35. https://doi.org/10.1016/j.clinthera.2014.02.014.
18. Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 american college of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis & rheumatology. (2016);68(1):1-26. https://doi.org/10.1002/art.39480.
19. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. Eular recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. (2017);76(6):960-77. https://doi.org/10.1136/annrheumdis-2016-210715.
20. Antin-Ozerkis D, Evans J, Rubinowitz A, Homer RJ, Matthay RA. Pulmonary manifestations of rheumatoid arthritis. Clin Chest Med. (2010);31(3):451-78. https://doi.org/10.1016/j.ccm.2010.04.003.
21. Sebastiani M, Manfredi A, Cerri S, Della Casa G, Luppi F, Ferri C. Radiologic classification of usual interstitial pneumonia in rheumatoid arthritis-related interstitial lung disease: Correlations with clinical, serological and demographic features of disease. Clin Exp Rheumatol. (2016);34(3):564-5.
22. Kiely P, Busby A, Nikiphorou E, Sullivan K, Walsh D, Creamer P, 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(5):e028466. https://doi.org/10.1136/bmjopen-2018-028466.
23. Van Der Linden MP, Knevel R, Huizinga TW, Van Der Helm-Van Mil AH. Classification of rheumatoid arthritis: Comparison of the 1987 american college of rheumatology criteria and the 2010 american college of rheumatology/european league against rheumatism criteria. Arthritis Rheum. (2011);63(1):37-42. https://doi.org/10.1002/art.30100.
24. Assayag D, Lee JS, King TE, Jr. Rheumatoid arthritis associated interstitial lung disease: A review. Medicina (B Aires). (2014);74(2):158-65.
25. Fragoulis GE, Nikiphorou E, Larsen J, Korsten P, Conway R. Methotrexate-associated pneumonitis and rheumatoid arthritis-interstitial lung disease: Current concepts for the diagnosis and treatment. Front Med (Lausanne). (2019);6:238. https://doi.org/10.3389/fmed.2019.00238.
26. Ibfelt EH, Jacobsen RK, Kopp TI, Cordtz RL, Jakobsen AS, Seersholm N, et al. Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: A nationwide population-based study. Rheumatology (Oxford). (2021);60(1):346-52. https://doi.org/10.1093/rheumatology/keaa327.
27. Manfredi A, Venerito V, Cazzato M, Sambataro G, Zanini U, Gozzi F, et al. Pulmonary progressive fibrosis in rheumatoid arthritis and primary sjogren syndrome: Similarities and differences. J Clin Med. (2024);13(21). https://doi.org/10.3390/jcm13216508.
28. Shaw M, Collins BF, Ho LA, Raghu G. Rheumatoid arthritis-associated lung disease. European Respiratory Review. (2015);24(135):1.
29. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. Rheumatic diseases clinics of North America. (2015);41(2):225.
30. Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: Manifestations and current concepts in pathogenesis and management. European Respiratory Review. (2021);30(160).
31. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid

arthritis disease activity predicting incident clinically apparent rheumatoid arthritis–associated interstitial lung disease: A prospective cohort study. Arthritis & Rheumatology. (2019);71(9):1472-82.

32. Casal A, Suárez-Antelo J, Riveiro V, Ferreiro L, Rodríguez-Núñez N, Toubes ME, et al. Smoking-related interstitial lung disease: A narrative review. Chronic Respiratory Disease. (2024);21:14799731241291538.
33. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: Analyses of disease activity, disease characteristics, and treatments in the quest-ra study. Arthritis Res Ther. (2009);11(1):R7. https://doi.org/10.1186/ar2591.
34. Ito Y, Ichikawa Y, Murashima S, Sakuma H, Nakajima A. Rheumatoid arthritis disease activity significantly impacts on the severity of interstitial lung disease. Arthritis Research & Therapy. (2024);26(1):95.
35. Zhang M, Yin J, Zhang X. Factors associated with interstitial lung disease in patients with rheumatoid arthritis: A systematic review and meta-analysis. PLoS One. (2023);18(6):e0286191. https://doi.org/10.1371/journal.pone.0286191.
36. Lee JS, Kim GJ, Ha YJ, Kang EH, Lee YJ, Goldin JG, et al. The extent and diverse trajectories of longitudinal changes in rheumatoid arthritis interstitial lung diseases using quantitative hrct scores. J Clin Med. (2021);10(17):3812. https://doi.org/10.3390/jcm10173812.
37. Dawson JK, Quah E, Earnshaw B, Amoasii C, Mudawi T, Spencer LG. Does methotrexate cause progressive fibrotic interstitial lung disease? A systematic review. Rheumatol Int. (2021);41(6):1055-64. https://doi.org/10.1007/s00296-020-04773-4.
38. Conway R, Low C, Coughlan RJ, O'donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis: A meta-analysis of randomized controlled trials. Arthritis Rheumatol. (2014);66(4):803-12. https://doi.org/10.1002/art.38322.