

## **Pulmonary Manifestations in Patients with Rheumatoid Arthritis Visiting Mardan Medical Complex Mardan, kpk**

**<sup>1</sup>Dr. Nabi Rahman, <sup>2</sup>Dr. Hamidullah, <sup>3</sup>Dr. Qasim Nawaz, <sup>4</sup>Dr. Amjad Ali, <sup>5</sup>Dr. Muhammad Qasim Khan, <sup>6</sup>Dr. Shah Muhammad Khan**

<sup>1</sup>Assistant Professor, Bacha Khan Medical College, Mardan Medical Complex, Mardan

<sup>2</sup>Assistant Professor, Bacha Khan Medical College, Mardan, Medicine Department, FCPS Medicine

<sup>3</sup>Assistant Professor Pulmonology, Gajju Khan Complex, Swabi

<sup>4</sup>Professor of Medicine, BKMC/MMC, Mardan

<sup>5</sup>Professor of Paediatrics, BKMC/MMC, Mardan

<sup>6</sup>Professor of Pharmacology, Rai Foundation Medical College, Sargodha

### **Corresponding Author: Dr. Hamidullah**

Assistant Professor, Bacha Khan Medical College, Mardan, Medicine Department, FCPS Medicine

## **Abstract**

### **Background:**

Rheumatoid arthritis (RA) often causes pulmonary symptoms, which are often overlooked yet greatly increase patient morbidity and death.

### **Objective:**

To determine the frequency and types of pulmonary manifestations in patients with RA attending a Mardan Medical Complex Mardan, kpk.

### **Methodology:**

This cross-sectional observational study was conducted at the Rheumatology and Pulmonology Departments of Mardan Medical Complex, Pakistan, from January to December 2023. The study used nonprobability convenience sampling to recruit 218 RA patients who met the ACR/EULAR 2010 criteria. Patients with lung issues linked to smoking or non-RA-related lung illnesses were not included. Clinical assessment, chest X-rays, pulmonary function tests, and high-resolution computed tomography (HRCT) where necessary were used to gather data. Demographic and clinical variables were described using

descriptive statistics, and the Chi-square test was used to evaluate the relationships between pulmonary involvement and clinical parameters; a p-value of less than 0.05 was deemed significant.

### **Results:**

Of the 218 patients, the majority (39.45%) were between the ages of 46 and 60, and 71.56% were female. Of the patients, 50.46% had pulmonary symptoms. The most frequent symptom was interstitial lung disease (ILD) (22.02%), which was followed by methotrexate-induced pneumonitis (3.21%), pleural effusion (9.63%), pulmonary nodules (6.42%), bronchiolitis (5.05%), and pulmonary hypertension (4.13%). Age group ( $p = 0.041$ ) and RA duration ( $p = 0.005$ ) were strongly correlated with pulmonary involvement, but not with gender or methotrexate usage.

### **Conclusion:**

Pulmonary involvement in RA is frequent and significantly associated with older age and longer disease duration, necessitating early screening and multidisciplinary management.

### **Keywords:**

Rheumatoid arthritis, pulmonary manifestations, interstitial lung disease, methotrexate, Pakistan, tertiary care.

### **Introduction**

The prevalence of rheumatoid arthritis (RA), a chronic, systemic inflammatory illness that mostly manifests as symmetrical polyarthritis, ranges from 0.5% to 1% worldwide [1]. Although the illness mostly affects synovial joints, its extra-articular symptoms, such as lung damage, are becoming more well acknowledged [2]. In RA, pulmonary involvement may occur before or at the same time as joint symptoms, and it greatly increases patient morbidity and death [3]. Among the various pulmonary diseases [4] are interstitial lung disease (ILD), pleural effusion, pulmonary nodules, bronchiolitis, and pulmonary hypertension. These problems may stay subclinical for extended periods of time, usually undetectable until they interfere with functioning or show up on routine imaging [5].

The etiology of pulmonary involvement in RA is multifarious. It covers environmental exposures like smoking, genetic predispositions (including HLA-DR4), immune-mediated inflammation, and adverse

effects of disease-modifying antirheumatic drugs (DMARDs [6]). Fascinatingly, a pillar of RA therapy, methotrexate has been related in certain patients to methotrexate-induced fibrosis and pneumonitis [7]. Furthermore promoted by ongoing systemic inflammation driven by cytokines such as TNF- $\alpha$  and IL-6 are fibrotic changes and pulmonary tissue remodeling [8].

Early diagnosis and monitoring of pulmonary issues are prerequisites for optimizing patient outcomes in RA. Clinical diagnosis of these presentations is still challenging, nevertheless, as respiratory symptoms may be modest or misinterpreted for another disease [9]. While high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) are valuable tools for evaluating lung involvement, their routine usage is usually limited in settings with low resources [10]. Moreover, regional, ethnic, and healthcare access all influence the incidence and pattern of pulmonary symptoms; thus, region-specific data are needed to guide clinical judgement [11].

Given that RA is often treated in tertiary care facilities, very little is known about the pulmonary effects of the disease in Pakistan. Lack of information and diagnostic limitations might lead to inadequate treatment, delayed diagnosis, or underreporting. Therefore, it is important to evaluate the kind and frequency of pulmonary symptoms among RA patients in local clinical environments in order to improve diagnosis knowledge and guide therapy regimens.

## **Research Objective**

To ascertain the prevalence and forms of pulmonary symptoms in RA patients visiting a Mardan Medical Complex Mardan, kpk

## **Methodology**

### **Study Design and Setting**

This was a cross-sectional observational study conducted at the Rheumatology and Pulmonology Departments of Mardan Medical Complex, Mardan, Pakistan. The research was conducted throughout one year, from January 2023 to December 2023.

## **Inclusion and Exclusion Criteria**

Included were individuals who visited outpatient or inpatient departments and were at least eighteen years old and had a confirmed diagnosis of RA based on the 2010 ACR/EULAR diagnostic criteria. Patients not included were those having a history of pre-existing non-RA-related pulmonary diseases like COPD, asthma, or TB as well as smoking-related lung illness. Participants without clinical records or those who refused to provide informed consent were also rejected in order to preserve the reliability and ethical integrity of the research.

## **Sample Size**

218 individuals in all were enrolled using a simple non-probability sampling technique. Selected depending on patient availability across the study period, the sample size was sufficient to provide a realistic picture of pulmonary symptoms in RA among the patient population of the hospital.

## **Data Collection**

Following informed permission, a systematic proforma was used to collect demographic information, clinical history, and pertinent physical examination results. Clinical examination, chest X-ray, PFTs, and HRCT were all part of the pulmonary assessment. ILD, pleural effusion, pulmonary nodules, bronchiolitis, pulmonary hypertension, and other pertinent findings were categorized as pulmonary symptoms.

## **Statistical Analysis**

SPSS version 25 was used for data entry and analysis. The data was compiled using descriptive statistics. Frequencies and percentages were used to display categorical information, such as the different kinds of pulmonary symptoms. Age and other continuous data were presented as means and standard deviations. Chi-square was used to evaluate relationships between clinical parameters and lung involvement; a p-value of less than 0.05 was deemed statistically significant.

**Ethical Approval**

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of Mardan Medical Complex, Mardan, Pakistan. Written informed consent was obtained from all participants prior to data collection. Confidentiality and anonymity were maintained throughout the study.

**Results**

The clinical and demographic details of the 218 RA patients who were included in the trial are reported in Table 1. Women made up 71.56% of the population, while men made up 28.44%. 39.45% of the patients were between the ages of 46 and 60, and 33.03 percent were between the ages of 31 and 45. Regarding the length of the illness, 43.58% of patients had RA for more than five years, while 47.71% had it for one to five years. 82.11% of patients were using methotrexate as part of their treatment plan.

Table 1: Demographic and Clinical Characteristics of Patients (n = 218)

Variable		Frequency (n)	Percentage (%)
Gender	Male	62	28.44
	Female	156	71.56
Age Group (years)	18–30	28	12.84
	31–45	72	33.03
	46–60	86	39.45
	>60	32	14.68
Duration of RA	<1 year	19	8.72
	1–5 years	104	47.71
	>5 years	95	43.58
Use of Methotrexate	Yes	179	82.11
	No	39	17.89

The frequency and kinds of pulmonary symptoms seen in RA patients are shown in Figure 1. The majority (49.54%) showed no signs of pulmonary involvement. The most prevalent condition among those impacted was ILD (22.02%), which was followed by methotrexate-induced pneumonitis (3.21%), pleural effusion (9.63%), pulmonary nodules (6.42%), bronchiolitis (5.05%), and pulmonary hypertension (4.13%).

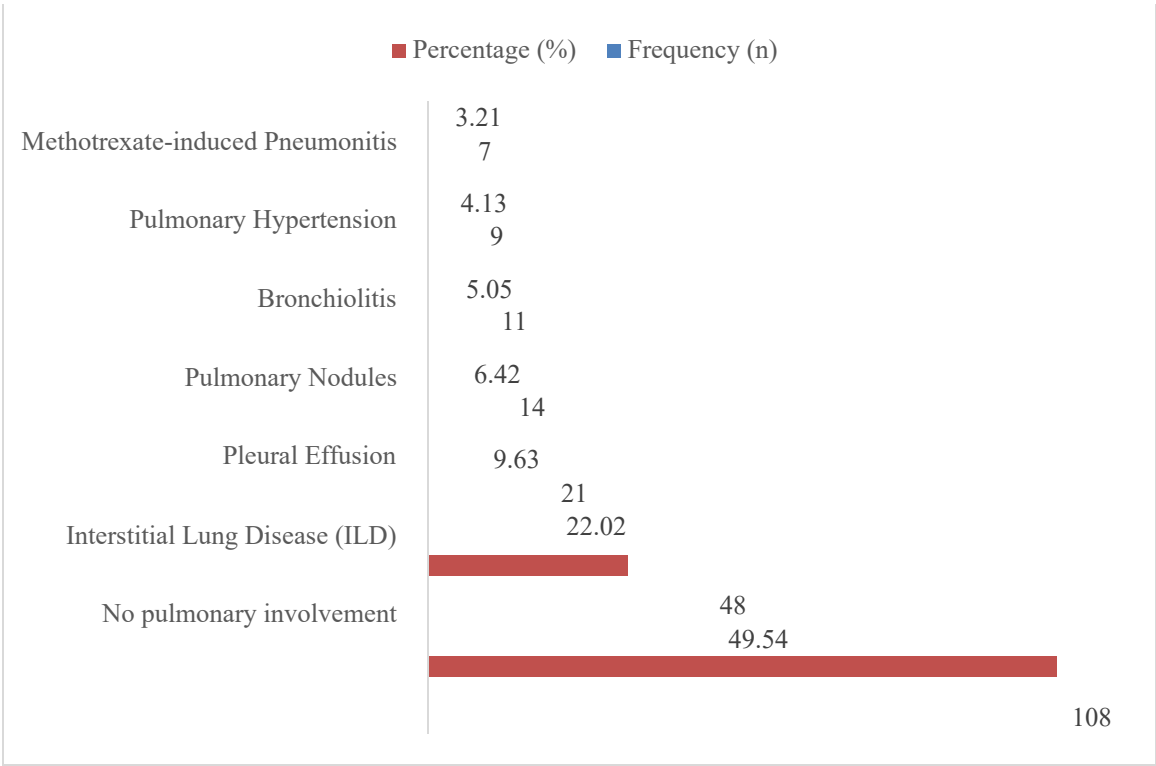


Figure 1: Frequency and Types of Pulmonary Manifestations in RA Patients (n = 218)

Of the 110 individuals with pulmonary symptoms, Figure 2 shows the pulmonary involvement by gender. Males were more likely than females to have pulmonary involvement (54.84% vs 48.72%), although the difference was not statistically significant.

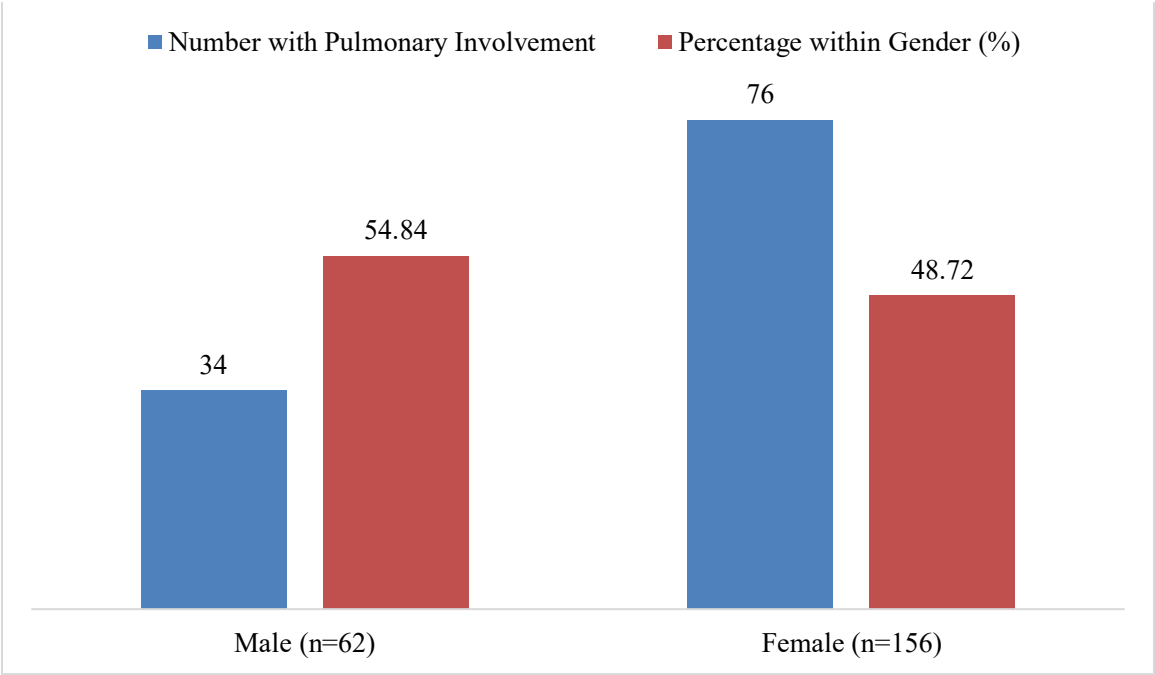


Figure 2: Pulmonary Involvement by Gender (n = 110 with Pulmonary Involvement)

The association between pulmonary involvement and RA duration is seen in Figure 3. Patients with RA for more than five years had a higher prevalence of pulmonary problems (69.47%), followed by those with RA for one to five years (39.42%), and those with RA for less than a year (15.79%).

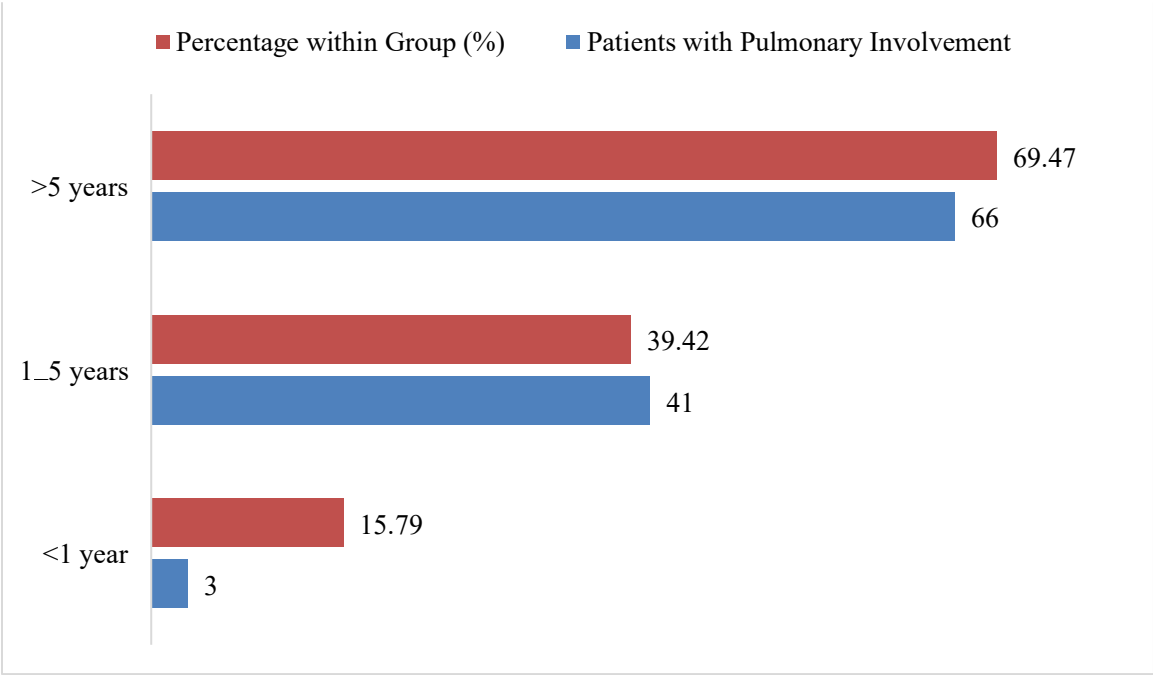


Figure 3: Pulmonary Involvement by Duration of RA (n = 110 with Pulmonary Involvement)

The statistical relationship between clinical indicators and pulmonary involvement is evaluated in Table 2. Age group ( $p = 0.041$ ) and RA duration ( $p = 0.005$ ) showed significant relationships, suggesting that lung problems are more likely to occur in older adults and those with longer illness durations. Methotrexate usage ( $p = 0.114$ ) and gender ( $p = 0.327$ ) did not significantly correlate.

Table 2: Association Between Clinical Parameters and Pulmonary Involvement (n = 218)

Clinical Parameter		Pulmonary Involvement Present (n = 110)	Pulmonary Involvement Absent (n = 108)	pvalue	Statistical Significance
Gender	Male (n = 62)	34 (54.84%)	28 (45.16%)	0.327	Not Significant
	Female (n = 156)	76 (48.72%)	80 (51.28%)		
Age Group	18–30 (n = 28)	6 (21.43%)	22 (78.57%)	0.041*	Significant
	31–45 (n = 72)	28 (38.89%)	44 (61.11%)		

	46–60 (n = 86)	52 (60.47%)	34 (39.53%)		
	>60 (n = 32)	24 (75.00%)	8 (25.00%)		
Duration of RA	<1 year (n = 19)	3 (15.79%)	16 (84.21%)	0.005*	<b>Significant</b>
	1–5 years (n = 104)	41 (39.42%)	63 (60.58%)		
	>5 years (n = 95)	66 (69.47%)	29 (30.53%)		
Methotrexate Use	Yes (n = 179)	86 (48.04%)	93 (51.96%)	0.114	Not Significant
	No (n = 39)	24 (61.54%)	15 (38.46%)		

## Discussion

A well-known but sometimes overlooked consequence of RA, especially in settings with limited resources, is pulmonary involvement. The most common pulmonary symptom in our research was ILD, which was seen in 50.46% of RA patients (22.02%). According to previous publications, ILD is the most frequent pulmonary consequence in RA, with a frequency that varies from 10% to 20% based on the demographic and diagnostic method [12]. This conclusion is consistent with those findings. For example, Zou et al. used HRCT to describe ILD in 19% of RA patients, which is similar to what we found [13].

9.63% of the individuals in our cohort had pleural effusion. Previous studies revealing pleural effusion in 10% of RA patients had practically exact results similar to these [14]. Reduced incidence in our study might have resulted from early use of disease-modifying antirheumatic drugs (DMARDs), particularly methotrexate, and simpler access to medical treatment. Pulmonary nodules were detected in 6.42% of patients, virtually in accordance with the results of previous studies [15]. Like in our studies, these frequently accidental nodules may not produce any symptoms. Though less prevalent, clinically important symptoms were bronchiolitis (5.05%) and pulmonary hypertension (4.13%). 3.21% of our patients had methotrexate-induced pneumonitis, which is almost in line with the results of the earlier research [16].

We found a statistically significant correlation between pulmonary involvement and RA duration ( $p = 0.005$ ) as well as age group ( $p = 0.041$ ). The greatest incidence of pulmonary symptoms (75%), seen in patients aged 60 and above, supports earlier findings that show aging is a risk factor for lung involvement

because of the cumulative inflammatory load [17]. Likewise, a 69.47% frequency of pulmonary problems was seen in individuals with RA for more than five years, supporting earlier results that prolonged illness duration was associated with higher lung involvement [18].

It's interesting to note that, although being taken by 82.11% of patients, methotrexate usage did not significantly correlate with pulmonary involvement ( $p = 0.114$ ). This might be the result of cautious patient selection and observation, which lowers the risk of unfavorable pulmonary outcomes. Additionally, gender did not substantially correlate with lung symptoms ( $p = 0.327$ ), even though a greater percentage of men (54.84%) had them. Results from earlier research on the impact of gender have been conflicting; some have shown that environmental exposures like smoking increase risk in men [19].

### **Study Strengths and Limitations**

This study's reasonably high sample size ( $n = 218$ ) and inclusion of thorough lung evaluations utilizing both imaging and functional assessments are among its main advantages. These factors improve the study's capacity to reliably detect different pulmonary symptoms in RA patients. In order to ensure thorough clinical evaluations, the research was carried out in a tertiary care facility with multidisciplinary input from the pulmonology and rheumatology departments. Additionally, it provides region-specific data from Pakistan, where illness trends may be influenced by local epidemiology and healthcare accessibility. The cross-sectional form of the research, however, limits its ability to evaluate causation or change over time. The exclusion of smokers, although methodologically sound, may restrict generalizability to other RA groups, and the use of non-probability convenience sampling may add selection bias. Furthermore, the accuracy of identifying subclinical illness may have been impacted by restricted availability to sophisticated imaging (such as HRCT for all patients) and the need for clinical judgment for some diagnosis.

### **Conclusion**

ILD is the most frequent consequence, followed by pleural effusion and lung nodules, as this research shows that pulmonary symptoms are common in RA patients. The need of early respiratory screening and careful long-term surveillance in the therapy of RA was underscored by the substantial correlation seen between lung involvement and older age and longer illness duration. Clinical awareness of possible drug-related lung toxicity is nevertheless crucial, even if methotrexate usage was not substantially associated with

pulmonary problems in this group. The results highlight the need of proactive diagnostic procedures, particularly in healthcare settings with limited resources.

## References

1. 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. [https://www.researchgate.net/profile/Imad-Hameed/publication/319421622\\_Rheumatoid\\_Arthritis\\_History\\_Stages\\_Epidemiology\\_Pathogenesis\\_Diagnosis\\_and\\_Treatment/links/59b8d0ebaca2724161893d2a/Rheumatoid-ArthritisHistory-Stages-Epidemiology-Pathogenesis-Diagnosis-and-Treatment.pdf](https://www.researchgate.net/profile/Imad-Hameed/publication/319421622_Rheumatoid_Arthritis_History_Stages_Epidemiology_Pathogenesis_Diagnosis_and_Treatment/links/59b8d0ebaca2724161893d2a/Rheumatoid-ArthritisHistory-Stages-Epidemiology-Pathogenesis-Diagnosis-and-Treatment.pdf).
2. Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, Giacomelli R, Cipriani P. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. *Autoimmunity reviews*. 2021 Feb 1;20(2):102735. <https://doi.org/10.1016/j.autrev.2020.102735>.
3. Wang D, Zhang J, Lau J, Wang S, Taneja V, Matteson EL, Vassallo R. Mechanisms of lung disease development in rheumatoid arthritis. *Nature Reviews Rheumatology*. 2019 Oct;15(10):581-96. <https://doi.org/10.1038/s41584-019-0275-x>.
4. Kadura S, Raghu G. Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. *European Respiratory Review*. 2021 Jun 23;30(160). <https://doi.org/10.1183/16000617.0011-2021>.
5. Sommer OJ, Kladosek A, Weiler V, Czemberek H, Boeck M, Stiskal M. Rheumatoid arthritis: a practical guide to state-of-the-art imaging, image interpretation, and clinical implications. *Radiographics*. 2005 Mar;25(2):381-98. <https://doi.org/10.1148/rg.252045111>.
6. Alivernini S, Firestein GS, McInnes IB. The pathogenesis of rheumatoid arthritis. *Immunity*. 2022 Dec 13;55(12):2255-70. <https://doi.org/10.1016/j.immuni.2022.11.009>.
7. 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. *Frontiers in medicine*. 2019 Oct 23;6:238. <https://doi.org/10.3389/fmed.2019.00238>.
8. Shrivastava AK, Pandey A. Inflammation and rheumatoid arthritis. *Journal of physiology and biochemistry*. 2013 Jun;69:335-47. <https://doi.org/10.1007/s13105-012-0216-5>.
9. Koduri G, Solomon JJ. Identification, monitoring, and management of rheumatoid arthritis-associated interstitial lung disease. *Arthritis & Rheumatology*. 2023 Dec;75(12):2067-77. <https://doi.org/10.1002/art.42640>.
10. Zrour SH, Touzi M, Bejia I, Golli M, Rouatbi N, Sakly N, Younes M, Tabka Z, Bergaoui N. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis: prospective study in 75 patients. *Joint bone spine*. 2005 Jan 1;72(1):41-7. <https://doi.org/10.1016/j.jbspin.2004.02.001>.
11. Strait A, Castillo F, Choden S, Li J, Whitaker E, Falasinnu T, Schmajuk G, Yazdany J. Demographic characteristics of participants in rheumatoid arthritis randomized clinical trials: a systematic review. *JAMA network open*. 2019 Nov 1;2(11):e1914745-. doi:10.1001/jamanetworkopen.2019.14745.

12. Huang S, Kronzer VL, Dellaripa PF, Deane KD, Bolster MB, Nagaraja V, Khanna D, Doyle TJ, Sparks JA. Rheumatoid arthritis–associated interstitial lung disease: current update on prevalence, risk factors, and pharmacologic treatment. Current treatment options in rheumatology. 2020 Dec;6:337-53. <https://doi.org/10.1007/s40674-020-00160-z>.
13. Zou YQ, Li YS, Ding XN, Ying ZH. The clinical significance of HRCT in evaluation of patients with rheumatoid arthritis-associated interstitial lung disease: a report from China. Rheumatology international. 2012 Mar;32(3):669-73. <https://doi.org/10.1007/s00296-010-1665-1>.
14. Antin-Ozerkis D, Evans J, Rubinowitz A, Homer RJ, Matthay RA. Pulmonary manifestations of rheumatoid arthritis. Clinics in chest medicine. 2010 Sep 1;31(3):451-78. DOI: [10.1016/j.ccm.2010.04.003](https://doi.org/10.1016/j.ccm.2010.04.003).
15. Anaya JM, Diethelm L, Ortiz LA, Gutierrez M, Citera G, Welsh RA, Espinoza LR. Pulmonary involvement in rheumatoid arthritis. In Seminars in arthritis and rheumatism 1995 Feb 1 (Vol. 24, No. 4, pp. 242-254). WB Saunders. [https://doi.org/10.1016/S0049-0172\(95\)80034-4](https://doi.org/10.1016/S0049-0172(95)80034-4).
16. Salaffi F, Manganelli P, Carotti M, Subiaco S, Lamanna G, Cervini C. Methotrexate-induced pneumonitis in patients with rheumatoid arthritis and psoriatic arthritis: report of five cases and review of the literature. Clinical rheumatology. 1997 May;16:296-304. <https://doi.org/10.1007/BF02238967>.
17. Wang HF, Wang YY, Li ZY, He PJ, Liu S, Li QS. The prevalence and risk factors of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. Annals of medicine. 2024 Dec 31;56(1):2332406. <https://doi.org/10.1080/07853890.2024.2332406>
18. Duarte AC, Porter JC, Leandro MJ. The lung in a cohort of rheumatoid arthritis patients—an overview of different types of involvement and treatment. Rheumatology. 2019 Nov 1;58(11):2031-8. <https://doi.org/10.1093/rheumatology/kez177>.
19. Hoovestol RA, Mikuls TR. Environmental exposures and rheumatoid arthritis risk. Current rheumatology reports. 2011 Oct;13:431-9. <https://doi.org/10.1007/s11926-011-0203-9>.