

THE FREQUENCY OF PULMONARY MANIFESTATIONS OF RHEUMATOID ARTHRITIS PATIENTS IN MOSUL, IRAQ

¹*Dr. Marwah Mahfoodh Shakir, ²Dr. Rami Mohammed Adil Al-Hayali and ³Dr. Sara Nassear Hassan

¹M.B.Ch.B.-DRMR (Rheumatology), Nineveh Rehabilitation Center.

²M.B.Ch.B.-FICMS-FRCP, College of Medicine-University of Mosul.

³M.B.Ch.B.-DRMR (Rheumatology), Nineveh Rehabilitation Center.

Article Received date: 08 July 2024

Article Revised date: 28 July 2024

Article Accepted date: 18 August 2024



*Corresponding Author: Dr. Marwah Mahfoodh Shakir

M.B.Ch.B.-DRMR (Rheumatology), Nineveh Rehabilitation Center.

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting synovial joints, leading to joint deformities and destruction. Pulmonary involvement is a significant extra-articular manifestation, contributing to morbidity and mortality. RA is more common in women and men with long-standing RA, positive rheumatoid factor, and subcutaneous nodules. **Aim:** To assess the frequency of pulmonary involvement of RA. **Patients and Methods:** A case series study was conducted at Ibn-Sina Teaching Hospital in Mosul and two private clinics, one specializing in rheumatology and the other in respiratory medicine, from January to December 2020. The study included 75 patients diagnosed with rheumatoid arthritis, including 12 males and 63 females. The study excluded patients with confirmed or suspected COVID-19 due to difficulty in distinguishing radiological findings from pulmonary manifestations of the disease. **Results:** The study found that 84.6% of patients with rheumatoid arthritis (RA) had pulmonary manifestations, including rheumatoid arthritis-interstitial lung disease (RA-ILD) in 23.1% of patients, rheumatoid nodules in 7.69%, pleural effusion in 1.28%, and bronchiectasis in 1.28%. Patients with RA-ILD had a higher proportion of males (23.1%) and were older (mean age of 56.7 years) than those without pulmonary manifestations (46.7 years). Patients with pulmonary manifestations were more likely to be smokers (34.6% versus 7.7%). Four patients (15.3%) had no clinical or spirometric abnormality, and the diagnosis was made on imaging. The study highlights the importance of understanding the pulmonary manifestations of RA in managing the disease. **Conclusion:** The study concluded that about one-third of RA patients had pulmonary manifestations. RA Patients with pulmonary manifestations are more likely to be males and smokers than RA patients without pulmonary manifestations.

KEYWORDS: Pulmonary Manifestations, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is defined as a chronic, systemic, inflammatory disease of unknown etiology that firstly affects synovial joints. The arthritis is usually symmetrical, if left untreated, usually leads to destruction of joints as a result of erosion of cartilage and bone, leading to joint deformities. One of the major extra-articular symptoms of RA is pulmonary involvement. A significant factor in morbidity and death is lung disease. Respiratory symptoms may occasionally appear before articular discomfort. One may also notice pulmonary illness as a harmful event that arises from RA medication.

Rheumatoid lung disease is more likely in males with long-standing rheumatoid illness, positive rheumatoid

factor, and subcutaneous nodules, even though RA is more common in women. In the first stages of the disease, pulmonary symptoms are quite prevalent in RA and can go unnoticed by the medical community. Except for pleural effusion, which is more common in the early stages of the disease, they rise with the length of RA and the patient's age.^[1]

Pulmonary manifestations of rheumatoid arthritis can be classified as follows:

1. Parenchymal lung disease, including interstitial lung disease (RA-ILD), pulmonary nodules and cryptogenic organizing pneumonia.
2. Bronchial diseases: including bronchiectasis, follicular bronchiolitis (FB) and bronchiolitis obliterans (BO).
3. Pleural disease including pleurisy and pleural effusion.

4. Pleuropulmonary infection, due to RA and immunosuppressive drugs.
5. Drug-associated lung disease caused by the drugs used to treat rheumatoid disease (like methotrexate).
6. Vascular disease including rheumatoid pulmonary vasculitis and pulmonary hypertension (rare).
7. Comorbid medical conditions (eg, thoracic cage immobility, venous thromboembolism, lung cancer).^[2]

No matter whether a patient exhibits respiratory symptoms, pulmonary assessment should be undertaken as soon as possible in RA patients since these individuals frequently remain clinically quiet, particularly in the early stages of the illness. Clinically significant pulmonary disease occurs in 10%-20% of patients with RA, while high resolution computed tomography (HRCT) may detect radiological abnormalities in up to 36% of cases. However, the prevalence of pulmonary manifestations of RA and its different presentations varies substantially among studies and in different countries.^[3]

The aim of the study

The aim of the study is to assess the frequency of pulmonary involvement of RA in Mosul and to know which complication are more prevalent and the proportion of each of these complications even in those patients without apparent symptoms.

PATIENTS AND METHODS

Study design, setting and time of study

This is a case series study conducted in Ibn-Sina Teaching Hospital in Mosul and 2 private clinics; one of special interest in rheumatology and the other in respiratory medicine during the period from January to December 2020. Interruption did occur at the time of lock down during COVID-19 initial spread.

A total of 75 consecutive patients (12 males and 63 females) diagnosed as RA were included in the study. These patients were recruited from the Rheumatology Consultation Clinic and the committee of biological agents in the hospital and those patients consulting the 2 above mentioned private clinics.

Inclusion and exclusion criteria

All adult rheumatoid arthritis patients with or without apparent symptoms were included. Any patient with

confirmed or suspected COVID-19 were excluded because of the difficulty in separating the radiological findings of this disease from the pulmonary manifestation of RA.

Methods of the study

The diagnosis of RA was reviewed according to the latest diagnostic criteria of European League against Rheumatism/American College of Rheumatology criteria. In order to make a firm diagnosis, we made use of the reports of the previous investigations and we asked for new investigations as required for each case. Information about the duration of the disease and the current medications were included. Each patient was carefully questioned regarding respiratory symptoms as detailed in the questionnaire below and examined for the presence of respiratory physical signs. chest radiograph was performed in all patients including asymptomatic patients to exclude early or asymptomatic pulmonary disease. Spirometry was also included in most patients. Those patients with abnormalities in these investigation received either PFT or a HRCT for better evaluation.

Ethical issue, approval and official permission

Prior to collection of data, a verbal consent from each of the participants was obtained after explaining the purpose of the study and ensuring privacy of data. Approval was obtained from the concerned health authorities.

Statistical Analysis

Descriptive statistics were used for categorical variables and the mean and standard deviation for quantitative variables. Analytic statistics included Chi-squared test and correlation coefficient (r).

RESULTS

A total number of 78 patients with RA were studied. Twelve of them were males (15.4%) and 66 of them were females (84.6%). Their age ranged from (23-82 years) with a mean of 50.7 years. The duration of their disease varied from (4 months–38 years), with a mean of 8.2 years. Most of these patients were on methotrexate (69 (88.4%)) and 52 of them were on biologics (66.6%). Twelve patients were smoker (14.4%), 66 of them were nonsmoker (83.3%) and 1 was an ex-smoker (1.3%).

Table (1): Personal characteristics of rheumatoid arthritis patients.

Parameters	Mean ± SD	Range	
Age (years)	50.7±11.94	23–82	
Duration of RA (years)	8.2±6.77	0.3–38.0	
BMI (kg/m ²)	33.1±7.56	20.0–62.8	
	No.	%	
Gender	Male	12	15.4
	Female	66	84.6
Smoking	Current smokers*	13	16.7
	Non-smokers	65	83.3

* One x-smoker was included.

Spirometry was performed in 61 patients (78.2%). It was normal in 49 patients (79.4%), restrictive in 6 patients (9.8%), obstructive in 4(6.5%) and mixed (restrictive and obstructive) in 2(3.3%). Pulmonary manifestations of RA were diagnosed in 26 patients (33.3%). These included rheumatoid arthritis-interstitial lung disease (RA-ILD) in 18 patients (23.1%), rheumatoid nodules in 6 patients (7.69%), pleural effusion in 1 patient (1.28%) and bronchiectasis in 1 patient (1.28%). More than one of these manifestation were present in some patients.

In patients with RA-ILD, 5 patients had UIP pattern on HRCT (27.78%) and 13 had a pattern on NSIP (72.22%). Of these 26 patients with documented pulmonary manifestation, 4 patients (15.3%) had no clinical or spirometric abnormality referring to the presence of pulmonary disease and the diagnosis was made on imaging. Two patients (7.69%) had presented with pulmonary disease and the diagnosis of RA was made subsequently.

Table (2): Pulmonary manifestations of RA patients.

Pulmonary manifestations	No.	%
RA-ILD	18	23.1
UIP	5	27.78
NSIP	13	72.22
Rheumatoid nodules	6	7.69
Pleural effusion	1	1.28

Patients with pulmonary manifestations of RA were significantly older (mean age of 56.7%) than those patients without pulmonary manifestations (46.7%) (p=0.001). These patients with pulmonary manifestations also had higher proportion of males (23.1%) compared with those without pulmonary manifestation (11.5%).

However, the difference did not reach statistical significance.

Patients with pulmonary manifestations of RA were more likely to be smokers than those patients without pulmonary manifestations (34.6% versus 7.7%) (p=0.003)

Table (3): Comparison of pulmonary manifestation among RA patients regarding age, gender and smoking.

Items		Pulmonary manifestation				P-value*
		Present		Absent		
		No.	%	No.	%	
Gender	Male	6	23.1	6	11.5	0.183
	Female	20	76.9	46	88.5	
Smoking	Current smokers	9	34.6	4	7.7	0.003
	Non-smokers	17	65.4	48	92.3	
Total		26	100.0	52	100.0	---
Age (Mean± SD)		56.7 ± 11.40		46.7 ± 11.10		0.001
Duration of RA (Mean ± SD)		9.6 ± 8.45		7.45 ± 5.21		0.189

* Chi-square test was used for categorical variables. Whereas, independent t-test for two means for quantitative data.

The effect of duration of RA on pulmonary symptoms and signs was demonstrated in table (4) which revealed that there were no statistically significant differences

between those with duration of the RA more or less than 10 years concerning pulmonary symptoms and signs.

Table (4): The effect of duration of RA on pulmonary symptoms and signs.

Pulmonary Manifestations		Duration of RA (years)				P-value*
		< 10 [n = 45]		≥ 10 [n = 33]		
		No.	%	No.	%	
Pulmonary symptoms	Cough	17	37.8	19	57.6	0.083
	Sputum	13	28.9	11	33.3	0.685
	Dyspnea	16	35.6	16	48.5	0.251
	Chest pain	10	22.2	12	36.4	0.125
Pulmonary sighs	Abnormal respiratory rate	8	17.8	11	33.3	0.114
	Abnormal chest expansion	8	17.8	12	36.4	0.063
	Abnormal percussion	8	17.8	12	36.4	0.063
	Abnormal breath sounds	10	22.2	14	42.4	0.056
	Added sounds	14	31.1	16	48.5	0.119

Spirometry was done in 22 of those patients with pulmonary complication and it was normal in 13 patients

(59%), restrictive in 5 patients (22.7%), obstructive in 2 patients (9%) and mixed in 2 patients (9%).

Table (5): The relationship between duration of RA and pulmonary radiological findings.

Radiological technique		Duration of RA (years)				P-value*
		< 10		≥ 10		
		No.	%	No.	%	
CXR	Positive	12	26.7	16	48.5	0.077
	Normal	33	73.3	17	51.5	
Total		45	100.0	33	100.0	---
CT	Positive	9	40.9	10	66.7	0.124
	Normal	13	59.1	5	33.3	
Total		22	100.0	15	100.0	---

*Chi square test

DISCUSSION

In this study the frequency of pulmonary manifestations were assessed in RA patients. For gender distribution, the current study presented with males (15.4%) and females (84.6%) in 78 RA patients. These findings are in consistent with finding of the Sandipan Banik *et al.*,^[4] that included 63 RA Patients with (66.6%) were females and (33.3%) were males, that found the incidence of RA disease was higher among females. The mean age of current study for RA patients was 50.7 years and these results were lower than what was reported by Sandipan Banik *et al.*^[4] with mean age of 45.22 years old. In this study for smoker and nonsmoker patient, twelve of patients were smoker (14.4%), 66 of them were nonsmoker (84.4%) and 1 was an ex-smoker (1.3%). Patients with pulmonary manifestations of RA were more likely to be smokers than those patients without pulmonary manifestations (34.6% versus 7.7%) ($p=0.003$). In the Stolt *et al.* research^[5], there was no significant increase in the risk of seropositive RA for current smokers, ex-smokers, or ever-smokers of either gender. For ever-smokers, the odds ratio was 1.7 (95% confidence interval (95% CI) 1.2 to 2.3) for women and 1.9 (95% CI 1.0 to 3.5) for men.

Since respiratory symptoms are the focus of this investigation, pulmonary involvement is one of the key extra-articular signs of RA. A significant factor in morbidity and death is lung disease. In many instances, pulmonary symptoms could appear before articular ones. One may also see pulmonary illness as a harmful event resulting from RA therapy. Men with subcutaneous nodules, positive rheumatoid factor, and long-standing rheumatoid illness are more likely to develop rheumatoid lung disease, even though RA is more common in women. By kadhum *et al.*,^[6] pulmonary involvement is a frequent and among the most severe extra-articular manifestations of rheumatoid arthritis. Rheumatoid arthritis can affect the lung parenchyma, airways and pleura. Pulmonary complications are directly responsible for 10-20% of all mortality in RA patients.

Spirometry was used in 61 patients (78.2%) in this study; it was normal in 49 patients (79.4%); restrictive in 6 patients (9.8%); obstructive in 4 patients (6.5%); and

mixed (restrictive and obstructive) in 2 patients (3.3%). The study was a case-control study carried out at the rheumatology unit of Al Sader teaching hospital, involving 40 RA patients [33 (82.5%) females and 7 (17.5%) males] along with sixty seemingly healthy subjects {50(83.3%) females and 10(16.7% males)}. Every participant had a pulmonary function test (PFT) to assess their lung function, on the pulmonary function test, nine patients had a restrictive pattern, and only one patient had an obstructive pattern. Conversely, all sixty healthy control subjects^[7] had normal pulmonary function tests. Out of the 5661 patients from a North Indian Town who had a history of arthritis, 27 patients (43%) had an abnormal PFT, with 18 (29%), 5 (8%) having an obstructive pattern, and 4 (6.4%) having a mixed pattern. HRCT indicated aberrant findings in 21 (33.8%) cases, with the most prevalent ones being sub pleural reticulations in 6 (9.6%), pleural thickening in 2 (3.2%), pulmonary vascular prominence in 1 (1.6%), and ground glass pattern in both lower lobes in 12 (19.3%) cases.^[8]

In this study pulmonary manifestations of RA were diagnosed in 26 patients (33.3%). These included rheumatoid arthritis-interstitial lung disease (RA-ILD) in 18 patients (23.1%), rheumatoid nodules in 6 patients (7.69%), pleural effusion in 1 patient (1.28%) and bronchiectasis in 1 patient (1.28%). More than one of these manifestation were present in some patients. In patients with RA-ILD, 5 patients had UIP pattern on HRCT (27.78%) and 13 had a pattern on NSIP (72.22%).

Of these 26 patients with documented pulmonary manifestation, 4 patients (15.3%) had no clinical or spirometric abnormality referring to the presence of pulmonary disease and the diagnosis was made on imaging. In past study, researchers in Boston analyzed 190 RA patients who underwent chest computed tomography (CT) for clinical indications from 2003 through 2017. Abnormal scans were reviewed independently by thoracic radiologists. Presumed RA-related lung disease was noted in 54 patients: Interstitial lung disease (16%), bronchiectasis (14%), and pleural disease (10%) were most common. Male sex and methotrexate use were associated with RA-related lung

disease, but rheumatoid-factor positivity was not a risk factor. Seven-year mortality among the patients with RA-related lung disease was significantly higher than that in patients with normal CT results.^[9]

In the current study, of the patients with RA-ILD, 5 had a UIP pattern on HRCT (27.78%), and 13 had a pattern on NSIP (72.22%). In contrast, of the patients with RA-ILD who were identified (n = 99), 84 had HRCT scans that were completed within a year of the first clinic visit and were available for review. Since neither of these patients exhibited diffuse illness, their HRCT patterns were classified as other (one with organizing pneumonia and the other with bronchiolitis). As a result, they were not included in further analysis. Out of the remaining 82 patients, 20 (24%; κ 0.54) had a clear UIP HRCT pattern, 19 (23%) had a probable NSIP pattern, and 43 (52%) had an uncertain pattern.^[10]

Out of the 26 patients in this research, two (7.69%) had pulmonary illness at initial presentation, and RA was later diagnosed. According to A Robles-Perez, the second study's findings indicate that PFT abnormalities are commonly found in individuals with recently diagnosed RA who do not exhibit any respiratory symptoms. Moreover, a potential link between lung involvement and the intensity of disease activity is suggested by the correlation between physiological lung abnormalities and rheumatoid activity markers. This implies that a few biological markers may be useful in identifying people who are more likely to get lung involvement. Most earlier research on pulmonary illness linked to RA involved people who had chronic articular disease. Similar to what is seen here, previous research on early RA indicates that physiological lung abnormalities are prevalent (33%–40%). This suggests that lung involvement occurs during a subclinical phase of RA illness and that the lung disease is already progressed when respiratory symptoms manifest clinically. Consequently, regardless of their clinical respiratory symptoms, including a pulmonary function evaluation might be beneficial for all RA patients from the time of first diagnosis.^[11]

In the current study, the patients with pulmonary manifestations of RA were significantly older (mean age of 56.7%) than those patients without pulmonary manifestations (46.7%) ($p=0.001$). These patients with pulmonary manifestations also had higher proportion of males (23.1%) compared with those without pulmonary manifestation (11.5%). However, the ($p=0.183$) did not reach statistical significance. Patients with pulmonary manifestations of RA were more likely to be smokers than those patients without pulmonary manifestations (34.6% versus 7.7%) (P -value = 0.003).

CONCLUSION

The study concluded that about one-third of RA patients had pulmonary manifestations. RA Patients with pulmonary manifestations are more likely to be males

and smokers than RA patients without pulmonary manifestations.

REFERENCES

1. Cavagna L, Monti S, Grosso V, et al. The multifaceted aspects of interstitial lung disease in rheumatoid arthritis. *Biomed Res Int.* 2013; 2013: 759760. doi: 10.1155/2013/759760.
2. Massey H, Darby M, Edey A. Thoracic complications of rheumatoid disease. *Clin Radiol.*, 2013 Mar; 68(3): 293-301. doi: 10.1016/j.crad.2012.07.007.
3. Turesson C, Jacobsson L, Bergstrom U. ExtraArticular Rheumatoid Arthritis: Prevalence and Mortality. *Rheumatology (Oxford)*, 1999; 38(7): 668-674. doi:10.1093/rheumatology/38.7.668
4. Banik S, Tapadar SR, Ray A, et al. A Study on Pulmonary Manifestations of Rheumatoid Arthritis. *Journal of Clinical and Diagnostic Research.* June 2018; 12(6): OC05-OC09. DOI:10.7860/JCDR/2018/3020 8.11625
5. Stolt P, Bengtsson C, Nordmark B, et al. EIRA study group. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. *Ann Rheum Dis.* 2003 Sep; 62(9): 835-841. doi: 10.1136/ard.62.9.835.
6. kadhun HJ, Al hamza AN, Abdualwahid AB. Pattern of pulmonary function test in rheumatoid arthritis patients. *The Medical Journal of Basrah University*, 2017; 35(2): 109-115
7. Fatima N, Shameem M, Malik A, et al. A Study on the Pulmonary Manifestations of Rheumatoid Arthritis from a North Indian Town. *Open Journal of Respiratory Diseases.* 2013; 3: 128-131. doi: 10.4236/ojrd.2013.33020.
8. Huang S, Doyle TJ, Hammer MM, et al. Rheumatoid arthritis-related lung disease detected on clinical chest computed tomography imaging: Prevalence, risk factors, and impact on mortality. *Seminars in Arthritis and Rheumatism*, 2020; 50(6): 1216-1225. <https://doi.org/10.1016/j.semarthrit.2020.08.015>
9. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J.*, 2010 Jun; 35(6): 1322-8. doi: 10.1183/09031936.00092309.
10. Robles-Perez A, Luburich P, Rodriguez-Sanchon B, et al. Preclinical lung disease in early rheumatoid arthritis. *Chron Respir Dis.*, 2016 Feb; 13(1): 75-81. doi: 10.1177/1479972315620746.