

# Prevalence of Pulmonary Manifestations in a Cohort of the Egyptian Patients with Rheumatoid Arthritis

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## ABSTRACT

**Background:** rheumatoid arthritis can affect the lung in many ways including lung parenchymal affection (Interstitial lung disease), pleural inflammation, upper and lower airways affection and pulmonary vasculature. **Aim of the work:** this study aimed to estimate the prevalence of pulmonary manifestations in Egyptian RA patients. **Patients and methods:** this study included seventy patients with RA. All patients were subjected to detailed medical history taking, general examination including chest examination, local musculoskeletal examination, laboratory investigations including CBC, ESR, CRP titre, ALT, AST, BUN and creatinine, rheumatoid factor titer (RF), Anti-CCP antibodies titer, radiological investigations including chest X ray, HRCT and PFT. **Results:** pulmonary manifestations were prevalent in 50% of patients. Spirometric abnormalities were detected in 45.7%, while HRCT abnormalities were detected in 42.85%. HRCT severity score was correlated with age, tender joint count (TJC), swollen joint count (SJC) and ESR. There was a statistically significant negative correlation between HRCT and FVC, FEV1. There was no correlation regarding other parameters. **Conclusion:** pulmonary affection was prevalent in RA and can be detected by radiological and pulmonary functions. There was correlation with age, ESR and pulmonary functions

**Keywords:** RA, RA-ILD, HRCT, PFT, TJC and SJC

## INTRODUCTION

Rheumatoid arthritis is considered as one of the most prevalent models of autoimmune inflammatory diseases. The joints are the main target of the disease producing articular manifestations; meanwhile other systems can be involved producing extraarticular manifestations<sup>(1)</sup>. The lung is one of the most common involved organs in RA contributing to morbidity and mortality affecting lung parenchyma, airways, pleura and vasculature<sup>(2)</sup>. This study aimed to estimate the prevalence of pulmonary manifestations in the Egyptian RA patients.

## PATIENTS AND METHODS

This study was an observational cross sectional study and it included seventy patients with RA fulfilling the American Colleague of Rheumatology / European league against Rheumatism (ACR/EULAR) 2010 classification criteria<sup>(3)</sup>. They were selected from Rheumatology Outpatient Clinic and Internal Medicine Department of Ain Shams University Hospital. The study was conducted in the period 7/2015-7/2017.

### All patients were subjected to the following

- Detailed medical history taking with special emphasis on age, smoking, articular symptoms and detailed chest symptoms

- General examination including chest examination
- local musculoskeletal examination
- Laboratory Investigations:
  - CBC, ESR, CRP titre, ALT, AST, BUN and Creatinine
  - Rheumatoid factor titer (RF) by using latex agglutination test kit
  - Anti-CCP antibodies titer using ELISA technique

### • Radiographic evaluation:

1. Plain chest x ray posterior-anterior (PA) view
2. Pulmonary high resolution computed tomography scan (HRCT): It was done using both techniques GE Light Speed Plus MSCT 4 channels set and Toshiba Aquilion MSCT 64 channels set. HRCT films were done in supine position with full inspiration without contrast enhancement.

1. Spirometric pulmonary function test: Spirometry was performed according to American Thoracic Society guidelines (ATS) with assessment of vital capacity, forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), FEV1/FVC ratio.

The study was approved by the Ethics Board of Ain Shams University.

### Data Analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 17.0.

➤ Description of quantitative variables as mean, standard deviation (SD) and range.

➤ Description of qualitative variables as number (no) and percentage (%).

- Chi-square test was used to compare qualitative variables.

- Unpaired t-test was used to compare two independent groups as regard a quantitative variables.

- Spearman & Pearson Correlation co-efficient rank test was used to rank different variables against each other's positively or inversely

- P value refers to level of significance as follows:

P value  $>0.05$  => insignificant.

Pvalue  $<0.05$  => significant.

Pvalue  $<0.01$  => highly significant

### RESULTS

This study was an observational cross sectional study that included 70 RA patients, 61 females (87.1%) and 9 males (12.9%). Age ranged between 24 to 76 years with mean of  $44 \pm 10.8$  years. Disease duration ranged from 0.17 to 23 years with a mean of  $7.3 \pm 6$  years. Only 7 patients (10%) were smokers (Table 1)

The commonest articular manifestations in our RA patients were arthralgia in 77.1%, active arthritis in 72.8%. Joint deformities were observed in 12.8%. The most prevalent pulmonary manifestations were dyspnea and cough as they were present in 37.14% and 34.29% of patients respectively.

All patients received steroids. Methotrexate was used by 85.7%. Hydroxychloroquine and leflunamide were used in 77.14% and 42.86% respectively. Sulfasalazine was used in 21.4%. Biologics were not used by any of our patients.

Thirty two patients (45.71%) had abnormal spirometric findings; 18.75% had mild restrictive pattern, 21.88% had moderate restrictive pattern, severe restrictive in 12.5%, mild obstructive in 3.13%, small airway (early obstructive) in 21.88% and mixed pattern in 18.75%.

**Table 2:** pattern of pulmonary function tests among RA pts

Parameter	Pts with abnormal spirometry (n=32)	Percent
<b>Abnormal spirometric patterns</b>	32	45.7
Mild restrictive	6	18.75
Moderate restrictive	7	21.88
Severe restrictive	4	12.50
Mild obstructive	1	3.13
Small airway (early obstructive)	7	21.88
Mixed	6	8.75

\*PFT: pulmonary function test\*\*DLCO: diffusion lung capacity of carbon monoxide

Chest X ray showed abnormal findings in 11.4% of the patients, while thirty patients (42.85%) had abnormal HRCT findings; twenty five patients of them (35.7%) had interstitial abnormalities. The most common HRCT abnormalities were reticulation and ground glass appearance found in 19 patients (27%) and 13 patients (18.5%) respectively, while honeycombing was present in 7 patients (10%), Bronchiectasis in 13 patients (18.5%), pleural effusion in 4 patients (5.7%) and rheumatoid nodules in 3 patients (4.2%)

**Table 3:** HRCT findings among the studied 70 RA patients

HRCT finding	No. of pts (70)	Percent
<b>Abnormal HRCT findings</b>	30	42.85
Ground glass appearance	13	18.5%
Pleural irregularities	11	15.7%
Reticulation	19	27%
Honey combing	7	10%
Subpleural cyst	2	2.8%
Airspace consolidation	1	1.4%
Nodules	3	4.2%
Emphysema	6	8.5%
Bulla	3	4.2%
Bronchiectasis	13	18.5%
Mosaic perfusion	4	5.7%
Pleural effusion	4	5.7%
Air trapping	5	7%

Comparison between RA patients with and without pulmonary manifestations showed that patients with pulmonary affection were older ( $P=0.006$ ) with more active arthritis ( $P= 0.005$ ), swollen joint count ( $p= 0.001$ ), dyspnea ( $P <0.001$ ), cough ( $P= 0.001$ ), crepitations ( $P=0.003$ ), chest pain ( $P=0.029$ ) and wheezing ( $P= 0.023$ )

RA patients with pulmonary affection by HRCT showed more affection regarding FVC ( $P= 0.004$ ) and FEV1 ( $P= 0.025$ ), but there was no significant difference regarding FEV1/FVC ratio ( $P= 0.653$ .) (Table 2)

Correlations between HRCT total score (Warrick score) and disease parameters revealed that there was a statistically highly significant positive correlation between HRCT score and age ( $r=0.378$ ,  $P=0.001$ ), tender joint count (TJC) ( $r=0.460$ ,  $P <0.001$ ), swollen joint count (SJC) ( $r=0.369$ ,  $P =0.002$ ), while there was a statistically significant positive correlation with ESR ( $r=0.254$ ,  $P= 0.034$ ). There was a statistically significant negative correlation between HRCT score and AST ( $r=-0.243$   $P= 0.043$ ) and a statistically highly significant negative correlation with FVC ( $r=-0.520$ ,  $P <0.001$ ) FEV1 ( $r=-0.437$ ,  $P <0.001$ ). There was no correlation regarding other parameters (Table 3).

## DISCUSSION

Rheumatoid arthritis (RA) is a disabling autoimmune systemic inflammatory disease of unknown etiology that can affect numerous tissues and organs, but predominantly attacks synovial joints causing symmetric affection of peripheral joints. It manifests as inflammatory polyarthritis and produces a wide range of extra-articular manifestations including the lung as one of the most commonly affected organs in RA patients<sup>(5)</sup>. All compartments of the respiratory system can be affected in RA patients including parenchyma, airways, pleura and vasculature. Interstitial lung disease (ILD), a diffuse progressive disease of the lung parenchyma, is the most serious manifestation of RA lung. ILD can occur in 10% of RA patients clinically and in 30% of patients subclinically. ILD can occur even before development of articular disease<sup>(2)</sup>.

Our study involved 61 females (87.14%) and 9 males (12.86%), their age ranged from 24 years to 76 years with mean age  $\pm$  SD  $44 \pm 10.8$  years. The disease duration ranged from 2 months to 23 years with mean  $\pm$  SD  $7.3 \pm 6$  years. **Zurour *et al.***<sup>(6)</sup> included 63 women (84%) and 12 men (16%). Age of patients ranged from 20-84 years with mean age 48 years and disease duration ranged

from 2 months to 27 years<sup>(6)</sup>. In our study smoking history was prevalent in 7 patients (10%). **Zurour *et al.***<sup>(6)</sup> recruited only 11 patients as smokers (14.6%). This small percentage may be explained by small number of male patient and most of female patients are non smokers due to cultural issues .

Our study showed that respiratory symptoms were encountered in 35 patients (50%). Regarding the most prevalent respiratory symptoms dyspnea was in 26 patients (37%), cough in 24 patients (34.3%) chest pain in 11 patients (15.7%) while wheezing in 9 patients (12.8%). **Zurour *et al.***<sup>(6)</sup> noted respiratory symptoms in only 32% of patients. Dyspnea was the most common symptom (25.3%), cough (13.3%), chest pain (10.7%) and wheezing in (6.7%).(6)

In the current study HRCT was found normal in 40 patients (57.2%) and abnormalities were found in 30 patients (42.8%) with ILD in 25 patients (35.7%). Ground glass appearance in 13 patients (18.5%), pleural irregularities in 11 patients (15.7%), septal or reticular lines in 19 patients (27%), honey combing in 7 patients (10%) and subpleural cysts in 2 patients (2.8%). Airway abnormalities were less prevalent with bronchiectasis in 18.5% of patients, mosaic perfusion (5.7%), air trapping (7%), emphysema in 6 patients (8.5%), bulla in 3 patients (4.2%) and airspace consolidation in 1 patient (1.4%). Pleural effusion was present in (5.7%) and pulmonary nodule in 3 patients (4.2%).

These results are in consistence with **Youssef *et al.***<sup>(9)</sup> who found abnormalities in 47% of RA patients with ILD the most common in (38.9%) of patients. Eight (22.2%) patients had reticular opacities, while 4 (11.1%) had ground-glass opacity and two (5.6%) had honeycombing. Bronchial abnormalities were detected in 13 (36.1%) patients, emphysema in 2 (5.6%), rheumatoid pulmonary nodules in 4 (11.1%) patients, and pleural effusion in 2 (5.6%) .

In contrast to the a previous study **Cortet *et al.***<sup>(10)</sup> reported airway predominance in a cohort of 68 French RA patients. Abnormal HRCT pattern was found in (80.9%). Bronchiectasis was the most common abnormality (30.5%) followed by nodules (28%), air trapping (25%), ground glass attenuation (17.1%), honeycombing (2.9%) and pleural effusion (1.5%). This variation can be due to inconsistency in the method and the criteria used to define the disease and the characteristics of the patients studied .

Our study revealed that PFTs were abnormal in 45.71% with restrictive pattern the most

common followed by small airway affection and the least is the obstructive pattern. This was agreed by **Farrag et al.**<sup>(12)</sup>. found PFT abnormalities in 37% mainly a restrictive pattern and small airway obstruction, whereas the obstructive pattern was observed the least. **Joshi et al.**<sup>(5)</sup>. observed restrictive pattern of PFT in (31.4%) patients whereas obstructive pattern was seen in (12.8%) patients. **Biomdo et al.**<sup>(14)</sup>. reported PFT abnormality in 38.5% but, in contrast to our study, obstructive pattern was the most common (20.4%) followed by restrictive pattern in 16.9% and mixed in 1.2%. They attributed these results to different environmental conditions including pollution and climatic conditions .

In our cohort of patients FVC and FEV1 were significantly correlated with HRCT score (P value <0.0001) **Zurour et al.**<sup>(6)</sup>. found the same strong association between FVC and FEV1 (P value <0.0001) . A good correlation was demonstrated between FEV1 % predicted values and HRCT findings in RA patients. In contrary to these reports **Bilgici et al.**<sup>(13)</sup> did not observe a statistically significant association between PFTs results and the presence of lung involvement by HRCT .

Our study revealed association between age and HRCT severity score. **Zhang et al.**<sup>(8,11)</sup> found association with age is closely related to RA-ILD. Hence, it is important to perform ILD screening in elderly RA patients. **Sakre et al.**<sup>(7)</sup> found no association with age .

Our results did not show correlation between severity score and disease duration. The same results were encountered by **Bilgici et al.**<sup>(13)</sup> and **Yilmazer et al.**,<sup>(8)</sup>. as they found no relation between the presence of lung involvement and longer disease duration. This suggests that HRCT abnormalities may also develop in the early stages of disease process in RA. **Joshi et al.**<sup>(5)</sup> found that ILD is more common in patients who had longer disease duration . This may be because of disease duration of their patients was longer than that of our patients.

Our study failed to find any association between smoking and pulmonary abnormalities. In agreement with our study, **Sakre et al.**<sup>(7)</sup> found no association to smoking **Bilgici et al.**<sup>(13)</sup> stated that smoking was not associated with physiological or HRCT abnormalities suggestive of RA ILD **Zhang et al.**<sup>(11)</sup>. concluded that smoking is a significant risk factor for the development of ILD in RA patients .

We found no association between HRCT severity and medications. Results of **Sakre et al.**<sup>(20)</sup>. **Bilgici et al.**<sup>(7)</sup> agreed with us and found no association with medications (20) (7). This result suggests that changes detected by HRCT may occur as a result of RA associated factors rather than treatment given.

**Conway et al.**<sup>(15)</sup> reported a small but significant risk for increased pulmonary damage in RA patients receiving methotrexate but it is still difficult to prove causality as patients with rheumatoid arthritis are prone to lung complications from infection, other medications and the disease itself.

In the current study rheumatoid factor was high in patients with HRCT abnormalities but it was not correlated with the total severity score (Warrick score). Meanwhile anti CCP showed neither difference between groups nor correlation to severity score. In agreement with this results of **Skare et al.**<sup>(7)</sup> found no association between HRCT abnormalities and RF, anti CCP . **Zhang et al.**<sup>(11)</sup> and **Joshi et al.**<sup>(5)</sup> found association with RF but not with anti CCP. **Zrour et al.**<sup>(6)</sup> found association with RF but anti CCP was not evaluated .

In contrast to these studies **Doyle** and his colleagues showed that titres of RF and anti-CCP antibodies were significantly higher in patients with RA-ILD. RF and anti-CCP showed them both to be significant predictors of ILD <sup>(17)</sup>. He reported that anti-citrullinated peptide antibody (ACPA) positivity correlates with the presence of ILD in RA, and higher titers of ACPA may be associated with more severe ILD. This difference may be related to smoking habits, male percentage and disease duration.

## CONCLUSION

Pulmonary affection in RA patients can be more prevalent than what was expected and can be increased with age, ESR, PFT abnormalities.

**Data availability:** the dataset on which the conclusions of the paper rely are available on request from the authors.

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