

## Pulmonary Function Abnormalities in Patients of Rheumatoid Arthritis and their Relation with Rheumatoid Disease Activity: An Observational Study from a Rural Tertiary Care Centre in North India

Romatoid Artritli Hastalarda Solunum Fonksiyonu Anormallikleri ve Romatoid Hastalık Aktivitesi ile İlişkisi: Kuzey Hindistan'daki Kırsal Üçüncü Basamak Bakım Merkezinden Gözlemsel Bir Çalışma

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### ABSTRACT

**Introduction-** Pulmonary involvement is a frequent and among the most severe extra-articular manifestations of Rheumatoid Arthritis. There may be variable involvement of almost all the components of lung structure. Early detection and management of pulmonary manifestations is important to decrease the overall morbidity and mortality of RA patients. PFTs may be a useful tool for early diagnosis of pulmonary involvement in patients of Rheumatoid Arthritis. The present study was conducted to investigate the frequency of pulmonary function abnormalities in Rheumatoid Arthritis patients presenting at a rural tertiary care centre in North India and to study its relation with rheumatoid disease activity.

**Materials and Methods-** The present study was a cross-sectional observational study performed on 55 diagnosed patients of Rheumatoid Arthritis. RA was diagnosed as per the 2010 ACR-EULAR Classification criteria. Disease activity of Rheumatoid Arthritis was assessed based on the DAS 28 score. Pulmonary Function Tests were conducted in all the patients by using a computerized Spirometer.

**Results and Observations-** The most common abnormalities observed on PFT were obstructive pattern (seen in 25.4% patients), restrictive pattern (16.4%) and mixed pattern (5.4%). The patients with abnormal PFTs had a significantly longer duration of illness ( $p<0.05$ ) and more severe disease activity as measured by DAS 28 score ( $p<0.05$ ).

**Conclusion-** Pulmonary Function Testing is a simple and easily available method to detect pulmonary involvement in patients of Rheumatoid Arthritis at an early stage. Impairment in PFTs correlates with the duration of disease and severity of disease activity.

**Keywords:** Pulmonary function tests; Rheumatoid arthritis; disease activity; DAS28 score

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### ÖZET

**Amaç:** Pulmoner tutulum, Romatoid Artrit sık görülen ve en şiddetli eklem dışı belirtileri arasındadır. Akciğer yapısının hemen hemen tüm bileşenlerinin değişken tutulumu olabilir. RA hastalarının genel morbidite ve mortalitesini azaltmak için pulmoner bulguların erken tespiti ve yönetimi önemlidir. SFT'ler, Romatoid Artrit hastalarında pulmoner tutulumun erken teşhisi için yararlı bir araç olabilir. Bu çalışma, Kuzey Hindistan'da kırsal bir üçüncü basamak bakım merkezine başvuran Romatoid Artrit hastalarında solunum fonksiyon anormalliklerinin sıklığını araştırmak ve romatoid hastalık aktivitesi ile ilişkisini araştırmak için yapılmıştır.

**Yöntem:** Bu çalışma, Romatoid Artrit tanısı almış 55 hasta üzerinde gerçekleştirilen kesitsel gözlemsel bir çalışmadır. RA, 2010 ACR-EULAR Sınıflandırma kriterlerine göre teşhis edildi. Romatoid Artrit hastalık aktivitesi, DAS 28 skoruna göre değerlendirildi. Tüm hastalara bilgisayarlı Spirometre ile Solunum Fonksiyon Testleri yapıldı.

**Bulgular:** SFT'de en sık gözlenen anormallikler obstrüktif patern (hastaların %25.4'ünde görüldü), restriktif patern (%16.4) ve mikst patern (%5.4) idi. Anormal SFT'leri olan hastalar, DAS 28 skoru ( $p<0.05$ ) ile ölçüldüğü üzere, anlamlı olarak daha uzun hastalık süresine ( $p<0.05$ ) ve daha şiddetli hastalık aktivitesine sahipti.

**Sonuç:** Pulmoner Fonksiyon Testi, Romatoid Artrit hastalarında pulmoner tutulumu erken bir aşamada saptamak için basit ve kolay ulaşılabilir bir yöntemdir. SFT'lerdeki bozulma, hastalık süresi ve hastalık aktivitesinin şiddeti ile ilişkilidir.

**Anahtar Sözcükler:** Solunum fonksiyon testleri; Romatizmal eklem iltihabı; hastalık aktivitesi; DAS28 puanı

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## INTRODUCTION

Rheumatoid Arthritis (RA) is one of the most common connective tissue disorders worldwide. It is a chronic inflammatory systemic disorder which most commonly manifests as a symmetrical, destructive and deforming polyarthritis affecting both small and large synovial joints. The prevalence of RA in the adult population is reported to be 0.5 to 1 percent (1). Although joint involvement is the most common and central pathological involvement in RA, but extra-articular manifestations are seen commonly and are important determinants of long term morbidity and disability in these patients. Studies have shown that more than 40% of RA patients may manifest one or more of extra-articular manifestations within a few years of development of joint manifestations (2).

Pulmonary involvement is a frequent and among the most severe extra-articular manifestations of RA. The epidemiological data suggests involvement of respiratory system in approximately 30-40% patients of RA (3). The onset of respiratory manifestations may even precede the onset of symptoms of arthritis. In 10-20% patients, respiratory involvement may be the first manifestation in RA (3). Respiratory involvement is also a major determinant of mortality in RA and may be responsible for 10-20% of all deaths in RA (4).

In the respiratory system, RA may variably involve almost all the components of lung structure including the pleura, lung parenchyma and airways (5). Radiological evaluation with High Resolution CT scan may show lung parenchyma involvement in a large number of RA patients (6). Histopathologically, the most common forms of Interstitial Lung Diseases associated with RA are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) (7). The other pulmonary manifestations include pleural involvement, rheumatoid nodules, Caplan's syndrome, vasculitis and pulmonary hypertension. Further, indirect complications in the form of respiratory infections and drug induced toxicity (specially with Methotrexate) are seen frequently in patients of RA (8,9).

Early detection and management of pulmonary manifestations is important to decrease the overall morbidity and mortality of RA patients. Pulmonary Function Tests (Spirometry) are inexpensive and readily available clinical tests which provide objective measures of respiratory physiology for detecting and quantifying pulmonary impairment in cardio-pulmonary diseases (10). PFTs may be a useful tool for diagnosis of early pulmonary involvement in patients of Rheumatoid Arthritis. The present study was conducted to investigate the frequency of pulmonary function abnormalities in Indian Rheumatoid Arthritis patients presenting at a rural tertiary care centre and to study its relation with rheumatoid disease activity.

## MATERIALS and METHODS

The present study was a cross-sectional observational study which was conducted in Department of Physiology at a rural tertiary care centre in North India. The study was performed on 55 patients of Rheumatoid Arthritis taken from the outpatient and inpatient facilities in Department of Medicine in the hospital. The study was conducted over a period of six months in 2018-19 after approval from the ethics committee of the institute. Patients who were more than 18 years of age and were clinically established cases of Rheumatoid Arthritis as per the 2010 ACR-EULAR Classification criteria for Rheumatoid Arthritis (11) were included in the study. Subjects who were active smokers and those having documented pulmonary disease (including COPD, Bronchial Asthma, Tuberculosis, and Pneumonia) or documented cardiac disorders (including CAD, Congestive Heart Failure) were excluded from the study. Patients with severe anemia, those diagnosed with other connective tissue disorders or having any other systemic disorder involving respiratory system were also excluded from the study.

Each participant in the study was explained about the aims and objectives of the study and an informed consent after explaining in patient's own vernacular language was taken prior to his/her inclusion in the study. Demographic data including age and sex of the patients was recorded. Detailed present and past medical history was recorded, followed by a thorough physical examination in all the subjects. Height, Weight and Body Mass Index of the patients was noted as per the standard protocol. Disease activity of Rheumatoid Arthritis was assessed based on the DAS 28 score. The number of swollen and tender joints (28 joint count) and patient's assessment of global health on Visual Analog Score (VAS) was recorded. Erythrocyte Sedimentation rate (ESR) of the patients was noted. DAS 28 score was calculated by applying these parameters in the standard equation ( $DAS28 = 0.56 \times (t28) + 0.28 \times (sw28) + 0.70 \times \ln(ESR) + 0.014 \times VAS$ ).

Pulmonary Function Tests were conducted in all the patients by using a computerized Spirometer (RMS Helios-401) available in the department of Physiology. The test procedure was explained in detail to all the subjects. The steps of spirometry were demonstrated and a trial run was conducted before starting the actual test. The test was done in the standing position. The subject was asked to take a deep inspiration and blow into the mouthpiece as rapidly, forcefully and completely as possible. A minimum of three forced expiratory maneuvers were performed and the best of three readings were selected for statistical analysis. Different parameters of spirometry including Forced vital capacity (FVC), Forced expiratory volume in 1 s (FEV1), FEV1/FVC ratio and Peak expiratory flow rate (PEFR) were recorded. Abnormalities on PFTs were categorized as i) Obstructive defect as decreased FEV1/FVC ratio < 70% of predicted, ii) Restrictive defect as reduced FVC with a normal FEV1/FVC ratio or iii) mixed as reduced FVC with a reduced FEV1/FVC ratio.

### Statistical Analysis

The statistical analysis was carried out with SPSS PC software version 21.0. Variables were expressed as mean  $\pm$  standard deviation and percentage. Mean differences for continuous variables between groups were examined by the independent Student t-test. Chi-square test was used for categorical variables. P value of < 0.05 was considered significant.

## RESULTS

The clinical and pulmonary function tests parameters of the Rheumatoid Arthritis patients are tabulated in Table 1. The mean age of the study population was  $41.1 \pm 11.8$  years. Eighty three percent of RA patients in our study were females. Mean duration of illness for RA was  $6.2 \pm 4.6$  years. Rheumatoid Factor was positive in 85.4% of our patients. As measured by the DAS 28 score, majority of the patients in our study had severe disease activity (38.2%), followed by moderate (36.4%) and mild (25.4%) disease activity. The pulmonary function tests of the study population showed that the mean percent predicted values for FVC, FEV1, FEV1/FVC, FEV25-75 and PEFR were  $85.4 \pm 12.3$ ,  $83.6 \pm 15.1$ ,  $98.0 \pm 10.4$ ,  $67.9 \pm 21.5$  and  $84.3 \pm 15.6$ , respectively.

**Table 1** Clinical and pulmonary function parameters of the study population

Parameter	Cases (55)
Age (in years) (Mean $\pm$ SD)	41.1 $\pm$ 11.8
Gender (n, %)	
Males	9 (16.4%)
Females	46 (83.6%)
Duration of Disease (in years) (Mean $\pm$ SD)	6.2 $\pm$ 4.6
Weight (in kg) (Mean $\pm$ SD)	56.6 $\pm$ 5.4
Height (in m) (Mean $\pm$ SD)	1.6 $\pm$ 0.1
BMI (in kg/m <sup>2</sup> ) (Mean $\pm$ SD)	21.1 $\pm$ 1.6
ESR (mm 1 <sup>st</sup> hr) (Mean $\pm$ SD)	43.3 $\pm$ 19.5
Rheumatoid Factor	
Positive (n, %)	47 (85.4%)
Negative (n, %)	8 (14.6%)
Treatment for Rheumatoid Arthritis (n, %)	
Methotrexate	43(78.1%)
Hydroxychloroquine	52(94.5%)
Sulfasalazine	6(10.9%)
Leflunamide	1(1.8%)
Disease Severity (DAS 28 Score) (n,%)	
Mild (2.6 - 3.2)	14 (25.4%)
Moderate (3.2 - 5.1)	20(36.4%)
Severe( >5.1)	21 (38.2%)
Pulmonary Function Tests	
FVC (% predicted) (Mean $\pm$ SD)	85.4 $\pm$ 12.3
FEV1 (%predicted)(Mean $\pm$ SD)	83.6 $\pm$ 15.1
FEV1/FVC (%predicted)(Mean $\pm$ SD)	98.0 $\pm$ 10.4
FEF25-75% (Mean $\pm$ SD)	67.9 $\pm$ 21.5
PEFR% (Mean $\pm$ SD)	84.3 $\pm$ 15.6

Table 2 shows the distribution of patterns on pulmonary function testing in the study population. PFTs were normal in 52.8% percent of Rheumatoid Arthritis patients. The most common abnormalities observed on PFT were obstructive pattern (seen in 25.4% patients), restrictive pattern (16.4%) and mixed pattern (5.4%).

**Table 2** Distribution of pulmonary function test abnormalities in RA patients

PFT result	Number of patients	Percentage
Normal	29	52.8%
Obstructive pattern	14	25.4%
Restrictive pattern	9	16.4%
Mixed blockage	3	5.4%
Total	55	100%

Table 3 compares the demographic and clinical characteristics in RA patients with or without abnormal Pulmonary Function Tests. The patients with abnormal PFTs had a significantly longer duration of illness ( $p < 0.05$ ) and more severe disease activity as measured by DAS 28 score ( $p < 0.05$ ). No significant difference was found between the two groups with respect to age, gender, BMI, Rheumatoid Factor positivity and DMARD therapy ( $p > 0.05$ ).

**Table 3** Comparison of demographic and clinical characteristics of RA patients with normal and abnormal pulmonary function tests

Parameter	Normal PFT (N=29)	Abnormal PFT (N=26)	p value
Age (in years) (Mean $\pm$ SD)	40.7 $\pm$ 11.3	41.5 $\pm$ 12.4	0.792
Males (n, %)	4(13.7%)	5 (19.2%)	0.430
BMI (in kg/m <sup>2</sup> ) (Mean $\pm$ SD)	21.3 $\pm$ 1.9	20.9 $\pm$ 1.2	0.310
Duration of Disease (in years) (Mean $\pm$ SD)	5.1 $\pm$ 4.1	7.7 $\pm$ 5.2	0.043*
ESR (mm 1 <sup>st</sup> hour)	42.8 $\pm$ 18.6	45.2 $\pm$ 21.2	0.659
Rheumatoid Factor (n, %)			
Positive	26 (89.6%)	21 (80.8%)	0.351
Negative	3 (10.4%)	5 (19.2%)	
Disease Severity (DAS 28 Score) (n, %)			
Mild (2.6 - 3.2)	11 (37.9%)	3 (11.6%)	0.030*
Moderate (3.2 - 5.1)	11 (37.9%)	9 (34.6%)	
Severe( >5.1)	7 (24.2%)	14 (53.8%)	
Treatment for Rheumatoid Arthritis (n)			
Methotrexate	21	22	0.274
Hydroxychloroquine	27	25	0.618
Sulfasalazine	3	3	0.887

(\*  $p < 0.05$ - significant)

## DISCUSSION

Although pathological evidence of lung involvement may be present in as many as 40% of patients of Rheumatoid Arthritis, majority of patients may not manifest clinically with respiratory symptoms (3). Therefore many patients of RA with pulmonary involvement are diagnosed when lung pathology is at an advanced stage. The present study was done to evaluate the abnormalities in Pulmonary Function Tests in patients of Rheumatoid Arthritis. Almost all of the RA patients (97.4%) included in this study didn't have any clinical symptom or sign pertaining to respiratory involvement. Three patients had clinical history of exertional dyspnea and dry cough, although no signs of ILD were noticed on respiratory examination.

In our study, pulmonary function tests were normal in 52.8% of Rheumatoid Arthritis patients. Obstructive airway involvement was the most common abnormality seen on PFT (25.4%) whereas restrictive pattern was seen in 16.4% patients. Five percent patients had mixed pattern on PFT. Previous studies done in different populations have shown variable results with regards to prevalence and abnormal patterns on the Pulmonary Function Tests (12-15). In a study done by Perez et al to evaluate the prevalence and characteristics of airways involvement in 50 patients of RA without interstitial lung disease, nine patients (18%) were shown to have obstructive disease on PFT while small airways disease was seen in 4 (8%) patients (12). In another cross-sectional study of pulmonary function tests done in Brazil, Kawasaka et al observed normal spirometry in 69.9% RA patients. Eleven percent patients showed obstructive and restrictive patterns in their study while mixed pattern seen in 4.9% RA patients (13). In a study done to evaluate the functional pulmonary involvement in RA patients in a semi-urban population of Eastern India, Chattopadhyay et al observed normal PFT in 56.6% patients, obstructive lung disease in 15.09% patients and restrictive lung involvement in 28.3% patients (14).

In a longitudinal study of pulmonary function tests in Rheumatoid Arthritis conducted in Tunisia, Avnon LS et al conducted PFTs in 82 patients (21 men, 61 women) which were repeated after five years in 38 out of the 67 surviving patients. The baseline PFT showed normal result in 36.6% patients. Restrictive ventilator defect was seen in 25.6% patients whereas 17% patients had a small airway abnormality. In the follow up study after 5 years, clinical symptoms were reported by 8 patients, while one patient had a new obstructive ventilatory defect, one patient developed a restrictive ventilatory defect, and 5 patients had a newly developed small airway defect. Their study concluded that regular monitoring with PFT is indicated in patients of Rheumatoid Arthritis which allows early detection of different ventilatory abnormalities (16).

We compared the demographic and clinical characteristics of RA patients with normal or abnormal PFTs. Patients with abnormal PFT had significantly longer duration of disease as compared to those with normal PFT ( $p < 0.05$ ). The impairment on PFT also correlated significantly with severity of disease activity as measured by DAS 28 score. Majority of patients with normal PFT had mild to moderate disease activity, whereas abnormal PFT was found in higher proportion of patients with moderate to severe disease activity ( $p < 0.05$ ). In a study done on 40 Iraqi patients of Rheumatoid arthritis, significant correlation of PFT parameters was seen with ESR, articular index and disease activity ( $p < 0.01$ ) (17). In another similar study, Biomdo I et al assessed the pulmonary function in rheumatoid arthritis patients attending Rheumatology clinics in Nairobi. Their findings suggested that age and RA disease activity were the two important factors which showed independent association with pulmonary function test abnormalities (18). In a study of 159 patients of Rheumatoid Arthritis without clinical cardiovascular disease, Pappas DA et al observed that presence of respiratory symptoms in combination with other patient and RA characteristics (BMI, current smoking, Anti-CCP titre and ongoing use of steroids) may be used as a simple clinical tool to predict pulmonary function tests abnormalities in patients of RA, thereby helping to identify the patients who require detailed pulmonary evaluation (19).

One of the limitations of our study was that radiological evaluation using high resolution CT was not done to collaborate the PFT findings. Also since it was only a cross-sectional study, the follow up of the patients regarding progression of pulmonary involvement was not included in the study.

## CONCLUSION

Involvement of the respiratory system is one of the most common extra-articular manifestations of Rheumatoid Arthritis. Pulmonary Function Testing is a simple and easily available method to detect pulmonary involvement in patients of Rheumatoid Arthritis at an early stage. Impairment in PFTs correlates with the duration of disease and severity of disease activity.

## Conflict of interest

No conflict of interest was declared by the authors.

## REFERENCES

1. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376(9746):1094–1108.
2. Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. *Curr Med Res Opin*. 2008 Feb;24(2):469-80.
3. Alunno A, Gerli R, Giacomelli R, Carubbi F. Clinical, Epidemiological, and Histopathological Features of Respiratory Involvement in Rheumatoid Arthritis. *Biomed Res Int*. 2017;2017:7915340.
4. Pinheiro FA, Souza DC, Sato EI. A Study of Multiple Causes of Death in Rheumatoid Arthritis. *J Rheumatol*. 2015 Dec;42(12):2221-8.
5. Ha YJ, Lee YJ, Kang EH. Lung Involvements in Rheumatic Diseases: Update on the Epidemiology, Pathogenesis, Clinical Features, and Treatment. *Biomed Res Int*. 2018 May 8;2018:6930297.
6. Cortet B, Flipo RM, Rémy-Jardin M, Coquerelle P, Duquesnoy B, Rémy J, et al. Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Ann Rheum Dis*. 1995 Oct;54(10):815-9.
7. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. *Chest*. 2005;127:2019–27.
8. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. *Arthritis Rheum*. 2006;54:628-34.
9. 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) 66:803–12.
10. Ranu H, Wilde M, Madden B. Pulmonary function tests. *Ulster Med J*. 2011 May;80(2):84-90.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569–2581.
12. Perez T, Remy-Jardin M, Cortet B. Airways involvement in rheumatoid arthritis: clinical, functional, and HRCT findings. *Am J Respir Crit Care Med*. 1998;157:1658-65.
13. Kawassaki AM, Pereira DA, Kay FU, Laurindo IM, Carvalho CR, Kairalla RA. Pulmonary involvement in rheumatoid arthritis: evaluation by radiography and spirometry. *J Bras Pneumol*. 2015 Jul-Aug;41(4):331-42.
14. Chattopadhyay K, Chaudhuri A, Hussain SA, Biswas A. A comparative study of functional pulmonary involvement in patients with rheumatoid arthritis in a semi-urban population of Eastern India. *Saudi J Sports Med* 2015;15:26-30.
15. Ben Fredj H, Ben Saad H, Mhaouech N, Bouajina I, Tabka Z, Rouatbi S. [Pulmonary function in rheumatoid arthritis in a Tunisian population]. *Tunis Med*. 2013 Apr;91(4):248-53.
16. Avnon LS, Manzur F, Bolotin A, Heimer D, Flusser D, Buskila D, Sukenik S, Abu-Shakra M. Pulmonary functions testing in patients with rheumatoid arthritis. *Isr Med Assoc J*. 2009 Feb;11(2):83-7.
17. Al-Assadi T, Al-Shemery A, Salman S. Correlation of Lung Function with Disease Activity Rheumatoid Arthritis. *Oman Medical Journal*. 2009;24(2):84-88.
18. Biomdo I, Oyoo GO, Mecha J, Chakaya M. Assessment of pulmonary function in rheumatoid arthritis patients attending rheumatology clinics in Nairobi. *Afr J Rheumatol*. 2013; 1(2): 64–69.
19. Pappas DA, Giles JT, Connors G. et al Respiratory symptoms and disease characteristics as predictors of pulmonary function abnormalities in patients with rheumatoid arthritis: an observational cohort study. *Arthritis Res Ther*. 2010; 12(3):R104.