Correlation With Disease Activity Score 28 (Das28) With Pulmonary Function Test In Rheumatoid Arthritis Patients

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic inflammatory disease of unknown etiology involving both small and large joints with many extra-articular manifestations. There may be a variety of pulmonary complications associated with RA based on its disease activity and levels of RF and anti-CCP titers. Pulmonary involvement may be seen at different levels of the respiratory system, with infection being the most common cause of mortality. Our study shows the association and degree of pulmonary involvement in patients with RA based on the pulmonary function test and its correlation with the DAS 28 score. The aim of our study was to assess the prevalence of pulmonary involvement in patients with Rheumatoid Arthritis. The study population was 100 patients with RA diagnosed based on the 2010 ACR/EULAR criteria following all the exclusion. The patients were subjected to a PFT on diagnosis and repeated at 6 and 18 months following treatment. In our study, there is a higher prevalence of pulmonary involvement seen in doing PFT, even in asymptomatic patients with RA when compared to other studies. Pulmonary complications occurring in patients with Rheumatoid Arthritis may be identified on doing a PFT or HRCT thorax. Pulmonary involvement carries significant mortality and morbidity. Disease duration and disease activity score 28 were found to have a significant association with pulmonary complications. Although our study brings out the incidence of higher risk of pulmonary involvement in patients with RA, more studies meta-analysis are required.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease of unknown etiology characterized by joint swelling, joint tenderness and destruction of synovial joints predominantly affecting the small joints with other extra-articular manifestations leading to severe disability and premature mortality (Aletaha *et al.*, 2010; Fatima *et al.*, 2013).

The prevalence of RA in the general population ranges from from0.5% to 2% (Anaya *et al.*, 1995). All races are affected and women are commonly affected. The onset of illness frequently occurs during the fourth and fifth decade (Zohal *et al.*, 2012).

Although RA is considered a disease of the joints, a variety of extra-articular manifestations result in an effect of immune-mediated mechanism. In some cases, the production of Rheumatoid Factor (RF) with the formation of immune complexes that fix complement causes extra-articular manifesta-

tions (Anaya *et al.*, 1995). Pulmonary disease is an important extra-articular manifestation of RA with autopsy studies suggesting that it is the second most common cause of death (10 to 20%) after infections (Wilsher *et al.*, 2012; Perez *et al.*, 1998). It has been estimated that nearly 50% of RA patients will develop some form of pulmonary abnormality during their lifetime (Hamblin and Horton, 2011).

RA can potentially affect all compartments of the lung (airways, parenchyma, vascular) or may coexist with the involvement of the pleura (Massey *et al.*, 2013). The mean age of onset of lung diseases is the fifth to the sixth decade (Al-Assadi *et al.*, 2009). Smokers and patients with high titer of Rheumatoid Factor (RF) are at higher risk of developing pulmonary complications (Lamblin *et al.*, 2001).

Aim & Objectives

The primary aim of the study is to detect a pulmonary pattern in an asymptomatic patient with a pulmonary function test in Rheumatoid arthritis and improvement in pulmonary function test following treatment and its correlation with DAS28. The objectives of the present study were, to identify the prevalence of lung involvement in patients with RA, other factors contributing for pulmonary diseases in patients with RA, to evaluate the clinical and spirometric features of pulmonary abnormalities in diagnosed cases of RA and evaluate the impact of treatment on pulmonary abnormality detected in RA.

MATERIALS AND METHODS

This was a hospital-based observational and descriptive study enrolling 100 consecutive patients with RA attending the rheumatology outpatient department in the Saveetha Medical College Hospital, Chennai, Tamilnadu, India from 01/04/2017 to 31/11/2018. In this study, a sample size of 100 patients diagnosed with rheumatoid arthritis (according to THE ACR/EULAR 2010 CLASSIFICATION CRITERIA\) will be assessed on the basis of the pulmonary function test and DAS28 on the day of diagnosis. The measurements used in data analysis are (1) FVC% (2) FEV1% and (3) FEV1: FVC ratio. The FVC and FEV1 are reported as a measured volume in liters and as a percentage of the predicted or reference value for an individual of that age, height, gender and ethnicity. FEV1: FVC ratio was calculated from the measured volume in liters and then the percentage was taken. Done using a single spirometry machine then repeated after 6 months and 18months.

The study included all patients during the period of study between the age of 18-70 years, patients attending clinics of the Medicine and Rheumatology departments and individuals satisfying 2010 ACR/EULAR classification criteria for RA. Patients were excluded for, not giving consent, patients with malignancy, post-transplant and post-radiotherapy immune suppression (due to potential confounding effects on data analysis), active infection and HIV/AIDS, patients with signs and symptoms of respiratory diseases(Cough, SOB, chest, pain, sputum production, cyanosis, edema and clubbing), systemic pulmonary diseases, Smoker and ex-smoker, chest wall and spinal deformity and failure to produce acceptable and reproducible spirograms.

Study method

Patients were confirmed to have RA according to the following 2010 ACR/EULAR criteria:

Joint involvement

Joints involved ——————— Score

1 large joint —————————— 0

2-10 large joints ————————— 1

1-3 small joints —————————— 2

4-10 small joints ———————— 3

>10 joints —————————————— 5

Serology

Serology ———————————— score

Negative rheumatoid factor and negative Anti-CCP ———— 0

Low positive rheumatoid factor and negative Anti-CCP ———— 2

High positive rheumatoid factor and negative Anti-CCP ———— 3

Acute phase reactants

Acute phase reactants ——————— score

Normal ESR ——————————— 0

Abnormal ESR ——————————— 1

Duration of symptoms

Duration of symptoms ——————— score

<6 weeks ——————————————— 0

>6 weeks ——————————————— 1

A score of more than 6/10 was necessary to confirm that a patient had definite RA.

Assessments

Disease Characteristics

In patients with RA, various disease characteristics like age, sex, duration, comorbidities, treatment history, ESR, Rheumatoid Factor and the presence of

deformities were assessed. In patients with RA disease activity was assessed by the Disease Activity Score (DAS28), calculated by using characteristics of RA: swollen joints and tender joints, visual analog scale (VAS) and ESR. Online calculator http://www.das-score.nl was used to calculate DAS28.

The following formula was used to calculate DAS:

$$DAS28 = 0.56 \times \sqrt{(28TJ)} + 0.28 \times \sqrt{(28SJ)} + 0.70 \times LN\,(ESR) + 0.014 \times VAS$$

(TJ = tender joints; SJ= swollen joints; VAS= patients general health on a visual analog scale)

A DAS28 score of >5.1 was considered to be high disease activity, a DAS28 score between 5.1 and 3.2 is considered moderate disease activity, a DAS28 score between 2.6 to 3.2 is considered low disease activity and DAS28 score below 2.6 considered remissions.

Assessment of Pulmonary Involvement

All the patients were evaluated with the history of previous diseases, pulmonary symptoms such as cough and phlegm, dyspnea, chest pain and wheezing. The Laboratory tests requested for the patients included: assessment of Rheumatoid Factor (RF), Erythrocyte Sedimentation Rate (ESR) and Anti-Cyclic Citrullinated Peptide (Anti CCP).

Statistics analysis

Descriptive statistics such as percentage, mean, standard deviation and median were used to describe the variables used in the study. Quantitative and qualitative data were analyzed using t-tests and chi-square tests, respectively. Logistic regression was used to calculate the Odds Ratio (OR) and confidence interval of the variables. *P* values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

On day 1, 75% of patients were normal, 22% of patients were restrictive and 3% of patients were obstructive. After 6 months, 78% of patients were normal, 19% of patients were restrictive and 3% of patients were obstructive. After 2 years, 85% of patients were normal, 12% of patients were restrictive and 3% of patients were obstructive. The comparison was made by the chi-square test. The results showed that there is no significant difference in pulmonary function tests with respect to time (p=0.456).

The chi-square test shows that there is a significant correlation between duration of illness and pulmonary functional test (day 1) (p< 0.001).

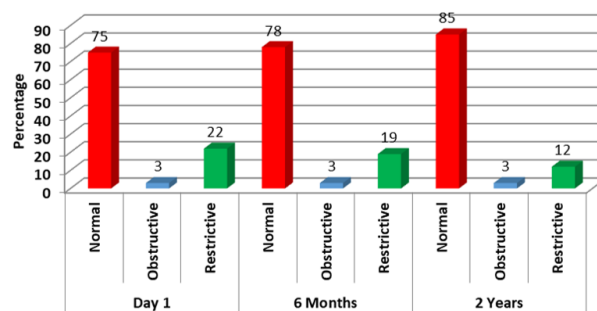The present prospective study enrolled 100 patients diagnosed with Rheumatoid Arthritis (RA) who
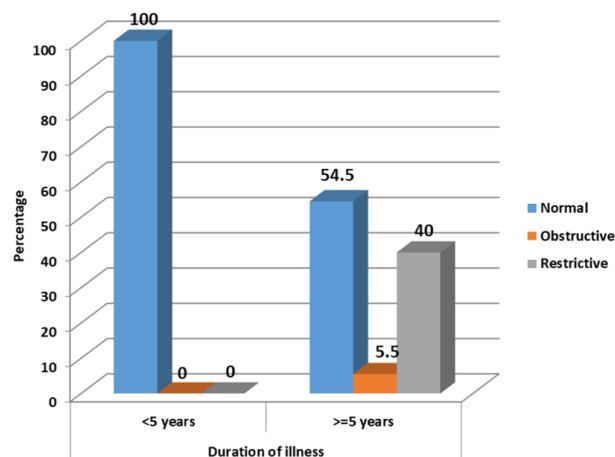

Figure 1: Pulmonary Function Test

Figure 2: Correlation of duration of illness and pulmonary functional test (day 1)

attended the Rheumatology Clinic at the Saveetha Medical College Hospital, Chennai, Tamilnadu, India with the objectives of defining their disease characteristics and ascertaining the prevalence of respiratory complications.

Demographics

The mean age group of the study population was 47.3 ± 11.2 years. In the study population majority of patients were between 30-50 years (58%). 35% of patients were more than >50 years and 7% of patients were less than <30 years (Table 1). The mean age of patients with pulmonary involvement was 50.6 ± 9.4 years and the mean age of patients without pulmonary involvement was 46.7±11.4 years.

In the study population, female patients predominated over males, 89% were females and 11% were males (Table 2). The study was done by (Zohal *et al.*, 2012), and (Chen *et al.*, 2013) supported the finding of females were more than males.

Characteristics of RA

In the study group, the mean duration of illness was 6.4 ± 5.5 years (Table 3). In our group, 55% of patients had a duration of more than 5 years and 45% of patients had a duration of less than 5 years.

Table 1: Age Distribution

Age	No. of cases	Percentage
<30 years	7	7%
30-50 years	58	58%
>50 years	35	35%
Total	100	100%

The majority of patients were between 30-50 years (58%). 35% of patients were more than >50 years and 7% of patients were less than <30 years

Table 2: Sex Distribution

Sex Distribution	No. of cases	Percentage
Male	11	11%
Female	89	89%
Total	100	100%

The maximum numbers of patients were females (89%). 11% of the patientswere males

Table 3: Duration of Illness

Duration of Illness	No. of cases	Percentage
<5 years	45	45%
>=5 years	55	55%
Total	100	100%

The maximum number of patients had the illness for more than 5 years (55%). 45% of patients had an illness for less than 5 years

Table 4: Treatment History

Treatment History	No. of Cases	Percentage
Steroids	90	90%
Methotrexate	80	80%
Sulphasalazine	60	60%
HCQ	50	50%
NSAIDs	10	10%
Vit D+C	60	60%
Leflunomadie	10	10%

The majority of patients had Steroids (90%), 80% of patients had Methotrexate and 50% of patients had HCQ

Table 5: Rheumatoid Factor (RF)

Rheumatoid Factor	No. of Cases	Percentage
Positive	87	87%
Negative	13	13%
Total	100	100%

Out of 100 patients, most of them had a positive Rheumatoid factor (87%)

Table 6: Anti CCP

Anti-CCP	No. of Cases	Percentage
Positive	73	73%
Negative	27	27%
Total	100	100%

The majority of patients had positive Anti-CCP (73%)

Table 7: Deformities

Deformities	No. of Cases	Percentage
Present	34	34%
Absent	66	66%
Total	100	100%

Deformities were presented in 34% of patients

Table 8: Pulmonary Function Test

Pulmonary Function Test		No. of Cases	Percentage
Day 1	Normal	75	75%
	Obstructive	3	3%
	Restrictive	22	22%
6 Months	Normal	78	78%
	Obstructive	3	3%
	Restrictive	19	19%
18 months	Normal	85	85%
	Obstructive	3	3%
	Restrictive	12	12%

Chi-Square Value = 3.645; P-value = 0.456; Not Significant

Table 9: Correlation of duration of illness and pulmonary functional test (day 1)

			Pulmonary Functional Test (Day 1)			Total
			Normal	Obstructive	Restrictive	
Duration of illness	<5 years	Count	45	0	0	45
		% within Duration of illness	100.0%	.0%	.0%	100.0%
	>=5 years	Count	30	3	22	55
		% within Duration of illness	54.5%	5.5%	40.0%	100.0%
Total		Count	75	3	22	100
		% within Duration of illness	75.0%	3.0%	22.0%	100.0%

Chi-Square Value = 27.273; P value = < 0.001; Significant

Table 10: Correlation between DAS score and PFT result on day 1

	Pulmonary Functional Test (Day 1)	N	Mean	Std. Deviation	Std. Error Mean	't' value	P-value
DAS (Day 1)	Obstructive	3	6.1400	.80672	.46576	0.986	0.334
	Restrictive	22	5.7577	.61022	.13010		

The results show that there is no significant difference in the DAS score with respect to the pulmonary function test on day 1 (p=0.334)

Table 11: Correlation between DAS score and PFT result on 6 months

	Pulmonary Functional Test (6 Months)	N	Mean	Std. Deviation	Std. Error Mean	't' value	P-value
DAS (6 Months)	Obstructive	3	5.8800	.86279	.49813	1.381	0.183
	Restrictive	19	5.3300	.61173	.14034		

The results show that there is no significant difference in DAS score with respect to pulmonary functional test after 6 months (p=0.183)

Table 12: Correlation between DAS score and PFT result on 18months

	Pulmonary Functional Test (18months)	N	Mean	Std. Deviation	Std. Error Mean	't' value	P-value
DAS (18 Months)	Obstructive	3	5.5233	.80649	.46563	1.792	0.096
	Restrictive	12	4.8675	.51149	.14765		

The results show that there is no significant difference in DAS score with respect to pulmonary functional test after 18months (p=0.096)

Table 13: Mean and SD of clinical parameters

	Mean	Std. Deviation	Std. Error of Mean
ESR	66.29	26.175	2.617
Hemoglobin	10.991	1.4352	0.1435
DAS (Day 1)	5.4867	0.68388	0.06839
DAS (6 Months)	4.6720	0.91034	0.09103
DAS (18 Months)	3.6339	1.16040	0.11604

3% of patients had a disease duration of less than one year (early RA). In our study, the mean duration of the disease of patients with RA with pulmonary complications was significantly longer (13.5 years vs. 5.3 years, p=0.00). The study done by (Al-Tayyar et al., 2012) from Baghdad showed a significant correlation between the duration of the disease and pulmonary complications.

In our study group, 34% of patients had deformities of RA (Table 7) reflecting the chronicity and inadequacy of therapy. 87% of our patients were seropositive for the RA factor (Table 5). In our study group, 73% were positive for Anti CCP (Table 6).

Pulmonary involvement

This was assessed by pulmonary function tests (Table 8). 15% of our patients had pulmonary complications. Pulmonary involvement was common in RA (Figure 1) and many studies reported that 1% to 40% of the patients were affected (Hamblin and Horton, 2011). In patients with RA, lung complications were the second most common of death (10%

to 20%) after infection (Ribéra et al., 2012).

Many studies published showed pulmonary involvement in patients with RA with lung physiology tests. The study by Remy-Jardin et al. (1994) in 84 patients showed pulmonary involvement in 49% of cases. The study by Suzuki et al. (1994) in 84 patients showed pulmonary involvement in 34.6% of patients. The study by Zrour et al. (2005) in 75 patients showed pulmonary involvement in 49.3% of patients. The study by Geddes et al. (1979) in 100 patients showed pulmonary involvement in 32% of cases. The study by Perez et al. (1998) in 50 patients showed pulmonary involvement in 70% of cases. The study by Fuld et al. (2003) in 52 patients showed pulmonary involvement in 8.7% of patients. In our study, lung involvement was found in 14% of patients with RA. Interstitial lung disease and bronchiectasis were the commonest types of lung involvement in RA.

The incidence of lung involvement in the above-mentioned studies was higher than the rate in our

study (15%) (Table 9), (Figure 2). These differences have been due to less disease duration, lower disease severity and a patient seeking treatment in the early phase.

In our study, abnormalities in the pulmonary function test was a sensitive indicator for the diagnosis of a pulmonary complication of RA. HRCT thorax is also a sensitive test to identify pulmonary complications of RA. Therefore we suggest obtaining HRCT thorax and Pulmonary function tests at regular intervals in all patients with RA to help decide on aggressive therapy to delay the progression of the disease.

In our study, the chi-square test shows that there is a significant correlation between duration of illness and pulmonary functional test ($p < 0.001$). The results show that there is no significant difference in the DAS score with respect to the pulmonary functional test ($p=0.183$) (Table 10, Table 11, Table 12, Table 13).

A population-based study by Bongartz *et al.* (2010) found a significant relationship between disease activity and ILD in RA patients. A study done by Al-Assadi *et al.* (2009) from Oman in 2009 found a significant relationship between disease activity and pulmonary involvement.

We found no significant relation between pulmonary complications and characteristics like RA factor, ESR, smoking, hemoglobin and drugs like methotrexate and steroids (Table 4). Larger studies, including more number of patients with RA, is required to answer these relations. (Terasaki *et al.*, 2004)

Limitations of this study

1. A small number of patients

2. Institution-based study

CONCLUSION

Pulmonary complications occur in patients with Rheumatoid Arthritis. Pulmonary involvement carries significant mortality and morbidity. Patients with RA should be evaluated with pulmonary function tests and HRCT thorax at regular intervals for early diagnosis and to delay the progression of the disease. In this study, Disease duration and disease activity score 28 were found to have a significant association with pulmonary complications. Larger studies, including more RA patients, are required to answer the relation of various other disease characteristics with pulmonary involvement.

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