Pulmonary function test with DAS28 score and duration of Rheumatoid arthritis: A comparative analysis

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Abstract:
Background: Pulmonary involment in Rheumatoid arthritis is major health concern in the field of rheumatology. Evidence suggests one of commonest cause of mortality in RA.
Objective: We found the abnormalities of pulmonary function test in patients with Rheumatoid Arthritis in tertiary care centre.
Patients and Methods: This is a comparative, analytical, cross sectional, Institution- based, single centre study.We included all adult willing patients of Rheumatoid arthritis (age >18) and selected them based on 2010 ACR/EULAR criteria. Severity was assessed by number of joints involve in both upper & lower limb, along with ESR, CRP, Anti CCP level. Pulmonary function tests were performed on RA patients with or without abnormal HRCT patterns using a standard protocol. Forced expiratory volume in the first second (FEV1), FEV1/FVC ratio (a sensitive index of overall airway obstruction), and forced expiratory flow from 25% to 75% of VC (FEF25–75, a specific index of small airway function).
Results: Present study conducted in 50 patients of Rheumatoid arthritis who meet the inclusion criteria.Out of 50 RA patients, pulmonary involvement was observed in 25 patients , identified by Spirometry, CXR, HRCT. Mean age of the patients was   35.01 ranging from 26 to 56 years.Out of 50 RA patients 14 was male and 36 was female. Though RA is more common in female sex but pulmonary involvement was more common in male sex.Pulmonary involvement is more common in age group < 40 years. There is a significant correlation between DAS28 score(indicator of disease activity) with pulmonary involvement. Patients having high disease activity , more is the pulmonary involvements. Most common form of pulmonary involvement is ILD followed by obstructive lung disease like chronic bronchitis, bronchiectasis etc. HRCT is the most common stool for detection of Pulmonary involvement in Rheumatoid arthritis.HRCT abnormality, most are Restrictive on spirometry (FEV1/FVC) < 80% of predicted value. And this relation is statiscally significant as P value is 0.001(<0.05) by Chi-Square test.Patients having more the disease duration, more the pulmonary involvement. This association is statically significant as p value is 0.001 (<0.05).
Conclusions: Pulmonary function test is the cheapest and bedside tool to detect the pulmonary involvement in rheumatoid arthritis.
Keywords: Rheumatoid arthritis, Pulmonary Function Test, Pulmonary involment

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I.   Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints.[1] It typically results in warm, swollen, and painful joints.[2] Pain and stiffness often worsen following rest.[3] Most commonly, the wrist and hands are involved, with the same joints typically involved on both sides of the body.[4] The disease may also affect other parts of the body.[5] This may result in a low red blood cell count, inflammation around the lungs, and inflammation around the heart.[6] Fever and low energy may also be present.[7] Often, symptoms come on gradually over weeks to months.[8]

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors.[9] The underlying mechanism involves the body's immune system attacking the joints.[10] This results in inflammation and thickening of the joint capsule.[11] It also affects the underlying bone and cartilage.[12] The diagnosis is made mostly on the basis of a person's signs and symptoms.[13] X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms.[14] Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others.[15]

RA affects approximately 0.8-1.2%of the adult population worldwide. The prevalence and incidence of RA varies based on geographic location, both globally and certain ethnic groups within a country. For example,

the Native American Yakima, Pima, and Chippewa tribes of North America have reported prevalence rates in some studies of nearly 7% . In contrast , many population studies from Africa and Asia show lower prevalence rates in the ranges of 0.2 – 0.4%. Like many other autoimmuno diseases, RA occures more commonly in female than in males, with a 2-3:1 ratio. Interestingly, studies of RA from some of the Latin American and African countries show an even greater predominance of disease in females compare to males, with ratio of 6-8: 1. Given this preponderence of females , various theories have been proposed to explain the possible role of estrogens in enhancing the immuno response. For example some experimental studies have shown that estrogen can stimulate production of tumor necrosis factor a(TNF-a), a major cytokine in the pathogenesis of RA[16].

The pulmonary involvement in RA can be due to various causes including infection ,drug toxicity and specific manifestation of immune processes. Pulmonary involvement contributes significantly to morbidity and mortality of patients with RA and is the 2nd most common cause of it.

It has been estimated that nearly 50% RA patients will develop some form of respiratory problem during their lifetime. Pleural disease (with or without pleural effusion) ,Interstitial lung disease(ILD) and Rheumatoid lung nodules are the most frequent manifestation with prevalence varying according to the investigation employed. Respiratory involved patient may be clinically asymptomatic, however spirometry, CXR, HRCT thorax is used to estimate course, prognosis and response to therapy. I have decided to conduct the study to see positive changes pulmonary function test in patients with rheumatoid arthritis.

II. Objectives

Aims of this study are to find out the abnormalities of pulmonary function test in patients with Rheumatoid Arthritis in tertiary care centre so as to take necessary steps for intervention and early detection and thereby reducing the chance of pulmonary dysfunction which leads to mortality and morbidity of the patient.

III. Patients and Methods

STUDY AREA: The study has been conducted in the Rheumatology unit and department of General Medicine of Midnapore Medical College and Hospital situated in Paschim Medinipur district of West Bengal. The main catchment area is rural with few township and Municipal area covering Purba and Paschim Medinipur, Purulia districts of West Bengal as well as adjoining areas of Orissa and Jharkhand. The study involves the Department of General Medicine, Biochemistry , Pathology, Radiology and chest medicine for necessary laboratory tests and investigation data.

STUDY PERIOD: Period of twelve months from February 2016 to January 2017.

SAMPLE SIZE: 50 Patients of Rheumatoid Arthritis were digonised according to the 2010 ACR/EULAR classification criteria for rheumatoid arthritis and clinically assessed by rheumatologist.

SAMPLE DESIGN: This is a comparative, analytical, cross sectional, Institution- based, single centre study. The study was approved by the Institutional Ethics Committee of the Hospital. Written and informed consent was taken from each of the study subjects. The subjects were selected randomly, only they had to satisfy the inclusion and exclusion criteria.

INCLUSION CRITERIA:

1) All adult patients(age>18 years)

2)All patients who are willing to participate in the study.

3)The subject to the study will be selected based on The 2010 ACR/EULAR classification criteria for rheumatoid arthritis.

EXCLUSION CRITERIA:

Subject with respiratory illness.

Subject with cardiac diseses.

Subject with thoracic abnormality.

Subject with vertebral abnormality.

Subject with Methotrexate theraphy.

Subject with congenital anomaly.

Subject with genetic disorder.

Smoker

In each case a full history was taken and a complete clinical examination done. Severity was assessed by number of joints involve in both upper & lower limb, along with ESR, CRP, Anti CCP level. Special enquiry was made regarding previous history of respiratory diseases including pneumonia, pleurisy, pulmonary tuberculosis and other chest illness. A record was made regarding smoking history. All patient underwent routine investigation including Hb, CBC, ECG , ESR, Urea and Creatinine. Titers of rheumatoid factor (RF) were determined by laser nephelometry. A titer 40 IU was considered to indicate seropositivity. Antinuclear

antibodies (ANAs) were detected by indirect immunofluorescence with the HEP2 cell line. Pulmonary function tests were performed on RA patients with or without abnormal HRCT patterns using a standard protocol. Forced expiratory volume in the first second (FEV1), FEV1/FVC ratio (a sensitive index of overall airway obstruction), and forced expiratory flow from 25% to 75% of VC (FEF25–75, a specific index of small airway function).

Results were expressed as percentages of predicted values[17], and FEV1 reversibility was defined as an increase in FEV1 as a percentage of the initial value. Airway obstruction was defined by a decrease in the FEV1/VC ratio of more than 11.8% from predicted values in men and 10.7% in women[17]. Small-airways disease (SAD) was defined by a decreased FEF25–75

All cases were subjected to Chest X-Ray both AP and lateral view.X-Ray of both palm & sole including wrist joint s elbow, knee joints also taken. High-resolution CT Scan examinations were performed with a Somatom Plus S CT unit (Siemens, Erlangen, Germany). Scans were obtained with 1-mm-thick sections at 10-mm intervals, extending from the lung apices to below the costophrenic angles.

Data collected during study was entered in Microsoft Excel spread sheet, analyzed statistically using appropriate biomedical software like SPSS for Windows 20.0 statistical package program. The quantitative data of the groups were compared using ANOVA (Analysis Of VAriance) and the qualitative data were compared using Chi-square tests.
A P value of <0.05 was considered statistically significant

IV. Results

Table No. 1 : Baseline characteristics of study patients (n=50)

PARAMETERS	VALUE
Age (in years, N50, mean ± SD)	35.01 ± 5.01
SEX (M::F)	28%::72%
Disease duration(<3yrs::>3yrs)	34%::66%
ESR (mean ± SD)	26.7 ±18.3
CRP (mean ± SD)	18.7 ± 13.82
DAS 28	5.04 ± 1.33
FEV1/FVC	96.46 ± 10.94
CXR (Normal :: Abnormal)	86% :: 14%
HRCT Normal :: Abnormal)	74% :: 26%
Spirometry (normal::rest::obst)	66.66% :: 25% :: 8.34%

Table no 2 : Age distribution of RA patients

Age Distribution	No.	%
20-40	39	78
>40	11	22

Table shows maximam RA patients between the age group of 20-40 years(78%).

Table no 3: Sex distribution of the patients.

Sex Distribution	No.	%
Male	14	28
Female	36	72

Table shows 72% of the patients are female and 28 % are male. That means RA is more common in female compare to male

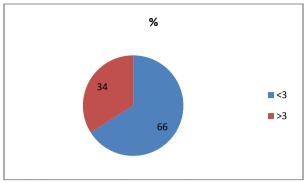**Table no 4:** Association of age with sex of the patients

Age Groups	Male		Female	
	No.	%	No.	%
20-40	10	20	29	58
>40	4	08	7	14

Table shows most RA patients is between age group of 20-40 in both male and female sex.

Table no 5: Distribution of patients according to disease duration .

Disease duration (yrs)	No.	%
<3	33	66
>3	17	34

Table shows majority of the RA patients having disease durations between 0- 3 years(66%) followed by disease durations >3 years in 34%.
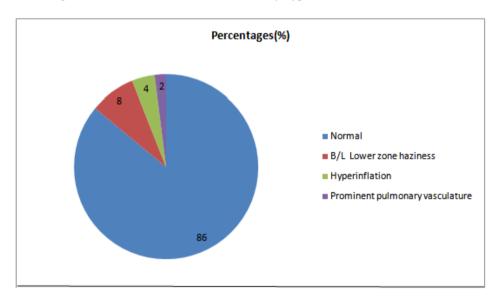
Pie diagram showing patients distribution as per disease durations.

Table no 6: Chest X ray findings.

Chest X Ray	No of patients(n)	Percentage(%)
Normal	43	86
B/L Lower zone haziness	4	8
Hyperinflation	2	4
Prominent pulmonary vasculature	1	2

Table shows majority of C-X-R are normal (86%).C-X-R abnormality observed in 14 % of patients. Most common CXR finding is B/L lower zone haziness followed by hyperinflation.
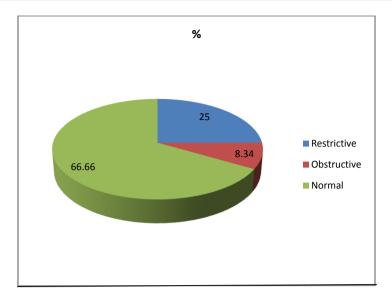

 Pie chart showing chest x ray findings in RA patients.

Table no 7 : Spirometric changes (FEV1/FVC) in RA patients

Spirometric pattern	No.	%
Restrictive	12	25
Obstructive	4	8.34
Normal	32	66.66

Table shows most common finding is Restrictive changes(25%) followed by obstructive changes(8.34%).
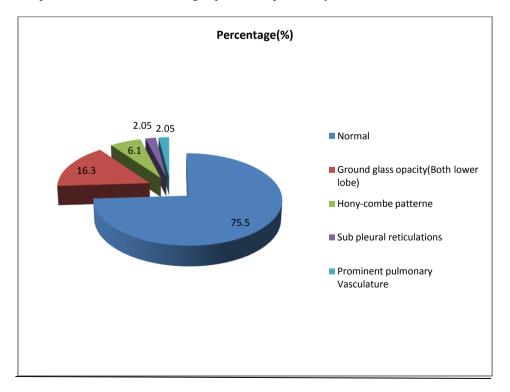
Pie chart shows spirometric changes (FEV1/FVC) in RA patients

Table no 8 : HRCT findings in RA patients.

HRCT Findings	No of patients	Percentage(%)
Normal	37	75.5
Ground glass opacity(Both lower lobe)	8	16.3
Honey-comb patterns	3	6.1
Sub pleural reticulations	1	2.05
Prominent pulmonary Vasculature	1	2.05

Table shows most common HRCT findings is ground glass opacity in both lower lobe of lung (16.3%) followed by honey comb patterns in 6.1%. least finding is prominent pulmonary vasculature.
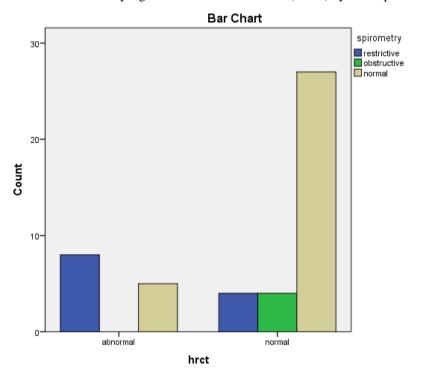

Pie diagram showing HRCT abnormality in RA patients.

Table No. 9 : Correlation of pulmonary involvement in relation of HRCT and Spirometry (FEV1/FVC) findings.

			Spirometry			Total	P Value (Chi Square test)
			restrictive	obstructive	Normal		
HRCT	Abnormal	Count	8	0	5	13	0.001
		% within hrct	61.5%	0.0%	38.5%	100.0%	
	Normal	Count	4	4	27	35	
		% within hrct	11.4%	11.4%	77.1%	100.0%	
Total		Count	12	4	32	48	
		% within hrct	25.0%	8.3%	66.7%	100.0%	

Table shows among HRCT abnormality, most are Restrictive on spirometry (FEV1/FVC) < 80% of predicted value. And this relation is statiscally significant as P value is 0.001(<0.05) by Chi-Square test.

Bar diagram shows association of HRCT findings with Spirometry(FEV1/FVC) findings.

Table No. 10 : Correlation of Chest-X-Ray(CXR) findings with Spirometry findings (FEV1/FVC)

			Spirometry			Total	P Value (Chi Square test)
			restrictive	obstructive	normal		
CXR	abnormal	Count	2	2	3	7	0.083
		% within cxr	28.6%	28.6%	42.9%	100.0%	
	normal	Count	11	2	30	43	
		% within cxr	25.6%	4.7%	69.8%	100.0%	
Total		Count	13	4	33	50	
		% within cxr	26.0%	8.0%	66.0%	100.0%	

Table shows among the 7 abnormal CXR spirometry findings are 2 restrictive and 2 obstructive lesions.And this finding is not statistically significant as p value is 0.083 by Chi-Square test (>0.05).

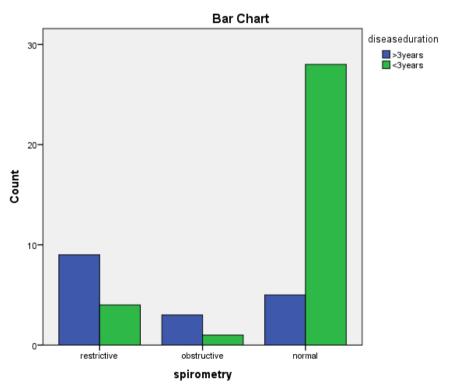**Table No 11 :** Correlation of Spirometry (FEV1/FVC) findings with DAS28 scorings

			DAS28scoring		Total	P Value (Chi Square test)
			>5.1	<5.1		
Spirometry	restrictive	Count	9	4	13	0.066
		% within spirometry	69.2%	30.8%	100.0%	
	obstructive	Count	1	3	4	
		% within spirometry	25.0%	75.0%	100.0%	
	Normal	Count	11	22	33	
		% within spirometry	33.3%	66.7%	100.0%	
Total		Count	21	29	50	
		% within spirometry	42.0%	58.0%	100.0%	

Table showing among the abnormal spirometry, most patient having DAS28 scoring more than 5.1 most spirometry abnormality are restrictive .But this correlation is not statically significant as p value is more than 0.05 .

Table No. 12 : Correlation of Spirometry (FEV1/FVC) with disease duration.

			Disease duration		Total	P Value (Chi Square test)
			>3years	<3years		
Spirometry	Restrictive	Count	9	4	13	0.001
		% within spirometry	69.2%	30.8%	100.0%	
	Obstructive	Count	3	1	4	
		% within spirometry	75.0%	25.0%	100.0%	
	Normal	Count	5	28	33	
		% within spirometry	15.2%	84.8%	100.0%	
Total		Count	17	33	50	
		% within spirometry	34.0%	66.0%	100.0%	

Table shows patients having more the disease duration, more the pulmonary involvement. This association is statically significant as p value is 0.001 (<0.05).

Bar diagram shows relationship of Spirometry with duration of disease.

V. Discussion

The prevalence of RA is around 1% worldwide. The information about prevalence of RA in India is scarce[18] . In a study on the prevalence of rheumatoid arthritis in the adult Indian population by Malviya *et al.*, a prevalence rate of 0.75% was found [19]. The Indian prevalence rate (0.9%) almost equals the world prevalence rate[20] . Our study showed a slightly higher prevalence rate (1.1%)(50 out of 4300 randamly selected patient in OPD and indoor). This could be because the patients included were those presenting with history of arthralgia.

RA predominantly occurs in females with women suffering 3 - 5 times more than males[21] . This study also revealed a much higher incidence rate (Female:male ratio 2.5:1) among females. The variation in the level of sex hormones of females (oestrogen and progesterone which regulate the inflammatory process) is the main cause of development of RA among them [22].

Of the RA cases studied for pulmonary involvement, nearly one-fourth (26%) gave history of dyspnoea and a productive cough. These symptoms are a common presentation in diffuse interstitial fibrosis of the lung [23]. Dyspnoea may also point towards pleural effusion, pulmonary vasculitis or to a chest infection [23], while wheeze seen in 16% patients may indicate an obstructive pulmonary disease. This finding is corroborated with the finding of Fatima et.al study. They found dyspnoea in 21% patients as a chief complain.[24]

In our study, we found that the most common age group involved by rheumatoid arthritis between 20 to 40, with the youngest being 26 years and the oldest being 46 years old. This result corroborates with previous studies, which show that the mean age is fourth to fifth decade of life in South Asian males. Also this finding is supported by some epidemiological studies done. Panda et.al shows most of the patients from both sexes belonged to the age group of 31 to 40 years (41.7%)

An overwhelming majority of the patients in our study belonged to low socio-economic class. This may be due to the existing demographical profile currently prevalent in this part of rural India. This data supported by study done by Melleet Et al.

Panda et al shows most of the patients having pulmonary involvement (41.7%) had their duration of illness between 5 to 10 years. 27.7% of patients had duration between 1 to 5 years. Mean disease duration was 8.1 years.
But in our study most patients having pulmonary involvement having duration of illness more than 3 years.

In our study the predominant presentation on X-ray Chest was a bilateral lower zone diffuse shadow (8%) predominantly reticular and nodular pattern and prominent pulmonary vasculature. These findings are suggestive of an underlying interstitial lung disease. This study is supported by some study like Gabbay and colleagues[25]   studied 36 patients with RA of less than 2 years' duration using chest films, high-resolution computed tomographic (HRCT) scans, pulmonary function tests (PFTs), BAL characteristics, and technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA) nuclear scan. Fiftyeight percent of the patients had findings suggestive of ILD by at least one of these modalities. In their study, chest radiographs were abnormal in 6%, HRCT in 33%, PFTs in 22%, BAL in 52%, and Tc-99m DTPA nuclear scan in 15% of the patients.

Majority of RA patients had a restrictive pattern on pulmonary function testing (Spirometry) 25%.Which again highlights the presence of lung fibrosis and an underlying interstitial lung disease . 8% of our RA cases had obstructive pattern with airflow obstruction that was most marked when respiratory volumes were low and trapping of air occurred. The mean forced expiratory volume in 1 second and forced vital capacity are reduced. The combination of tobacco smoking and RA is associated with a much higher prevalence of obstructive pulmonary disease [26]. This finding in our study is supported by some other study. F.R Lake et .al showes most common lung abnormality in spirometry in patients of RA is restrictive followed by obstructive[27].

A longitudinal study by Fuld. Et al evaluating asymptomatic nonsmoking patients with rheumatoid arthritis found a slightly higher rate of PFT abnormalities at baseline (8.7% versus 5% of the reference population), but this number did not significantly change over the course of 10 years, leading the authors to question the significance of PFT abnormalities in patients without respiratory symptoms [28].

In the present study a positive correlation is observed between spirometry (FEV1/FVC) findings and DAS28 scoring. Out of 21 patients having DAS28 score > 5.1, spirometry abnormality observed in the form of restrictive or obstructive is 10. That is near about 50%.compare to 29 patients having DAS28 score<5.1 is 7(24%). That means patients having higher DAS28 score , more is spirometry abnormality. Although the association is not statistically significant(p value 0.066) but trend is towards 0.05. this is because of smaller number of sample size in the study. This is new finding in our study.

VI. Conclusion

Though pulmonary function test is not so sensitive to detect very early pulmonary involment in rheumatoid arthritis but it should be done in every case of rheumatoid arthritis because it is cheap and portable tool.

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