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A CROSS-SECTIONAL STUDY OF PULMONARY MANIFESTATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS IN A TERTIARY CARE CENTRE

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ABSTRACT

Background: Rheumatoid Arthritis (RA) is a systemic inflammatory condition, influenced by the interplay of genetic and environmental factors that impact its development and expression. A typical extra-articular symptom of RA is pulmonary involvement, which encompasses diseases of the airways, parenchymal nodules, pleurisy, and interstitial involvement. Among these, RA-related interstitial lung disease (RA-ILD) detected in up to 60% of RA patients through high-resolution computed tomography (HRCT), is the most prevalent lung issue with the worst prognosis and mortality, affecting 30–40% of patients. Mortality in RA is highest within the first 5 to 7 years following diagnosis. In addition to pulmonary function tests (PFTs), other non-invasive methods, such as HRCT lungs, have proven valuable in assessing rheumatoid lung disease. However, the study between PFT parameters and HRCT findings in RA patients in this part of India, Manipur has not been thoroughly reported. Therefore, this study aims to investigate the pulmonary manifestations in RA patients using both HRCT and PFTs. **Materials and Methods:** This is a cross sectional Hospital based study conducted in the Department of Medicine RIMS, Imphal for a period of two years from April, 2023 to February, 2025. Patients of age 18 years and above, diagnosed RA having pulmonary manifestation, attending Medicine OPD, Chest medicine OPD and patients admitted in Medicine wards, RIMS, Imphal were enrolled. Routine blood tests included complete Blood Count (CBC), Liver function test (LFT),Kidney function test (KFT),Urine Routine analysis, Rheumatoid Factor (RF), Anti-Cyclic Citrullinated Peptide (Anti-CCP),C-Reactive Protein (CRP) Erythrocyte Sedimentation Rate (ESR) and Electrocardiogram (ECG). Pulmonary involvement was assessed using a combination of chest X-rays, pulmonary function tests (PFTs), and high-resolution computed tomography (HRCT) scans. A p value<0.05 was considered as statistically significant. **Result:** A total of 130 patients diagnosed with RA and associated pulmonary manifestations were assessed with the mean age being 48.32±12.40 years and majority (106, 81.5%) were females. Cough was the predominant symptom (68, 52.3%) followed by wheeze (26, 20%) and dyspnoea (43,33.1%). Most of the patients (64, 49.2%) had been living with RA for 5-10 years, and (40, 30.8%) patients had the disease >10 years. X-ray revealed bilateral lower zone haziness in (79, 60.8%) subjects, reticulo-nodular pattern in (39, 30%) patients and prominent vascular markings in (12, 9.2%) patients. Pulmonary function tests (PFTs) revealed a restrictive pattern in majority (80, 61.5%) of the patients. The spectrum of HRCT abnormalities were as follows: decreased attenuation ((108, 83.1%), bronchiectasis ((76, 58.5%), bronchial wall

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thickening (68, 52.3%), ground glass opacification (32, 24.6%), and reticulo-nodular pattern (36, 27.7%). Pleural effusion was seen in (44, 33.8%) and pleural thickening in (20, 18.5%) patients. **Conclusion:** The study concluded that pulmonary manifestations are very common in RA and often remain clinically silent, especially in the early stages of the disease. These findings underscore the importance of early pulmonary screening using chest X-rays ,PFTs and HRCT scans and monitoring in RA patients particularly older individuals, those with long-standing disease, males, and those with co-morbidities, to facilitate timely diagnosis and management of respiratory complications. The study emphasizes that physicians should always consider the possibility of pulmonary manifestations when evaluating RA patients to ensure optimal treatment and management.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the synovium, leading to joint damage and bone destruction and causes severe disability and increases mortality.[1]It is a common multisystemic disease that characteristically affects small, diarthrodial joints in a progressive, symmetric and erosive fashion affecting approximately 0.5–1% of the population. The prevalence of RA in the general population ranges from 0.5% to 2%, and women 40 years old and over is more commonly affected. The most common extra-articular manifestation of longstanding RA and the second cause of death after infection is pleuro-pulmonary involvement.[2]Although the majority of RA-related deaths is associated with cardiovascular disease, 10 to 20% of all mortality were seen with pulmonary complications. After the initial diagnosis within the first 5 years, lungs are commonly involved. All anatomic compartments of the lung are affected by RA, which includes the lung parenchyma, large and small airways, pleura and to lesser extent the vasculature.[3] The greatest concern is interstitial lung disease (ILD) with fibrotic ILD being the most severe form.[4]

There can be identification of lung disease in early symptomatic RA as well as before the articular symptoms onset of RA.[5] It is not clear whether all of the pulmonary manifestations of RA are present at the outset or indeed precede the articular manifestations of the disease.[6] Lung disorders, particularly ILD or certain airways diseases (e.g., bronchiolitis or bronchiectasis), are common in patients with RA and may also predate the articular manifestations of RA.[7]

Lung involvement is the most common extra-articular manifestation of RA affecting up to 60% of patients with RA during the course of the disease. Any lung compartment can be involved in RA: interstitial lung disease (ILD) or rheumatoid nodules (parenchyma); pleural inflammation and/or effusions;cricoarytenoiditis, constrictive or follicular bronchiolitis and bronchiectasis (involving small and large airways); vasculitis and pulmonary hypertension (where pulmonary vasculatures are affected).[8]

Rheumatoid arthritis- interstitial lung disease (RA-ILD), is associated with significant morbidity and mortality, seen more commonly in men, especially with high titres of rheumatoid factor (RF), and greater articular disease severity. Although ILD is a well-known manifestation of RA, small-airway involvement may be the most common form of RA lung involvement.[9,10] Interstitial lung disease, pulmonary nodules and pleural effusions are the common manifestations of lung involvement while rheumatoid pulmonary vasculitis is rare. Although previous studies commonly describe interstitial involvement of the lungs such as fibrosing alveolitis, in practice a wide range of pathological changes have been noted in the interstitium of the lungs in patients with RA. Invasive investigations have been previously required to establish affirm histological diagnosis in such patients and to provide guidance as to therapy and prognosis. However, the advent of high-resolution computed tomography (HRCT) offers the possibility of a non-invasive assessment of ILD. Bronchiectasis seems to be one of the most frequent lung manifestations particularly in patients complaining of respiratory symptoms and its frequency ranges from 20% to 30%. Interstitial lung disease (ILD) and subclinical alveolitis have been found in up to 40% of RA patients. Another approach for the assessment of pulmonary involvement is to use pulmonary function tests (PFT). PFT abnormalities include airflow obstructions associated with bronchiectasis, obliterative bronchiolitis, or smoking. Airway obstruction was reported in the majority of RA patients with respiratory symptoms.[11,12] Pharmacological options include steroids, disease-modifying antirheumatic drugs (DMARDs), immunosuppressants, and biologic agents. Non-pharmacological treatments encompass conservative management, supplemental oxygen therapy, pulmonary rehabilitation, smoking cessation, and lung transplantation.

Rheumatoid arthritis (RA) is associated with a variety of pulmonary manifestations, which can be detected through HRCT scans and PFTs. However, the relationship between these pulmonary function parameters and HRCT findings has not been extensively studied in RA patients with pulmonary symptoms. The aim of this study is to evaluate the

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pulmonary manifestations in RA patients using HRCT and PFTs and evaluate the potential of these assessments in determining patient prognosis.

MATERIALS AND METHODS

This is a cross sectional Hospital based study conducted in the Department of Medicine, Regional Institute of Medical Sciences (RIMS), Imphal for a period of two years from April, 2023 to February, 2025. Patients of age 18 years and above attending Medicine OPD, Chest medicine OPD and those admitted in Medicine wards, RIMS, Imphal and who fulfilled the inclusion criteria were recruited in the study.

Inclusion criteria included patients of aged 18 years and above, diagnosed Rheumatoid arthritis having pulmonary manifestation and who give consent to participate in the study.

Exclusion criteria included those patients with Bronchial asthma, Chronic Obstructive Pulmonary Disorder (COPD), Occupational Lung diseases, Sarcoidosis, pregnant women and those not giving consent for the study.

Sample size was calculated using the formula:

n = Z2 x PQ/L2 (Taking the prevalence of pulmonary manifestation in patients with RA as 32.5% from a cohort study done by A Robles Perez et al).[13]

Where, n = Sample size, Z= 1.96, P = Prevalence = 32.5%,L = Absolute Allowable error = 8

So, n = 3.8 x 32.5 (100-32.5)/64, n =130. Therefore, sample size (n)=130.

Study Procedure: After taking informed consent, every participant answered a questionnaire, had their medical histories thoroughly reviewed, and had a detailed physical examination. Routine blood tests included complete Blood Count (CBC), Liver function test (LFT),Kidney function test (KFT),Urine Routine analysis, Rheumatoid Factor (RF), Anti-Cyclic Citrullinated Peptide (Anti-CCP),C-Reactive Protein (CRP) Erythrocyte Sedimentation Rate (ESR), Pulmonary function test (PFT),Electrocardiogram (ECG), chest radiography and HRCT of the thorax were performed on all participants, along with additional tests based on clinical suspicion. Confidentiality was ensured by coding patient information throughout the study.

Working definition

Diagnostic Criteria: The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis [14]

Joints affected:
1 large joint -0,
2-10 large joints -1,
1-3 small joints -2,
4-10 small joints -3 and
More than 10 joints (including at least 1 small joint) -5

Serology: Negative RF* and ACPA -0, low positive RF or ACPA -2 and high positive RF or ACPA-3

Duration of symptoms: <6 weeks -0 and >6 weeks -1

Acute phase reactants: Normal CRP# and ESR@ -0 and abnormal CRP or ESR- 1

Patients with a score of > 6 are defined as Rheumatoid Arthritis

*RF-Rheumatoid factor

#CRP-C Reactive protein

@ESR-Erythrocyte sedimentation rate

Statistical analysis was done using windows based statistical package for social sciences [SPSS] version 26.0 (Armonk, NY: IBM Corp). The data was analysed and summarized using descriptive statistics like percentages, mean and standard deviation, student's t test for continuous data and Chi-square test were used for testing the categorical variables association and p value<0.05 was considered as statistically significant.

Approval of research ethics board: Ethical approval for this study was obtained from the Research Ethics Board, Regional Institute of Medical Sciences, Imphal[No.A/206/REBComm(SP)/RIMS/2015/1012/43/2023].

RESULTS

In this study, one hundred and thirty (130) patients diagnosed with Rheumatoid Arthritis (RA) and associated pulmonary manifestations were assessed at the Department of General Medicine, Regional Institute of Medical Sciences (RIMS) in Imphal. The baseline characteristics of the study subjects were shown in [Table 1]. The participants' ages ranged from 18 to 87 years, with the mean age being 48.32±12.40 years, maximum (52, 40%) participants belong to 46-55 years age group. Maximum participants were females (106, 81.5%) while (24, 18.5%) were males. Cough was the predominant symptom (68, 52.3%) followed by wheeze (26,20%) and dyspnoea (43,33.1%). Regarding the duration of the disease, almost half of the patients (64, 49.2%) had been living with RA for 5-10 years, with a significant portion (40, 30.8%) having had the disease for more than 10 years. About one-fifth (26, 20%) of the patients had been diagnosed with RA for < 5 years. These figures suggest that the majority of patients had long-standing RA, which may have contributed to the development of pulmonary complications over time. Laboratory parameters of the study subjects were shown in [Table 2]. Among blood investigations, ESR, anti CCP, RF and CRP were found elevated with mean values of 48.61+33.48, 250.73+173.35, 61.43+32.74 and 41.15+25.43 respectively.

Radiological findings as given in [Table 3], were critical in understanding the extent of pulmonary involvement in these patients. X-ray findings revealed that almost two-thirds (79, 60.8%) of the participants exhibited bilateral lower zone haziness, indicating widespread pulmonary involvement. Additionally, (39, 30%) patients had a reticulo-

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nodular pattern, and (12, 9.2%) presented with prominent vascular markings on their chest X-rays. Pulmonary function tests (PFTs) revealed a restrictive pattern in (80, 61.5%) of the patients, while (50, 38.5%) had a constrictive pattern (shown in table 4), further emphasizing the significant impact of RA on pulmonary function. HRCT parameters were briefly given in [Table 5].In HRCT thorax, decreased attenuation was seen in (108, 83.1%) of the patients, bronchiectasis in (76, 58.5%) patients, bronchial wall thickening in (68, 52.3%) patients and a reticulo-nodular pattern, which is indicative of ILD, was found in (36, 27.7%) of the patients. Air trapping was observed in (48, 36.9%) patients, pulmonary nodules were seen in (16, 12.3%) patients and ground-glass opacities (GGO) were present in (32, 24.6%) of the patients, indicating partial lung consolidation or regions of inflammation. Pleural effusion was found in (44, 33.8%) patients and pleural thickening was observed in (20,18.5%) patients. This comprehensive evaluation of both clinical and radiological findings underscores the extensive pulmonary manifestations associated with rheumatoid arthritis, which can significantly impact the quality of life of affected individuals and plays a key role in early detection and management.

Table 1: Baseline characteristics of the study subjects (N = 130).

Characteristics	Study subjects (n, %)
Age (in years)	
<35	16(12.3%)
35-45	12(9.2%)
46-55	52(40%)
Gender	
Male	24(18.5%)
Female	106(81.5%)
Address	
Urban	62(47.7%)
Rural	68(52.3%)
Duration of illness (in years)	
<5	26(20%)
5-10	64(49.2%)
>10	40(30.8%)
Symptoms	
Cough	68(52.3%)
Wheezing	26(20%)
Dyspnoea	43(33.1%)

Table 2:Laboratory parameters of the study subjects (N = 130).

Parameters	Mean + SD
Erythrocyte sedimentation Rate (ESR) (Normal: 5-15mm/ 1st hour)	448.61+33.48
Anti Citrullinatede Protein (Anti CCP) (Normal <17U/ml)	250.73+173.35
Rheumatoid factor (RF) (Normal 1-20 IU/ml)	61.43+32.74
6 C Reactive Protein (CRP) (Normal :0-6 mg/L)	41.15+25.43

Table 3: Distribution of patients by X-Ray Findings (N=130).

X-Ray Findings	Frequency (n)	Percentage (%)
BL Lower zone Haziness	79	60.8%
Reticulo-nodular Pattern	39	30%
ProminentVascular Marking	12	9.2%

Table 4: Distribution of participants according to Pulmonary Function Test (PFT) (N=130)

PFT	Frequency (n)	Percentage (%)
Restrictive	80	61.5%
Constrictive	50	38.5%

Table 5: Distribution of participants according to HRCT Findings (N=130).

HRCT parameters	Frequency (n)	Percentage (%)
Decreased Attenuation	108	83.1%
Bronchiectasis	76	58.5%
Bronchial wall thickening	68	52.3%
Reticulo-Nodular Pattern	36	27.7%
Air trapping	48	36.9%
Pulmonary Nodules	16	12.3%
Ground Glass Opacities	32	24.6%
Pleural Effusion	44	33.8%
Pleural Thickening	20	18.5%

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DISCUSSION

Rheumatoid arthritis (RA) is a prevalent systemic condition that primarily impacts small, synovial joints in a progressive, symmetrical, and destructive manner, affecting roughly 0.5–1% of the population. The most frequent extra-articular complication of long-term RA, and the second leading cause of death after infections, is pleuro-pulmonary involvement.[2] In this study, 130 patients diagnosed with RA and associated pulmonary manifestations were assessed. Rheumatoid arthritis (RA) predominantly affects females, with women experiencing the condition 3 to 5 times more frequently than men.[15] This gender disparity in RA prevalence is well-documented and has been a focus of various studies, which suggest that hormonal, genetic, and immune system differences between the sexes may contribute to the higher incidence in women.

In the present study, the age of the participants ranged from 18 to 87 years, with the mean age being 48.32±12.40 years. The age distribution indicated that more than one-third (40%) of the participants were in the 46-55 years age group, which was in concordance with the studies done by Banotra P et al,[16] (mean age :49.5±13.51) and Banik S et al,[17] (mean age of 45.22 years).

Regarding the duration of the disease, almost half of the patients (49.2%) had been living with RA for 5-10 years, with a significant portion (30.8%) having had the disease for more than 10 years. An Indian study, reported that the extent of lung involvement increased threefold when comparing patients with a disease duration of 6-10 years to those with a duration of >10 years. Literatures also suggested that a longer duration of illness was found to significantly affect lung involvement.[18] These figures suggested that the majority of patients had long-standing rheumatoid arthritis, which may have contributed to the development of pulmonary complications over time.

In the present study, the most common symptom was cough (52.3%), followed by dyspnoea (33.1%) and wheezing (20%). Similar findings were reported by Fatima N et al,[19] and Shah SA et al.[20] These symptoms are commonly seen in diffuse interstitial lung fibrosis. Dyspnoea may suggest presence of pleural effusion, pulmonary vasculitis, or a chest infection, while wheezing in patients may be a sign of obstructive pulmonary disease.

Radiological findings were critical in understanding the extent of pulmonary involvement in these patients. X-ray findings revealed that almost two-thirds (60.8%) of the participants exhibited bilateral lower zone haziness, indicating widespread pulmonary involvement. Additionally, 30% of patients had a reticulo-nodular pattern, and 9.2% presented with prominent vascular markings on their chest X-rays which were consistent with study done by Sen S et al,[21] and Fatima N et al,[19] Prominent pulmonary vasculature could be due to pulmonary vasculitis which is a less common pulmonary manifestation of RA.

Restrictive pattern was observed in (80, 61.5%) of the patients, while constrictive pattern was seen in (50, 38.5%) subjects, suggesting the significant impact of RA on pulmonary function in the present study. Rheumatoid arthritis (RA) is recognized as being linked to restrictive lung diseases, such as RA-ILD in various literatures.[22-24] On the contrary, Banik S et al,[17] reported obstructive pattern of PFT to be more common among their patients.

In our study, HRCT was instrumental in providing a detailed assessment of pulmonary manifestations among the patients. Decreased attenuation was observed in 83.1% of the patients, suggesting widespread parenchymal involvement. Bronchiectasis, another significant finding, was seen in 83.1% of the patients, indicating damage to the airways. Bronchial wall thickening, which is often associated with chronic inflammation, was present in more than half of the patients (52.3%). Air trapping, a feature of small airway obstruction, was observed in 36.9% of patients. A reticulo-nodular pattern, which is indicative of interstitial lung disease, was found in 27.7% of the patients. Ground-glass opacities were present in 24.6% of the patients, suggesting areas of inflammation or partial consolidation in the lungs and pulmonary nodules, which can indicate the presence of inflammation or neoplastic changes, were seen in 12.3% of the patients.

Pleural effusion was found in 33.8% of the patients and pleural thickening, another indication of chronic inflammation, was observed in 18.5% of the patients. Our study findings regarding HRCT are similar to studies conducted by Sen S et al,[21] and Hyldgaard C et al.[22] This comprehensive evaluation of both clinical and radiological findings underscores the extensive pulmonary manifestations associated with rheumatoid arthritis, which can significantly impact the quality of life of affected individuals and highlight the importance of early detection and management.

In both studies, decreased attenuation was the most common HRCT abnormality, with bronchiectasis being the second most frequent finding. Bronchial wall thickening in HRCT thorax typically occurs after prolonged airway inflammation. The presence of reticulo-nodular shadows and ground-glass opacities (GGO) in HRCT suggests interstitial involvement. Other studies done by Tanaka et al,[25] found GGO to be the most frequent finding in their study (90%), while Skare et al,[26] reported it in 39%. Additionally, Akira et al,[27]noted that reticulation was the most common finding (72%) in their study.

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CONCLUSION

Pulmonary manifestations are common in RA and often remain clinically silent, especially in the early stages of the disease. Most patients with respiratory symptoms have a long duration of RA. Therefore, pulmonary evaluation should be conducted early in RA patients, regardless of the presence of respiratory symptoms. It is recommended that respiratory symptoms and abnormalities in pulmonary function tests (PFTs) can serve as indicators of lung disease. Thus, to ensure optimal treatment, healthcare providers should always consider the potential for associated pulmonary manifestations when evaluating RA patients.

Limitations: Our study was conducted in a tertiary care centre, so referral bias could not be completely excluded. Additionally, it was a cross-sectional study from a limited geographic region. Prospective, multicentric studies involving a larger number of patients would offer more conclusive insights into the types and prevalence of various pulmonary manifestations in RA and their associations with different factors.

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