

## Assessment of Characteristics of ILD Associated with RA

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### Abstract

**Background:** The aim is to assess the characteristics of ILD associated with RA. **Subjects and Methods:** One hundred six patients with RA of either gender were divided into 2 groups. Group I were RA with ILD and group II were RA without ILD. Parameters such as erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP), hepatitis B surface antigen (HBsAg), anti-nuclear antibodies (ANA), immunoglobulin (Ig) G, IgA, IgM, complement (C) 3, C4 were noted. History of smoking was recorded. **Results:** Group I comprised of 40 and group II 66 patients. Group I had 18 males and 22 females and group II had 26 males and 40 females. The mean age was 58.2 years in group I and 50.6 years in group I. The age of onset of RA was 51.4 years in group I and 45.2 years in group II. The mean disease duration was 7.6 years in group I and 5.3 years in group II. There were 14 smokers in group I and 20 in group II. IgA (g/L) level found to be 2.98 and 2.90, IgG (g/L) was 13.9 and 13.2, IgM (g/L) was 1.08 and 1.02, C3 (g/L) was 1.27 and 1.23, C4 (g/L) was 0.27 and 0.28, LDH (U/L) was 153.2 and 156.3, RF (IU/ml) was 654.2 and 350.6, anti CCP (RU/ml) was 911.2 and 713.9, CRP (mg/L) was 52.1 and 41.8 and ESR (mm/h) was 75.3 and 65.7 in group I and II respectively. History of medication such as methotrexate was seen in 8 and 15, sulfasalazine in 12 and 18, leflunomide in 5 and 22, combination of methotrexate+ sulfasalazine in 6 and 4 and methotrexate+ leflunomide in 4 and 2 in group I and II respectively. **Conclusion:** The risk factors of RA-ILD were age, age at RA onset and smoking. HRCT should be carried out to confirm abnormalities in these patients.

**Keywords:** Interstitial lung disease, Rheumatoid arthritis, Smoking.

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### Introduction

Rheumatoid arthritis (RA) is a commonly occurring inflammatory disease characterized by symmetric polyarthritis. It is the leading cause of functional disability. Near about 1% of general people are affected from it. It is estimated that about 55% patients with RA show involvement of lungs, heart, eye and skin.<sup>[1]</sup> Common manifestation is lung involvement. RA-associated interstitial lung disease (RA-ILD) is commonly encountered. It is linked with high mortality. It is characterized by subclinical inflammation to end-stage pulmonary fibrosis. Interstitial lung disease is seen in within 3 years in patients with RA.<sup>[2]</sup> It is found that high-resolution computed tomography (HRCT) is very effective diagnostic modality for assessment of ILD.<sup>[3]</sup> Clinically, RA can essentially affect any lung compartment including: the parenchyma, manifesting as interstitial lung disease (ILD) or rheumatoid nodules; pleura, resulting in pleural inflammation and/or effusions; small and large airways (cricoarytenoiditis, constrictive or follicular bronchiolitis and bronchiectasis); and pulmonary vasculature (vasculitis and pulmonary hypertension).<sup>[4]</sup> Lung involvement, particularly RA-ILD, is associated with significant morbidity and mortality. Though lung involvement in RA typically occurs following articular

manifestations, pulmonary manifestations may occasionally precede joint symptoms.<sup>[5]</sup>

The etiology and risk factors of RA is still not well known. Environmental factors are involved in the development of RA-ILD.<sup>[6]</sup> It is also established that some disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX) and leflunomide (LEF), are also associated with an increased risk of RA-ILD.<sup>[7]</sup> Considering this, we assess the characteristics of ILD that are associated with RA.

### Subjects and Methods

One hundred six patients with RA of either gender were selected for this observational, prospective study. Patients with history of pregnancy, history of any autoimmune disease, lung disease other than ILD were excluded. The approval for the study was obtained from institutional ethical clearance and review committee. All enrolled subjected were informed in their vernacular language and their written consent was taken before commencing the study.

A thorough clinical examination was carried out inn all enrolled patients. Demographic profile of each patient such as age, sex, etc. was recorded. Patients were divided into 2 groups. Group I were RA with ILD and group II were RA without ILD. Parameters such as erythrocyte sedimentation

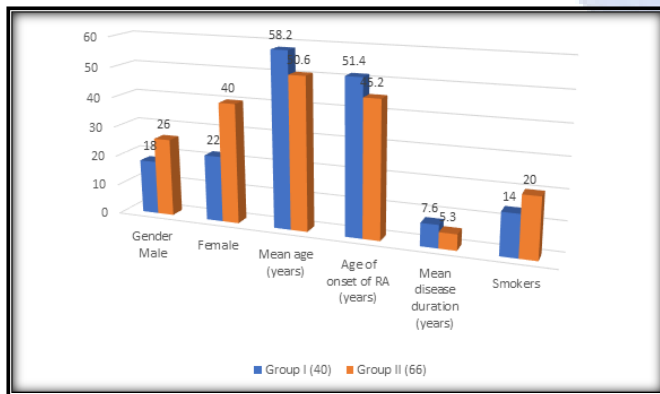
rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), anti-cyclic citrullinated peptide (anti-CCP), hepatitis B surface antigen (HBsAg), anti-nuclear antibodies (ANA), immunoglobulin (Ig) G, IgA, IgM, complement (C) 3, C4 were noted. History of smoking was recorded. HRCT scan was obtained with Siemens 16-spiral CT scanner. Results of the study was compiled and studied using Mann Whitney U test and the level of significance was set below 0.05.

**Results**

**Table 1: Demographic data**

| Parameters                    | Group I (40) | Group II (66) | P value |
|-------------------------------|--------------|---------------|---------|
| Gender Male                   | 18           | 26            | <0.05   |
| Female                        | 22           | 40            | <0.05   |
| Mean age (years)              | 58.2         | 50.6          | <0.05   |
| Age of onset of RA (years)    | 51.4         | 45.2          | <0.05   |
| Mean disease duration (years) | 7.6          | 5.3           | <0.05   |
| Smokers                       | 14           | 20            | <0.05   |

Group I comprised of 40 and group II 66 patients. Group I had 18 males and 22 females and group II had 26 males and 40 females. The mean age was 58.2 years in group I and 50.6 years in group I. The age of onset of RA was 51.4 years in group I and 45.2 years in group II. The mean disease duration was 7.6 years in group I and 5.3 years in group II. There were 14 smokers in group I and 20 in group II. The difference found to be significant (P< 0.05) [Table 1, Figure 1].



**Figure 1: Demographic data**

**Table 2: Laboratory parameters in both groups**

| Parameters       | Group I (40) | Group II (66) | P value |
|------------------|--------------|---------------|---------|
| IgA (g/L)        | 2.98         | 2.90          | >0.05   |
| IgG (g/L)        | 13.9         | 13.2          | >0.05   |
| IgM (g/L)        | 1.08         | 1.02          | >0.05   |
| C3 (g/L)         | 1.27         | 1.23          | >0.05   |
| C4 (g/L)         | 0.27         | 0.28          | >0.05   |
| LDH (U/L)        | 153.2        | 156.3         | >0.05   |
| RF (IU/ml)       | 654.2        | 350.6         | <0.05   |
| Anti CCP (RU/ml) | 911.2        | 713.9         | <0.05   |
| CRP (mg/L)       | 52.1         | 41.8          | >0.05   |
| ESR (mm/h)       | 75.3         | 65.7          | <0.05   |

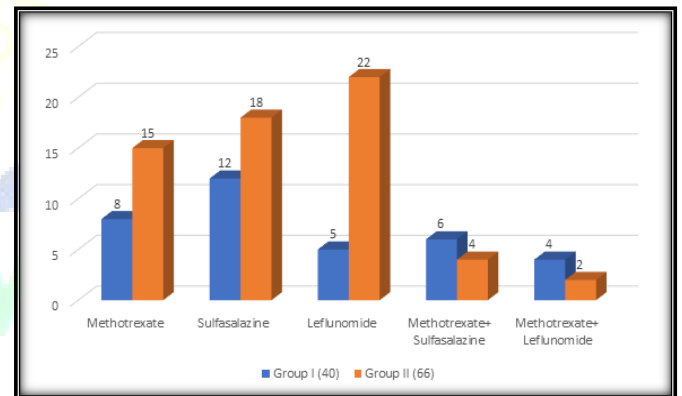
IgA (g/L) level found to be 2.98 and 2.90, IgG (g/L) was

13.9 and 13.2, IgM (g/L) was 1.08 and 1.02, C3 (g/L) was 1.27 and 1.23, C4 (g/L) was 0.27 and 0.28, LDH (U/L) was 153.2 and 156.3, RF (IU/ml) was 654.2 and 350.6, anti CCP (RU/ml) was 911.2 and 713.9, CRP (mg/L) was 52.1 and 41.8 and ESR (mm/h) was 75.3 and 65.7 in group I and II respectively. The difference found to be significant (P< 0.05) [Table 2].

**Table 3: Comparison of treatment**

| Treatment                  | Group I (40) | Group II (66) | P value |
|----------------------------|--------------|---------------|---------|
| Methotrexate               | 8            | 15            | <0.05   |
| Sulfasalazine              | 12           | 18            | >0.05   |
| Leflunomide                | 5            | 22            | <0.05   |
| Methotrexate+Sulfasalazine | 6            | 4             | >0.05   |
| Methotrexate+Leflunomide   | 4            | 2             | >0.05   |

History of medication such as methotrexate was seen in 8 and 15, sulfasalazine in 12 and 18, leflunomide in 5 and 22, combination of methotrexate+ sulfasalazine in 6 and 4 and methotrexate+ leflunomide in 4 and 2 in group I and II respectively. The difference found to be significant (P< 0.05) [Table 3, Figure 2].



**Figure 2: Comparison of treatment**

**Discussion**

Interstitial lung disease (ILD) is a progressive fibrotic disease of the lung parenchyma. Occurring in association with several connective tissue diseases, it is the commonest and most important pulmonary manifestation of rheumatoid arthritis (RA).<sup>[8,9]</sup> RA-associated ILD (RA-ILD) may be a consequence of the chronic immune activation and inflammation that occurs in RA and which subsequently promotes aberrant fibroproliferation, or can be due to drug-related or infectious precipitants.<sup>[10]</sup> RA-ILD contributes significantly to decreased quality of life, progressive chronic disability, high utilization of healthcare resources and poorer mortality, with mean survival under 3 years.<sup>[11,12]</sup> The most common patterns found are usual interstitial pneumonia (UIP), accounting for 44–66% and nonspecific interstitial pneumonia (NSIP) (24–44%), followed by mixed disease (0–12%). Cryptogenic organizing pneumonia (COP) and acute interstitial pneumonia (AIP/diffuse alveolar damage (DAD))

are uncommon (0–11%), while lymphocytic interstitial pneumonia and desquamative interstitial pneumonia are rare.<sup>[13,14]</sup> In this study we assessed the characteristics of ILD that are associated with RA.

Our results showed that Group I comprised of 40 and group II 66 patients. Group I had 18 males and 22 females and group II had 26 males and 40 females. The mean age was 58.2 years in group I and 50.6 years in group I. The age of onset of RA was 51.4 years in group I and 45.2 years in group II. The mean disease duration was 7.6 years in group I and 5.3 years in group II. There were 14 smokers in group I and 20 in group II. Wang et al,<sup>[15]</sup> in their study patients with RA-ILD or with RA alone were compared in terms of age, sex distribution, duration of disease, clinical and laboratory parameters, history of smoking and medication. Based on HRCT imaging, 83 (15.26%) patients with RA were diagnosed with ILD. ILD was more frequent in older patients, in those with a longer duration of disease ( $7.46 \pm 7.40$  vs.  $5.27 \pm 6.32$  years,  $P=0.013$ ) and in male patients. RA-ILD was found to be associated with hepatitis B surface antigen (HBsAg) positivity and smoking. Higher levels of C-reactive protein, anti-cyclic citrullinated peptide (CCP) and rheumatoid factor were detected in association with RA-ILD. RA-ILD was more frequently observed in patients treated with steroids or *Tripterygium wilfordii*, age at RA onset, anti-CCP, and steroid use were independently associated with RA-ILD in multivariate analysis.

We found that IgA (g/L) level found to be 2.98 and 2.90, IgG (g/L) was 13.9 and 13.2, IgM (g/L) was 1.08 and 1.02, C3 (g/L) was 1.27 and 1.23, C4 (g/L) was 0.27 and 0.28, LDH (U/L) was 153.2 and 156.3, RF (IU/ml) was 654.2 and 350.6, anti CCP (RU/ml) was 911.2 and 713.9, CRP (mg/L) was 52.1 and 41.8 and ESR (mm/h) was 75.3 and 65.7 in group I and II respectively. Bilgici et al,<sup>[16]</sup> reported abnormal HRCT findings in 67.3% of RA patients.

Our results showed that History of medication such as methotrexate was seen in 8 and 15, sulfasalazine in 12 and 18, leflunomide in 5 and 22, combination of methotrexate+sulfasalazine in 6 and 4 and methotrexate+ leflunomide in 4 and 2 in group I and II respectively. Several studies have reported that smoking, older age, male sex, disease severity, high RF, subcutaneous nodules, and long-standing RA might be risk factors for the development of ILD.<sup>[17,18]</sup>

## Conclusion

The risk factors of RA-ILD were age, age at RA onset and

smoking. HRCT should be carried out to confirm abnormalities in these patients.

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