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RESEARCH ARTICLE

DEMOGRAPHIC AND SEROLOGIC FACTORS PREDICT RHEUMATOİD ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE

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ABSTRACT

Purpose: Interstitial lung disease (ILD) stands as a prominent reason of morbidity and mortality in rheumatoid arthritis (RA). Certain demographic and serologic elements have been attributed in the risk of RA-ILD; however, the available data may not be sufficient to fully clarify this association. Our objective was to analyze the relationship of demographic features and serologic factors with RA-ILD.
Material and Methods: We examined clinical data from RA patients between January 2015-January 2020. Chest computed tomography (CT) examinations were assessed for ILD. The association between age, gender, smoking, RF and anti-CCP titers and the existence of RA-ILD was analyzed. The same factors were analyzed for the existence of usual interstitial pneumonia (UIP) pattern in RA-ILD patients.
Results: RA patients with ILD were notably older (p=0.005), male (p<0.001), and smokers (p=0.027). Higher RF titers were found in RA-ILD group (p=0.022). Although anti-CCP (cyclic citrullinated peptide) rates and titers were elevated in RA-ILD patients, the variation was not significant. Male sex was linked with the UIP pattern (p=0.029), but other factors did not vary significantly between UIP and non-UIP patterns.
Conclusion: Advanced age, being male, smoking, and elevated RF titers were spotted as significant indicators of RA-ILD. Except for male gender, no significant risk factor predicted UIP pattern.

Keywords: anti-cyclic citrullinated peptide, interstitial lung disease, smoking, rheumatoid arthritis, rheumatoid factor

INTRODUCTION

While bilateral polyarthritis is the primary presentation of rheumatoid arthritis (RA), most RA patients also develop extra-articular symptoms affecting various organs, including heart, eyes, lungs, and skin (1). Pulmonary involvement is common and can affect various lung components, incorporating air passages, lung tissue, pleural layers, and vascular structures. Interstitial lung disease (ILD) is a prevalent complication related to lungs in RA, identified through high-resolution computed tomography (HRCT) in approximately 60% of RA patients, with clinical significance evident in 10% of instances (1-3). RA patients with ILD are prone to have an unfavorable prognosis (2). Interestingly, patients may remain asymptomatic for long periods despite evidence of pulmonary involvement (4). Therefore, screening all RA patients for ILD is recommended, given its status as a leading cause of morbidity and mortality in RA. Despite its importance, there is still limited

Table 1. Comparative characteristics of RA patients with and without ILD

	RA-ILD (n=)	RA-no ILD (n=)	P value
Demographic parameters			
Age, mean ± SD	64.5 ± 9.3	60.1 ± 13.6	0.005
Male sex n (%)	33 (47)	32 (19.8)	0.000
Smoker, n (%)	38 (54.3)	63 (39)	0.027
Pack-years of smoking, mean ± SD	33 ± 18.5	25.8 ± 15	0.056
Autoantibody tests			
Rheumatoid factor positive, n (%)	52 (74.3)	112 (69.1)	0.229
Rheumatoid factor, median ± SD	69 ± 349	37 (205)	0.022
Anti-CCP positive, n (%)	39 (55.7)	84 (51.8)	0.308
Anti-CCP, median ± SD	177 ± 379	59.5 ± 370	0.126

understanding of the underlying causes and risk factors of RA-ILD (5). The pathogenesis of RA-ILD has been linked to factors such as autoantibodies, smoking, and gene mutations; nevertheless, the available evidence is insufficient to reach a conclusive conclusion (6).

Currently, HRCT imaging is the primary method for evaluating ILD in RA patients. HRCT is superior to chest radiography as it can identify subtle structural abnormalities in lung tissue during the initial phases of the disease (7). It also replaces the need for biopsy, as HRCT findings correlate well with histopathologic changes (8). The usual interstitial pneumonia (UIP) pattern identified in RA patients with ILD mirrors that seen in individuals with idiopathic pulmonary fibrosis (IPF) and is correlated with a more unfavorable prognosis in comparison to other patterns of RA-ILD (9).

Among the demographic and environmental factors studied, there is strong evidence to support cigarette smoking, advanced age and male gender are identified as risk factors for the onset of RA-ILD (3). Rheumatoid factor (RF), which is an autoantibody targeting immunoglobulin G (IgG) Fc fragments, particularly of the IgM class, is linked to RA-associated ILD (RA-ILD) (10). Elevated serum levels of RF, even when there is no evident clinical presence of RA, might contribute to lung injury and inflammation, thereby elevating the risk of ILD (11). Anti-citrullinated peptide antibodies (anti-CCP), specifically directed against citrullinated peptides, demonstrate higher specificity for RA compared to RFs. Elevated serum levels of anti-CCP IgG might be associated with RA-ILD, although additional validation studies are required (5,12).

In our present study, we explored the relationship between age, gender, smoking habits, and serum autoantibodies (RF and anti-CCP) and their association with RA-ILD within our patient cohort. We also evaluated the relationship between these factors and the observed ILD pattern.

MATERIAL AND METHODS

A total of 251 consecutive outpatients meeting standard diagnostic criteria for rheumatoid arthritis (13) were enrolled between January 2015 and January 2022. After excluding patients with rheumatologic comorbidities, congestive heart failure, and those with indeterminate ILD status, the study included 232 patients.

Each patient underwent a thorough clinical evaluation with careful review of their medical records. An experienced thoracic radiologist visually reviewed the most recent chest CT scans for evidence of ILD. Individuals with ILD were sorted into two categories depending on whether a UIP pattern was present or absent (Figure 1A and Figure 1B, respectively). Demographic information, encompassing age, gender, and smoking history, was obtained through a questionnaire during the initial visit. Antibody titers were determined through ELISA at the initial assessment, expressed in IU/mL, and considered

Table 2. Comparative characteristics of RA-ILD patients with UIP and non-UIP paterns

	UIP (n=13)	Non-UIP (n=57)	P value
Demographic parameters			
Age, mean ± SD	67.5 ± 7.9	63.7 ± 9.5	0.149
Male sex n (%)	10 (76.9)	23 (40.3)	0.029
Smoker, n (%)	8 (61.5)	30 (52.6)	0.71
Pack-years of smoking, mean ± SD	35 ± 13.8	32.5 ± 19.6	0.77
Autoantibody tests			
Rheumatoid factor positive, n (%)	10 (76.9)	42 (73.7)	0.186
Rheumatoid factor, median ± SD	144 ± 363	63 ± 347	0.094
Anti-CCP positive, n (%)	6 (46)	33 (57.9)	0.17
Anti-CCP, median ± SD	202 ± 587	149 ± 347	0.164

positive for RF at a threshold of 10 IU/mL and for anti-CCP at 20 IU/mL.

Patient age and gender were analyzed to assess their association with RA-ILD. The impact of smoking on RA-ILD was evaluated by examining both smoking status (former-current smoker versus never smoker) and cumulative smoking exposure (evaluated based on pack-years) in patients with and without ILD. Furthermore, age, sex, and smoking details were compared between RA-ILD patients with UIP pattern and RA-ILD patients with any pattern other than UIP. An analysis of autoantibody positivity and titers was conducted in RA patients with and without ILD. Similarly, RF and anti-CCP positivity and levels were compared among RA-ILD patients with a UIP pattern and those with a pattern other than UIP.

Demographic characteristics and autoantibody titers among RA patients were compared using chi-squared test and Mann-Whitney U test. A p-value below 0.05 was considered indicative of a statistically significant difference.

Ethical Considerations

Dokuz Eylül University Non-Interventional Research Ethics Committee approved this retrospective study (Date: 02.06.2021, Decision number: 2021/17-01), and the requirement for a consent form was waived.

RESULTS

In the present study, from the original cohort of 232 RA patients, 70 individuals (30%) were identified with RA-ILD by chest CT scan. Of these, 33 were male and 37 were female. Thirteen of the patients with RA-ILD had a UIP pattern. The overall mean age of the patient population was 61.4±13.6 years and 28% were male. Among the patients, 59% were either current or former smokers, while 41% had never smoked. Smokers within the group had a median pack-years of 30, ranging from 2 to 87. RF titers ranged from 7 to 1794 IU/mL, and anti-CCP titers ranged from 0.8 to 2001 IU/mL. The median of anti-CCP was 73.5 U/mL with an IQR of 188 U/mL, and the median value of RF was 44 U/mL with an IQR of 119 U/mL.

RA patients with ILD tended to be older (p=0.005) and male (p=0.000) compared to those without ILD. In addition, a substantially larger number of patients with ILD were smokers (p=0.027) and had more pack-years of smoking, even though this disparity was not significant (p=0.056). An increased percentage of RA-ILD patients tested positive for RF (p=0.229), and the median RF level was significantly elevated compared to those without ILD (p=0.022). Despite a more frequent occurrence of anti-CCP positivity and

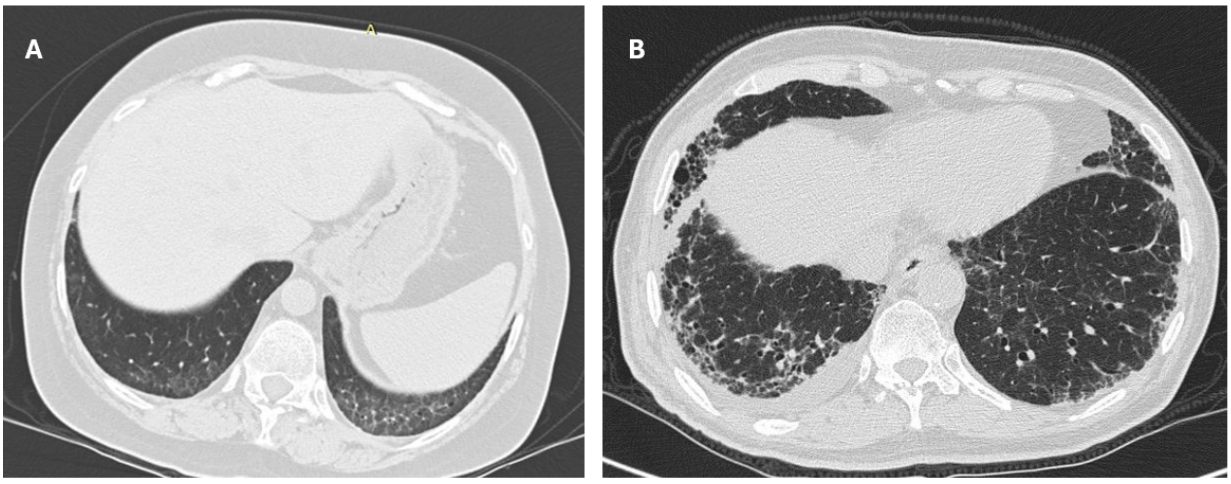

Figure 1. CT images of two patients with rheumatoid arthritis-associated interstitial lung disease. (A) Axial CT image of a 55-year-old male patient shows bilateral subpleural reticular opacities, honeycombing with peripheral and lower lobe predominance, consistent with a usual interstitial pneumonia pattern. (B) Axial CT image of a 49-year-old female patient shows bilateral subpleural ground-glass opacities, more prominent on the left, consistent with a non-specific interstitial pneumonia pattern.

higher antibody titers in patients with ILD, these distinctions did not achieve statistical significance. A summary of the comparative findings is presented in Table 1.

No statistically meaningful distinction in age was identified between patients exhibiting and not exhibiting a UIP pattern (p=0.149). The male gender exhibited a statistically pronounced correlation with the UIP pattern (p=0.029). The UIP pattern did not show a significant association with smoking status or pack-years of smoking. Although the median RF titer was higher in the UIP group than in the non-UIP group, this distinction was not statistically significant (p=0.094). The association of RF positivity with the UIP pattern was not more robust than what was noted for RF levels (p=0.186). Although anti-CCP titers were slightly higher in the UIP group (202 ± 587 vs. 149 ± 347 IU/mL), there was not a significant correlation between anti-CCP positivity or titer and ILD pattern. Comparative findings of patients with RA-ILD with and without UIP pattern are presented in Table-2.

DISCUSSION

In this study, we noted significant connections between RA-ILD and advanced age, male gender, and smoking. Additionally, we detected a significant correlation between higher RF levels and ILD in patients with RA. Although elevated anti-CCP titers were more common in RA-ILD patients, this association did not attain statistical significance. Male sex was correlated with the UIP pattern in RA-ILD, but we did not reveal a significant correlation between the UIP pattern and autoantibody titers.

ILD is a fatal outcome in patients diagnosed with RA. RA-ILD patients have a three times elevated risk of mortality in comparison to RA patients without ILD (14). Although the exact mechanisms contributing to the onset of RA-ILD remain elusive, certain demographic and external factors appear to play a noteworthy role in its occurrence in RA patients. Our study aligns with prior research, which have consistently found that ILD is more commonly seen in males, elderly patients, and smokers (5,6,14-16). Zhang et al. found that the onset of ILD is most common between the ages of 50 and 69, with a 59.9% elevate in the risk of ILD with each additional decade of age (14). Another study showed that individuals aged 65 years and older experience a quadruple increase in the incidence of ILD (17). Therefore, it is imperative to evaluate ILD in elderly RA patients.

Studies by Saag et al. have shown a correlation between cigarette smoking and the progression of RA-ILD (18). Another study also showed that the occurrence of ILD rose with the quantity of cigarettes consumed (19). In the present research, the frequency of ILD was significantly higher in smokers. While we observed a greater pack-years of smoking in ILD patients, we did not identify a significant correlation between pack-years and RA-ILD. One possible mechanism contributing to the association

between cigarette smoking and RA-ILD is that cigarette smoking facilitates protein citrullination in the lung. It is theorized that citrullinated proteins within the lung may initiate an autoimmune response, causing the generation of anti-CCP antibodies (20). Considering the correlation between elevated serum titers of anti-CCP antibodies and an elevated risk of RA-ILD, it is conceivable that smoking-induced protein citrullination in the lung might contribute to RA-ILD (1).

We compared anti-CCP and RF titers between RA-ILD group and RA patients with no evidence of ILD. We observed a significant elevation in RF antibody levels among patients with ILD, indicating a potential association between high RF levels and the pathogenesis of ILD. Nevertheless, we did not observe noteworthy disparities in the rates of positivity for anti-CCP or RF antibodies between individuals with and without ILD. Restrepo et al. found higher titers of anti-CCP and increased disease activity in RA-ILD patients, supported by the discovery of citrullinated proteins in lungs (5,21). Giles et al. also documented a correlation between higher titers of anti-CCP and the presence of ILD (22,23). However, Mori et al. found significantly elevated titers of anti-CCP in RA patients with airway disease but not in patients with ILD (24). In our study, although we observed higher positivity rates and increased titers of anti-CCP in RA-ILD patients, we did not detect a meaningful distinction compared to RA patients without ILD. Inui et al. did not identify a significant correlation between anti-CCP and ILD, aligning with the findings of our study (25). Additional investigation is required to tackle the diversity in data concerning the association between anti-CCP and RA associated ILD.

The most prevalent histopathological subtypes of RA-ILD include UIP and nonspecific interstitial pneumonia (NSIP) (26). UIP, which has been identified as more prevalent and associated with poorer survival outcomes compared to non-UIP ILD patterns, is a critical focus. The identification of ILD and its specific pattern relies primarily on HRCT scans. A crucial diagnostic criterion for definitively identifying the UIP pattern is the presence of honeycombing. While the presence of honeycombing in the absence of conflicting features such as widespread ground-glass opacities or significant mosaic perfusion indicates high specificity, its sensitivity in detecting the histopathologic UIP pattern may be limited. This radiologic presentation of UIP is referred to as "radiologic UIP", with reported survival rates akin to those of idiopathic pulmonary fibrosis (IPF) (27). In the field of RA-associated ILD (RA-ILD), there is a greater prevalence of patients exhibiting the UIP pattern in comparison to other ILDs associated with connective tissue diseases, where the NSIP pattern is more prevalent. However, our study showed a greater prevalence of the NSIP pattern than previous cohorts. These differences in findings may be due to differences in the methods used to diagnose ILDs, including clinical assessment, imaging studies, pulmonary function testing, or lung biopsy.

In our investigation, no significant relationship was found between rheumatoid factor (RF) and anti-CCP positivity/titer and ILD pattern (UIP versus non-UIP) in RA-ILD patients. Therefore, our results suggest that RF and anti-CCP antibodies may not serve as reliable biomarkers to diagnose ILD pattern, particularly UIP, in RA-ILD patients. Nevertheless, it is crucial to recognize specific limitations in our study, particularly the sample size, leading to a smaller number of patients for each RA-ILD pattern. This limitation could potentially lead to false negative results or underestimation of the observed associations.

CONCLUSION

In conclusion, this study enhances our comprehension of the features and risk factors associated with RA-ILD, potentially contributing to enhanced patient care. The findings underscore the significance of factors such as advanced age, male sex, and smoking as risk factors for ILD in individuals with RA. We also observed a notable association between elevated RF levels and the occurrence of ILD. It's worth noting that demographic and serologic markers, other than male gender, may not be reliable for predicting the UIP pattern. Nevertheless, further research should address limitations such as sample size for validation.

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Conflict of interests: None.

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