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ANTI-RO ANTIBODY POSITIVITY AND ITS RELATIONSHIP WITH PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS

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Abstract

Aim: Pulmonary involvement is a major contributor to both morbidity and mortality in systemic sclerosis (SSc). While specific autoantibodies, such as anti-Scl-70 and anti-centromere, have been linked to distinct disease subtypes and organ complications, the role of anti-Ro antibodies in SSc—particularly in relation to pulmonary manifestations—has not been fully elucidated. Understanding this relationship may provide insights into disease stratification and risk assessment for lung involvement in SSc patients. This study aimed to determine the prevalence of anti-Ro antibodies in patients with SSc and to investigate their potential association with pulmonary complications, including interstitial lung disease and pulmonary arterial hypertension.

Material and Methods: We retrospectively reviewed 73 patients with SSc who underwent anti-Ro antibody testing, chest X-rays, and high-resolution computed tomography (HRCT). Serum levels of anti-Scl-70, anti-centromere, anti-Ro, and anti-La antibodies were measured using enzyme-linked immunosorbent assay, with a positivity threshold of ≥21 IU/mL, while antinuclear antibodies (ANA) were assessed via indirect immunofluorescence. Pulmonary changes were evaluated by imaging, with particular attention to reticular patterns, ground-glass opacities, and honeycombing.

Results: ANA positivity was observed in 94.5% of patients. Anti-Scl-70 and anti-centromere antibodies were detected in 52.8% and 18.8% of patients, respectively. Anti-Ro antibodies were positive in six patients (8.2% of the cohort); all were also ANA-positive. Two patients (2.7% of the cohort) were positive for anti-Scl-70, while none exhibited anti-centromere antibodies. Pulmonary abnormalities were more frequently observed in anti-Ro-positive patients on both chest radiographs and HRCT, although these differences did not reach statistical significance.

Conclusion: Anti-Ro antibodies were uncommon in SSc, but were associated with a non-significant trend toward increased pulmonary involvement. Larger prospective studies, especially evaluating anti-Ro52, are needed to clarify their clinical relevance.

Keywords: Systemic sclerosis, anti-Ro antibodies, interstitial lung disease, pulmonary involvement, autoantibodies

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INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease characterized by microvascular injury, immune activation, and fibrosis of the skin and internal organs (1). While cutaneous thickening is often the most apparent manifestation, internal organ involvement—particularly of the lungs—plays a decisive role in disease progression and patient prognosis. Among pulmonary manifestations, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) represent two of the most frequent and clinically significant complications (2,3).

ILD is associated with SSc affects approximately 40-60% of patients and typically develops insidiously, often progressing to pulmonary fibrosis and, ultimately, respiratory failure (4). PAH may initially present without symptoms but can advance to exertional dyspnea, right ventricular dysfunction, and reduced survival. Given their substantial impact on morbidity and mortality, early detection of pulmonary involvement and identification of predictive biomarkers are crucial components of effective disease management.

Autoantibodies not only aid in the diagnosis of SSc but also provide valuable insights into disease subsets, prognosis, and organ-specific involvement. Antinuclear antibodies (ANA) are present in the vast majority of patients, while more specific autoantibodies—such as anti-Scl-70, anti-centromere, and anti-RNA polymerase III—are strongly associated with distinct clinical phenotypes and organ complications (5). Among these, anti-Ro [Sjögren's disease antigen A (SSA)] antibodies are detected in a subset of SSc patients and have gained increasing attention for their potential association with particular clinical manifestations, including pulmonary involvement.

Although anti-Ro antibodies are most commonly associated with Sjögren's disease and systemic lupus erythematosus, they have been reported in roughly 10-20% of SSc patients (6,7). Their presence has been linked to earlier disease onset, increased systemic inflammation, musculoskeletal symptoms, digital ulcers, and involvement of certain internal organs (8,9). However, the connection between anti-Ro positivity and pulmonary complications—particularly ILD and PAH—remains uncertain, with previous studies reporting inconsistent findings (10).

This study aims to assess the prevalence of anti-Ro antibodies in patients with SSc and to examine whether their presence correlates with an increased risk of pulmonary involvement, especially ILD and PAH, thereby informing their potential role as predictive markers for lung complications.

MATERIAL AND METHODS

Study Design and Participants

Baseline demographic and clinical data, including age, sex, disease duration, time interval between SSc diagnosis and ILD onset, and pulmonary artery pressure (PAP) values, were collected from medical records. ILD subtypes were classified based on high-resolution computed tomography (HRCT) patterns (ground-glass opacity, reticular pattern, honeycombing) according to international guidelines.

Anti-Ro-positive patients were systematically assessed for overlap with Sjögren's disease using a combination of clinical history (sicca symptoms), serological testing (anti-La/Sjögren's disease antigen B), and salivary gland evaluation, when available. Patients meeting established Sjögren's criteria were excluded from the anti-Ro-positive SSc subgroup analysis. Data were extracted retrospectively from hospital charts and patient files. The study protocol was approved by the Fırat University Non-Invasive Research Ethics Committee (approval number: 39433, date: 24.09.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Laboratory Assessments

Serum levels of anti-Scl-70, anti-centromere, anti-Ro, and anti-La antibodies had been measured previously under standardized laboratory conditions using enzyme-linked immunosorbent assay, with values ≥21 IU/mL considered positive according to reference ranges. ANA were evaluated using the indirect immunofluorescence technique.

Pulmonary Assessment

Pulmonary involvement was evaluated by reviewing chest radiographs and thoracic HRCT scans. Radiographs were assessed for changes in hilar prominence, lung parenchymal density, and contour. HRCT scans were analyzed for features suggestive of ILD, including ground-glass opacities, reticular patterns, and honeycombing. Two experienced radiologists, blinded to serological results, independently assessed the extent and severity of abnormalities using a semiquantitative scoring system as described by Goh et al. (11).

Statistical Analysis

Descriptive statistics were reported as mean ± standard deviation for normally distributed continuous variables and median with interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented as frequencies and percentages. Fisher's exact test was used to compare categorical variables, and the Mann-Whitney U test was used for continuous

variables that were not normally distributed. Associations between anti-Ro positivity and clinical or imaging findings were initially examined using univariable logistic regression. Variables with $p<0.10$ in univariable analysis (including age, sex, disease duration, and anti-Scl-70 positivity) were entered into a multivariable logistic regression model. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported for univariable analyses in Table 1. Statistical significance was defined as $p<0.05$. All analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 73 patients with SSc were included in the analysis. The mean age was 48.6±12.4 years, and 63% of the patients were female. The median disease duration was 7 years (IQR: 4-12). The median time interval between SSc diagnosis and ILD onset was 3 years (IQR: 2-6). PAP measurements were available for 60 patients; the median systolic PAP was 28 mmHg (IQR: 25-34 mmHg).

ANA positivity was detected in 94.5% of participants. Regarding disease-specific autoantibodies, anti-Scl-70 antibodies were present in 52.8% (n=38), anti-centromere antibodies in 18.8% (n=13), anti-Ro antibodies in 8.2% (n=6), and anti-La antibodies in 1.4% (n=1). Among the six anti-Ro positive patients, two (2.7%) were also positive for anti-Scl-70, and none had anti-centromere antibodies. Importantly, none of the anti-Ro-positive patients met criteria for Sjögren's disease overlap based on clinical assessment, anti-La testing, and salivary gland evaluation.

Pulmonary involvement was observed more frequently among patients with anti-Ro antibodies compared to those without. Chest radiographs of anti-Ro-positive patients showed findings, including prominent pulmonary hilar, reticular opacities, and basal parenchymal irregularities. HRCT scans revealed ground-glass opacities, reticular patterns, and, in some cases, honeycombing, suggestive of fibrotic ILD.

Overall, 83.3% (n=5) of anti-Ro-positive patients exhibited pulmonary abnormalities, compared with 63.2% (n=42) of anti-Ro-negative patients. Chest X-ray findings included pulmonary conus prominence in 2 (25%) anti-Ro positive patients versus 10 (15%) anti-Ro negative patients (OR: 2.8, 95% CI: 0.5-17.7, p=0.26), and a reticular pattern in 3 (50%) anti-Ro positive patients versus 19 (28%) anti-Ro negative patients (OR: 2.5, 95% CI: 0.5-13.6, p=0.28). HRCT findings included ground-glass opacity in 4 (75%) anti-Ro positive patients versus 28 (42%) anti-Ro negative patients (OR: 2.8, 95% CI: 0.5-16.3, p=0.26) and honeycombing in 3 (50%) anti-Ro positive patients versus 11 (16%) anti-Ro negative patients (OR: 5.1, 95% CI: 0.9-28.6, p=0.065). Although none of these differences reached statistical significance, a trend toward increased pulmonary involvement in anti-Ro positive patients was observed (Table 1).

Regarding respiratory symptoms, including dyspnea, dry cough, and reduced exercise tolerance, 66.7% of anti-Ro positive patients reported these symptoms compared with 40.3% in the anti-Ro negative group (p=0.12), suggesting a higher symptom burden in the anti-Ro positive subgroup.

Univariable logistic regression analyses were performed to examine associations between anti-Ro antibody positivity and individual pulmonary findings. Variables with $p<0.10$ in univariable analysis (age, sex, disease duration, and anti-Scl-70 positivity) were included in a multivariable logistic regression model. The Hosmer-Lemeshow test indicated a good model fit (p=0.72). The OR presented in Table 1 reflect the univariable associations between anti-Ro positivity and each pulmonary finding.

Table 1. Pulmonary findings according to anti-Ro antibody status in patients with systemic sclerosis

Variable	Anti-Ro positive (n=6)	Anti-Ro negative (n=67)	OR (95% CI)	p-value
Baseline characteristics				
Age, mean ± SD	49.2±11.6	48.5±12.6	-	0.81
Female sex, n (%)	4 (66.7%)	42 (66.7%)	1.1 (0.3-4.1)	0.89
Disease duration, median (IQR)	7 (5-11)	7 (4-12)	-	0.76
Pulmonary findings				
Pulmonary conus prominence, n (%)	2 (33.3%)	10 (14.9%)	2.8 (0.5-17.7)	0.26
Reticular pattern, n (%)	3 (50.0%)	19 (28.4%)	2.5 (0.5-13.6)	0.28
Ground-glass opacity, n (%)	4 (66.7%)	28 (41.8%)	2.8 (0.5-16.3)	0.26
Honeycombing, n (%)	3 (50.0%)	11 (16.4%)	5.1 (0.9-28.6)	0.065

OR: Odds ratio, CI: Confidence interval, SD: Standard deviation, IQR: Interquartile range

Collectively, these findings indicate a potential association between anti-Ro antibody positivity and an elevated risk of pulmonary manifestations in patients with SSc, emphasizing the importance of close monitoring and early imaging in this subgroup.

DISCUSSION

In this study, we aimed to evaluate the prevalence of anti-Ro antibodies and their association with pulmonary involvement in patients with SSc. Anti-Ro antibodies were present in a minority of patients (8.2%). Their presence was associated with a trend toward increased pulmonary abnormalities on both chest X-ray and HRCT, as well as more pronounced respiratory symptoms, although this association was not statistically significant. These findings suggest that anti-Ro positivity may identify a subgroup of SSc patients at higher risk for lung involvement. To our knowledge, this study contributes to the limited literature on the clinical relevance of anti-Ro antibodies in SSc, indicating a potential link with ILD and underscoring the importance of vigilant pulmonary monitoring in this subset of patients.

Several studies have investigated the prevalence and pulmonary implications of anti-Ro antibodies, particularly the anti-Ro52 (TRIM21) subtype, in autoimmune diseases (12). Anti-Ro52 antibodies have been frequently associated with ILD in conditions such as idiopathic inflammatory myopathies, mixed connective tissue disease, and Sjögren's disease, suggesting a potential pathogenic role in fibrotic lung involvement (13,14). In SSc, data are more limited, but emerging evidence indicates that anti-Ro52 positivity may identify patients at higher risk of ILD or progressive pulmonary manifestations (15).

For instance, a meta-analysis of 59 observational studies reported that anti-Ro52/SSA positivity in SSc was associated with ILD (OR: 1.71; 95% CI: 1.04-2.83; p=0.036) (12). A large multicenter cohort of 963 patients identified anti-Ro52/TRIM21 antibodies in approximately 20% of patients and suggested a potential association between these antibodies and ILD and overlap syndromes (16). In a longitudinal study of 43 early SSc ILD patients, 23% were anti-Ro52 positive, and these patients exhibited a significantly faster decline in vital capacity (VC) (-2.41% predicted VC per year; 95% CI: -4.28 to -0.54; p=0.013), with anti-Ro52 levels showing a dose-response relationship with lung function decline (-0.03% predicted VC per arbitrary unit per mL per year; 95% CI: -0.05 to -0.02; p<0.001) (14). More recently, dual positivity for anti-Ro52 and anti-Ro60 was shown to substantially increase the risk of ILD (adjusted OR: 2.27; 95% CI: 1.02-5.14) and disease progression (adjusted hazard ratio: 2.20; 95% CI: 1.36-3.57) compared with double-negative patients (17). Together, these findings suggest that anti-Ro52 positivity may serve as a biomarker to identify a subgroup of SSc patients at higher risk for pulmonary complications (14). Clinically, this could inform closer monitoring, earlier imaging, and potentially more proactive management strategies for ILD (12). Nevertheless, the observed associations should be interpreted cautiously, given the heterogeneity in assays, cohort sizes, and follow-up durations. Future large-scale prospective studies are needed to validate these observations and to clarify whether anti-Ro52 positivity has predictive value for disease progression or response to therapy in SSc (11,14).

The potential mechanisms linking anti-Ro antibodies, particularly anti-Ro52, to pulmonary involvement in SSc remain incompletely understood, but several hypotheses have been proposed (16). Anti-Ro52 is known to target the TRIM21 protein, which plays a role in regulating innate immune responses, including type I interferon pathways, cytokine production, and antiviral defense (18). Dysregulation of these pathways may contribute to chronic inflammation, endothelial injury, and fibroblast activation, which are central to the development of ILD in SSc (18,19). Furthermore, anti-Ro52 positivity has been associated with more severe pulmonary phenotypes in other connective tissue diseases, suggesting a potential shared pathogenic mechanism underlying autoimmune-related lung fibrosis (20). Clinically, these findings highlight the value of serologic profiling in risk stratification, as anti-Ro positive patients may benefit from closer pulmonary surveillance, including regular imaging and pulmonary function testing, even in the absence of overt respiratory symptoms (12). Early identification of at-risk patients could facilitate timely intervention, potentially mitigating disease progression and improving long-term outcomes (15).

In our cohort, anti-Ro positivity was associated with higher rates of radiographic and HRCT abnormalities, suggesting that these patients may represent a subgroup with an intermediate or overlapping risk of pulmonary complications, warranting vigilant monitoring and timely imaging (21).

Study Limitations

Despite the insights gained from our study, several limitations should be acknowledged. First, the retrospective design and relatively small sample size, particularly the low number of anti-Ro positive patients, limit the statistical power to detect significant associations and may contribute to type II errors. Second, the study did not distinguish anti-Ro52 from anti-Ro60 subtypes in all patients, which may have diluted potential subtype-specific associations with pulmonary involvement. Third, although imaging and clinical assessments were systematically reviewed,

the absence of longitudinal follow-up for pulmonary function and ILD progression constrains our ability to evaluate temporal relationships and draw causal inferences. Finally, single-center data may limit the generalizability of our findings to broader SSc populations with different demographic or ethnic characteristics. Future research should focus on prospective, multicenter studies with larger cohorts, detailed anti-Ro subtyping, serial HRCT scans, and standardized pulmonary function testing to clarify the prognostic value of anti-Ro52 antibodies and inform risk stratification and early intervention strategies in SSc-associated ILD.

CONCLUSION

In this study, anti-Ro antibodies were detected in 8.2% of patients with SSc. Individuals with these antibodies had a higher frequency of pulmonary abnormalities on imaging and more frequent respiratory symptoms than those without anti-Ro positivity, although the differences were not statistically significant. These results indicate a possible association between the presence of anti-Ro antibodies and increased pulmonary risk in SSc.

Ethics

Ethics Committee Approval: The study protocol was approved by the Fırat University Non-Invasive Research Ethics Committee (approval number: 39433, date: 24.09.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.A., Z.A.A., A.K., B.Ö., Concept: Z.A.A., Design: Z.A.A., A.K., B.Ö., Data Collection or Processing: U.A., Z.A.A., B.Ö., Analysis or Interpretation: Z.A.A., A.K., B.Ö., Literature Search: U.A., Z.A.A., A.K., B.Ö., Writing: Z.A.A., A.K.

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