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Title: Risk factors and biomarkers for ınterstitial lung disease and pulmonary arterial hypertension in systemic sclerosis: experience of two tertiary centers in Türkiye.

Short title: Risk factors and biomarkers in systemic sclerosis.

Abstract

Purpose: To define the clinical and laboratory characteristics of patients with systemic sclerosis (SSc), and to investigate the risk factors affecting the prevalence of interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), which are important causes of morbidity and mortality.

Patients and methods: 88 patients with SSc were compared according to the presence of ILD and PAH. ILD was confirmed by chest high-resolution computed tomography, and PAH was suspected and considered probable PAH when right ventricular systolic pressure was >40 mmHg according to echocardiography during rest.

Results: Of the 88 patients, 44.3% had diffuse-type and 55.7% had limited-type SSc. Diffuse type, percentages of positive anti-scleroderma-70 (anti-Scl70) antibody and anti-centromere antibody, white blood cell (WBC), platelet, erythrocyte sedimentation rate (ESR), smoking, and presence of the sclerodactyly and telangiectasia differed significantly in SSc with ILD group. The positive titer of anti-Scl70 antibody (odds ratio (OR)=6.124, *p*=0.004), platelet count (OR=0.138, *p*=0.002), ESR (OR=1.042, *p*=0.035) and presence of telangiectasia (OR=10.571, *p*=0.001) were associated with ILD in patients with SSc. Also, while diffuse-type (OR=0.223, *p*=0.010), the presence of sclerodactyly (OR=11.112, *p*=0.028) and telangiectasia (OR=3.861, *p*=0.020) were risk factors for the development of ILD in nonspecific interstitial pneumonia pattern, anti-Scl-70 antibody positivity (OR=12.921, *p*=0.019) and high ESR (OR=1.034, *p*=0.030) were found to be risk factors for the development of usual interstitial pneumonia pattern. When evaluated in terms of PAH, the only risk factor was found to be advanced age (OR=1.073, 95% CI:1.012-1.139, *p*=0.019).

Conclusion: Positive titer of the anti-Scl70 antibody, diffuse type, presence of telangiectasia, and high ESR were independently associated with ILD in SSc patients.
Keywords: Interstitial lung disease, NSIP, pulmonary arterial hypertension, systemic sclerosis, UIP.

Başlık: Sistemik sklerozda interstisyel akciğer hastalığı ve pulmoner arteriyel hipertansiyon için risk faktörleri ve biyobelirteçler: Türkiye'de iki tersiyer merkezin deneyimi.

Kısa başlık: Sistemik sklerozda risk faktörleri ve biyobelirteçler.

Öz

Amaç: Sistemik skleroz (SSk) hastalarının klinik ve laboratuvar özelliklerini tanımlamak, önemli morbidite ve mortalite nedenleri olan interstisyel akciğer hastalığı (İAH) ve pulmoner arteriyel hipertansiyon (PAH) prevalansını etkileyen risk faktörlerini araştırmak.

Hastalar ve yöntemler: Sistemik skleroz tanısı olan 88 hasta İAH ve PAH varlığına göre karşılaştırıldı. Akciğerin yüksek rezolüsyonlu bilgisayarlı tomografisi ile İAH doğrulandı ve istirahatte uygulanan ekokardiyografiye göre sağ ventriküler sistolik basınç >40 mmHg olduğunda olası PAH olarak değerlendirildi ve kaydedildi.

Bulgular: 88 hastanın %44,3'ünde yaygın tipte ve %55,7'sinde sınırlı tipte SSk vardı. Diffüz tip, pozitif anti-skleroderma-70 (anti-Scl70) antikoru ve anti-sentromer antikor yüzdeleri, beyaz kan hücresi, trombosit sayısı, eritrosit sedimantasyon hızı (ESH), sigara içme ve sklerodaktili ve telanjiektazi varlığı İAH olan grupta anlamlı farklı saptandı. Anti-Scl70 antikorunun pozitif titresi (odds oranı (OR)=6,124, *p*=0,004), trombosit sayısı (OR=0,138, *p*=0,002), ESH (OR=1,042, *p*=0,035) ve talenjiektazi varlığı (OR=10,571, *p*=0,001), SSk'li hastalarda İAH ile ilişkili bulundu. Ayrıca diffüz tip (OR=0,223, *p*=0,010), sklerodaktili (OR=11,112, *p*=0,028) ve talenjiektazi (OR=3,861, *p*=0,020) varlığı nonspesifik interstisyel pnömoni paterninde İAH gelişimi için risk faktörleri iken, anti Scl-70 antikor pozitifliği (OR=12,921, *p*=0,019) ve yüksek ESH'nın (OR=1,034, *p*=0,030) usual interstisyel pnömoni paterni gelişimi için risk faktörleri olduğu saptandı. PAH açısından değerlendirildiğinde ise tek risk faktörünün ileri yaş olduğu görüldü (OR=1,073, %95 GA:1,012-1,139, *p*=0,019).

Sonuç: Anti Scl-70 antikorunun pozitif titresi, yaygın tip, talenjiektazi varlığı ve yüksek ESH, SSk hastalarında İAH'nın varlığı ile bağımsız olarak ilişkilendirildi.

Anahtar kelimeler: İnterstisyel akciğer hastalığı, NSIP, pulmoner arteriyel hipertansiyon, sistemik skleroz, UIP.

Introduction

Systemic sclerosis (SSc) is a chronic multisystem disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs [1]. SSc occurs as a result of triggering by environmental factors in genetically susceptible individuals [2]. SSc is associated with autoantibody positivity; antinuclear antibodies (ANA) may be present in more than 90% of SSc cases, and at least one of the more specific autoantibodies (anti-centromere antibody, anti-Scleroderma 70 (Scl70) antibody and anti-RNA polymerase III antibody) is present in up to 70% [3]. SSc affects the internal organs and musculoskeletal system and has a significant impact on morbidity, mortality, and quality of life [4, 5]. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) associated with SSc are the most important causes of mortality and morbidity in the course of this disease [6].

Pulmonary arterial hypertension occurs due to loss of pulmonary microvascularity as a result of vasculopathy and progressive pulmonary fibrosis [3]. Although it is a mortal complication, early intervention and treatment optimization provides a better prognosis [7]. Recently, the definition of PAH has been revised by the 6th World Symposium on Pulmonary Hypertension (WSPH). According to the updated definition, PAH is characterized by pulmonary artery wedge pressure (PAWP) ≤15 mmHg, pulmonary vascular resistance (PVR) ≥3 Wood units, and mean pulmonary artery pressure (mPAP) >20 mmHg as determined by right heart catheterization [8]. Classically, doppler echocardiography (DE) has served as the main screening tool for PAH, but can cause misleading overestimation of pulmonary artery pressures [9]. Although right-heart catheterization is mandatory for a definitive diagnosis, echocardiography (resting and exercise) represents a key noninvasive imaging test on the diagnostic-prognostic-therapeutic PAH algorithm [10]. It has been reported that the presence of PAH can be mentioned if the pulmonary artery systolic pressure (PASP) is >40 mmHg in DE [11]. While the incidence of PAH in SSc on echocardiography is reported to be 10-15% [12, 13] in the PHAROS study conducted with SSc patients, PAH was found in 69% of the patients, and in the DETECT study, this rate was 60% [14, 15].

Interstitial lung disease is characterized by chronic inflammation and fibrosis that progresses to respiratory failure and death [16]. Risk factors associated with the development and progression of ILD include older age at disease onset, presence of diffuse cutaneous SSc, African-American ethnicity, presence of anti-Scl-70/anti-topoisomerase I antibodies and/or absence of anticentromere antibodies [17, 18]. The most common pulmonary involvement in SSc is non-specific interstitial pneumonia (NSIP) and the second most common is usual interstitial pneumonia (UIP), which has a

worse prognosis [3]. Evidence of ILD has been observed in 40-75% of SSc patients based on lung function changes and in more than 90% in autopsy series [19, 20].

It is estimated that the prevalence has increased significantly recently due to advances in imaging and evaluation methods. The purpose of this study; to describe the clinical and laboratory characteristics of SSc patients and to investigate the prevalence of ILD and PAH, which are important causes of morbidity and mortality, and the risk factors affecting them.

Material and method

A total of 88 patients (9 males, 79 females, mean age 53.35±13.92 years) who applied between January 2016 and January 2021, were over 18 years old, and met the classification criteria for Systemic Sclerosis (SSc) by the American College of Rheumatology [21] were retrospectively examined for this study. From data obtained from medical records, demographic information, disease subset (diffuse or limited skin involvement), clinical findings (sclerodactyly, talingiectasia, Raynaud's phenomenon, digital ulcer, arthralgia, dysphagia, presence of lung, heart and kidney involvement), disease duration, concomitant Comorbidities and medications used were recorded.Laboratory data included complete blood cell counts [hemoglobin, white blood cell (WBC), platelet (PLT)], including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The presence and titers of autoantibodies, including ANA, anti-Scl70 antibody, anti-centromere antibody, anti-SSA antibodies, and anti-SSB antibodies, were collected.

Specific investigations including two-dimensional ECHO, pulmonary function tests, X-ray chest and high-resolution computed tomography (HRCT) chest were conducted to evaluate cardiopulmonary involvement. By examining the HRCT reports evaluated by the radiologist, the presence of ILD in patients with ground-glass opacities, reticular pattern or honeycomb findings and the presence of probable PAH in those with pulmonary artery systolic pressure (PASP) >40 mmHg on echocardiography during rest were accepted and recorded [11].

This study was conducted in accordance with the Helsinki Declaration. All participants were informed and their consent was obtained. The study was approved by the local ethics committee.

Statistical analysis

The Statistical Package for Social Sciences version 22.0 software was used to evaluate the data. Descriptive statistical data are expressed as frequency (percentage), number and mean±standard deviation, or median (min-max). The distribution properties

of the numeric variables were evaluated by Kolmogorov–Smirnov test. Independent-samples t-test was used for inter group comparisons of numeric variables with normal distribution, and Mann–Whitney's U test was used for variables without normal distribution. The estimates of the strengths of associations were demonstrated by the odds ratio (OR) with a 95% confidence interval (CI). Categorical data were evaluated using chi-square test. A *p*-value of <0.05 was considered statistically significant.

Results

The mean age of patients was 53.35±13.92 years and the median duration of disease was 4 (0.5-38) years. Out of 88 patients, 79 were females and 9 patients were males; female/male ratio was 8.7/1. Based on the extent of skin involvement, patients were classified as diffuse cutaneous systemic sclerosis 39 (44.3%) and limited cutaneous systemic sclerosis 49 (55.7%). 86 (97.7%) were ANA-positive, 39 patients (44.3%) had positive titers of anti-Scl70 antibody, and 37 patients (42%) had positive titers of anti-centromere antibody (Table 1). While only PAH detected in 3 patients, both ILD and PAH were detected in 7 (8%) patients.

Patients with SSc who had PAH were older than patients without a diagnosis of PAH (62.91±8.72 vs. 51.99±14.03, *p*=0.014). In SSc patients with ILD, more patients had positive titers of anti-Scl70 antibody (68.4% vs. 26%, *p*<0.001) and less patients had positive titers of anti-centromere antibody (21.1% vs. 58%, *p*=0.001) compared to those without ILD. SSc patients with ILD had significantly higher ESR, WBC and PLT levels (Table 2). While ILD was detected in 11 (22.4%) patients with limited cutaneous type, ILD was detected in 27 (69.2%) patients with diffuse cutaneous type (*p*<0.001).

Considering the subtypes of ILD, 25 patients had NSIP (65.8%), while 12 patients had UIP (31.6%) and 1 patient had cryptogenic organizing pneumonia (2.6%). Diffuse involvement, presence of telangiectasia, anti scl-70 antibody positivity and high ESR were found to be risk factors for ILD. While diffuse involvement, presence of sclerodactyly and telangiectasia were risk factors for the development of ILD in NSIP pattern, anti Scl-70 antibody positivity and high ESR were found to be risk factors for the development of UIP pattern. Univariate and multivariate logistic regression analysis showing associate parameters of ILD in table 3, NSIP and UIP in table 4. When evaluated in terms of PAH, the only risk factor was found to be advanced age (OR=1.073, 95% CI:1.012-1.139, *p*=0.019).

Discussion

Systemic sclerosis is a rare autoimmune connective tissue disease and the presence of cardiopulmonary involvement is associated with poor prognosis; It increases mortality and morbidity. Therefore, it is important to quickly diagnose ILD or PAH and start early treatment. However, diagnosis is often delayed as disease findings can develop gradually without symptoms such as dyspnea or cough and typical findings on PFT or chest radiography [22]. Therefore, in this study, to define the clinical and laboratory characteristics of SSc patients, the risk factors affecting ILD and PAH, which are important causes of morbidity and mortality, and the prevalence of PAH and ILD were investigated. Diffuse cutaneous type, smoking, presence of sclerodactyly, presence of telangiectasia, anti-scl70 positivity and anti-centromere negativity were found to be significantly higher in the ILD group. Diffuse cutaneous type, presence of telangiectasia, anti-scl70 antibody positivity and high ESR at the time of diagnosis were found to be important risk factors for the development of ILD. Regarding ILD involvement patterns, diffuse involvement type, presence of sclerodactyly and thalangiectasia were determined as risk factors for NSIP pattern, presence of anti scl-70 antibody and high ESR at the time of diagnosis were determined as risk factors for development of UIP pattern.

In this study, the most common features detected in SSc patients were ANA positivity, Raynaud's syndrome and abnormal capillaroscopic findings, respectively. Similarly, in the update published by The European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) group, the most prominent features of the disease are Raynaud's phenomenon (96.3%), antinuclear antibodies (93.4%) and a typical capillaroscopic pattern (90%) has been reported [23].

The incidence of ILD, an important involvement pattern of SSc, is higher in patients with the diffuse cutaneous type than in those with the limited type of SSc. The European Scleroderma Trials and Research group reported that in 3,656 SSc patients, the incidence of ILD was 53% in patients with diffuse type SSc and 35% in patients with limited type [24]. Although our results for the incidence of ILD were not the same according to subtype, according to the findings in this study, the prevalence of ILD was found to be higher in patients with diffuse type SSc.

Lung involvement has been reported to be associated with specific ethnic, socioeconomic and behavioral factors in SSc [25]. It has been reported that significant abnormalities are frequently detected in nail videocapillaroscopy in patients with SSc with concomitant cardiopulmonary disease, and it has been stated that pulmonary involvement should be suspected if there are abnormal nail videocapillaroscopy patterns or digital ulcers in a patient with SSc [26, 27]. However, in our study, no significant

difference was found in patients with ILD and/or PAH in terms of the presence of either digital ulcer or abnormal capillaroscopy.

Risk factors associated with progressive ILD in patients with SSc include diffuse cutaneous type, male gender, African American race, presence of anti-Scl70 antibodies, absence of anti-centromere antibodies [28-30]. Although a number of potential biomarkers have been identified that may be indicative of lung involvement in patients with SSc [31], autoantibodies are currently the only blood markers available in routine clinical practice. In line with other studies showing a strong relationship between anti-Scl70 antibody and ILD, in this study, SSc patients with ILD had higher anti-Scl70 antibody positivity and lower anti-centromere antibodies than those without ILD [27, 32]. Additionally, anti-Scl70 antibody positivity was found to be an independent risk factor for ILD in SSc patients.

Blood cell counts and inflammatory marker levels of SSc patients with ILD were found to be different from those of patients without ILD. There were no secondary infections such as pneumonia in our patients, but WBC and ESR were significantly higher in SSc patients with ILD compared to those without ILD. Therefore, it is thought that increased WBC and ESR may represent a non-infective chronic inflammatory state in the pulmonary tissue. It should be kept in mind that it may be necessary to be careful in terms of the development of ILD in patients with increased ESR and WBC despite the absence of an infective focus during follow-up. A large cohort showed that baseline CRP was associated with shorter survival and decreased forced vital capacity in SSc patients with ILD [33]. Similar to our findings, in a study conducted in Korea, WBC and ESR were found to be significantly higher in SSc patients with ILD; it has been noted that WBC is widely used as other inflammatory markers, including ESR and CRP, and such data may represent circulating markers that may predict inflammation in the lung interstitium [27]. In this study, CRP levels were found to be high in ILD patients, although it did not have statistical power.

The common HRCT pattern seen in SSc-associated ILD is NSIP, with a greater proportion of ground-glass opacities and a lower degree of reticulation [27]. up to two-thirds of patients, ground-glass opacities progress to fibrosis, even with treatment. Honeycomb cysts, a marker for UIP and pulmonary fibrosis, can be seen in up to one-third of patients with ILD and are more common in patients with limited cutaneous SSc. The pattern of HRCT findings correlates well with histology. Ground glass opacities/consolidation correlate with active inflammation, and reticular opacities/honeycombing are associated with fibrotic lesions [34]. In this study, the NSIP pattern was present in 65.8% of the 25 patients, while the UIP pattern was present in

31.6% of the 12 patients, which was similar to the study conducted by Mulkoju et al. [34]. In addition, in our study, the type of diffuse involvement, the presence of sclerodactyly and telangiectasia were found to be independent risk factors for the development of the NSIP pattern, and the presence of anti-scl-70 antibodies and high ESR at the time of diagnosis were found to be independent risk factors for the development of the UIP pattern.

The reported prevalence of pulmonary hypertension in systemic sclerosis varies between 5% [35, 36] and 30% [37] depending on the definition and exclusion criteria used in previous studies. It has been previously reported that organ involvement may be more frequent and begin earlier in SSc patients with diffuse involvement [38]. The only exception is that PAH can occur equally frequently in both diffuse and limited skin involvement [39], although some studies have reported it to be more common in limited skin involvement [34]. In our study, although the prevalence of PAH was not equal in the groups with limited and diffuse skin involvement, no significant difference was found. Pulmonary hypertension caused by SSc usually occurs after 10 to 15 years. However, PAH can occur at any stage in patients with limited or diffuse disease [34]. In our study, no significant effect of disease duration on the development of PAH was found, but the only risk factor for PAH was found to be advanced age. It has been reported in various studies that advanced age is a risk factor together with anti-centromere antibodies and limited cutaneous SSc [40, 41].

Limitations of this study include its retrospective nature, a small number of recorded patients, incomplete data on the progression or survival of Systemic Sclerosis (SSc), and the absence of right heart catheterization data for evaluating PAH. Additionally, the threshold value of PASP >40 mmHg for PAH may be considered high, and therefore, the prevalence of PAH may be underestimated compared to the actual value.

Consequently, the characteristics of patients with SSc, a rare disease, were analyzed and it was found that the positive value of anti-Scl70 antibody was more frequent in patients with SSc with ILD, the positive value of anti-centromere antibody was less frequent, and the WBC, ESR and platelet count were higher. In addition, while diffuse involvement type, presence of telangiectasia, anti-Scl70 positivity and high ESR at diagnosis were found to be independent risk factors for ILD, the risk factor for PAH was determined to be advanced age. It should be kept in mind that ILD may develop in patients who develop elevated WBC, ESR and PLT during their follow-up.

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References

1. Barsotti S, Orlandi M, Codullo V, et al. One year in review 2019: systemic sclerosis. Clin Exp Rheumatol 2019;119:3-14.
2. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res 2019;20:13. https://doi.org/10.1186/s12931-019-0980-7
3. Adigun R, Goyal A, Hariz A. Systemic Sclerosis. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430875/. Accessed March 14, 2024
4. Kowal Bielecka O, Fransen J, Avouac J, et al. EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327-1339. https://doi.org/10.1136/annrheumdis-2016-209909
5. Elhai M, Meune C, Boubaya M, et al. EUSTAR group. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897-1905. https://doi.org/10.1136/annrheumdis-2017-211448
6. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-1699. https://doi.org/10.1016/S0140-6736(17)30933-9
7. Sobanski V, Launay D, Hachulla E, Humbert M. Current Approaches to the treatment of Systemic-Sclerosis-Associated Pulmonary Arterial Hypertension (SSc-PAH). Curr Rheumatol Rep 2016;18:10. https://doi.org/10.1007/s11926-015-0560-x
8. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913. https://doi.org/10.1183/13993003.01913-2018
9. Vachiéry JL, Brimioulle S, Crasset V, Naeije R. False-positive diagnosis of pulmonary hypertension by Doppler echocardiography. Eur Respir J 1998;12:1476-1478. https://doi.org/10.1183/09031936.98.12061476
10. Ferrara, F, Zhou X, Gargani L, et al. Echocardiography in pulmonary arterial hypertension. Curr Cardiol Rep 2019;21:22. https://doi.org/10.1007/s11886-019-1109-9
11. Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: a controlled study of 100 consecutive patients. Arthritis Rheum 2008;58:1803-1809. https://doi.org/10.1002/art.23463
12. Yang X, Mardekian J, Sanders KN, Mychaskiw MA, Thomas J 3rd. Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a

systematic review of the literature. Clin Rheumatol 2013;32:1519-1531. https://doi.org/10.1007/s10067-013-2307-2

13. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792-3800. https://doi.org/10.1002/art.21433
14. Hinchcliff M, Fischer A, Schiopu E, Steen VD, PHAROS Investigators. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. J Rheumatol 2011;38:2172-2179. https://doi.org/10.3899/jrheum.101243
15. Coghlan JG, Denton CP, Grünig E, et al. DETECT study group. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340-1349. https://doi.org/10.1136/annrheumdis-2013-203301
16. Kalchiem Dekel O, Galvin JR, Burke AP, Atamas SP, Todd NW. Interstitial lung disease and pulmonary fibrosis: a practical approach for general medicine physicians with focus on the medical history. J Clin Med 2018;7:476. https://doi.org/10.3390/jcm7120476
17. Jaeger VK, Wirz EG, Allanore Y, et al. EUSTAR co-authors. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR Study. PLoS One 2016;11:e0163894. https://doi.org/10.1371/journal.pone.0163894
18. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. Arthritis Rheum 2012;64:2986-2994. https://doi.org/10.1002/art.34482
19. Varga J. Systemic sclerosis: an update. Bull NYU Hosp Jt Dis 2008;66:198-202.
20. Bussone G, Mouthon L. Interstitial lung disease in systemic sclerosis. Autoimmun Rev 2011;10:248-255. https://doi.org/10.1016/j.autrev.2010.09.012
21. Masi AT, Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581-590. https://doi.org/10.1002/art.1780230510
22. Giacomelli R, Liakouli V, Berardicurti O, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. Rheumatol Int 2017;37:853-863. https://doi.org/10.1007/s00296-016-3636-7
23. Meier FM, Frommer KW, Dinser R, et al. EUSTAR Co-authors. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research

group database. Ann Rheum Dis 2012;71:1355-1360. https://doi.org/10.1136/annrheumdis-2011-200742

24. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754-763. https://doi.org/10.1136/ard.2006.062901
25. McNearney TA, Reveille JD, Fischbach M, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum 2007;57:318-326. https://doi.org/10.1002/art.22532
26. Markusse IM, Meijs J, de Boer B, et al. Predicting cardiopulmonary involvement in patients with systemic sclerosis: complementary value of nailfold videocapillaroscopy patterns and disease-specific autoantibodies. Rheumatology (Oxford) 2017;56:1081-1088. https://doi.org/10.1093/rheumatology/kew402
27. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with ınterstitial lung disease. Arch Rheumatol 2018;33:322-327. https://doi.org/10.5606/ArchRheumatol.2018.6630
28. Ashmore P, Tikly M, Wong M, Ickinger C. Interstitial lung disease in South Africans with systemic sclerosis. Rheumatol Int 2018;38:657-662. https://doi.org/10.1007/s00296-017-3893-0
29. Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N, Louthrenoo W. Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: inception cohort study. Mod Rheumatol 2016;26:588-593. https://doi.org/10.3109/14397595.2015.1115455
30. Ho KT, Reveille JD. The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther 2003;5:80-93. https://doi.org/10.1186/ar628
31. Kennedy B, Branagan P, Moloney F, et al. Biomarkers to identify ILD and predict lung function decline in scleroderma lung disease or idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2015;32:228-236.
32. Liaskos C, Marou E, Simopoulou T, et al. Disease-related autoantibody profile in patients with systemic sclerosis. Autoimmunity 2017;50:414-421. https://doi.org/10.1080/08916934.2017.1357699
33. Liu X, Mayes MD, Pedroza C, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res (Hoboken) 2013;65:1375-1380. https://doi.org/10.1002/acr.21968

34. Mulkoju R, Saka VK, Rajaram M, et al. Pulmonary manifestations in systemic sclerosis: hospital-based descriptive study. Cureus 2020;12:e8649. https://doi.org/10.7759/cureus.8649
35. Avouac J, Airò P, Meune C, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290-2998. https://doi.org/10.3899/jrheum.100245
36. Erken Pamukcu H, Tunca Ç, Özişler C, et al. Pulmonary hypertension screening in patients with systemic sclerosis, in a tertiary center, in Turkey; a cross-sectional original study. TJCL 2020;11:146-155. https://doi.org/10.18663/tjcl.630633
37. McGoon MD, Benza RL, Escribano Subias P, et al. Pulmonary arterial hypertension: epidemiology and registries. J Am Coll Cardiol 2013;62:51-59. https://doi.org/10.1016/j.jacc.2013.10.023
38. Hachulla E, Launay D. Diagnosis and classification of systemic sclerosis. Clin Rev Allergy Immunol 2011;40:78-83. https://doi.org/10.1007/s12016-010-8198-y
39. Hachulla E, de Groote P, Gressin V, et al. Itinér AIR-Sclérodermie Study Group. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009;60:1831-1839. https://doi.org/10.1002/art.24525
40. Jiang Y, Turk MA, Pope JE. Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). Autoimmun Rev 2020;19:102602. https://doi.org/10.1016/j.autrev.2020.102602
41. Morrisroe K, Huq M, Stevens W, Rabusa C, Proudman SM, Nikpour M; Australian Scleroderma Interest Group (ASIG). Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. BMC Pulm Med 2016;16:134. https://doi.org/10.1186/s12890-016-0296-z

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Authors' contributions to the article

M.P., T.I.D., and H.U. contributed to the study conception and design. Material preparation and data collection were performed by M.P. and H.U., and analysis by T.I.D. The first draft of the manuscript was written by M.P. and T.I.D. All authors commented on previous versions of the manuscript and read and approved the final manuscript. All co-authors take full responsibility for the integrity of the study and the final version of the manuscript.

Table 1. Characteristics of patients with systemic sclerosis (n=88)

Parameters		Patients group (n=88)
Age, years (mean±SD)		53.35±13.92
Gender, F/M (n)		79/9
Disease duration, years, median (min-max)		4 (0.5-38)
Limited/Diffuse type, n		49/39
Smoker, n (%)		9 (10.2%)
Raynaud's Syndrome, n (%)		76 (86.4%)
Digital ulcer, n (%)		15 (17%)
Abnormal nailfold capillaroscopy finding, n (%)		65 (73.9%)
Sclerodactyly, n (%)		60 (68.2%)
Telangiectasia, n (%)		31 (35.2%)
Arthralgia, n (%)		23 (26.1%)
Dysphagia, n (%)		21 (23.9%)
PAB, mmHg, (mean±SD)		26.11±11.41
Pulmonary Arterial Hypertension, n (%)		11 (12.5%)
Interstitial Lung Disease, n (%)		38 (43.2%)
Rheumatoid factor, n (%)		20 (22.7%)
Anti Nuclear Antibody, n (%)	Negative	2 (2.3%)
	1/160	11 (12.5%)
	1/320	19 (21.6%)
	1/1000	46 (52.3%)
	1/3200	10 (11.4%)
Anti-Scl70, n (%)		39 (44.3%)
Anti Centromer, n (%)		37 (42%)
Anti SS-A, n (%)		11 (12.5%)
Anti SS-B, n (%)		2 (2.3%)
ESR, mm/h, (mean±SD)		24.39±19.68
CRP, mg/L, (mean±SD)		6.87±8.08

Anti-Scl70: Anti-Scleroderma70, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate PAB: Pulmonary Arterial Pressure

Table 2. Comparison of systemic sclerosis patients according to interstitial lung disease (İAH) and pulmonary arterial hypertension (PAH)

Parameters	SSc-ILD (n=38)		*p*	SSc-PAH (n=11)		*p*
	Presence	Absence		Presence	Absence	
Age, years, (mean±SD)	56.11±12.5	51.26±14.7	0.106	62.91±8.72	51.99±14.03	**0.014**
Female, n (%)	36 (94.7%)	43 (86%)	0.180	10 (90.9%)	69 (89.6%)	0.894
Disease duration, years, median (min-max)	5 (0.5-38)	4 (0.5-21)	0.334	9 (2-20)	4 (1-38)	0.102
Diffuse type, n (%)	23 (71.1%)	12 (24%)	**<0.001**	2 (18.2%)	37 (48.1%)	0.062
Smoker, n (%)	7 (18.4%)	2 (4%)	**0.027**	1 (9.1%)	8 (10.4%)	0.894
Raynaud's Syndrome, n (%)	35 (92.1%)	41 (82%)	0.171	9 (81.8%)	67 (87%)	0.639
Digital ulcer, n (%)	5 (13.2%)	10 (20%)	0.398	2 (18.2%)	13 (16.9%)	0.915
Abnormal nailfold capillaroscopy finding, n (%)	29 (76.3%)	36 (72%)	0.648	9 (81.8%)	56 (72.7%)	0.521
Sclerodactyly, n (%)	33 (86.8%)	27 (54%)	**0.001**	7 (63.6%)	53 (68.8%)	0.729
Telangiectasia, n (%)	21 (55.3%)	10 (20%)	**0.001**	5 (45.5%)	26(33.8%)	0.448
Arthralgia, n (%)	11 (28.9%)	12 (24%)	0.601	-	23 (100%)	**0.035**
Dysphagia, n (%)	10 (26.3%)	11 (22%)	0.638	4 (36.4%)	17 (22.1%)	0.298
PAB, mmHg, (mean±SD)	28.64±13.22	24.26±9.47	0.105	47.63±13.32	23.08±6.98	**<0.001**
Rheumatoid factor, n (%)	10 (26.3%)	10 (20%)	0.484	13 (65%)	7 (35%)	0.620
Anti-Scl70, n (%)	26 (68.4%)	13 (26%)	**<0.001**	5 (45.5%)	34(44.2%)	0.935
Anti Centromer, n (%)	8 (21.1%)	29 (58%)	**0.001**	2 (18.2%)	35 (45.5%)	0.110
Anti SS-A, n (%)	5 (45.5%)	6 (54.5%)	0.871	1 (9.1%)	10 (13%)	0.715

ESR, mm/h, (mean±SD)	33.08±24.6	17.78±11.30	**0.004**	21.45±13.28	24.81±20.46	0.910
CRP, mg/L (mean±SD)	8.43±10.33	5.69±5.67	0.264	5.12±3.95	7.12±8.50	0.557
WBC, K/uL, (mean±SD)	7.56±1.98	7.36±2.09	**0.046**	8.23±1.37	7.34±2.09	0,076
PLT, K/uL, (mean±SD)	309.39±90.91	275.10±94.61	**0.031**	281.36±51.32	291.12±98.84	0.820

Anti-Scl70: Anti-Scleroderma 70, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PAB: Pulmonary Arterial Pressure, PLT: Platelet WBC: White blood cell

Table 3. Univariate and multivariate logistic regression analysis showing associate parameters of ILD

	Univariate analysis			Multivariate regression analysis		
	HR	**CI**	***p***	**HR**	**CI**	***p***
Diffuse type	0.129	0.049-0.334	**<0.001**	0.138	0.040-0.474	**0.002**
Smoker	0.185	0.036-0.947	**0.043**			
Presence of Sclerodactyly	5.622	1.885-16.767	**0.002**			
Presence of Telangiectasia	4.941	1.925-12.686	**0.001**	10.571	2.750-40.644	**0.001**
Anti-Scl70 antibody	6.167	2.430-15.649	**<0.001**	6.124	1.757-21.348	**0.004**
Anti Centromer antibody	0.193	0.074-0.505	**0.001**			
ESR	1.050	1.019-1.081	**0.001**	1.042	1.003-1.083	**0.035**

Anti-Scl70: Anti-Scleroderma 70, ESR: Erythrocyte sedimentation rate

Table 4. Univariate and multivariate logistic regression analysis showing associate parameters of NSIP and UIP

	Univariate analysis			Multivariate regression analysis		
	HR	**CI**	***p***	**HR**	**CI**	***p***
NSIP						
Diffuse type	0.253	0.094-0.678	**0.006**	0.223	0.072-0.695	**0.010**
Presence of Sclerodactyly	18.000	2.290-141.464	**0.006**	11.112	1.299-95.064	**0.028**
Presence of Telangiectasia	5.689	2.090-15.488	**0.001**	3.861	1.235-12.073	**0.020**
UIP						
Diffuse type	0.217	0.054-0.217	**0.031**			
Anti-Scl70 antibody	18.857	2.310-153.914	**0.006**	12.921	1.513-110.370	**0.019**
ESR	1.047	1.017-1.078	**0.002**	1.034	1.003-1.065	**0.030**
CRP	1.070	1.007-1.137	**0.029**			

Anti-Scl70: Anti-Scleroderma 70, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NSIP: Nonspecific interstitia lpneumonia
UIP: Usual interstitial pneumonia

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İzci Duran T, Pamukçu M, Ulusoy H. Sistemik sklerozda interstisyel akciğer hastalığı ve pulmoner arteriyel hipertansiyon için risk faktörleri ve biyobelirteçler: Türkiye'de iki tersiyer merkezin deneyimi. Pam Tıp Derg 2024;17:…-…

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