Clinical distinctions of anti-topoisomerase positive limited cutaneous systemic sclerosis in early disease: results from the early Systemic sclerOsis Longitudinal Assessment Registry from Turkey

M.E. Yayla[1], B. Okyar[2], E.D. Ersözlü[2], D.S. Özgür[3], C. Bes[3], A. Çefle[4], B. Firlatan Yazgan[5], G. Kimyon[6], T.M. Turgay[1], M.A. Baltaci[7], A. Avanoglu Guler[8], I. Vasi[9], A. Erden[9], R. Bilici[10], B. Sulu[11], G. Varkal[12], D. Arslan[12], Z. Uğurlu[13], A. Doğru[13], A. Avcu[14], F. Alibaz-Oner[14], B. Yurttaş[15], S.C. Güven[16], Ş. Erten[16,17], O. Küçükşahin[17], T. Kahraman Denizhan[18], S. Şenel[18], G. Yamancan[19], A. Karatas[19], E. Genç[20], M.E. Tezcan[20], Ö. Dogan Agbuga[21], S. Amikishiyev[22], A. Babayigit[23], A. Şahin[23], R. Yildirim[24,25], T. Kaşifoğlu[24], B. Aslan[26], T.S. Öğüt[27], O. Zengin[28], F. Albayrak[28], E. Er Gülbezer[29], V. Yazısız[30], M. Birlik[31], G. Hatemi[11], Y. Yalçınkaya[22], M. Inanç[22], S.S. Koca[19], D. Temiz Karadağ[4], M. Erdogan[14], A. Sarı[7], A. Akdogan[5]

Abstract

Objective

Anti-topoisomerase I antibody (ATA) is typically associated with diffuse cutaneous systemic sclerosis (dcSSc). However, subset of limited cutaneous SSc (lcSSc) patients also present with ATA positivity. Emerging data suggest that ATA-positive lcSSc may represent a distinct or intermediate clinical phenotype. This study aimed to compare the demographic, clinical, and treatment features of early ATA-positive lcSSc patients with those of ACA-positive lcSSc and ATA-positive dcSSc patients.

Methods

Patients were recruited from the multicentre Turkish SOLAR cohort (Systemic sclerOsis Longitudinal Assessment Registry). Among 295 SSc patients screened, 172 were included: 74 ACA-positive lcSSc, 55 ATA-positive lcSSc, and 43 ATA-positive dcSSc. Demographic, clinical, and treatment-related variables were analysed and compared across groups.

Results

ATA-positive lcSSc patients were younger at the onset of Raynaud's phenomenon (RP) ($p=0.042$), the first non-RP symptom ($p=0.016$), and at diagnosis ($p=0.018$) compared with ACA-positive lcSSc patients. Interstitial lung disease (ILD) was significantly more frequent in ATA-positive lcSSc (74.5%) than ACA-positive lcSSc (8.1%, $p<0.001$) and was comparable to ATA-positive dcSSc. Modified Rodnan skin scores were highest in ATA-positive dcSSc but were also significantly elevated in ATA-positive lcSSc ($p<0.001$). Pitting scars were more frequent in dcSSc. Among patients with ILD, ATA-positive lcSSc and ATA-positive dcSSc showed similar HRCT patterns. ATA-positive lcSSc patients were more frequently treated with glucocorticoids and mycophenolate mofetil than ACA-positive lcSSc, whereas cyclophosphamide was highest in dcSSc.

Conclusion

ATA-positive lcSSc patients exhibit a clinically distinct phenotype characterized by a substantial risk of internal organ involvement, despite having less extensive skin disease. Their overlap with dcSSc and divergence from ACA-positive lcSSc highlight the importance of incorporating both skin involvement and serologic subtyping into the early management and risk stratification of SSc.

Key words

scleroderma, interstitial lung disease, mRSS, disease subset

Affiliations: see page 1568.

Müçteba Enes Yayla, MD
Burak Okyar, MD
Emine Duygu Ersözlü, MD
Duygu Sevinç Özgür, MD
Cemal Bes, MD
Ayşe Çefle, MD
Büşra Fırlatan Yazgan, MD
Gezmiş Kimyon, MD
Tahsin Murat Turgay, MD
Mehmet Akif Baltaci, MD
Aslihan Avanoglu Guler, MD
İbrahim Vasi, MD
Abdulsamet Erden, MD
Reyhan Bilici, MD
Bercemhan Sulu, MD
Gizem Varkal, MD
Didem Arslan, MD
Zübeyde Uğurlu, MD
Atalay Doğru, MD
Aysegul Avcu, MD
Fatma Alibaz-Oner, MD
Berna Yurttaş, MD,
Serdar Can Güven, MD
Şükran Erten, MD,
Orhan Küçükşahin, MD
Tuğba Kahraman Denizhan, MD
Soner Şenel, MD
Gülsah Yamancan, MD
Ahmet Karatas, MD
Esra Genç, MD
Mehmet Engin Tezcan, MD
Özlem Dogan Agbuga, MD
Shirkhan Amikishiyev, MD
Arif Babayigit, MD
Ali Şahin, MD
Reşit Yildirim, MD
Timuçin Kaşifoğlu, MD
Bengisu Aslan, MD
Tahir Saygın Öğüt, MD
Orhan Zengin, MD
Fatih Albayrak, MD
Elif Er Gülbezer, MD,
Veli Yazısız, MD
Merih Birlik, MD
Gülen Hatemi, MD
Yasemin Yalçınkaya, MD
Murat İnanç, MD
Süleyman Serdar Koca, MD
Duygu Temiz Karadağ, MD
Mustafa Erdogan, MD
Alper Sarı, MD
Ali Akdogan, MD

Please address correspondence to:
Müçteba Enes Yayla
Ankara University Faculty of Medicine,
Division of Rheumatology,
Department of Internal Medicine,
06230 Ankara, Turkey.
E-mail: enesyayla@hotmail.com

Received on December 6, 2025; accepted in revised form on February 27, 2026.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2026.

Competing interests: see page 1568.

Introduction

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterised by autoimmunity, fibrosis and microvascular damage, with its aetiology not yet fully elucidated. Fibrosis in the skin and internal organs is the hallmark of SSc (1-3). Disease subtype based on the extent of skin involvement into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) is a cornerstone for prognostic stratification (4). Pulmonary arterial hypertension (PAH) is more prevalent in lcSSc patients, whereas interstitial lung disease (ILD), primary cardiac involvement, and scleroderma renal crisis occur more frequently in dcSSc patients (4, 5). Consistent with this, the survival rates are significantly poorer in dcSSc patients compared to those with lcSSc (6, 7).

Although classification based on the extent of skin involvement provides a general perspective, it is insufficient on its own to fully capture the complexity of SSc or to accurately predict prognosis, given the disease's marked heterogeneity. Recent studies have highlighted the significance of autoantibodies in shaping clinical manifestations and prognosis of the disease, emphasising their importance in subclassifying SSc (8-11). The most widely known disease-specific antibodies detected in approximately 50-80% of SSc patients are anti-centromere (ACA), anti-topoisomerase I (ATA), and anti-RNA polymerase III antibodies (12, 13). ACA is frequently detected in lcSSc patients and has been associated with PAH. In contrast, ATA is predominantly observed in dcSSc patients and is strongly associated with ILD (11). Although ATA is classically associated with dcSSc, ATA positivity has been detected in approximately 13-23.5% of patients with lcSSc (14-17). The current knowledge regarding ATA-positive lcSSc patients is derived from a limited number of studies. Male gender, presence of ILD, and higher modified Rodnan skin scores (mRSS) are more prevalent in ATA-positive lcSSc patients. Of particular importance, these patients appear to exhibit an intermediate disease severity between ACA-positive lcSSc and ATA-positive dcSSc patients (16-19). However, data on ATA-positive lcSSc patients in the early disease stages remain scarce and clinical decision-making at this stage is particularly challenging, as phenotypic manifestations may not yet be fully established. This study aims to define the distinct clinical phenotype of ATA-positive lcSSc by comparing demographic, clinical, and laboratory features with those of ACA-positive lcSSc and ATA-positive dcSSc patients in a multicentre cohort of early-stage systemic sclerosis patients across Turkey, defined as ≤3 years from the onset of the first non-Raynaud's phenomenon (non-RP) manifestation.

Materials and methods

Participants

In the current study, patients were recruited from the early Systemic SclerOsis Longitudinal Assessment Registry (SOLAR). SOLAR is a nationwide, multicentre, prospective cohort initiated in 2023 and involving 25 centres across Turkey. The cohort enrols patients with SSc who are within three years of the onset of non-RP, symptoms and who meet either the 2013 American College of Rheumatology (ACR)/ European Alliance of Associations for Rheumatology (EULAR) classification criteria for SSc or the very early diagnosis of systemic sclerosis (VEDOSS) definition (20, 21). Patients were classified as lcSSc and dcSSc according to the extent of skin involvement (4). A total of 295 patients registered in the database from inception through August 2024 were evaluated. Fifty-five patients fulfilling the VEDOSS definition and 8 patients with SSc-sine scleroderma were excluded. Two hundred thirty-two SSc patients were further evaluated. Nineteen patients who were negative for both ATA and ACA, 4 patients who were positive for both ACA and ATA, 6 patients positive for other SSc-related antibodies, 7 patients with unknown antibody profiles, and 24 ATA-negative dcSSc patients were excluded from the analysis (Fig. 1). A total of 74 ACA-positive lcSSc patients were compared with 55 ATA-positive lcSSc patients and 43 ATA-positive dcSSc.

Definitions

Disease onset was defined as the time of the first non–RP symptom manifestation and the age at disease onset was calculated accordingly. Disease duration was defined as the interval between the onset of non-RP symptoms and the date of study enrolment. Age at diagnosis was determined as the age at which the patients fulfilled the 2013 ACR/EULAR classification criteria for SSc and were diagnosed by a rheumatologist. The presence of RP, digital ulcer, pitting scar, calcinosis, telangiectasia and arthritis were recorded at the time of enrolment if ever present. Skin thickness was determined using mRSS (22). SSc-related organ involvement was defined according to the SOLAR criteria (Supplementary Table S1) (23-26). Nailfold videocapillaroscopy was performed when equipment was available at participating centres. Missing capillaroscopy data were mainly related to the lack of equipment in some centres rather than patient- or disease-related factors. To ensure standardisation, investigators involved in data collection underwent structured capillaroscopy training during a national meeting prior to study initiation. Capillaroscopic findings were evaluated according to the standardised assessment recommended by the EULAR Study Group on Microcirculation in Rheumatic Diseases and the Scleroderma Clinical Trials Consortium Group on Capillaroscopy (27). The use of at least one of following agents was considered immunosuppressive therapy: glucocorticoids, mycophenolate mofetil, methotrexate, azathioprine, rituximab, or cyclophosphamide.

Ethical approval for the study was obtained from the Kocaeli University Non-Interventional Clinical Research Ethics Committee on May 4, 2023, under decision number KÜ GOKAEK-2023/08.29. Written informed consent was obtained from all participants.

Statistical analysis

Statistical analyses were performed using SPSS version 21 (SPSS Inc., 2015). Normally distributed continuous variables were expressed as mean ± standard deviation, whereas non-normally distributed data were presented as median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. For comparisons among the three groups, the Chi-square or Fisher's exact test was used for categorical variables, as appropriate and either the Kruskal-Wallis or one-way ANOVA test was applied for continuous variables, depending on the distribution of the data. For pairwise comparisons between ATA-positive lcSSc and ACA-positive lcSSc or ATA-positive dcSSc, Student's t test or the Mann-Whitney U-test was used for quantitative variables, while the Chi-square or Fisher's exact test was applied for categorical variables, as appropriate. Bonferroni correction was applied to adjust for multiple comparisons and a two-sided p value <0.05 was considered statistically significant.

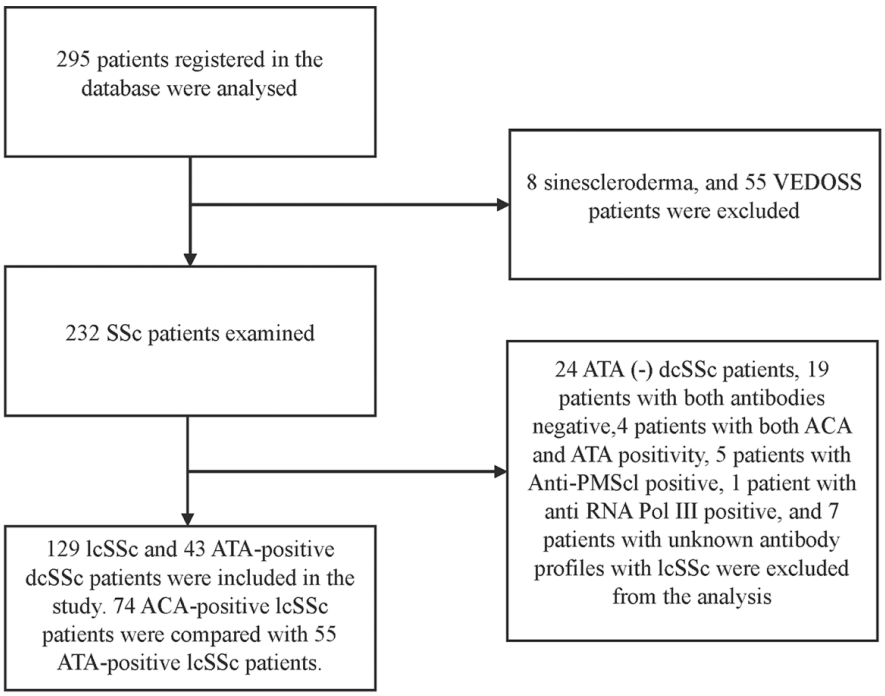

Fig. 1. Schematic representation of included and excluded patients in the study.

Results

A total of 172 SSc patients, including 129 lcSSc (74 ACA-positive and 55 ATA-positive) and 43 ATA-positive dcSSc patients were included in the study.

Comparison of ACA-positive lcSSc and ATA-positive lcSSc patients

The proportion of female patients was comparable between the two groups. The age of onset for RP (47.5 IQR 23.3 *vs*. 41.3 IQR 20.5 years, p=0.042), the age of onset for non-RP symptoms (49.6 IQR 23.4 *vs*. 41.3 IQR 20.5 years, p=0.016), and the age at diagnosis (52.2±13.8 *vs*. 44.9±13.9, p=0.018) were earlier in ATA-positive lcSSc patients.

The duration from the onset of RP to the emergence of non-RP symptoms was shorter in ATA-positive lcSSc patients (1.6 IQR 2.3 *vs*. 1.2 IQR 2.3 years, p=0.120) but the difference did not reach statistical significance. ILD was more frequent (8.1% *vs*. 74.5%, p<0.001) and the mRSS was higher (3 IQR 3 *vs*. 7 IQR 7, p<0.001) in ATA-positive lcSSc patients. Other clinical findings and laboratory results were similar between the two groups. (Table I, Fig. 2).

Immunosuppressive therapy was more frequently administered to ATA-positive lcSSc patients compared to ACA-positive lcSSc patients (83.6% *vs*. 25.7%, p<0.001). Within immunosuppressive treatments, use of mycophenolate mofetil (63.6% *vs*. 6.8%, p<0.001) and glucocorticoids (29.1% *vs*. 13.5%, p=0.058) were more frequent in ATA-positive lcSSc patients but glucocorticoid use did not reach a statistically significant difference.

Table I. Comparison of demographic, clinical and laboratory characteristics in ACA-positive and ATA-positive lcSSc and dcSSc patients.

	All lcSSc patients n=129	ACA (+) lcSSc n=74	ATA (+) lcSSc n=55	ATA (+) dcSSc n=43	*p*
Sex, female, n (%)	122 (94.6)	70 (94.6)	52 (94.5)	31 (72.1)	**<0.001**‡¶
Disease duration, years, median (IQR)	1.2 (1.5)	1.2 (1.4)	1.25 (1.8)	1.6 (1.3)	0.195
Age at the onset of RP symptoms, year, median (IQR)	45.9 (23.6)	47.5 (23.3)	41.3 (20.5)	47.1 (15.3)	0.055†
Age at onset of non-RP, year, median (IQR)	48.4 (22.1)	49.6 (23.4)	44.9 (21.3)	49.4 (16.4)	0.027†
Age at diagnosis, year, mean ± std	48.7 (21.8)	52.2 ± 13.8	44.9 ± 13.9	49.3 ± 11.1	**0.010**†
Time between non-RP symptoms and RP, year, median (IQR)	1.5 (2.45)	1.6 (2.3)	1.2 (2.3)	0.4 (1.5)	**0.001**¶
Clinical features					
RP, n (%)	123 (95.3)	71 (95.9)	52 (94.5)	42 (97.7)	0.739
Pitting scar, n (%)	28 (21.7)	14 (18.9)	14 (25.5)	22 (51.2)	**0.001**‡¶
Digital ulcer, n (%)	24 (18.6)	11 (14.9)	13 (23.6)	18 (41.9)	0.005¶
Telangiectasia, n (%)	60 (46.5)	33 (44.6)	27 (49.1)	19 (45.2)	0.871
Arthritis, n (%)	26 (20.2)	14 (18.9)	12 (21.8)	12 (27.9)	0.527
ILD, n (%)	47 (36.4)	6 (8.1)	41 (74.5)	28 (65.1)	**<0.001**†¶
PAH, n (%)	5 (3.9)	3 (4.1)	2 (3.7)	2 (4.7)	0.973
SRC, n (%)	0	0	0	1 (2.3)	0.224
Gastrointestinal involvement, n (%)	37 (28.7)	21 (28.4)	16 (29.6)	19 (44.2)	0.180
Cardiac involvement, n (%)	3 (2.3)	0	3 (5.7)	6 (14)	**0.005**¶
mRSS, median (IQR)	4 (5.5)	3 (3)	7 (7)	17 (17.2)	**<0.001**†‡¶
Capillaroscopy findings					
Abnormal capillaroscopy findings, n (%)	97/109 (75.2)	55/62 (88.7)	42/47 (89.4)	35/40 (87.5)	0.963
Early SSc pattern, n (%)	47/97 (48.5)	26/55 (47.2)	21/42 (50)	4/35 (11.4)	**0.001**‡¶
Active SSc pattern, n (%)	45/97 (46.4)	27/55 (49.1)	18/42 (42.9)	26/35 (74.3)	**0.015**‡
Late SSc pattern, n (%)	5/97 (5.2)	2/55 (3.6)	3/42 (7.1)	5/35 (14.3)	0.175
Laboratory findings					
CRP, mg/L, median (IQR)	3 (6.1)	3 (5.9)	3 (7.7)	3.3 (8.1)	0.535
CRP >5 mg/L, n (%)	36/114 (31.6)	18/65 (27.7)	18/49 (36.7)	17/40 (42.5)	0.276
ESR, mm/h, median (IQR)	13 (13.8)	14 (13.5)	13 (15)	19 (19)	**0.010**‡
Hypocomplementemia, n (%)	1/90 (1.1)	1/52 (1.9)	0/38	1/37 (2.7)	0.621

ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ILD: interstitial lung disease; IQR: interquartile range; lcSSc: limited cutaneous systemic sclerosis; mRSS: modified Rodnan skin score; n: number of patients; PAH: pulmonary arterial hypertension; RP: Raynaud's phenomenon; SRC: scleroderma renal crisis; SSc: systemic sclerosis; Std: standard deviation.
†, ‡, ¶ denote Bonferroni-adjusted pairwise comparisons ($p<0.05$): † ACA-positive lcSSc *vs*. ATA-positive lcSSc; ‡ ATA-positive lcSSc *vs*. ATA-positive dcSSc; ¶ ACA-positive lcSSc *vs*. ATA-positive dcSSc.

Nintedanib was used in 5 ATA-positive lcSSc patients (9.1%), whereas none of the ACA-positive lcSSc patients received it (p=0.026). The frequency of use of other medications was similar between the two groups (Table II).

Comparison of ATA-positive lcSSc and ATA-positive dcSSc patients

Male sex was more prevalent in ATA-positive dcSSc patients compared to ATA-positive lcSSc patients (27.9% *vs*. 5.5%, $p=0.004$). The age at RP onset, the age at non-RP symptom onset, and the age at diagnosis were comparable between the two groups; however, the duration from RP onset to the onset of non-RP symptoms (0.4 IQR 1.5 *vs*. 1.2 IQR 2.3, $p=0.134$) was shorter in ATA-positive dcSSc patients although not statistically significant. Pitting scars (51.2% *vs*. 25.5%, $p=0.018$) were more frequent and the mRSS (17 IQR 17.2 *vs*. 7 IQR 7, $p<0.001$) was higher in ATA-positive dcSSc patients. The frequency of ILD (p=0.610) and cardiac involvement ($p=0.582$) was similar in the two groups. Capillaroscopic evaluation revealed that the early SSc pattern was more common in ATA-positive lcSSc patients (11.4% *vs*. 50%, $p<0.001$), whereas the active SSc pattern (74.3% *vs*. 42.9%, $p=0.012$) was more frequently observed in ATA-positive dcSSc patients. Erythrocyte sedimentation rate was higher in ATA-positive dcSSc patients (19 IQR 19 *vs*. 13 IQR 15 mm/h, $p=0.012$), while other laboratory characteristics were comparable between the two groups (Table I). With respect to treatment characteristics, cyclophosphamide (30.2% *vs*. 5.5%, $p=0.003$) was the only therapy administered more frequently in ATA-positive dcSSc patients compared to ATA-positive lcSSc patients. The utilisation rates of other medications were comparable between the two groups (Table II).

Comparison of ILD features across ATA-positive subgroups: ATA-positive lcSSc, and ATA-positive dcSSc patients

ILD was present in 74.5% of ATA-positive lcSSc patients and 65.1% of ATA-positive dcSSc patients. Baseline HRCT and pulmonary function test characteristics were compared between the groups. ACA-positive patients with ILD were excluded from this analysis due to the small sample size. No significant differences were observed in HRCT patterns or pulmonary function test parameters between the two groups (Table III).

Discussion

This multicentre study demonstrates that ATA-positive lcSSc in early-stage

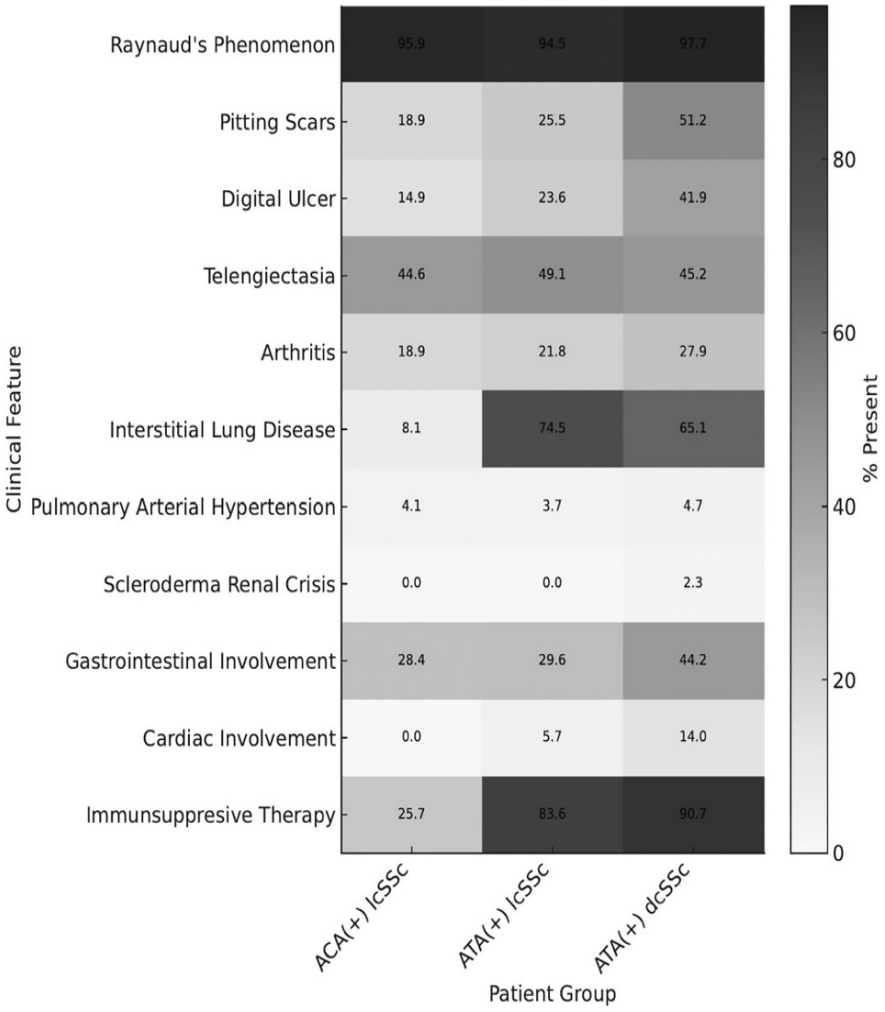

Fig. 2. Comparison of clinical characteristics in ACA-positive and ATA-positive lcSSc and dcSSc patients.

disease represents a distinct clinical subset rather than a mild form of lcSSc. Compared with ACA-positive lcSSc, these patients had a higher prevalence of ILD, earlier onset of both RP and non-RP symptoms, and higher mRSS values, indicating a more aggressive disease profile despite limited skin involvement. In contrast to ATA-positive dcSSc, they were more frequently female, had lower mRSS values (a known adverse prognostic marker for ILD), and exhibited a longer interval between RP and non-RP manifestations. Together, these findings place ATA-positive lcSSc in an intermediate but high-risk position between ACA-positive lcSSc and ATA-positive dcSSc.

In patients with early stage lcSSc, the presence of ATA may be associated with an earlier onset of both RP and non-RP symptoms, a shorter interval between the onset of RP and non-RP manifestations, a higher prevalence of ILD, and increased mRSS. This indicates that ATA-positive lcSSc patients have a more severe clinical course compared to ACA-positive lcSSc patients. Traditionally, classification based on the extent of skin involvement has been central to the clinical evaluation of patients with systemic sclerosis. However, increasing evidence indicates that skin-based classification alone is not sufficient and that autoantibody status plays a critical role in shaping disease phenotype and prognosis (15-19). Furthermore, these studies suggest that autoantibody profiles in patients with lcSSc may influence the timing of symptom onset. In line with this concept, in our study, RP and non-RP symptoms appeared earlier in ATA-positive lcSSc patients, and although not statistically significant, the time from RP onset to non-RP symptom onset was shorter in ATA-positive patients. These findings are consistent with several previous reports (17-19), although others have found no differences in the age at onset of RP or non-RP symptoms between ATA- and ACA-positive lcSSc patients (16, 28). Additionally, Kranenburg et al. reported no difference in the interval between RP and non-RP symptoms (16). Moreover, we demonstrated that the age of onset for RP and non-RP symptoms was comparable between ATA-positive lcSSc and ATA-positive dcSSc patients, whereas the interval from the onset of RP to non-RP symptoms was shorter in ATA-positive dcSSc patients. ATA positivity appears to precipitate the onset of symptoms earlier than in ACA positive patients. Although ATA positivity in lcSSc patients seems to shorten the interval between RP and non-RP symptoms, it is insufficient to explain the rapid progression observed in dcSSc, implicating additional modifying mechanisms in disease evolution.

The strongest and most clinically relevant finding of this study is the high prevalence of ILD among ATA-positive lcSSc patients, which was comparable to that observed in ATA-positive dcSSc and markedly higher than in ACA-positive lcSSc. Consistent with previous reports, despite not being specifically focused on early-stage systemic sclerosis (15-19, 28), our findings support that ATA positivity is a key determinant of pulmonary involvement in early SSc, independent of the extent of skin involvement. Although our study was not designed to assess ILD prognosis and did not evaluate the extent of fibrosis on HRCT, the higher proportion of male patients and greater mRSS in ATA-positive dcSSc, both recognised adverse prognostic factors, suggest a potentially worse ILD course in this subgroup (17, 29). These results suggest that patients with early SSc should be cautious about the presence and progression of ILD in the presence of ATA positivity, regardless of the extent of skin involvement.

Beyond lung involvement, ATA-positive lcSSc also demonstrated a more severe cutaneous phenotype than ACA-positive lcSSc. Although ATA-positive

Table II. Comparison of treatment characteristics in ACA-positive and ATA-positive lcSSc and dcSSc patients.

	All lcSSc patients n=129	ACA (+) lcSSc n=74	ATA (+) lcSSc n=55	ATA (+) dcSSc n=43	*p*
Immunosuppressive treatments, n (%)	65 (50.4)	19 (25.7)	46 (83.6)	39 (90.7)	**<0.001**†¶
Glucocorticoids, n (%)	26 (20.2)	10 (13.5)	16 (29.1)	18 (41.9)	**0.002**¶
Mycophenolate mofetil, n (%)	40 (31)	5 (6.8)	36 (63.6)	29 (67.4)	**<0.001**†¶
Methotrexate, n (%)	5 (3.9)	8 (10.8)	10 (18.2)	11 (25.6)	0.115
Azathioprine, n (%)	6 (4.7)	2 (2.7)	4 (7.3)	4 (9.3)	0.290
Rituximab, n (%)	5 (3.9)	1 (1.4)	4 (7.3)	4 (9.3)	0.126
Cyclophosphamide, n (%)	5 (3.9)	2 (2.7)	3 (5.5)	13 (30.2)	**<0.001**‡¶
Other treatments					
Calcium channel blockers, n (%)	83 (64.3)	49 (66.2)	34 (61.8)	30 (69.8)	0.707
Acetylsalicylic acid, n (%)	93 (72.1)	56 (75.7)	37 (67.3)	30 (69.8)	0.555
Hydroxychloroquine, n (%)	73 (56.6)	42 (56.8)	31 (56.4)	20 (46.5)	0.517
Iloprost, n (%)	15 (11.6)	8 (10.8)	7 (12.7)	6 (14)	0.873
PDE5 inhibitors, n (%)	8 (6.2)	4 (5.4)	4 (7.3)	3 (7)	0.898
Endothelin receptor antagonist, n (%)	7 (5.4)	4 (5.4)	3 (5.5)	1 (2.3)	0.705
Pentoxifylline, n (%)	10 (7.8)	6 (8.1)	4 (7.3)	1 (2.3)	0.444
Nintedanib, n (%)	5 (3.9)	0	5 (9.1)	0	**0.004**†

ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; n: number of patients; PDE5: phosphodiesterase-5.
†, ‡, ¶ denote Bonferroni-adjusted pairwise comparisons ($p<0.05$): † ACA-positive lcSSc *vs*. ATA-positive lcSSc; ‡ ATA-positive lcSSc *vs*. ATA-positive dcSSc; ¶ACA-positive lcSSc *vs*. ATA-positive dcSSc.

Table III. Comparison of HRCT and pulmonary function test findings between ATA-positive lcSSc and ATA-positive dcSSc patients with ILD.

	ATA-positive lcSSc with ILD n=41	ATA-positive dcSSc with ILD n=28	ATA (+) lcSSc *vs*. ATA (+) dcSSc P
HRCT findings			
Ground-glass opacities, n (%)	34/40 (85)	21/27 (77.8)	0.524
Traction bronchiectasis, n (%)	10/40 (25)	9/27 (34.6)	0.399
Honeycomb, n (%)	2/39 (5.1)	0/26	0.513
Septal thickening	18/40 (45)	12/27 (46.2)	0.927
Increased reticular density, n (%)	25/40 (62.5)	19/27 (70.4)	0.506
Pleural effusion, n (%)	6/40 (15)	7/27 (25.9)	0.267
Pulmonary function test			
Basal FVC %, median (IQR)	81 (31)	73.5 (29.3)	0.077
Basal FEV1 %, median (IQR)	86 (35)	74.5 (23.3)	0.088
Basal FEV1/FVC %, median (IQR)	96 (18)	103 (19)	0.185
Basal DLCO %, median (IQR)	77 (31.5)	88 (22)	0.052

ACA: anti-centromere antibody; ATA: anti-topoisomerase I antibody; DLCO: diffusing capacity for carbon monoxide; FEV1: forced expiratory volume 1; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IQR: interquartile range; lcSSc: limited cutaneous systemic sclerosis; n: number of patients.

lcSSc demonstrated higher mRSS values, other clinical features were largely comparable with ACA-positive lcSSc. In contrast, ATA-positive dcSSc patients showed more advanced skin disease and more frequent pitting scars than ATA-positive lcSSc. Our results suggest that ATA positivity alone does not fully account for cutaneous severity and that skin extent remains an important modifier of phenotype. Previous studies have reported heterogeneous findings regarding clinical manifestations in ATA-positive disease subtypes. With respect to digital ulcers and pitting scars, several studies have shown similar frequencies in lcSSc patients regardless of ACA or ATA positivity, whereas others, including data from the RESCLE registry, have reported higher rates in ATA-positive subgroups, in line with our findings (17, 19, 28). In addition, nailfold capillaroscopy patterns differed across groups, with ATA-positive dcSSc more frequently exhibiting the active scleroderma pattern, in line with the findings of Arandia *et al*. (26). Collectively, these data support that ATA-positive lcSSc occupies an intermediate clinical position between ACA-positive lcSSc and ATA-positive dcSSc.

In ATA-positive patients, the earlier onset of symptoms, combined with a higher frequency of ILD and elevated mRSS, appears to be associated with a greater need for immunosuppressive therapy and the use of nintedanib. In our cohort, immunosuppressive therapies were used significantly more frequently in ATA-positive lcSSc patients compared to ACA-positive lcSSc patients, particularly mycophenolate mofetil and, to a lesser extent, nintedanib. Interestingly, the frequency of immunosuppressive use in ATA-positive lcSSc patients was comparable to that in ATA-positive dcSSc patients, except for cyclophosphamide use, despite the lower mRSS scores and absence of marked differences in pulmonary function tests. These findings may indicate that the high rate of immunosuppressive therapy in ATA-positive lcSSc reflects not only the clinical severity of the patients but also the increasing awareness of the prognostic significance of ATA positivity and its potential to influence the disease course even at early stages.

Our study has several limitations. First, although it included a cohort of patients with early SSc, the follow-up period remains relatively short. As a result, some ATA-positive patients initially

classified as having lcSSc may evolve into dcSSc over time, potentially representing a transitional phenotype not yet captured in our analysis. Second, due to the multicentre design of the study, ATA and ACA assessments were performed in different laboratories, which may have introduced variability. Third, the other SSc-related antibodies (such as anti-RNA polymerase III, anti-Th/To antibodies) were not assessed in most of the patients, and their potential effect on cutaneous subtypes may therefore have been underestimated. However, the coexistence of these antibodies is considered to be rare. Despite these limitations, the study has notable strengths, including its multicentre design, which enhances the generalisability of the findings to the Turkish SSc population, and its specific focus on the early-stage disease, allowing characterisation of ATA-positive lcSSc before full phenotypic evolution.

In conclusion, this multicentre study demonstrates that ATA-positive lcSSc patients, even at an early disease stage, represent a distinct clinical subset with features overlapping those of both ACA-positive lcSSc and ATA-positive dcSSc patients. Despite this intermediate clinical phenotype, the comparable frequency of immunosuppressive treatment to that in ATA-positive dcSSc patients, suggests that clinicians may perceive this subgroup as higher risk. These findings underscore the need for prospective longitudinal registries with systematic follow-up to clarify disease trajectories, evaluate treatment strategies, and determine long-term outcomes in this antibody-defined subgroup.

Competing interests

M.E. Yayla has received lecture fees from AbbVie, UCB Pharma, Bohringer Ingelheim and Pfizer. G. Hatemi has received research grant, lecture fees and fees for serving on an advisory board from Celgene, receiving consulting fees from UCB Pharma, Bayer, Johnson & Johnson, lecture fees from Novartis, AbbVie, Amgen and UCB Pharma. D. Temiz Karadag has received fees for serving on an advisory board from Boehringer Ingelheim, lecture fees from AbbVie, Sandoz and UCB Pharma. The other authors have declared no competing interests.

Affiliations

[1]Ankara University Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Ankara;
[2]University of Health Sciences, Adana City Training and Research Hospital, Dept. of Internal Medicine, Division of Rheumatology, Adana;
[3]University of Health Sciences Basaksehir Cam and Sakura City Hospital, Dept. of Rheumatology, Istanbul;
[4]Kocaeli University, Dept. of Internal Medicine, Division of Rheumatology, Kocaeli;
[5]Hacettepe University School of Medicine, Dept. of Internal Medicine, Division of Rheumatology, Ankara;
[6]Hatay Mustafa Kemal University School of Medicine, Dept. of Internal Medicine, Division of Rheumatology, Hatay;
[7]Etlik City Hospital, Clinic of Rheumatology, Etlik, Ankara;
[8]Ufuk University Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Ankara;
[9]Gazi University Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Ankara;
[10]Dept. of Rheumatology, Faculty of Medicine, Necmettin Erbakan University, Konya;
[11]Istanbul University Cerrahpaşa Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Istanbul;
[12]Çukurova University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Adana;
[13]Süleyman Demiral University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Isparta;
[14]Marmara University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Istanbul;
[15]Tekirdağ İsmail Fehmi Cumalıoğlu City Hospital, Clinic of Rheumatology, Tekirdağ;
[16]Ankara Bilkent City Hospital, Clinic of Rheumatology, Ankara;
[17]Ankara Yıldırım Beyazıt University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Ankara;
[18]Erciyes University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Kayseri;
[19]Fırat University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Elazığ;
[20]Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Rheumatology, Istanbul;
[21]Van Training and Research Hospital, Clinic of Rheumatology, Van;
[22]Istanbul University, Istanbul Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Istanbul;
[23]Sivas Cumhuriyet University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Sivas;
[24]Eskişehir Osmangazi University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Eskişehir, Turkey;
[25]Royal Wolverhampton NHS Trust, Dept. of Rheumatology, Wolverhampton, UK;
[26]Antalya Training and Research Hospital, Clinic of Rheumatology, Antalya, Turkey;
[27]Antalya City Hospital, Clinic of Rheumatology, Antalya, Turkey;
[28]Gaziantep University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Gaziantep, Turkey;
[29]Koç University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Istanbul, Turkey;
[30]Akdeniz University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, Antalya, Turkey;
[31]Dokuz Eylül University, Faculty of Medicine, Division of Rheumatology, Dept. of Internal Medicine, İzmir, Turkey.

References

1. DENTON CP, KHANNA D: Systemic sclerosis. *Lancet* 2017; 390(10103): 1685-99. https://doi.org/10.1016/S0140-6736(17)30933-9
2. ALLANORE Y, SIMMS R, DISTLER O *et al.*: Systemic sclerosis. *Nat Rev Dis Primers* 2015; 1: 15002. https://doi.org/10.1038/nrdp.2015.2
3. DI BATTISTA M, LEPRI G, CODULLO V *et al.*: Systemic sclerosis: one year in review 2025. *Clin Exp Rheumatol* 2025; 43(8): 1369-79. https://doi.org/10.55563/clinexprheumatol/upbjl2
4. LEROY EC: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-6.
5. LEROY EC, MEDSGER TA: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28(7): 1573-76.

6. TYNDALL AJ, BANNERT B, VONK M *et al*.: Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69(10): 1809-15. https://doi.org/10.1136/ard.2009.114264
7. MAYES MD, LACEY JV, BEEBE-DIMMER J *et al*.: Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheumatol* 2003; 48(8): 2246-55. https://doi.org/10.1002/art.11073
8. SOBANSKI V, GIOVANNELLI J, ALLANORE Y *et al*.: Phenotypes determined by cluster analysis and their survival in the prospective European Scleroderma Trials and Research Cohort of Patients with Systemic Sclerosis. *Arthritis Rheumatol* 2019; 71(9): 1553-70. https://doi.org/10.1002/art.40906
9. MAHLER M, HUDSON M, BENTOW C *et al*.: Autoantibodies to stratify systemic sclerosis patients into clinically actionable subsets. *Autoimmun Rev* 2020; 19(8): 102583. https://doi.org/10.1016/j.autrev.2020.102583
10. PHILIP SS, JANARDANA R, SHENOY P *et al*.: Exploratory clinical subgroup clustering in systemic sclerosis: results from the Indian Progressive Systemic Sclerosis Registry. *J Scleroderma Relat Disord* 2024; 9(1): 29-37. https://doi.org/10.1177/23971983231215470
11. NIHTYANOVA SI, DENTON CP: Autoantibodies as predictive tools in systemic sclerosis. *Nat Rev Rheumatol* 2010; 6(2): 112. https://doi.org/10.1038/nrrheum.2009.238
12. KUWANA M: Circulating anti-nuclear antibodies in systemic sclerosis: utility in diagnosis and disease subsetting. *J Nippon Med Sch* 2017; 84(2): 56-63. https://doi.org/10.1272/jnms.84.56
13. MECOLI CA, CASCIOLA-ROSEN L: An update on autoantibodies in scleroderma. *Curr Opin Rheumatol* 2018; 30(6): 548-53. https://doi.org/10.1097/bor.0000000000000550
14. STEEN VD: Autoantibodies in systemic sclerosis. *Semin Arthritis Rheum* 2005; 35(1): 35-42. https://doi.org/10.1016/j.semarthrit.2005.03.005
15. NIHTYANOVA SI, SARI A, HARVEY JC *et al*.: Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. *Arthritis Rheumatol* 2020; 72(3): 465-76. https://doi.org/10.1002/art.41153.
16. KRANENBURG P, VAN DEN HOMBERGH WM, KNAAPEN-HANS HK, VAN DEN HOOGEN FH, FRANSEN J, VONK MC: Survival and organ involvement in patients with limited cutaneous systemic sclerosis and anti-topoisomerase-I antibodies: determined by skin subtype or auto-antibody subtype? A long-term follow-up study. *Rheumatology* (Oxford) 2016; 55(11): 2001-8. https://doi.org/10.1093/rheumatology/kew298
17. ZANATTA E, HUSCHER D, ORTOLAN A *et al*.: Phenotype of limited cutaneous systemic sclerosis patients with positive anti-topoisomerase I antibodies: data from the EUSTAR cohort. *Rheumatology* (Oxford) 2022; 61(12): 4786-96. https://doi.org/10.1093/rheumatology/keac188
18. SANTOS CS, MORALES CM, CASTRO CA, ALVAREZ ED: Clinical phenotype in scleroderma patients based on autoantibodies. *Rheumatol Adv Pract* 2023; 7(Suppl 1): i26-i33. https://doi.org/10.1093/rap/rkad010
19. SRIVASTAVA N, HUDSON M, TATIBOUET S *et al*.: Thinking outside the box – the associations with cutaneous involvement and autoantibody status in systemic sclerosis are not always what we expect. *Semin Arthritis Rheum* 2015; 45(2): 184-9. https://doi.org/10.1016/j.semarthrit.2015.04.009
20. HOOGEN F, KHANNA D, FRANSEN J *et al*.: 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheumatol* 2013; 65(11): 2737-47. https://doi.org/10.1136/annrheumdis-2013-204424
21. MINIER T, GUIDUCCI S, BELLANDO-RANDONE S *et al*.: Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. *Ann Rheum Dis* 2014; 73(12): 2087-93. https://doi.org/10.1136/annrheumdis-2013-203716
22. KHANNA D, FURST DE, CLEMENTS PJ *et al*.: Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. *J Scleroderma Relat Disord* 2017; 2(1): 11-18. https://doi.org/10.5301/jsrd.5000231
23. HOFFMANN-VOLD AM, PETELYTSKA L, BARUA I *et al*.: POS0203 evidence-based expert consensus definition of organ involvement in systemic sclerosis – a EUSTAR study. *Ann Rheum Dis* 2024; 83(Suppl 1): 331-32.
24. HUMBERT M, YAICI A, DE GROOTE P *et al*.: Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum* 2011; 63(11): 3522-30. https://doi.org/10.1002/art.30541
25. BRUNI C, BUCH MH, FURST DE *et al*.: Primary systemic sclerosis heart involvement: a systematic literature review and preliminary data-driven, consensus-based WSF/HFA definition. *J Scleroderma Relat Disord* 2022; 7(1): 24-32. https://doi.org/10.1177/23971983211053246
26. HUDSON M, BARON M, TATIBOUET S *et al*.: Exposure to ACE inhibitors prior to the onset of scleroderma renal crisis-results from the International Scleroderma Renal Crisis Survey. *Semin Arthritis Rheum* 2014; 43(5): 666-72. https://doi.org/10.1016/j.semarthrit.2013.09.008
27. SMITH V, HERRICK AL, INGEGNOLI F *et al*.: Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmun Rev* 2020; 19(3): 102458. https://doi.org/10.1016/j.autrev.2020.102458
28. INIESTA ARANDIA N, ESPINOSA G, TOLOSA VILELLA C *et al*.: Serodiscordant patients with systemic sclerosis: when antibody does not correspond to skin involvement. *Clin Exp Rheumatol* 2020; 38 (Suppl 125): S106-14.
29. HOFFMANN-VOLD A-M, ALLANORE Y, ALVES M *et al*.: Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. *Ann Rheum Dis* 2021; 80(2): 219-27. https://doi.org/10.1136/annrheumdis-2020-217455