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Original Research

The clinical phenotype of anti-Th/To+ patients in systemic sclerosis: a case-control study within the European Scleroderma Trials and Research cohort

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Abstract

Background: Systemic sclerosis (SSc) is a heterogeneous autoimmune disease, where autoantibody profiling plays a central role in defining disease subsets and guiding personalized management.

Objectives: To investigate the clinical phenotype and long-term outcomes of anti-Th/To positive SSc patients in an international cohort, focusing on interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), malignancy association, organ damage accrual, and mortality within a precision medicine framework.

Design: Multicenter case-control study.

Methods: Data prospectively collected from 28 European Scleroderma Trial and Research centers were analyzed (CP144). For each anti-Th/To+ case, two anti-Th/To– controls were matched by sex, age at onset, and disease duration to enable detailed phenotypic comparisons.

Results: A total of 102 anti-Th/To+ patients were compared to 204 anti-Th/To– matched controls. Anti-Th/To+ patients had a higher prevalence of concomitant anti-Ro52+, lower frequency of diffuse cutaneous involvement, digital ulcers, pitting scars, and telangiectasias. ILD on high-resolution computed tomography and ILD functional progression events were less frequent in anti-Th/To+ patients, and anti-Th/To positivity was not independently associated with ILD in multivariable analysis. Instead, ILD presence was significantly associated with anti-Topoisomerase-1 (anti-Topo1) and anti-Ro52 positivity, and lack of anticentromere antibodies. Similarly, myocarditis was less frequently observed in anti-Th/To+ cases, although myositis had a higher rate than in anti-centromere+ or other lcSSc patients. Other SSc manifestations, including PAH, and malignancies synchronous to SSc onset had similar frequencies between cases and controls. Anti-Th/To+ patients accrued mild organ damage during the disease course, with lower damage index scores than anti-Topo1+ matched controls. No SSc-related deaths occurred in anti-Th/To+ patients, who had survival curves slightly better, although not significantly different, than matched controls.

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Conclusion: Anti-Th/To+ SSc patients are characterized by low prevalence of major organ involvement, including ILD, when compared to matched controls, mild organ damage, and good survival. These results reinforce the ongoing use of autoantibody profiling—including rarer antibodies—in precision medicine for SSc.

Plain language summary

Understanding the features of systemic sclerosis patients with anti-Th/To antibodies: a study comparing patients within the European EUSTAR network

Why was the study done? Systemic sclerosis (SSc) is a complex autoimmune disease that affects the skin and internal organs. Doctors use specific antibodies detected in the blood to help predict how the disease might progress. However, some rare antibodies, like anti-Th/To, are not well understood. This study was done to better understand what anti-Th/To antibodies mean for patients with SSc, especially regarding lung and heart complications, cancer risk, and overall health outcomes.

What did the researchers do? The researchers collected and analyzed medical data from a large group of patients with systemic sclerosis across multiple centers in Europe. They compared patients who had anti-Th/To antibodies with similar patients who did not have these antibodies, looking closely at differences in lung disease, heart complications, cancer occurrence, organ damage, and survival over time.

What did the researchers find? They found that patients with anti-Th/To antibodies had less severe lung disease and fewer major organ complications compared to those without these antibodies. These patients also showed milder organ damage over time and had better overall survival rates. Some differences in other disease features were noted, but the presence of these antibodies was linked to a generally more favorable disease course.

What do the findings mean? The findings show that patients with anti-Th/To antibodies tend to have less severe organ involvement, especially less lung disease, and generally better health outcomes compared to similar patients without these antibodies. This information helps doctors better understand and predict disease progression in systemic sclerosis, supporting more personalized care based on patients' specific antibody profiles.

Keywords: anti-Th/To antibodies, clinical phenotype, precision medicine, systemic sclerosis

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Introduction

Anti-nuclear autoantibodies are detected in 95% of patients affected by Systemic Sclerosis (SSc), serving as valuable markers to identify distinct disease subsets.[1,2] The clinical significance of SSc-specific antibodies (anti-centromere (ACA), anti-topoisomerase 1 (anti-Topo1), anti-RNA-polymerase 3 (anti-RNAP3)) is well established and routinely applied in clinical practice to guide prognosis and management. However, the significance of rarer autoantibodies remains less clearly defined, and further research is needed. Among these, antibodies directed to the Th/To complex—which are associated with a characteristic homogeneous nucleolar pattern on HEp-2 indirect immunofluorescence—are found in 2%–5% of patients with SSc.[3] The Th/To antigens were first described in 1983 as 8–2 and 7–2 ribonucleo-proteins, which are components of RNase P and RNase MRP, respectively, two endonucleases involved in processing ribosomal, mitochondrial, and transfer RNA.[4,5] The gold standard test

for anti-Th/To antibody detection is RNA immunoprecipitation,[6,7] but, more recently, recombinant proteins have been used as antigenic targets in immunoassays such as Enzyme-Linked Immunosorbent Assays (ELISA) or line blots. Their specificity to SSc was estimated to be 97%, and their negative predictive value was 0.92.[8]

Anti-Th/To+ SSc patients have been described so far as a subgroup with limited cutaneous (lc) involvement but with worse survival compared to other lcSSc patients, which was attributed to a higher frequency of cardio-pulmonary involvement.[9–12] Interstitial lung disease (ILD) was reported in nearly half of anti-Th/To+ SSc patients[3,9,12,13]; however, data on its functional progression are limited[14] and no data on its radiologic features are available. Additionally, a higher frequency of pulmonary hypertension (PH), especially pulmonary arterial hypertension (PAH), was reported in the largest cohort of anti-Th/To+ patients so far described,[15] but not confirmed in other case series.[9,14,16,17] Data concerning organ damage,[18] that is associated with morbidity, mortality, and worse quality of life, are also scarce.[14] Finally, conflicting data on a possible increased incidence of cancer in anti-Th/To+ SSc patients have also been reported.[19,20]

Therefore, several clinically relevant issues concerning anti-Th/To antibodies still need to be clarified. Considering the low prevalence of these antibodies, only the analysis of a large multicentric cohort, and comparison with matched SSc controls not carrying these antibodies may provide meaningful information. Thus, the objective of the present study was to evaluate the clinical phenotype of anti-Th/To+ SSc patients, with focus on prevalence of organ involvement, disease progression and prognosis, including organ damage accrual and mortality, by taking advantage of the European Scleroderma Trial and Research (EUSTAR) network. These insights are essential for advancing precision medicine in SSc, as continuing to integrate autoantibody profiling, even with rarer specificities, into personalized risk stratification models can improve patient management and therapeutic decision-making in this heterogeneous disease.

Methods

Study design

A case-control study of prospectively collected data from 28 EUSTAR centers was performed (EUSTAR CP144). For every anti-Th/To+ SSc case, centers provided two anti-Th/To− SSc controls matched by sex, age at SSc onset (±5 years), and disease duration (±24 months).

Anti-Th/To cases with simultaneous positivity for other SSc-specific antibodies were excluded, while patients with concomitant positivity for anti-Ro52 antibodies, which are not SSc-specific and are often associated with other SSc-specific antibodies, were allowed in the study. Autoantibodies were detected by each center according to local practice. In particular, anti-Th/To were detected by immunoblotting assays in 74.0% patients, by RNA immunoprecipitation in 19.0%, and by ELISA in 7.0%.

To collect supplementary clinical and laboratory variables not covered by the EUSTAR registry, an additional dedicated form was created and distributed to the participating centers.

Clinical and laboratory data were retrieved from clinical charts and defined according to the minimal essential datasets of the EUSTAR registry, as previously described.[21]

In line with previous literature,[22] malignancies were classified as "synchronous" with SSc, when the diagnosis occurred within 24 months before and after SSc onset. In the analysis regarding cancer, anti-RNAP3+ SSc patients, known as having an increased risk of synchronous malignancies,[23] were excluded from the control group.

ILD severity (HRCT-defined pattern and extent) and outcome (functional progression, oxygen supply requirement, PH development, ILD-related mortality) were analyzed in ILD+ patients.

ILD functional progression was evaluated through pulmonary function tests (PFTs). A progressive ILD event was defined as either one of the following two statements:

> A relative decline in predicted forced vital capacity (pFVC) ⩾10%, or a relative decline in pFVC of 5%–10% along with a relative decline in predicted diffusion of the lung for carbon monoxide (pDLCO) ⩾15%, over 12 ± 3 months, according to Goh et al.[24] and Hoffmann-Vold et al.[25,26]
> Absolute decline in pFVC ⩾5% and/or pDLCO >10% over 12 ± 3 months, according to the American Thoracic Society/European

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Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society (ATS/ERS/JRS/ALAT) recommendations.[27]

The rate of ILD progressive events among the total available PFTs was calculated. A single patient was considered a progressor if they experienced at least ⩾1 ILD progression event during the disease course.

Organ damage was evaluated through the Scleroderma Clinical Trials Consortium Damage Index (SCTC-DI),[18] categorizing damage into mild (0–4), moderate (5–12), and severe (>12).

PFTs values and SCTC-DI scores were evaluated at different timepoints: at baseline (T0), every year during the first 5 years (T1, T2, T3, T4, T5), then after 10 (T10) and 15 (T15) years.

T0 was referred to SSc onset/first non-Raynaud symptom occurrence.

Subgroup analysis

A subgroup analysis compared lcSSc anti-Th/To+ with lcSSc anti-Th/To− controls; a further separated analysis evaluated anti-Th/To+ cases in comparison with anti-Topo1+ and ACA+ controls.

Statistical analysis

Continuous variables were presented as median (first–third quartile). Categorical variables were presented as number (percentages) and were compared using the Chi-square test, or Fisher's exact test when appropriate. Odds ratios (ORs) with their 95% confidence intervals were calculated; Haldane's correction was applied when needed. For the multivariable analysis, logistic regression models were used with a priori selection of variables based on expert opinion for their clinical relevance. The predictive performance of the logistic regression model was assessed by calculating the area under the receiver operating characteristic curve. Model calibration was evaluated using the Hosmer–Lemeshow goodness-of-fit test. The Mann–Whitney *U* test was performed to evaluate between-group differences in quantitative variables. For all the study variables, two-tailed *p* values smaller than 0.05 were considered statistically significant. The statistical analysis was performed with GraphPad Prism and SPSS programs.

The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[28]

Ethics approval was obtained from the respective local ethics committees (local ethics approval at ASST Spedali Civili di Brescia, n.1072). The study was conducted in accordance with Helsinki Declaration principles.

Results

In total, 306 SSc patients from 28 contributing EUSTAR centers were included in the study: 87.3% were females, and 91.7% Caucasians; median age at SSc onset was 53.0 (41.0–62.0) years, and median disease duration was 7.0 (3.0–12.0) years at the last available follow-up (Table 1).

One-hundred two anti-Th/To+ patients were compared to 204 anti-Th/To− controls (ACA+: 73 (35.8%); anti-Topo1+: 76 (37.3%); anti-RNAP3+: 10 (4.9%); other SSc-specific- or SSc-associated- autoantibodies: 31 (15.2%)). Anti-Ro52 antibody positivity was found in 53 of 256 evaluable patients (20.7%): in 40 was associated with SSc-specific antibodies and in 13 was an isolated finding (Table 1). Compared to anti-Th/To− controls, anti-Th/To+ patients had higher rate of concomitant anti-Ro52 positivity (31.7% vs 15.3%, OR: 2.54 (1.37–4.70)), lower frequency of diffuse cutaneous involvement, myocarditis, digital ulcers, pitting scars, and telangiectasias, whereas similar frequencies of gastrointestinal involvement, scleroderma renal crisis, and other cardiac manifestations were observed (Table 1).

Interstitial lung disease

ILD was detected in 39 (42.4%) anti-Th/To+ patients (vs 55.1% in anti-Th/To−, *p*: 0.046; Table 1), and was associated with anti-Ro52 positivity (16/35, 45.7% among anti-Th/To+ ILD+ patients vs 10/48, 20.8%, in anti-Th/To+ without ILD, *p*: 0.016; Table 2). Notably, the usual interstitial pneumonia (UIP) pattern on HRCT was more frequent in cases than in controls (23.1% vs 6.2%, *p*: 0.029), although the non-specific interstitial pneumonia pattern remained the most frequent pattern in both groups (71.8% vs 87.8% in anti-Th/To−, *p*: 0.027). Radiological ILD extent on HRCT was ⩾20% in nearly half of the patients in both groups. Among anti-Th/To+ ILD patients,

Table 1. Demographic and clinical features of anti-Th/To+ patients compared with sex-, age at disease onset-, and disease duration-matched anti-Th/To– SSc controls.

Demographic and clinical features	All the patients *n* = 306	Anti-Th/To+ *n* = 102	Anti-Th/To– *n* = 204	*p* Value OR (95% CI)
Females	267/306 (87.3)	88/102 (86.3)	179/204 (87.8)	0.716
Caucasian ethnicity	277/302 (91.7)	92/102 (90.2)	185/200 (92.5)	0.273
Anti-Th/To+	102/306 (33.3)	102/102 (100.0)	0/204 (0.0)	–
Anti-centromere+	73/306 (23.9)	0/102 (0.0)	73/204 (35.8)	–
Anti-topoisomerase 1+	76/306 (24.8)	0/102 (0.0)	76/204 (37.3)	–
Anti-RNA polymerase 3+	10/306 (3.3)	0/102 (0.0)	10/204 (4.9)	–
Other SSc specific/associated autoantibodies	31/306 (10.1)	0/102 (0.0)	31/204 (15.2)	–
Anti-Ro52+	53/256 (20.7)	27/86 (31.4)	26/170 (15.3)	0.003 2.54 (1.37–4.70)
Age at SSc onset,[a] years	53.0 (41.0–62.0)	54.0 (41.3–61.0)	53.0 (42.8–63.0)	0.998
Disease duration, years	7.0 (3.0–12.0)	6.0 (3.0–10.0)	7.0 (3.0–12.0)	0.659
Limited cutaneous subtype	212/306 (69.3)	79/102 (77.5)	133/204 (65.2)	0.028 1.83 (1.06–3.17)
mRSS at first evaluation	3.0 (1.0–9.0)	2.0 (0.0–4.3)	4.0 (2.0–11.0)	<0.001
mRSS at the last evaluation	3.0 (0.8–7.0)	2.0 (0.0–4.0)	4.0 (2.0–7.0)	<0.001
Digital ulcers	116/306 (37.9)	23/102 (22.5)	93/204 (45.6)	<0.001 0.35 (0.20–0.60)
Pitting scars	96/304 (31.6)	19/102 (18.6)	77/202 (38.1)	0.001 0.37 (0.21–0.66)
Telangiectasias	152/303 (50.2)	43/102 (42.2)	109/201 (54.2)	0.047 0.62 (0.38–0.99)
Calcinosis	49/300 (16.3)	13/101 (12.9)	36/199 (18.1)	0.234
Myositis	31/296 (10.5)	13/102 (12.7)	18/194 (9.3)	0.355
Synovitis	74/303 (24.4)	25/102 (24.5)	49/201 (24.4)	0.980
Joint contractures	36/302 (11.9)	7/102 (6.9)	29/200 (14.5)	0.053
Esophageal symptoms	177/303 (58.4)	55/102 (53.9)	122/201 (60.7)	0.258
GAVE	6/303 (2.0)	2/102 (2.0)	4/201 (2.0)	1.000
ILD (HRCT)	142/279 (50.9)	39/92 (42.4)	103/187 (55.1)	0.046 0.60 (0.36–0.99)
PH (RHC)	31/306 (10.1)	8/102 (7.8)	22/204 (10.7)	0.415
Group 1 PH (PAH)	14/306 (4.6)	4/102 (3.9)	10/204 (4.9)	0.781
Group 3 PH	11/306 (3.6)	2/102 (1.9)	9/204 (4.4)	0.347

(Continued)

Table 1. (Continued)

Demographic and clinical features	All the patients *n* = 306	Anti-Th/To+ *n* = 102	Anti-Th/To− *n* = 204	*p* Value OR (95% CI)
Cardiac involvement	95/294 (32.3)	34/102 (33.3)	61/192 (31.8)	0.758
Myocarditis	17/302 (5.6)	2/102 (2.0)	15/200 (7.5)	0.048 0.25 (0.06–1.10)
Pericarditis	5/301 (1.7)	2/102 (2.0)	3/199 (1.5)	0.771
Pericardial effusion	26/299 (8.7)	10/102 (9.8)	16/197 (8.1)	0.625
Arrhythmia	23/302 (7.6)	8/102 (7.8)	15/200 (7.5)	0.915
Diastolic dysfunction	81/290 (27.9)	31/102 (30.4)	50/188 (26.6)	0.915
Heart failure	12/292 (4.1)	4/102 (3.9)	8/190 (4.2)	0.906
Scleroderma renal crisis	10/304 (3.3)	3/102 (2.9)	7/202 (3.5)	0.809
Malignancies	45/285 (15.8)	17/100 (17.0)	28/185 (15.1)	0.680
Synchronous[b] malignancies	20/285 (7.0)	9/100 (9.0)	11/185 (5.9)	0.335
Death	41/306 (13.4)	9/102 (8.8)	32/204 (15.7)	0.097
Death due to SSc	10/306 (3.2)	0/102 (0.0)	10/204 (4.9)	0.023
Death due to SSc-ILD	8/306 (2.6)	0/102 (0.0)	8/204 (3.9)	0.043
Death due to cancer	10/306 (3.3)	6/102 (5.9)	4/204 (2.0)	0.069
Age at death, years	71.0 (60.0–78.0)	71.0 (61.0–82.0)	71.0 (58.0–76.8)	0.701
Disease duration at death, years	9.0 (4.0–17.0)	9.0 (6.0–15.0)	8.0 (3.3–17.8)	0.980

Continuous variables are presented as median (first–third quartile) and compared with Mann–Whitney test; categorical variables are presented as number/number available data (%) and compared with Chi-square test/Fisher's exact test. ORs were calculated, Haldane's correction was applied when needed.
[a]SSc onset = onset of first non-Raynaud manifestation.
[b]Synchronous malignancies = ±2 years from SSc onset.
CI, confidence interval; GAVE, gastric antral vascular ectasia; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; mRSS, modified Rodnan Skin Score; OR, odds ratio; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; SSc, systemic sclerosis.

immunosuppressive therapy was administered in 50.0%, oxygen supplementation in 15.4%, and anti-fibrotic drugs in 8.9%, with similar rates observed in the control group (Table 2). PFTs results were also comparable between groups at all evaluated time points (Tables S1 and S2).

According to the definition by Goh et al.,[24] 17 progressive ILD events were recorded among anti-Th/To+ patients (14.5% of 117 available PFT measurements), with 15 individuals (38.5%) defined as progressors. The proportion of progressive ILD events was lower than that observed in anti-Th/To− controls, in which 57 progressive events were recorded (24.2% of 236 available PFT measurements, *p*: 0.037) and 43 patients were defined progressors (41.7%; Table 2).

When applying the ATS/ERS/JRS/ALAT criteria, 25 anti-Th/To+ patients (64.1%) were classified as progressors, with 44 progressive ILD events recorded out of 117 PFT measurements (36.6%). In comparison, 62 anti-Th/To− patients (60.2%) were classified as progressors, with 98 ILD progressive events out of 236 measurements (41.5%). These differences were not significant (*p*: 0.670 and *p*: 0.480, respectively; Table 2). Only 1.9% of anti-Th/To+ patients developed group 3 PH;

Table 2. ILD characteristics and functional progression of anti-Th/To+ patients compared with sex-, age at disease onset-, and disease duration-matched anti-Th/To– SSc controls.

ILD characteristics and functional progression data	ILD+ anti-Th/To+ *n* = 39	ILD+ anti-Th/To– *n* = 103	*p* Value OR (95% CI)
NSIP pattern	28/39 (71.8)	79/90 (87.7)	0.027 0.35 (0.14–0.91)
UIP pattern	9/39 (23.1)	8/90 (8.9)	0.029 3.08 (1.09–8.70)
Other HRCT patterns	3/39 (7.7)	3/90 (2.9)	0.280
HRCT extent >20%	18/39 (46.2)	43/91 (47.3)	0.908
Immunosuppressive × ILD	24/48 (50.0)	57/115 (49.6)	0.960
Nintedanib	9/101 (8.9)	12/186 (6.5)	0.270
O_2 supply	6/39 (15.4)	14/91 (15.4)	1.000
Anti-Ro52+	16/35 (45.7)	15/87 (17.2)	0.001 4.04 (1.69–9.62)
Functional progressive ILD patients (Goh)	15/39 (38.5)	43/103 (41.7)	0.722
Total functional progressive events (Goh)	17/117 (14.5)	57/236 (24.2)	0.037 0.53 (0.29–0.97)
Functional progressive ILD patients, first 5 years (Goh)	14/39 (35.9)	35/103 (33.9)	0.830
Total functional progressive events, first 5 years (Goh)	16/102 (15.7)	47/208 (22.6)	0.178
Functional progressive ILD patients (ATS/ERS/JRS/ALAT)	25/39 (64.1)	62/103 (60.2)	0.670
Total functional progressive events (ATS/ERS/JRS/ALAT)	44/117 (36.6)	98/236 (41.5)	0.480
Functional progressive ILD patients, first 5 years (ATS/ERS/JRS/ALAT)	24/39 (61.5)	50/103 (48.5)	0.166
Total functional progressive events, first 5 years (ATS/ERS/JRS/ALAT)	38/101 (37.6)	78/208 (37.5)	0.983

Continuous variables are presented as median (first–third quartile) and compared with Mann–Whitney test; categorical variables are presented as number/number available data (%) and compared with Chi-square test/Fisher's exact test. ORs were calculated, Haldane's correction was applied when needed.
ATS/ERS/JRS/ALAT, American Thoracic Society American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society; CI, confidence interval; HRCT, high resolution computed tomography; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; O_2, oxygen supply; OR, odds ratio; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

none of the anti-Th/To+ patients died due to SSc-ILD (Table 1).

Analysis of factors associated with ILD presence and functional progression

To identify factors associated with the presence of ILD, a multivariable analysis was performed including variables selected for their clinical relevance, that is, cutaneous subset, age at SSc onset, sex, and antibody profile. Positivity for anti-Topo I and anti-Ro52 antibodies was independently associated with an increased likelihood of ILD, as was older age at disease onset. Conversely, ACA positivity was associated with a lower frequency of ILD, and anti-Th/To antibodies showed no significant impact on this complication (Table 3, Model 1). Given the established association of anti-Topo I antibodies with ILD, we explored the role of anti-Th/To antibodies in the subgroup of anti-Topo I-negative patients (Table S3). In this subset, the multivariable model yielded findings

Table 3. Multivariable analyses.

Model 1	**ILD presence**		
	***p*-Value**	**OR**	**95% CI**
dcSSc	0.844	0.92	0.41–2.08
Age at SSc onset	0.026	1.03	1.00–105
Female sex	0.298	0.60	0.23–1.57
Anti-Th/To+	0.189	0.55	0.23–1.34
Anti-Topo1+	<0.001	5.75	2.10–15.73
ACA+	0.005	0.23	0.08–0.64
Anti-Ro52+	0.023	2.43	1.12–5.22
Model 2	**ILD functional progression (according to Goh)**		
	***p*-Value**	**OR**	**95% CI**
Anti-Th/To+	0.662	0.76	0.22–2.62
Anti-Topo1+	0.826	0.88	0.27–2.83
Anti-Ro52+	0.974	0.98	0.34–2.88
UIP pattern on HRCT	0.497	0.64	0.17–2.36
ILD extent ⩾20%	0.001	4.41	1.81–10.75
%pFVC (T0)	0.784	0.99	0.08–5.09

Logistic regression models with a priori selection of variables to evaluate factors potentially associated with ILD development (Model 1) and ILD functional progression (Model 2). Model 1: The AUC for the logistic regression model was 0.81 (95% CI: 0.75–0.86), indicating a good level of discrimination. The Hosmer–Lemeshow goodness-of-fit test was not statistically significant ($\chi^2 = 10.19$, df = 8, $p = 0.25$), suggesting a good overall model fit. Model 2: The AUC for the logistic regression model was 0.70 (95% CI: 0.59–0.81), indicating an acceptable level of discrimination. The Hosmer–Lemeshow goodness-of-fit test was not statistically significant ($\chi^2 = 3.54$, df = 8, $p = 0.89$), suggesting a good overall model fit.
ACA, anti-centromere; AUC, area under the receiver operating characteristic curve; CI, confidence interval; dc, diffuse cutaneous; HRCT, high resolution computed tomography; ILD, interstitial lung disease; OR, odds ratio; pFVC, predicted forced vital capacity; SSc, systemic sclerosis; T0, baseline; Topo1, topoisomerase 1; UIP, usual interstitial pneumonia.

consistent with the overall cohort: anti-Ro52 positivity and older age at SSc onset were independently associated with ILD, whereas ACA positivity remained protective. Anti-Th/To antibodies did not show a significant association.

A further multivariable analysis was performed to evaluate factors associated with ILD functional progression (according to Goh definition, recorded at least once during the overall follow-up observation) and included the baseline HRCT pattern and extent, %pFVC, and antibody profiles. A baseline ILD extent on HRCT ⩾20% was the only variable showing a positive independent association with ILD functional progression (Table 3, Model 2).

Pulmonary hypertension

PH was confirmed at right heart catheterization in 8 (7.8%) anti-Th/To+ cases, not different than in anti-Th/To− controls. In particular, 4 (3.9%) cases belonged to group I PH (PAH), 2 cases (1.9%) to group II, and 2 cases (1.9%) to group III PH (Table 1).

Cancer

Malignancies were diagnosed in 17 (17.0%) anti-Th/To+ patients, not different from controls. In 9 (9.0%) anti-Th/To+ patients, cancer was diagnosed synchronously with SSc onset (vs 11, 5.9%, in anti-Th/To− controls; *p*: 0.335), the most common being breast cancer ($n = 4$), followed by

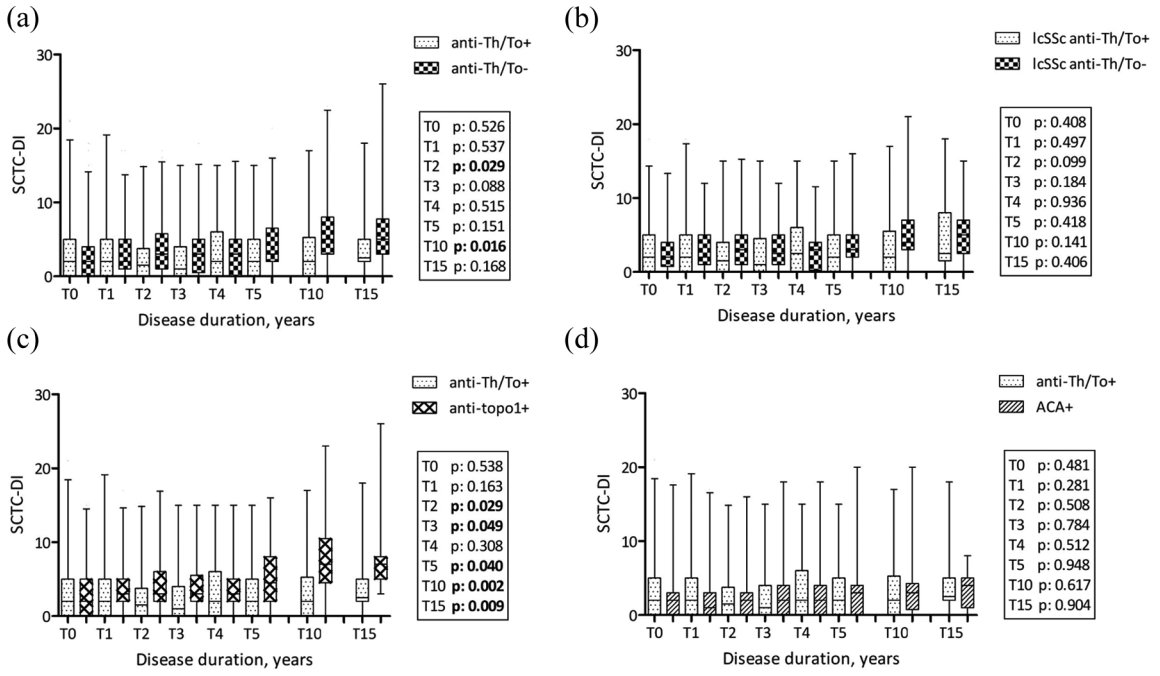

Figure 1. Organ damage accrual analysis, comparing anti-Th/To+ SSc patients with (a) anti-Th/To– matched controls, (b) anti-Th/To– lcSSc controls, (c) anti-topo1+ patients, and (d) ACA+ patients. Comparisons made with Mann–Whitney test.
ACA, anti-centromere; SCTC-DI, Scleroderma Clinical Trials Consortium Damage Index.

liver ($n=2$), pancreas, colon, and lung ($n=1$ each). No difference was observed in the frequency of anti-Ro52 antibodies between anti-Th/To-positive and -negative patients with cancer (data not shown).

Damage index

Anti-Th/To+ patients accrued mild organ damage (SCTC-DI <5) during the disease course, with scores significantly lower than controls at T2 and T10 (Figure 1(a)).

Mortality

Eight (7.8%) anti-Th/To+ patients died at a median age of 71.0 (61.0–82.0) years and with a median disease duration of 9.0 (6.0–15.0) years, with no deaths attributable to SSc-ILD or other SSc complications (Table 1). Survival curves are depicted in Figure 2(a): anti-Th/To+ patients had a survival rate of 98.9% at T1, 94.8% at T5, 89.9% at T10, and 76.4% T20, slightly better, although not significantly different, than matched controls (100.0% at T1, 94.3% at T5, 87.3% at T10, and 67.3% at T20).

Subgroup analysis 1: lcSSc

Among 212 patients with lcSSc included in this analysis, 79 were anti-Th/To+ and were compared to 133 anti-Th/To− (Table S4). Consistent with the findings in the overall cohort, anti-Th/To+ lcSSc patients exhibited fewer digital ulcers, pitting scars, and telangiectasias. Conversely, they demonstrated a significantly higher prevalence of myositis compared to other lcSSc patients (15.2% vs 4.6%, p: 0.008). No differences were recorded when evaluating gastrointestinal, cardiac, and renal involvements, as well as PAH and cancer (Table S4).

ILD was detected in 44.4% anti-Th/To+ lcSSc patients (vs 49.2% in controls, p: 0.528) with functional progression occurring in 34.4% according to Goh definition, and in 59.4% according to ATS/ERS/JRS/ALAT criteria, similar to lcSSc controls (Table S4).

Anti-Th/To+ lcSSc patients accrued mild organ damage during the disease course, with DI scores comparable to controls (Figure 1(b)). Survival curves (depicted in Figure 2(b)) were also not significantly different in the two groups.

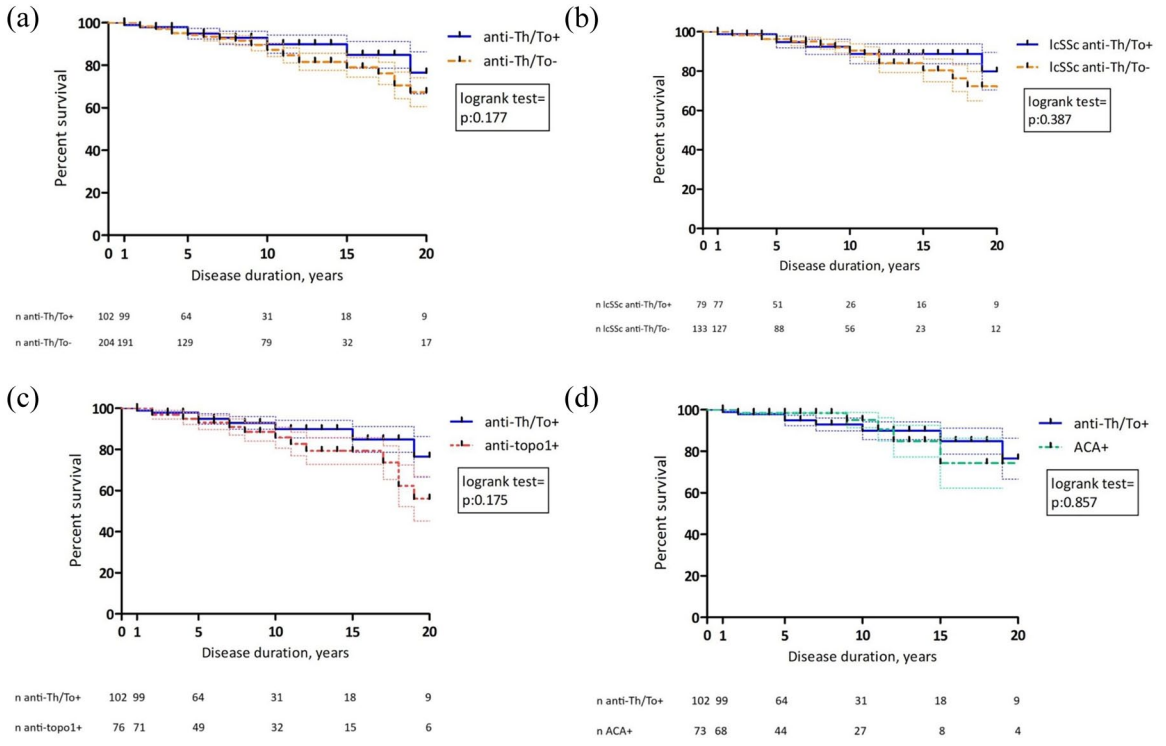

Figure 2. Survival analysis comparing anti-Th/To+ patients with controls, the latter including: (a) all anti-Th/To–, (b) lcSSc anti-Th/To–, (c) anti-topo1+, and (d) ACA+.
ACA, anti-centromere.

Subgroup analysis 2: Anti-Th/To+ versus anti-Topo1+ and versus ACA+

When compared with 76 anti-Topo1+ patients, anti-Th/To+ patients showed lower rates of dcSSc, digital ulcers, pitting scars, ILD, myocarditis, and joint contractures (Table 4). Anti-Th/To+ patients also showed lower scores of SCTC-DI, especially after 5, 10, and 15 years of disease duration (Figure 1(c)), and lower rates of deaths due to SSc, deaths due to ILD, and overall death (Table 4).

By comparing anti-Th/To+ patients with 73 ACA+ patients, the former suffered less frequently from digital ulcers and telangiectasias, but more frequently had myositis (12.7% vs 1.4%, p: 0.008) and ILD (42.4% vs 16.4%, p: <0.001; Table 4). No significant differences were observed in the SCTC-DI scores, which remained low in every timepoint assessed and in both groups (Figure 1(d)), as well as in the survival rates (Figure 2(d)).

Discussion

The aim of this study was to characterize the clinical phenotype of SSc patients positive for anti-Th/To antibodies, using data from the multicenter international EUSTAR cohort. Particular focus was placed on clarifying several unresolved aspects of this rare subset, including the radiologic features and progression of ILD, the prevalence of PAH and synchronous malignancies, as well as the trajectory of organ damage and overall survival. Understanding these distinct clinical patterns supports more tailored patient management, aligning with the goals of precision medicine in SSc.

In line with previous reports, anti-Th/To+ patients from our cohort mostly presented with lcSSc and showed ILD in nearly half of cases, while other major organ involvements, such as PAH, scleroderma renal crisis, and primary myocardial involvement, occurred in less than 5% of patients. All anti-Th/To+ patients accrued mild

Table 4. Demographic and clinical features of anti-Th/To+ patients compared with sex-, age at disease onset- and disease duration-matched anti-Topo1+ and ACA+ SSc controls.

Demographic and clinical features	Anti-Th/To+ *n* = 102	Anti-Topo1+ *n* = 76	*p* Value OR (95% CI)	ACA+ *n* = 73	*p* Value OR (95% CI)
Anti-Ro52+	27/86 (31.4)	6/68 (8.8)	0.001 4.73 (1.82–12.27)	6/64 (9.4)	0.001 4.42 (1.70–11.51)
Limited cutaneous subtype	79/102 (77.5)	40/76 (52.6)	0.001 3.901 (1.62–5.90)	61/73 (83.6)	0.319
mRSS at first evaluation	2.0 (0.0–4.3)	8.0 (2.3–14.0)	<0.001	2.0 (0.0–4.0)	0.835
mRSS at last evaluation	2.0 (0.0–4.0)	6.0 (3.0–11.5)	<0.001	2.0 (0.0–4.0)	0.434
Digital ulcers	23/102 (22.5)	45/76 (59.2)	<0.001 0.20 (0.11–0.39)	28/73 (38.4)	0.023 0.47 (0.24–0.91)
Pitting scars	19/102 (18.6)	39/76 (51.3)	<0.001 0.22 (0.11–0.43)	22/71 (31.0)	0.060
Telangiectasias	43/102 (42.2)	43/76 (56.6)	0.057	42/72 (58.3)	0.036 0.52 (0.28–0.96)
Calcinosis	13/101 (12.9)	14/76 (18.4)	0.296	13/69 (18.8)	0.276
Myositis	13/102 (12.7)	5/74 (6.7)	0.430	1/69 (1.4)	0.008 9.93 (1.27–77.80)
Synovitis	25/102 (24.5)	25/75 (33.3)	0.238	10/72 (13.9)	0.085
Joint contractures	7/102 (6.9)	17/76 (22.4)	0.003 0.26 (0.10–0.65)	4/72 (5.6)	0.727
Esophageal symptoms	55/102 (53.9)	45/75 (60.0)	0.420	48/71 (67.6)	0.071
GAVE	2/102 (2.0)	1/76 (1.3)	1.000	3/71 (4.2)	0.402
ILD (HRCT)	39/92 (42.4)	63/76 (82.9)	<0.001 0.15 (0.073–0.31)	12/73 (16.4)	<0.001 3.74 (1.78–7.87)
NSIP pattern	27/39 (69.2)	52/63 (82.5)	0.118	7/12 (9.6)	0.484
UIP pattern	9/39 (23.1)	5/63 (7.9)	0.031 3.48 (1.07–11.31)	1/12 (0.0)	0.261
Functional progressive ILD (ATS/ERS/JRS/ALAT)	25/39 (64.1)	38/63 (60.3)	0.252	4/12 (33.3)	0.060
Functional progressive ILD (Goh)	15/39 (38.5)	27/63 (42.9)	0.661	3/12 (25.0)	0.502
Cardiac involvement	34/102 (33.3)	25/74 (33.8)	0.950	22/69 (31.9)	0.843
Myocarditis	2/102 (2.0)	8/76 (10.5)	0.014 0.17 (0.04–0.32)	3/70 (4.3)	0.650
Pericarditis	2/102 (2.0)	2/76 (2.6)	1.000	1/69 (1.5)	1.000
Pericardial effusion	10/102 (9.8)	7/76 (9.2)	1.000	4/69 (5.8)	0.348
Arrhythmia	8/102 (7.8)	9/76 (11.8)	0.369	4/70 (5.7)	0.590

(Continued)

Table 4. (Continued)

Demographic and clinical features	Anti-Th/To+ *n* = 102	Anti-Topo1+ *n* = 76	*p* Value OR (95% CI)	ACA+ *n* = 73	*p* Value OR (95% CI)
Diastolic dysfunction	31/102 (30.4)	23/72 (31.9)	0.872	18/66 (27.3)	0.664
Heart failure	4/102 (3.9)	2/72 (2.8)	0.684	3/66 (4.6)	0.843
PH (RHC)	7/102 (6.9)	11/76 (14.5)	0.096	7/73 (9.6)	0.070
Group 1 PH (PAH)	4/102 (3.9)	2/76 (2.6)	1.000	6/73 (8.2)	0.323
Group 3 PH	2/102 (1.9)	6/76 (7.8)	0.074	0/73 (0.0)	0.511
Disease duration at RHC	8.0 (7.0–16.0)	7.0 (5.0–10.0)	0.426	2.0 (0.0–9.5)	0.159
Scleroderma renal crisis	3/102 (2.9)	4/76 (5.3)	0.462	0/71 (0.0)	0.145
Malignancies	17/100 (17.0)	10/73 (13.7)	0.555	10/68 (14.7)	0.831
Synchronous[a] malignancies	9/100 (9.0)	5/73 (6.8)	0. 608	3/68 (4.4)	0.364
Disease duration at K	2.0 (–1.0 to 6.0)	3.0 (–1.0 to 4.0)	0.691	5.0 (–1.75 to 9)	0.481
Disease duration, years	6.0 (3.0–10.0)	7.5 (2.8–12.3)	0.541	6.0 (3.0–11.0)	0.853
Follow-up duration, years	3.5 (2.0–7.0)	6.0 (2.0–10.5)	0.024	4.0 (2.0–10.0)	0.495
Deaths	9/102 (8.8)	15/76 (19.7)	0.035 0.40 (0.16–0.95)	6/73 (8.2)	0.888
Death due to SSc	0/102 (0.0)	6/76 (7.9)	0.004	1/73 (1.4)	0.417
Death due to SSc-ILD	0/102 (0.0)	5/76 (6.6)	0.013	0/73 (0.0)	1.000
Death due to cancer	6/102 (5.9)	3/76 (3.9)	0.560	0/73 (0.0)	0.035
Age at death, years	71.0 (61.0–82.0)	66.5 (53.0–71.5)	0.431	73.0 (62.0–78.5)	0.877
Disease duration at death, years	9.0 (6.0–15.0)	9.5 (3.5–16.3)	0.753	8.5 (2.0–18.5)	1.000

Continuous variables are presented as median (first–third quartile) and compared with Mann–Whitney test; categorical variables are presented as number/number available data (%) and compared with Chi-square test/Fisher's exact test. ORs were calculated, Haldane's correction was applied when needed.
[a]Synchronous malignancy = ±2 years from SSc onset.
ATS/ERS/JRS/ALAT, American Thoracic Society American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Society; CI, confidence interval; GAVE, gastric antral vascular ectasia; HRCT, high resolution computed tomography; ILD, interstitial lung disease; K, cancer; mRSS, modified Rodnan Skin Score; NSIP, nonspecific interstitial pneumonia; OR, odds ratio; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization; SSc, systemic sclerosis; UIP, usual interstitial pneumonia.

organ damage over 15 years of follow-up observation and had favorable survival rate of nearly 90% at 10 years, with no deaths attributable to SSc.

Our data provide new insights into ILD occurrence in anti-Th/To+ patients, revealing a lower frequency of ILD compared to SSc controls matched by sex, age at disease onset, and disease duration. In multivariable analysis, anti-Th/To antibodies were not significantly associated with ILD, suggesting that they do not serve as reliable biomarkers to raise suspicion for ILD in SSc patients, even in anti-Topo1-negative patients.

Notably, our findings suggest that the presence of ILD in anti-Th/To+ patients might be partly

attributable to co-existing anti-Ro52 positivity. Anti-Ro52 antibodies were more prevalent in anti-Th/To+ SSc patients compared to matched controls and were associated with a fourfold increased risk of ILD within this subset. These observations further support the established association between anti-Ro52 and ILD across different connective tissue diseases, including SSc.[29,30]

Additional insights from this analysis include the observation of a higher prevalence of the UIP pattern among anti-Th/To+ patients. However, in multivariable analysis, ILD extent at HRCT was the only factor associated with functional progression. The prognostic significance of UIP pattern as an indicator of progression in SSc remains uncertain and should be further clarified.[27,31]

In this wide multicenter cohort, no association of anti-Th/To with PH or PAH was observed, in line with other single-center studies,[9,14,16,17] but in contrast with the results from the wide Pittsburgh cohort (17% with PAH at the first visit, and additional 6% during the follow-up).[9] Possible referral bias, with selection of more severe cases and higher prevalence of unfavorable prognostic factors (including male sex, non-Caucasian ethnicity, and longer disease duration at baseline) might explain the findings observed in the latter.

Importantly, even after the exclusion of anti-RNAP3+ SSc patients from controls, we did not observe increased rates of overall or synchronous malignancies in anti-Th/To+ patients. Indeed, a possible association of anti-Th/To antibodies with a reduced risk of cancer diagnosis within the first 3 years after disease onset has been previously suggested.[20] Moreover, a recent case-control study of two prospective observational SSc cohorts with long-term follow-up reported an overall increased risk of malignancies in SSc patients with isolated anti-Ro52 positivity, but a decreased risk when anti-Ro52 positivity was detected together with anti-U1RNP or anti-Th/To positivity.[32–34] However, a small Japanese study reported an increased long-term incidence of cancer history in anti-Th/To+ patients,[19] highlighting potential differences across patients with different ethnicities and geographical origins.

The overall relatively favorable prognosis observed in anti-Th/To+ SSc patients was further supported by the mild organ damage accrual observed over the disease course, which was comparable to that seen in ACA+ controls, confirming our previous findings.[14]

Accordingly, survival analysis suggested a trend toward better outcomes in anti-Th/To+ SSc patients, as compared to matched controls, even when restricting the analysis to the lcSSc subgroup. Unfortunately, the relatively small number of patients included in our study and their limited median follow-up duration might have prevented to reach statistical significance. Anyway, it should be remarked that no death due to SSc was observed in this cohort of anti-Th/To+ patients.

Limitations

The main limitations of our study are explained by its multicenter design with retrospective evaluation of prospectively collected data and the additional retrospective collection of items not routinely included in the EUSTAR database. We acknowledge that there might be center-related differences in data collection and methods for auto-antibody identification. Complete data regarding the timing and the effects of treatments, especially for the long-term outcome of ILD were not available. Nevertheless, despite known inter-center differences in immunosuppressive or anti-fibrotic choices, in practice treatment algorithms for SSc-ILD remain broadly comparable across EUSTAR centers,[35,36] so that the interpretation of our findings can adequately reflect this reality. Therefore, despite methodological heterogeneity, we think that uniform therapeutic principles across centers may strengthen the external validity of our results.

Although we succeeded in collecting 102 anti-Th/To+ SSc patients (the second largest cohort so far described), the relatively small number of enrolled patients and the limited follow-up duration did not allow us to draw solid conclusions from survival curves analysis. Finally, the large majority of included patients were Caucasian, and this may limit the generalizability of these results to other ethnicities.

Conclusion

The combination of a large, well-characterized cohort and detailed ILD data provides one of the most comprehensive analyses of anti-Th/

To-positive SSc to date. In these patients, lower prevalence of major organ involvement, including ILD, compared to appropriately matched controls, along with mild organ damage and favorable survival outcomes were demonstrated. Our findings are supportive in risk stratification of anti-Th/To patients and further reinforce the personalized medicine strategies according to the autoantibody phenotype.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the respective local ethics committees (local ethics approval at ASST Spedali Civili di Brescia, n.1072). The study was conducted in accordance with Helsinki Declaration principles.

Consent for publication

Not applicable.

Author contributions

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María Martín-López: Investigation; Methodology.

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Antonio Tonutti: Investigation; Methodology; Writing – review & editing.

Francesco Del Galdo: Investigation; Methodology; Project administration.

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Marie Elise Truchetet: Investigation; Methodology; Project administration; Supervision.

Yannick Allanore: Investigation; Methodology; Supervision.

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Competing interests

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Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author (L.M.).

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Supplemental material

Supplemental material for this article is available online.

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