

The clinical profile of systemic sclerosis without a ‘scleroderma pattern’ at nailfold capillaroscopy: results from the multicenter SPRING registry of the Italian Society of Rheumatology

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ABSTRACT

Background: Microvascular alterations can be detected with nailfold videocapillaroscopy, useful for systemic sclerosis (SSc) diagnosis upon identification of the "scleroderma pattern" (NVC-SP). However, this pattern is missing in a subset of SSc patients.

Methods: This retrospective analysis on the multicenter Italian SPRING cohort of SSc patients assessed the prevalence and characteristics of patients without NVC-SP. Associations with demographic and clinical features were evaluated using logistic regression (cross-sectional) and mixed-effects models (longitudinal).

Results: Out of 1689 SSc patients with available NVC information, 90 (5.3%) did not have the NVC-SP. These patients were older at SSc onset (53 vs. 49 years) and more frequently sine scleroderma (31% vs 12%, $p < 0.001$). The overall burden of vascular complications was milder in this subset, with a lower prevalence of pitting scars (33% vs 48%), telangiectasias (52% vs 74%), and calcinosis (3.4% vs 12%). During the follow-up, mRSS remained lower (60-month mean 4 vs 7, $p = 0.002$), as well as the estimated probability of vascular complications. Moreover, despite comparable values at baseline, DLCO remained significantly higher in patients without NVC-SP at the following time points (12, 24, and 60 months, $p < 0.05$). The presence of "late" NVC-SP was independently associated with ILD (OR 1.83, 95% CI 1.05-3.18).

Conclusions: The absence of NVC-SP in 5.3% of SPRING SSc patients may identify a subset characterized by milder disease, with a lower burden of vascular and organ complications. Conversely, lung involvement was more frequently observed in patients with more severe NVC microangiopathy.

1. Introduction

In systemic sclerosis (SSc), the microvascular alterations are a hallmark of the vascular involvement [1], which includes skin telangiectasias, pitting scars, digital ulcers, pulmonary arterial hypertension (PAH), and renal crisis [2]. Modifications of the microcirculation can be observed on nailfold videocapillaroscopy (NVC), for which a qualitative classification of the 'scleroderma pattern' (SP) has been provided [3,4] and is part of the 2013 SSc classification criteria [5]. Remarkably, the presence of a NVC-SP is also a criterion for the very early diagnosis of SSc (i.e., VEDOSS) [6].

Nonetheless, patients may be diagnosed with—and fulfil the classification criteria for—SSc even in the absence of NVC-SP in approximately 10% cases [7], yet it remains poorly defined whether these subjects harbor a distinct clinical profile. Preliminary evidence suggests a correlation between the presence of 'active' or 'late' NVC-SP and the likelihood of onset and progression of visceral manifestations in SSc [8]. However, it is less clear whether the risk of developing distinct complications differs when comparing patients with or without NVC-SP [8]. The SSc Progression Investigation (SPRING) project, started in 2015 under the endorsement of the Italian Society of Rheumatology (SIR), includes more than 1900 classified SSc patients, along with more than

250 VEDOSS cases. Within the SPRING cohort, our study aimed to: [1] determine the prevalence of SSc without NVC-SP; [2] characterize the cross-sectional clinical, serological, and therapeutic profile of these patients compared to those with NVC-SP, including comparisons with 'early', 'active', and 'late' NVC-SP subgroups; [3] assess longitudinal disease trajectories over a five-year follow-up; and [4] perform an exploratory comparison of VEDOSS patients with and without NVC-SP. Notably, while patients without NVC-SP were included in a previous SPRING-SIR publication as a comparator group [9], no dedicated analysis of this subset has been performed to date.

2. Methods

2.1. Study design, data source, and setting

SPRING is a retrospective, multicenter, nationwide cohort involving 38 tertiary referral centers for SSc. Data were collected using the REDCap (Research Electronic Data Capture) platform. Clear definitions for all variables were established and shared "a priori" to minimize heterogeneity across participating centers, and periodic quality checks were performed by the coordinating team [9]. The study was approved by the Ethics Committee of the Azienda Ospedaliera Universitaria

Careggi (Florence), reference number OSS 15.010. All participants provided informed consent prior to enrollment. The extracted data includes information entered up to July 15, 2022. For each patient, follow-up visits were scheduled annually (± 2 months) after enrolment (hereafter referred to as 'baseline' visit), with a maximum follow-up duration of five years.

2.2. Study population and recorded variables

Patients from the SPRING registry were eligible for inclusion in this study if they were aged ≥ 18 years at enrollment, met the 2013 SSc classification criteria [5] or the VEDOSS criteria [6,10]. These patients underwent NVC, and were classified as: 'without NVC-SP' vs. 'with NVC-SP,' which was further categorized as 'early', 'active', or 'late' [3,4]. The NVC data were recorded at baseline, and NVC patterns were classified by trained rheumatologists at each center according to the standardized criteria published [3,4]. Patients lacking NVC information at enrolment were excluded from the analysis. SSc onset was defined as the time of appraisal of the first non-Raynaud's phenomenon manifestation [11].

Collected data included demographic [12] and clinical characteristics at baseline and at yearly intervals thereafter. These included: skin subsets (diffuse cutaneous—dcSSc, limited cutaneous—lcSSc, and sine scleroderma—ssSSc) [13]; oesophageal (dysphagia, reflux) and intestinal symptoms (diarrhoea, abdominal bloating, constipation, malabsorption); sicca syndrome (dry eyes and/or mouth); scleroderma renal crisis (sudden onset of severe arterial hypertension with acute renal failure); skin and peripheral vascular signs (puffy fingers, calcinosis, telangiectasia, pitting scars, digital ulcers); and musculoskeletal involvement (tenosynovitis and/or arthritis, defined as inflammatory changes observed in more than two joints; joint contractures; tendon friction rubs—TFR; clinically defined muscle weakness and atrophy). The Unified Vascular Phenotype (UVP) score was calculated by assigning one point each for the presence of puffy hands, skin telangiectasias, pitting scars, and digital ulcers (range 0–4), as described elsewhere [14, 15].

Further variables included: the modified Rodnan skin score (mRSS); predicted forced vital capacity (FVC%) and diffusion capacity for carbon monoxide (DLCO%); presence of interstitial lung disease (ILD) on high-resolution computed tomography (HRCT); systolic pulmonary artery pressure (sPAP, mmHg), left ventricular ejection fraction (LVEF%) and diastolic dysfunction on echocardiography [9,13,16]; antinuclear (ANA) and SSc-related antibodies (anticentromere—ACA, anti-topoisomerase I—TOPO1, and anti-RNA polymerase III—POLR3). Pulmonary arterial hypertension (PAH) was confirmed by right heart catheterization and classified as WHO group 1, in accordance with the diagnostic criteria in use at the time of data collection [17]: PAH was absent when there was no suspicion according to the low probability of pulmonary hypertension on the DETECT algorithm [18], or when right heart catheterization excluded PAH.

Comorbidities included ischemic heart disease, stroke, arterial hypertension, dyslipidaemia, and diabetes mellitus [19,20]. Treatment data included use of immunosuppressive agents (cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil, rituximab, tocilizumab) and vasoactive/vasodilating therapies (endothelin receptor antagonists—bosentan, macitentan; phosphodiesterase-5 inhibitors—sildenafil, tadalafil; intravenous iloprost; calcium channel blockers). No patient in the study group was on prednisone or its equivalent at doses of 10 mg/day or more.

The VEDOSS case report form was shared with the one adopted for patients with established SSc, provided that no patient presented with skin sclerosis or sclerodactyly, nor fulfilled the 2013 SSc classification criteria.

2.3. Exposure and outcomes

The main exposure was the absence of NVC-SP [3,4] in patients classified as SSc [5].

In the cross-sectional analysis, the outcomes of interests were baseline characteristics of patients with SSc, including demographic, clinical and therapeutic features. A sensitivity analysis was performed to compare the characteristics of patients with SSc without NVC-SP vs. those of patients with 'early', 'active', or 'late' NVC-SP.

In the longitudinal analysis, the outcomes of interest were changes in disease manifestations (expressed as expected prevalence for categorical variables and expected means for continuous variables, as detailed in the statistical methods), evaluated at 12, 24, and 60 months of follow-up from the baseline visit.

A cross-sectional comparison between VEDOSS patients with and without the NVC-SP was performed as a complementary analysis.

2.4. Statistical analysis

Given the retrospective registry-based design, no formal a priori sample size calculation was performed. The study included all eligible patients with available baseline NVC and the effective sample size was determined by existing data.

After assessing for normality using the Shapiro-Wilk test, continuous variables were summarized as means ($\pm$ standard deviation—SD) or medians (interquartile range—IQR), as appropriate. Categorical variables were expressed as numbers and counts and percentages (n/N, %).

Group comparisons were performed using appropriate statistical tests: Pearson's chi-square or Fisher's exact test for categorical variables, and Student's t-test or Mann-Whitney *U* test for continuous variables. To account for multiple comparisons, p-values were adjusted using the Benjamini-Hochberg procedure.

Multivariable logistic regression was used to explore associations of SSc without NVC-SP with the outcomes of interest. For binary logistic regression, results were reported as odds ratios (OR) with 95% confidence intervals (CI); for multinomial logistic regression, results were reported as relative risk ratios (RRR) with 95% CIs for each outcome category relative to the reference category (base outcome). In multivariable models, the UVP score was considered as an ordinal variable (0–4). Individual components of the UVP score were also evaluated separately to reduce reliance on the composite vascular index. Vasoactive treatment was considered a descriptive variable reflecting clinical management and vascular disease burden, rather than a core confounder in the primary adjusted models, because its prescription may occur downstream of peripheral vascular manifestations and NVC.

Multivariable models were fitted using clinically informed adjustment sets defined a priori, based on prior literature and expert opinion. Core covariates included age at SSc onset, sex, disease duration, cutaneous subset, and SSc-related autoantibodies, where appropriate according to the outcome under investigation. The specific adjustment set was adapted to each outcome to avoid overadjustment or adjustment for variables lying on the causal pathway. Exploratory univariable analyses were used to characterize the cohort and contextualize the clinical relevance of observed associations but were not used as an automated variable-selection procedure.

To evaluate the impact of SSc without NVC-SP on repeated measurements over time, longitudinal analyses were performed.

For binary outcomes (arthritis, calcinosis, digital ulcers, pitting scars, ILD, evidence of sPAP > 40 mmHg on echocardiography), generalized estimating equations (GEE) were used to account for within-subject correlations. For continuous outcomes (predicted FVC% and DLCO%, mRSS, UVP score), mixed-effects models with random intercepts for participants were adopted. Although the UVP score is an ordinal variable (range 0–4), it was included in mixed-effects models as an approximately continuous measure for exploratory purposes, consistent with published applications of this score. Predicted marginal means and differences between groups were estimated, and contrasts were used to derive ORs (for binary outcomes) or mean differences (for continuous outcomes) with corresponding 95% CIs. For longitudinal analyses, the number of available observations was reported by NVC-SP group and

Table 1

Cross-sectional comparison of demographic, clinical, serological, and therapeutic features between SSc patients with and without the NVC scleroderma pattern (NVC-SP) at enrollment in the SPRING-SIR registry. Categorical variables are reported as counts (percentages); continuous variables as medians (IQR) [number of patients with available data].

	SSc SPRING cohort (N = 1903)	NVC-SP present (N = 1599)	NVC-SP absent (N = 90)	p	Adj.p
Demographic features					
Sex, n/N (%)	1681/1893 (88.8)	1409/1595 (88.3)	83/90 (92.2)	0.339	0.694
Age at entry, median (IQR)	60 (50-70) [1895]	60 (49-69) [1597]	63 (52-72) [90]	0.067	0.328
Age at RP onset, median (IQR)	45 (34-56) [1879]	45 (34-56) [1586]	48 (35-60) [89]	0.323	0.694
Age at SSc onset, median (IQR)	50 (39-60) [1745]	49 (39-59) [1488]	53 (45-63) [81]	0.008	0.087
Disease duration, median (IQR)	8 (4-15) [1744]	8 (4-14) [1487]	9 (4-14) [81]	0.969	>0.99
RP to SSc onset, median (IQR)	1 (0-4) [1741]	1 (0-4) [1485]	1 (0-5) [80]	0.088	0.388
Smoke, n/N (%)	559/1693 (33)	477/1451 (32.9)	29/77 (37.7)	0.456	0.746
Comorbidities					
Coronary artery disease, n/N (%)	55/1903 (2.9)	44/1599 (2.8)	5/90 (5.6)	0.181	0.556
Stroke, n/N (%)	17/1903 (0.9)	15/1599 (0.9)	2/90 (2.2)	0.228	0.560
Arterial hypertension, n/N (%)	450/1903 (23.6)	390/1599 (24.4)	20/90 (22.2)	0.734	0.915
Peripheral artery disease, n/N (%)	103/1903 (5.4)	81/1599 (5.1)	4/90 (4.4)	>0.99	>0.99
Dyslipidemia, n/N (%)	209/1903 (11)	184/1599 (11.5)	6/90 (6.7)	0.214	0.560
Diabetes mellitus, n/N (%)	56/1903 (2.9)	45/1599 (2.8)	6/90 (6.7)	0.050	0.302
Overlap AT disease, n/N (%)	204/1889 (10.8)	166/1593 (10.4)	11/90 (12.2)	0.715	0.915
Clinical features					
LeRoy subset, n/N (%)				<0.001	<0.001
ssSSc	229/1849 (12.4)	190/1582 (12)	27/88 (30.7)		<0.001
lcSSc	1255/1849 (67.9)	1063/1582 (67.2)	56/88 (63.6)		0.487
dcSSc	365/1849 (19.7)	329/1582 (20.8)	5/88 (5.7)		<0.001
mRSS, median (IQR)	4 (2-9) [1736]	4 (2-9) [1469]	3 (0-6) [85]	0.001	0.013
Pitting scars, n/N (%)	880/1867 (47.1)	760/1591 (47.8)	30/90 (33.3)	0.010	0.094
Digital ulcers, n/N (%)	407/1873 (21.7)	344/1596 (21.6)	14/90 (15.6)	0.222	0.560
Telangiectasias, n/N (%)	1135/1872 (60.6)	983/1595 (61.6)	47/90 (52.2)	0.095	0.388
UVP score, median (IQR)	2 (1-3) [1875]	2 (1-3) [1597]	1 (1-2) [90]	0.001	0.013
Calcinosis, n/N (%)	219/1866 (11.7)	193/1591 (12.1)	3/89 (3.4)	0.020	0.137
Arthritis, n/N (%)	209/1858 (11.2)	181/1583 (11.4)	9/88 (10.2)	0.861	>0.99
Tendon friction rubs, n/N (%)	156/1868 (8.4)	145/1592 (9.1)	4/90 (4.4)	0.185	0.556
Muscle weakness, n/N (%)	267/1867 (14.3)	228/1591 (14.3)	10/90 (11.1)	0.486	0.750
Muscle atrophy, n/N (%)	96/1866 (5.1)	83/1590 (5.2)	0/90 (0)	0.020	0.137
Oesophageal symptoms, n/N (%)	937/1872 (50.1)	801/1595 (50.2)	39/90 (43.3)	0.245	0.575
Intestinal symptoms, n/N (%)	366/1868 (19.6)	325/1592 (20.4)	13/90 (14.4)	0.215	0.560
Sicca syndrome, n/N (%)	542/1869 (29)	467/1594 (29.3)	27/90 (30)	0.981	>0.99
Scleroderma renal crisis, n/N (%)	22/1868 (1.2)	16/1592 (1)	1/90 (1.1)	0.609	0.885
LVEF <50%, n/N (%)	23/1489 (1.5)	22/1288 (1.7)	1/77 (1.3)	>0.99	>0.99
Diastolic dysfunction, n/N (%)	343/1514 (22.7)	308/1318 (23.4)	13/74 (17.6)	0.312	0.694
sPAP >40 mmHg, n/N (%)	168/1553 (10.8)	138/1345 (10.3)	9/79 (11.4)	0.896	>0.99
PAH on RHC, n/N (%)	31/1421 (2.2)	27/1240 (2.2)	1/71 (1.4)	>0.99	>0.99
ILD, n/N (%)	660/1903 (34.7)	562/1599 (35.1)	24/90 (26.7)	0.126	0.425
FVC%, median (IQR)	102 (87-116) [1411]	102 (87-116) [1214]	107 (89-123) [74]	0.064	0.328
DLC0%, median (IQR)	69 (55-82) [1342]	69 (55-82) [1158]	72 (59-85) [68]	0.115	0.414
Autoantibodies					
ACA, n/N (%)	771/1903 (40.5)	669/1599 (41.8)	37/90 (41.1)	0.979	>0.99
anti-TOP01, n/N (%)	666/1858 (35.8)	552/1592 (34.7)	26/89 (29.2)	0.347	0.694
anti-POLR3, n/N (%)	40/1569 (2.5)	34/1348 (2.5)	3/77 (3.9)	0.448	0.746
Therapy					
Immunosuppressants, n/N (%)	712/1633 (43.6)	599/1378 (43.5)	26/78 (33.3)	0.101	0.388
Vasoactive treatments, n/N (%)	1621/1858 (87.2)	1395/1565 (89.1)	67/89 (75.3)	<0.001	0.004

AT: autoimmune; ACA: anticentromere antibodies; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; ssSSc: systemic sclerosis sine scleroderma; DLC0%: predicted diffusing capacity of the lungs for carbon monoxide; FVC%: predicted forced vital capacity; ILD: interstitial lung disease; LVEF: left ventricle ejection fraction; mRSS: modified Rodnan's skin score; NVC-SP: nailfold videocapillaroscopy scleroderma pattern; PAH: pulmonary arterial hypertension; POLR3: anti-RNA polymerase III; RHC: right heart catheterization; RP: Raynaud's phenomenon; sPAP: systolic pulmonary artery pressure; TOP01: topoisomerase 1; UVP: unified vascular phenotype score.

follow-up timepoint. Given the retrospective registry-based design, missing follow-up data reflected real-world data availability across visits and outcomes. To assess the potential impact of missing follow-up data, a complete-case/available-case sensitivity analysis was performed using observations available at each follow-up timepoint. Because of the limited number of patients without NVC-SP at later visits, this analysis was considered exploratory.

A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were conducted using RStudio (version 2024.12.0 + 467; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Characteristics of SSc patients without NVC-SP at baseline

The SPRING registry enrolled 1903 SSc patients: 88.8% female (1681/1893), median age at disease onset 50 years-IQR 39-60, median disease duration at entry 8 years, IQR 4-15. Cutaneous subsets were dcSSc in 19.7% (365/1849) of patients, lcSSc in 67.9% (1255/1849), and ssSSc in 12.4% (229/1849). Disease manifestations included digital ulcers in 21.7% (407/1873) of patients, telangiectasias in 60.6% (1135/1872), calcinosis in 11.7% (219/1866), arthritis in 11.2% (209/1858),

ILD in 34.7% (660/1903), PAH on right heart catheterization in 2.2% (31/1421), and oesophageal involvement in 50.1% (937/1872). SSc-specific autoantibodies included ACA in 40.5% (771/1903), anti-TOPO1 in 35.8% (666/1858), and anti-POLR3 in 2.5% (40/1569). Immunosuppressive treatments were administered to 43.6% (712/1633) of patients, and vasoactive/vasodilating therapies to 87.2% (1621/1858) (Table 1).

In 1689 patients, NVC data were available and 90 had SSc without NVC-SP (5.3%). Compared to those with NVC-SP, these patients had a higher median age at SSc onset (53 years, IQR 45-63 vs. 49 years, IQR 39-59; $p = 0.008$), while the disease duration at entry, sex, and comorbidities distribution were similar.

Notably, SSc patients without NVC-SP were more frequently ssSSc (30.7%, 27/88 vs 12%, 190/1582; $p < 0.001$) and less frequently dcSSc (5.7%, 5/88 vs 20.8%, 329/1582; $p < 0.001$), while the prevalence of lcSSc was similar in the two groups (63.6%, 56/88 vs 67.2%, 1063/1582; $p = 0.487$). Pitting scars (33.3%, 30/90 vs 47.8%, 760/1591; $p = 0.010$) and calcinosis cutis (3.4%, 3/89 vs 12.1%, 193/1591; $p = 0.020$) were significantly less frequent in this group, and the UVP score was lower (1, IQR 1-2 vs 2, IQR 1-3; $p = 0.001$), reflecting a lower overall burden of vascular complications. Accordingly, vasoactive treatments were less frequently prescribed in this disease subset (75.3%, 67/89 vs 89.1%, 1395/1565; $p < 0.001$).

After adjustment for confounders (Table 2), SSc without NVC-SP remained positively associated with the ssSSc phenotype (multinomial RRR 2.97, 95% CI 1.74-5.06; $p < 0.001$) and negatively with dcSSc (RRR 0.36, 95% CI 0.14-0.94; $p = 0.036$), compared to lcSSc as the reference category.

On binary logistic models, no association was observed for pitting scars and calcinosis, while telangiectasias were less common in patients without NVC-SP (OR 0.62, 95% CI 0.39-1.00; $p = 0.047$). Most importantly, we observed a negative association between the UVP score and the lack of NVC-SP (OR 0.57, 95% CI 0.38-0.86; $p = 0.007$). In adjusted models, absent NVC-SP was associated with lower odds of puffy hands (OR 0.62, 95% CI 0.39-0.98; $p = 0.040$), whereas no significant association was observed with digital ulcers (OR 0.71, 95% CI 0.34-1.36; $p = 0.333$).

3.2. Characteristics of SSc without NVC-SP versus 'early', 'active', and 'late' NVC-SP

Supplementary Table 1 shows the comparison of baseline demographic and clinical features of SSc without NVC-SP versus patients showing 'early', 'active', or 'late' NVC-SP. Patients without a NVC-SP had a lower burden of cutaneous and visceral manifestations when compared to those with a 'late' and 'active' NVC-SP, while no major differences were observed with those showing a 'early' NVC-SP.

On multivariable logistic regression (Supplementary Table 2), patients with 'early' (OR 0.55, 95% CI 0.31-0.97; $p = 0.038$), 'active' (OR 0.29, 95% CI 0.17-0.51; $p < 0.001$), and 'late' (OR 0.11, 95% CI 0.06-0.23; $p < 0.001$) NVC-SP were less likely to be ssSSc compared to those without NVC-SP. The UVP score was significantly higher with 'active' (OR 2.35, 95% CI 1.26-4.39; $p = 0.007$) and 'late' (OR 2.40, 95% CI 1.19-4.85; $p = 0.015$) NVC-SP, while ILD remained associated with the 'late' NVC-SP (OR 1.83, 95% CI 1.05-3.18; $p = 0.033$).

3.3. Longitudinal phenotype of patients with SSc without NVC-SP

According to generalized effects models, the estimated probability of experiencing vascular outcomes (new evidence of calcinosis, pitting scars, digital ulcers, or sPAP >40 mmHg on echocardiography) during follow-up was numerically lower in patients with SSc without NVC-SP than in those with NVC-SP. In particular, at the 12-month follow-up, patients without NVC-SP showed a significantly lower probability of having pitting scars (32%, 95% CI 22-43 vs 47%, 95% CI 45-50), corresponding to an absolute risk reduction of 15% (OR 0.52, 95% CI 0.32-

Table 2

Multivariable logistic regression models evaluating the association of absent NVC-SP with clinical outcomes showing $p < 0.10$ on univariable analysis. For cutaneous subsets, multinomial logistic regression was fit, lcSSc represented the reference category.

Outcomes	Covariates	OR/RRR	95% CI	p
ssSSc vs. lcSSc	Age at SSc onset	0.98	0.97-0.99	<0.001
	Disease duration	0.92	0.90-0.94	<0.001
	Sex	1.95	1.07-3.57	0.030
	Anti-TOPO1	0.56	0.38-0.82	0.003
	Absent NVC-SP	2.97	1.74-5.06	<0.001
dcSSc vs. lcSSc	Age at SSc onset	0.98	0.97-0.99	<0.001
	Disease duration	0.98	0.96-1.00	0.021
	Sex	0.65	0.44-0.95	0.027
	Anti-TOPO1	4.64	3.51-6.14	<0.001
	Absent NVC-SP	0.36	0.14-0.94	0.036
Pitting scars	Age at SSc onset	0.98	0.98-0.99	<0.001
	Disease duration	1.06	1.04-1.07	<0.001
	Sex	0.53	0.38-0.75	<0.001
	Anti-TOPO1	1.81	1.42-2.31	<0.001
	dcSSc	3.04	2.26-4.11	<0.001
Telangiectasias	Absent NVC-SP	0.73	0.43-1.19	0.208
	Age at SSc onset	1.01	1.00-1.02	0.002
	Disease duration	1.08	1.06-1.10	<0.001
	Sex	1.19	0.86-1.65	0.296
	Anti-TOPO1	0.88	0.69-1.12	0.297
Calcinosis	dcSSc	1.56	1.17-2.09	0.003
	Absent NVC-SP	0.62	0.39-1.00	0.047
	Age at SSc onset	0.99	0.98-1.00	0.185
	Disease duration	1.07	1.05-1.09	<0.001
	Sex	1.39	0.81-2.56	0.262
UVP score	Anti-TOPO1	0.51	0.33-0.75	0.001
	dcSSc	2.46	1.63-3.68	<0.001
	Absent NVC-SP	0.37	0.09-1.02	0.096
	Age at SSc onset	1.00	0.99-1.00	0.143
	Disease duration	1.05	1.03-1.06	<0.001
Puffy fingers	Sex	0.72	0.54-0.95	0.021
	Anti-TOPO1	1.20	0.97-1.48	0.089
	dcSSc	1.94	1.52-2.49	<0.001
	Absent NVC-SP	0.57	0.38-0.86	0.007
	Age at SSc onset	1.00	0.99-1.01	0.533
Digital ulcers	Disease duration	0.97	0.95-0.98	<0.001
	Sex	0.95	0.69-1.3	0.734
	Anti-TOPO1	0.65	0.52-0.81	<0.001
	Absent NVC-SP	0.62	0.39-0.98	0.041
	Age at SSc onset	0.99	0.98-1.00	0.005
	Disease duration	1.04	1.03-1.06	<0.001
	Sex	0.65	0.45-0.95	0.023
	Anti-TOPO1	1.68	1.27-2.23	<0.001
	dcSSc	1.91	1.41-2.59	<0.001
	Absent NVC-SP	0.71	0.34-1.36	0.333

dcSSc: diffuse cutaneous SSc; NVC-SP: nailfold videocapillaroscopy scleroderma pattern; OR: odds ratio of the binomial logistic regression; RRR: relative risk ratio of the multinomial logistic regression; ssSSc: SSc sine scleroderma; TOPO1: topoisomerase 1; UVP: unified vascular phenotype score.

0.87; $p = 0.012$). Likewise, their probability of having calcinosis was significantly lower at both 24 months (2.7%, 95% CI 0.7-10 vs 14%, 95% CI 11-16; absolute risk reduction 11%; OR 0.18, 95% CI 0.04-0.76; $p = 0.020$) and 60 months (3.1%, 95% CI 0.7-13 vs 15%, 95% CI 11-19; absolute risk reduction 12%; OR 0.18, 95% CI 0.04-0.86; $p = 0.031$). Notably, no association was found between SSc without NVC-SP and ILD or arthritis over time (Fig. 1).

Compared to patients with the NVC-SP, those without NVC-SP exhibited a significantly lower burden of skin and vascular involvement throughout the follow-up. Mean mRSS values were consistently lower at 12 months (4, 95% CI 2-6 vs 7, 95% CI 6.5-7; mean difference -3, $p = 0.001$), 24 months (4, 95% CI 2-6 vs 7, 95% CI 7-8; mean difference -3, $p = 0.001$), and 60 months (4, 95% CI 1-6 vs 7, 95% CI 7-8; mean difference -4, $p = 0.002$). UVP scores also remained significantly lower at 12 months (mean UVP 1.4, 95% CI 1.1-1.6, vs 1.8, 95% CI 1.7-1.9; mean difference -0.4, 95% CI -0.7 to -0.2; $p = 0.001$), at 24 months

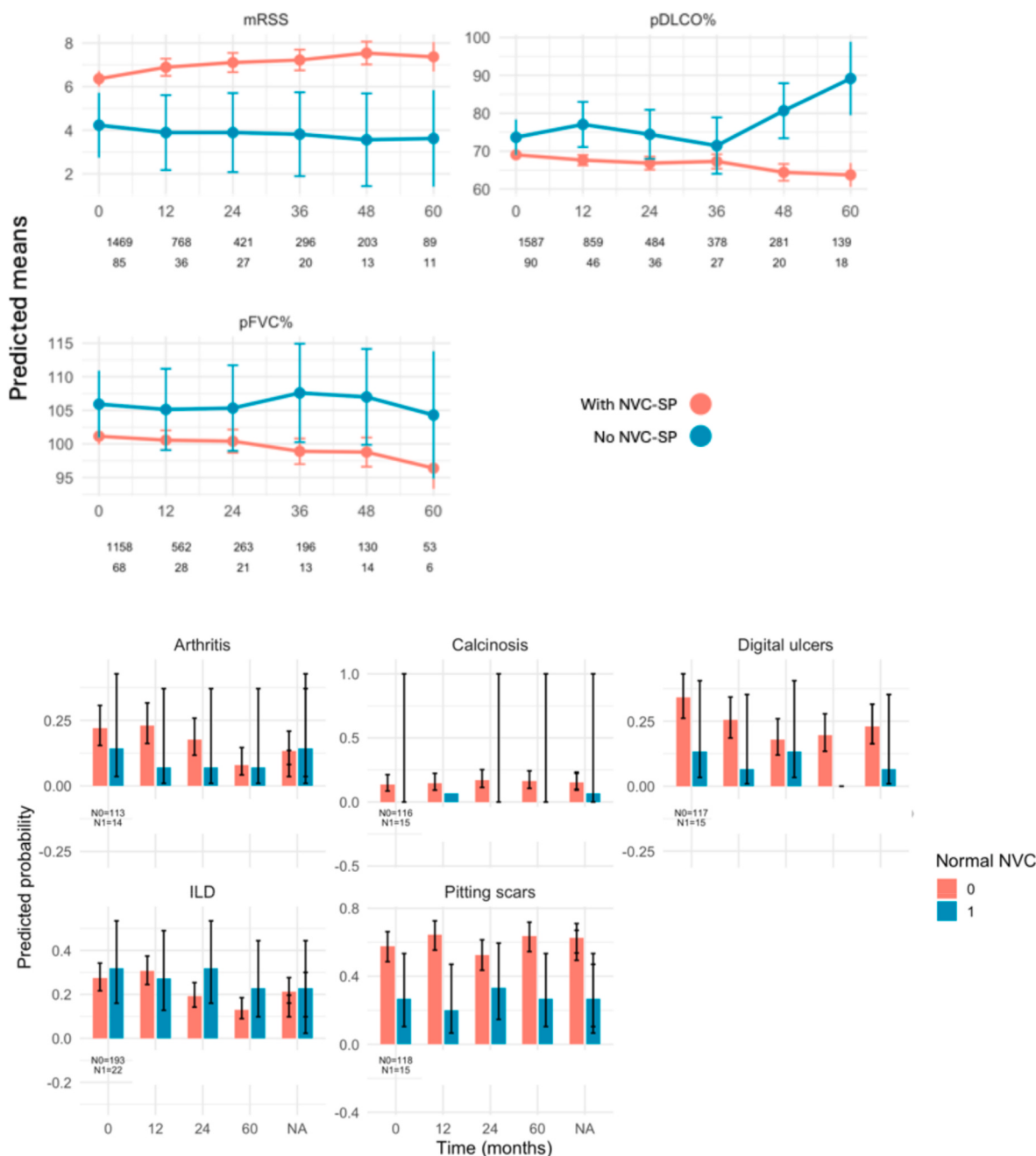


Fig. 1. Predicted mean values of continuous variables at 12, 24, and 60 months in SSc without NVC-SP (green) or with the NVC-SP (coral). Patient numbers at each timepoint are reported below each panel and correspond to the number of available observations contributing to the outcome-specific model at that visit. The upper row refers to patients with NVC-SP, whereas the lower row refers to patients without NVC-SP. Estimated probability (from GEE models) of having selected disease manifestations at 12, 24, and 60 months of follow up in patients with SSc without NVC-SP (green) or with the NVC-SP (coral).

(mean UVP 1.4, 95% CI 1.1-1.7, vs 1.7, 95% CI 1.6-1.8; mean difference -0.3 , 95% CI -0.6 to 0.0 ; $p = 0.047$), and at 60 months (mean UVP 1.4, 95% CI 1.0-1.7, vs 1.8, 95% CI 1.7-1.9; mean difference -0.4 , 95% CI -0.8 to -0.1 ; $p = 0.024$).

Predicted DLCO% was significantly higher in SSc without NVC-SP at all time points: 12 months (77%, 95% CI 71-83, vs 68%, 95% CI 66-69; mean difference 9.4%, 95% CI 3.3-16; $p = 0.003$), 24 months (74%, 95% CI 68-81, vs 67%, 95% CI 65-69; mean difference 7.6%, 95% CI 0.9-14; $p = 0.026$), and 60 months (89%, 95% CI 79-99, vs 64%, 95% CI 61-67; mean difference 25%, 95% CI 15-36; $p < 0.001$). By contrast, no significant differences in predicted FVC% were observed between the two groups at any time point (Fig. 1).

Since the number of available observations decreased over time in both groups, a complete-case/available-case sensitivity analysis was performed and reported in [Supplementary Fig. 1](#). Although the small number of patients without NVC-SP at later timepoints prevents robust statistical inference, the observed trajectories were qualitatively similar to those obtained in the primary longitudinal models.

3.4. Clinical relevance of absent NVC-SP in VEDOSS patients

SPRING included 268 patients with VEDOSS (Table 3): 92% were females, and the median age at RP onset was 44 years (IQR 32-56); ANA were detected in 97.7% (255/261) patients, with ACA in 45.1% (121/

Table 3

Comparison of baseline characteristics of VEDOSS patients with and without the NVC scleroderma pattern.

	SPRING-VEDOSS cohort (N = 268)	NVC-SP present (N = 162)	NVC-SP absent (N = 85)	p	adj.p
Demographic features					
Age at entry, median (IQR)	54 (43-66) [267]	52 (41-64) [162]	54 (44-65) [85]	0.474	>0.99
Age at RP onset, median (IQR)	44 (32-56) [265]	43 (30-54) [162]	46 (33-56) [84]	0.352	>0.99
Sex, n/N (%)	245/266 (92.1)	146/160 (91.2)	80/85 (94.1)	0.584	>0.99
Smoke, n/N (%)	84/239 (35.1)	49/148 (33.1)	30/75 (40)	0.385	>0.99
Menopause, n/N (%)	131/222 (59)	75/133 (56.4)	46/75 (61.3)	0.584	>0.99
Comorbidities					
Arterial hypertension, n/N (%)	37/268 (13.8)	21/162 (13)	13/85 (15.3)	0.760	>0.99
Dyslipidaemia, n/N (%)	27/268 (10.1)	12/162 (7.4)	13/85 (15.3)	0.084	0.745
Diabetes mellitus, n/N (%)	6/268 (2.2)	4/162 (2.5)	1/85 (1.2)	0.662	>0.99
COPD, n/N (%)	2/268 (0.7)	1/162 (0.6)	0/85 (0)	>0.99	>0.99
Cancer, n/N (%)	17/268 (6.3)	9/162 (5.6)	6/85 (7.1)	0.850	>0.99
Clinical features					
Oesophageal symptoms, n/N (%)	89/257 (34.6)	51/158 (32.3)	33/83 (39.8)	0.310	>0.99
Intestinal symptoms, n/N (%)	31/257 (12.1)	19/159 (11.9)	10/83 (12)	>0.99	>0.99
Sicca syndrome, n/N (%)	75/257 (29.2)	44/158 (27.8)	24/83 (28.9)	0.981	>0.99
Pitting scars, n/N (%)	6/257 (2.3)	4/159 (2.5)	1/83 (1.2)	0.663	>0.99
Digital ulcers, n/N (%)	4/257 (1.6)	2/159 (1.3)	1/83 (1.2)	>0.99	>0.99
Telangiectasias, n/N (%)	29/256 (11.3)	14/158 (8.9)	13/83 (15.7)	0.169	0.865
UVP score, n/N (%)	0 (0-1) [256]	0 (0-1) [158]	1 (0-1) [83]	0.002	0.060
Calcinosis, n/N (%)	5/256 (2)	2/158 (1.3)	1/83 (1.2)	>0.99	>0.99
Arthritis, n/N (%)	19/256 (7.4)	11/157 (7)	6/83 (7.2)	>0.99	>0.99
ILD, n/N (%)	26/268 (9.7)	16/162 (9.9)	7/85 (8.2)	0.848	>0.99
FVC%, median (IQR)	107 (93-120) [187]	111 (92-122) [116]	107 (98-118) [62]	0.839	>0.99
DLCO%, median (IQR)	78 (68.75-88.25) [192]	78 (68-89) [121]	80 (70-87) [62]	0.938	>0.99
Conduction block, n/N (%)	2/130 (1.5)	2/85 (2.4)	0/39 (0)	>0.99	>0.99
Arrhythmia, n/N (%)	6/130 (4.6)	4/85 (4.7)	0/39 (0)	0.307	>0.99
PASP >40 mmHg, n/N (%)	6/185 (3.2)	2/116 (1.7)	2/62 (3.2)	0.611	>0.99
LVEF <50%, n/N (%)	4/177 (2.3)	2/112 (1.8)	2/59 (3.4)	0.609	>0.99
Diastolic dysfunction, n/N (%)	24/171 (14)	10/105 (9.5)	13/62 (21)	0.066	0.745
Autoantibodies					
ANA, n/N (%)	255/261 (97.7)	155/161 (96.3)	84/84 (100)	0.097	0.745
ACA, n/N (%)	121/268 (45.1)	67/162 (41.4)	45/85 (52.9)	0.109	0.745
anti-TOPO1, n/N (%)	36/261 (13.8)	21/161 (13)	12/84 (14.3)	0.942	>0.99
anti-POLR3, n/N (%)	6/234 (2.6)	4/142 (2.8)	1/79 (1.3)	0.657	>0.99
Treatments					
Immunosuppressants, n/N (%)	30/231 (13)	21/146 (14.4)	5/68 (7.4)	0.215	0.978
Vasoactive treatments, n/N (%)	154/253 (60.9)	102/158 (64.6)	44/77 (57.1)	0.339	>0.99

ACA: anticentromere antibodies; ANA: antinuclear antibodies; COPD: chronic obstructive pulmonary disease; DLCO%: predicted diffusing capacity of the lungs for carbon monoxide; FVC%: predicted forced vital capacity; ILD: interstitial lung disease; POLR3: RNA polymerase III; RP: Raynaud's phenomenon; sPAP: systolic pulmonary artery pressure; TOPO1: topoisomerase 1; UVP: unified vascular phenotype score.

268), anti-TOPO1 in 13.8% (36/261), and anti-POLR3 in 2.6%. Gastrointestinal manifestations included oesophageal and intestinal symptoms in 34.6% (89/257) and 12.1% (31/257), respectively; 29.2% (75/257) patients complained of sicca syndrome and 7.4% (19/256) of arthritis. ILD was recorded in 9.7% (26/268) patients, the median FVC% predicted values being 107% (IQR 93-120) and DLCO% predicted 78 (IQR 69-88). Pitting scars were reported in 2.3% (6/234) of subjects, telangiectasias in 11.3% (29/256), calcinosis in 2% (5/256), and digital ulcers in 1.6% (4/257); the median UVP score was 0 (IQR 0-1).

Among VEDOSS patients, 32% had no detectable NVC-SP. Overall, the characteristics of VEDOSS patients with and without NVC-SP were similar, despite the latter group showing a lower burden of vascular manifestations, represented by the UVP score (Table 3). After adjusting for age at RP onset, sex, and anti-TOPO1 positivity, multivariable logistic regression confirmed that the absence of NVC-SP was associated with decreasing UVP score in VEDOSS (OR 2.44, 95% CI 1.41-4.22; $p = 0.001$).

4. Discussion

Our data show that in some SSc patients NVC capillary modifications may be not yet detectable, suggesting a very slow progression of the microvascular disease [1,9,21]. The prevalence and clinical relevance of absent NVC-SP among patients fulfilling the 2013 SSc classification criteria has been poorly described. In a previous EUSTAR study, 13.7% of patients did not have a NVC-SP [7], and similar results were reported

in another well-characterized monocentric cohort [22]. Herein, we report a prevalence of SSc without NVC-SP as high as 5.3% in the Italian SPRING registry, relatively lower but still representing a relevant proportion of SSc patients. The cross-sectional baseline data were partially and preliminarily presented [9]; however, that study did not include longitudinal analyses, UVP score assessments, or VEDOSS comparisons for this subgroup. [12].

In our study, aligning with smaller cohorts [8,22], SSc without NVC-SP was associated with a lower prevalence of peripheral vascular manifestations (telangiectasias, pitting scars, and calcinosis). However, we could not detect significant associations between NVC findings and digital ulcers [7,23], possibly due to class imbalance and the relatively small size of the group without NVC-SP. Nevertheless, the use of vasoactive medications and the overall vascular burden—reflected by the proposed UVP score—were significantly lower in patients without NVC-SP compared to those with NVC-SP. Overall, such vascular findings could be due to differences observed between patients without NVC-SP compared to those with ‘active’ and ‘late’—but not ‘early’—NVC-SP [22].

NVC-SP is a VEDOSS criterion and might represent a potential hallmark of progression to established SSc, particularly in cases that were negative at disease onset. Our explorative analysis identified that the NVC-SP was absent in 32% SPRING-VEDOSS cases, in agreement with the EUSTAR-VEDOSS data [6]. Remarkably, the association between the presence of NVC-SP and the increased overall vascular burden was confirmed in VEDOSS cases. Therefore, despite the sample size prevents

any sound conclusion, these results may first suggest that the correlation between capillary alterations and vascular burden—observed in established SSc—may be already present in the very early disease phases. Further evidence is required to assess whether NVC-SP could help stratify VEDOSS patients at higher risk of long-term vascular complications, since these subjects might represent a target population more likely to benefit from preventive pharmacological and non-pharmacological measures.

Previous works have postulated that SSc patients without a NVC-SP have a lower chance of developing vascular complications during follow-up, compared to those with pathologic NVC changes [8]. In our study, peripheral vascular manifestations were consistently more prevalent among patients with a NVC-SP at 12, 24, and 60 months after baseline, despite a statistical significance being reached only in selected comparisons. Nonetheless, the trend of the UVP score throughout the follow-up remained lower in SSc patients without NVC-SP compared to those showing the NVC-SP.

We observed that SSc patients without NVC-SP had a milder cutaneous phenotype. Indeed, the absence of NVC-SP was positively associated with the ssSSc phenotype and negatively with dcSSc, aligning with previous evidence from EUSTAR [7]. Interestingly, a higher prevalence of skin sclerosis was also reported among patients with mixed connective tissue disease and NVC-SP, compared to patients without specific NVC alterations [24]. Thus, an association between microvascular alterations and the severity of skin involvement across scleroderma spectrum disorders may be postulated [25]. Remarkably, in our analysis, SSc patients without NVC-SP retained lower mRSS values across follow-up visits compared to their counterpart.

The recent, single-center study on a mixed connective tissue disease, ILD was associated with reduced NVC capillary density but not with the presence of the NVC-SP [24]. In SPRING-SIR, we could not describe any difference comparing the prevalence of ILD in patients with or without NVC-SP. Nevertheless, ILD was associated with the 'late' NVC-SP after adjusting for notable risk factors like dcSSc and anti-TOPO1. Aligning with previous reports [21,22], we observed significantly decreased values of predicted DLCO% but not FVC% over time in patients with the NVC-SP compared to those without. Despite this finding might suggest a sufferance of the pulmonary microvasculature, we were not able to demonstrate that patients with and without NVC-SP differed in terms of right-heart catheterization-diagnosed PAH or increased echocardiographic sPAP [26].

Several limitations should be discussed. First, referral bias should be considered, since all SPRING centers were tertiary care units, likely selecting patients with a more severe SSc phenotype, generally linked with more severe NVC findings as confirmed in this analysis [11,12,14,23]. Second, while information on NVC was available for most patients, class imbalance could have affected the statistical power of our analysis, despite the genuine prevalence of microvascular alterations in SSc patients. This also applies to selected outcomes, such as PAH and SRC, which are underrepresented in the SPRING registry [9,12,13,16]. Third, the UVP score includes vascular manifestations that conceptually overlap with NVC-captured microangiopathy, raising the risk of circular interpretation. To partially address this, associations between absent NVC-SP and individual vascular components were tested, yielding inconsistent results. Additionally, vasoactive therapy may act as a confounder, mediator, or effect modifier in this context, and this distinction could not be formally tested. Fourth, the small size of the SSc without NVC-SP group — particularly at later follow-up visits, where the number of available observations decreased substantially — prevented confounder-adjusted longitudinal analyses and introduced sensitivity to attrition bias. A complete-case/available-case sensitivity analysis showed qualitatively similar trajectories, but without robust statistical confirmation; accordingly, all longitudinal estimates should be considered exploratory. In particular, apparent fluctuations in the model-predicted probability of ILD and calcinosis likely reflect selective loss to follow-up of patients with more severe disease, rather than

genuine disease remission. Additionally, the follow-up duration was limited to five years, which may be insufficient to capture long-term complications. Fifth, we could not evaluate the longitudinal trend of NVC alterations in patients without a baseline NVC-SP, since these were not recorded in the CRF of the registry. Sixth, due to the sample size and the cross-sectional design, our findings on VEDOSS patients must be interpreted cautiously and as purely speculative to inform further research.

In conclusion, the present analysis from the SPRING-SIR registry demonstrates that approximately 5% of classified SSc patients lack the NVC-SP, and that this subset is characterized by a milder overall phenotype, with lower vascular burden, lower mRSS, and better-preserved DLCO over time. The relationship with pulmonary vascular disease and fibrosing manifestations remains less clear, since a more severe skin involvement is observed in patients with the NVC-SP, while ILD shows only signals restricted to the 'late' NVC-SP. Notably, the absence of NVC-SP might have a prognostic implication, as these patients have a lower probability of developing new vascular complications, calcinosis, and worsening mRSS. Further multicenter studies with repeated assessment [25–27] should assess the longitudinal trend of NVC alterations and their correlation with the incidence and progression of SSc-related complications. Continued research is needed to elucidate the mechanistic interplay between vasculopathy and fibrosing manifestations of the SSc disease.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtauto.2026.100381>.

Data availability

Data will be made available on request.

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