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Original article

Digital pitting scars are associated with a severe disease course and death in systemic sclerosis: a study from the EUSTAR cohort

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Abstract

Objective. Digital pitting scars (DPS) are frequent, but little studied in SSc to date.

Methods. An analysis of SSc patients enrolled in the EUSTAR database. Primary objectives were to (i) examine DPS prevalence; (ii) examine whether DPS are associated with digital ulcers (DUs) and active digital ischaemia (DUs or gangrene); and (iii) describe other associations with DPS including internal organ complications. Secondary objectives were whether DPS are associated with (i) functional impairment; (ii) structural microvascular disease; and (iii) mortality. Descriptive statistics and parametric/non-parametric tests were used. Binary logistic regression was used to examine the association between DPS and DUs, active digital ischaemia and mortality.

Results. A total of 9671 patients were included with reported DPS at any time point ($n = 4924$) or 'never' DPS ($n = 4747$). The majority (86.9%) were female and mean age was 55.7 years. DPS were associated with longer disease and Raynaud's duration (both $P \leq 0.001$). DPS were associated with interstitial lung disease, pulmonary hypertension, conduction blocks, telangiectases, calcinosis (all $P \leq 0.001$) and joint synovitis ($P = 0.021$). Patients were more likely to have more severe capillaroscopic abnormality and greater hand functional impairment. Multivariable logistic regression analyses showed that DPS were associated (odds ratio) with DUs: 22.03 (19.51–24.87), active digital ischaemia: 6.30 (5.34–7.42) and death: 1.86 (1.48–2.36).

Conclusion. DPS are associated with a severe disease course including death. The impact of DPS on hand function and ischaemia is significant. The presence of DPS should alert the clinician to a poor prognosis and need to optimize the therapeutic strategy.

Key words: SSc, scleroderma, digital pitting scars, vasculopathy, digital ischaemia, death

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Rheumatology key messages

- Digital pitting scars (DPS) have not been investigated in SSc to date, unlike digital ulcers.
- DPS are associated with digital ulcers/acute digital ischaemia, organ involvement and mortality.
- Ischaemia likely drives DPS pathogenesis and DPS impact on hand function.

Introduction

Digital pitting scars (DPS) are common in patients with SSc, with a reported prevalence of ~30–50% [1, 2]. DPS appear as areas of concave depression with hyperkeratosis and typically occur on the fingertips [1, 3]. The cardinal importance of DPS in SSc is reflected by the assignment of three points (out of nine) that are required to fulfil the ACR/EULAR classification criteria [4]. DPS form part of a spectrum of digital vasculopathy in SSc but this characteristic cutaneous manifestation has not been the focus of significant investigation to date.

Although the pathogenesis of DPS in SSc is unresolved, it is generally believed that digital pitting occurs secondary to digital ischaemia with subsequent tissue atrophy [5–7]. Recurrent trauma has also been proposed to potentially contribute to the pathogenesis of DPS [1].

Digital vasculopathy [digital ulcers (DUs) and gangrene] are a major cause of pain and disability in patients with SSc, and despite treatment, many patients often experience recurrent vasculopathic events [8]. Like DUs in SSc, DPS have been reported to be painful and impact on the activities of daily living [7]. Furthermore, DUs are also associated with a more severe disease course in SSc including in patients with very early SSc [2, 9, 10]. However, the potential similar clinical utility of DPS has not been investigated in SSc to date.

Based on this knowledge, our primary objectives regarding DPS in SSc were to: (i) describe the prevalence of DPS in patients with SSc; (ii) examine whether DPS is associated with DUs and acute digital ischaemia (DUs or gangrene); and (iii) describe other associations with DPS including internal organ complications.

Secondary objectives were to assess whether DPS are associated with: (i) structural microvascular disease (as assessed by capillaroscopy); (ii) functional impairment [as assessed by the Cochin Hand Function Scale (CHFS) and HAQ]; and (iii) mortality.

Methods

Data sampling

An analysis of patients enrolled in the prospective European Scleroderma Trials and Research group (EUSTAR) database who fulfilled the 2013 ACR EULAR SSc classification criteria was performed [4]. The structure of the database has been previously described in detail, including the collected data sets and definitions of the clinical variables [11]. We included patients for whom the DPS status could be categorized into either 'never' or 'current/previous' DPS. Disease duration was based upon the timing of the first non-Raynaud feature of disease. Interstitial lung disease was defined as the presence of lung fibrosis on plain chest radiography and/or high-resolution computed tomography imaging. For the purpose of our current analysis, we considered both 'vasodilatory' (calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) and 'vasoactive' (phosphodiesterase type-5 inhibitors, endothelin receptor antagonists and prostanoids).

EUSTAR is part of the World Scleroderma Foundation, which has patient representatives from the Federation of European Scleroderma Associations in its governing board. All of the patients included in our analysis agreed to participate in the EUSTAR cohort by signing informed consent forms that were approved by the local ethics committees centers.

Statistical analysis

Descriptive statistics are used to describe the baseline demographic and clinical variables between patients with never or current/previous DPS. We included the first visit, at which the DPS status was known. Several of the variables had considerable missingness; to enable us to include these in the models without reducing the sample size included massively, we utilized an 'unknown' value label for covariates that had between 5% and 40% missingness. The statistical analysis for each of the objectives was as follows.

Primary objectives

(i) The frequency and percentage of patients with DPS, taken from the baseline demographics table. For this table, baseline refers to the first visit where DPS is recorded or can be inferred. The exception to this is for the HAQ and CHFS score where the first available score per patient was taken instead of the first visit where their DPS status is recorded.

(ii) In separate analyses, we considered whether DUs, and acute digital ischaemia (DUs and gangrene) are associated with DPS both at baseline and after accounting for numerous possible confounding variables. Each patient had several recorded visits, and all of those were included in the multivariable analysis: we therefore used binary logistic regression with standard errors adjusted for clustering at the patient level. The following potential confounding variables we included were pre-specified: age at visit, sex, smoking status (never or current/

previous), disease subtype (limited or diffuse), disease duration and telangiectasias. Further post-hoc confounders were included at the request of the reviewers: interstitial lung disease (ILD), pulmonary hypertension and for the DU analysis, anti-Scl-70 and vasodilatory therapy status. All variables were used in the model regardless of statistical significance. From these, the odds ratios (ORs) and accompanying 95% CIs are reported.

(iii) A χ^2 test, independent *t* test or Mann–Whitney *U* test was used to test whether the summary statistics of these other variables differed between the DPS and non-DPS groups.

Secondary objectives

(iv & v) For these we used multivariable logistic regression with DPS as the outcome and CHFS, HAQ and capillaroscopy as the independent variables of interest and including the following potential confounding variables: age, sex, disease subtype, smoking ever, and for the CHFS and HAQ, joint synovitis. As with (ii), all of the patient's visits were included in the analysis.

(vi) Multivariable logistic regression with 'dead' as the dependent variable, DPS as the independent variable of interest and including the following potential confounding variables: age, sex and disease subtype. At the reviewer's request, we also included further potential confounding variables: anti-Scl-70, interstitial lung disease, pulmonary hypertension and vasodilatory therapy status. We did not include smoking status as it massively reduced (by half) the number of available observations for our analysis. For this analysis, only the patient's last visit was used.

Results

Primary objectives

Patient population and prevalence of DPS

In our analysis, 9671 SSc patients from the EUSTAR database were included. Of these patients, 4924 (51%) had either current or previous DPS at baseline (Table 1). The majority (84.4%) of patients were female and the mean (S.D.) age was 55.7 (13.8) years. Just under half of patients (48.3%) had the limited subset of the disease.

Association between DPS and DUs and active digital ischaemia

At baseline: DPS were significantly ($P \leq 0.001$) associated with DUs (Table 2). Patients with (or have had) DPS were significantly more likely to have either current DUs (24.8% *vs* 4.4%) or previous DU (52.3% *vs* 9.3%) and less likely to have never developed DUs (22.9% *vs* 86.3%) compared with those who never had DPS. DPS were also associated with gangrene (8.4% *vs* 1.5%). Multivariable analysis (Table 3) also showed that that DPS were significantly associated with DUs: OR =

Table 1 Patient characteristics associated with DPS in SSc at baseline

	Never DPS (*n* = 4747)	DPS current/previous (*n* = 4924)	*P*-value
Age, mean (S.D.), years	56.2 (13.6)	55.2 (13.9)	0.001
Sex (female, %)	4123/4747 (86.9%)	4041/4924 (82.1%)	<0.001
Disease duration, median (IQR), years	4 (1–9)	9 (4–16)	<0.001
Raynaud's duration, median (IQR), years	6 (2–15)	9 (3–18)	<0.001
Smoking	1623/4507 (36.0%)	1747/4671 (37.4%)	0.167
Subtype			<0.001
Diffuse	947/3442 (27.5%)	1579/3752 (42.1%)	
Limited	2495/3442 (72.5%)	2173/3752 (57.9%)	
Capillaroscopy			<0.001
Early	6190/1996 (31.0%)	328/2008 (16.3%)	
Active	989/1996 (49.6%)	808/2008 (40.2%)	
Late	388/1996 (19.4%)	872/2008 (43.4%)	
Antibodies			
Anti-Scl-70	1164/4351 (26.8%)	1859/4368 (42.6%)	<0.001
Anticentromere	1949/4316 (45.2%)	1515/4297 (35.3%)	<0.001
Anti-RNA-Pol-3	221/2508 (8.8%)	163/2677 (6.1%)	<0.001
Anti-SSA	57/350 (16.3%)	59/337 (17.5%)	0.67
Anti-SSB	8/341 (2.4%)	15/340 (4.4%)	0.14
ANA	4435/4611 (96.2%)	4512/4651 (97.0%)	0.028
Vasodilatory therapy	4164/4747 (87.7%)	3489/4924 (89.1%)	0.029
CCBs	4146/4747 (87.3%)	4376/4924 (88.9%)	0.020
Vasoactive therapy	4640/4747 (97.7%)	4819/4924 (97.9%)	0.042
Prostanoids	471/4747 (9.9%)	468/4929 (9.5%)	0.521
Immunosuppression	1062/4685 (22.7%)	1149/4844 (23.7%)	0.224

DPS: digital pitting scars; IQR: interquartile range.

Table 2 Disease characteristics associated with DPS in SSc at baseline

	Never DPS ($n = 4747$)	DPS ($n = 4924$)	*P*-value
Digital ulceration			<0.001
Current	146/3295 (4.4%)	1183/4778 (24.8%)	
Previously	305/3295 (9.3%)	2500/4778 (52.3%)	
Never	2844/3295 (86.3%)	1095/4778 (22.9%)	
Gangrene	21/1437 (1.5%)	112/1327 (8.4%)	<0.001
CRP median (mg/l)	0.28 (0.10–0.65)	0.30 (0.10–0.70)	0.044
CK elevation	326/3653 (8.9%)	318/3800 (8.4%)	0.39
Conduction blocks	367/3769 (9.8%)	618/3794 (16.3%)	<0.001
Diastolic dysfunction	722/3772 (19.1%)	934/3617 (25.8%)	<0.001
Pulmonary hypertension	445/3577 (12.4%)	577/3503 (16.5%)	<0.001
Calcinosis	25/487 (5.1%)	172/813 (21.2%)	<0.001
Interstitial lung disease	1148/3974 (28.9%)	1702/3950 (43.1%)	<0.001
Renal involvement	80/4691 (1.7%)	87/4859 (1.8%)	0.750
Telangiectases	1743/3252 (53.6%)	3200/4697 (68.1%)	<0.001
Joint synovitis	537/4668 (11.5%)	628/4808 (13.1%)	0.021
Cochin Hand Function Scale, median (IQR)	3 (0–14)	9 (2–26)	<0.001
HAQ	0.63 (0.13–1.13)	0.75 (0.25–1.34)	0.013

Manifestations defined according to EUSTAR definitions [11, 12]. CK: creatine kinase; DPS: digital pitting scars; IQR: interquartile range.

Table 3 Association between DPS and structural microvascular disease (as assessed by capillaroscopy), functional impairment (Cochin Hand Function Scale and HAQ) and mortality

Outcome	Independent variable of interest	Odds ratio	95% CI	*P*-value	Variables accounted for	Number of observations	Number of patients
DPS	DU (current/previously)	22.03	19.51, 24.87	<0.001	Age, sex, smoking ever, disease subtype,[a] telangiectases, anti-Scl-70, interstitial lung disease, pulmonary hypertension, vasodilatory therapies	22 069	8804
DPS	Active digital ischaemia (DUs and gangrene)	6.30	5.34, 7.42	<0.001	Age, sex, smoking ever, disease subtype, telangiectases, interstitial lung disease, pulmonary hypertension	18 761	7775
DPS	Cochin Hand Function Scale	1.02	1.01, 1.03	<0.001	Age, sex, smoking ever, disease subtype, joint synovitis	2713	1376
DPS	HAQ	1.14	0.81, 1.60	0.451	Age, sex, disease subtype, smoking ever, joint synovitis	501	499
DPS	Capillaroscopy				Age, sex, smoking ever, disease subtype	8018	4332
	Early	0.59	0.50, 0.71	<0.001			
	Late	2.79	2.40, 3.24	<0.001			
Mortality	DPS status at last visit	1.87	1.48, 2.36	<0.001	Age at last visit, sex, disease subtype, anti-Scl-70, interstitial lung disease, pulmonary hypertension, vasodilatory therapies	6649	6649 (only last visit used)

DPS: digital pitting scars; DU: digital ulcer. [a]Disease subtype refers to diffuse *vs* limited *vs* unknown, any other subtypes excluded.

22.03 (95% CI: 19.51, 24.87) and active digital ischaemia (DU and gangrene): OR: 6.30 (95% CI: 5.34, 7.42).

Clinical associations of DPS

Patient characteristics associated with DPS are presented in Table 1. Patients with DPS were younger (55.2 *vs* 56.2 years) and had longer SSc disease (9 *vs* 4 years) and Raynaud's (9 *vs* 6 years) duration. DPS were less common in females (82.1% *vs* 86.9%) and more common in smokers (37.4% *vs* 36.0%). Patients with DPS (compared with never DPS) were significantly more likely to have the diffuse SSc subset than those without (42.1% *vs* 27.5%), and less likely to have the limited subset (57.9% *vs* 72.5%). DPS were associated with SSc-associated autoantibodies. Those with DPS had higher prevalence of anti-Scl-70 (42.6% *vs* 26.8%) and ANA (97.0% *vs* 96.2%) and lower prevalence of anticentromere (35.3% *vs* 45.2%), anti-RNA polymerase III (6.1% *vs* 8.8%). No association between DPS was observed with anti-SSA or anti-SSB (Table 1). Patients with DPS were more likely to be receiving treatment with vasodilators (89.1% *vs* 87.7%) including calcium channel blockers (88.9% *vs* 87.3%) and vasoactive therapy (97.9% *vs* 97.7%).

Disease associations with DPS

Disease characteristics associated with DPS are presented in Table 2. DPS were associated with pulmonary hypertension (based on echocardiography) (16.5% *vs* 12.4%), interstitial lung disease (43.1% *vs* 28.9%), conduction blocks (16.3% *vs* 9.8%) and diastolic dysfunction (25.8% *vs* 19.1%). No association with renal involvement was observed (1.8% *vs* 1.7%). DPS were more prevalent with telangiectases (68.1% *vs* 53.6%), calcinosis (21.2% *vs* 5.1%), joint synovitis (13.1% *vs* 11.5%) and c-reactive peptide (0.30 *vs* 0.28) to varying degrees of significance. No association was observed between DPS and elevated creatine kinase (CK).

Secondary objectives

Association between DPS and functional impairment

Increasing CHFS total was associated with increased odds of DPS [OR 1.02 (95% CI 1.01, 1.03)] but not HAQ [OR 1.14 (95% CI 0.81, 1.60)] after accounting for confounding variables (Table 3).

Association between DPS and structural microvascular disease

As compared with 'active', those with early capillaroscopy were less likely to be associated with DPS [OR 0.59 (95% CI 0.50, 0.71)] after accounting for confounding variables (Table 3). Those with 'late' capillaroscopy however were more likely to have DPS [OR 2.79 (95% 2.40–3.24)].

Association between DPS and mortality

Patients with DPS were more likely to die than those who never had DPS [OR 1.87 95% CI (1.48, 2.36) $P \leq 0.001$] after accounting for the specified potential confounding variables.

Conclusions

The key findings of our study are that DPS are common in patients with SSc affecting ~50% of patients and are associated with a severe disease course including internal organ and digital complications, function and death. To our knowledge, this is the largest study to comprehensively examine the burden and impact of DPS in SSc including disease course and impact on mortality.

In SSc, DPS were associated with major cardiopulmonary complications namely pulmonary hypertension, interstitial lung disease and conduction blocks. Furthermore, DPS were associated with major musculocutaneous disease; specifically, telangiectases, calcinosis and synovitis. DPS were associated with functional impairment as assessed by CHFS, the association between impairment and the HAQ is unclear, likely owing to the much smaller sample size who completed this measure. These findings highlight the high potential clinical impact of DPS in SSc akin to (and may exceed) DU. Therefore, our data suggest that DPS could represent a valuable clinical sign that should alert the clinician to likely more severe disease phenotype course or organ involvement and the need to review the therapeutic strategy.

Another major clinical finding is that DPS were significantly associated with DU [OR = 22.03 (95% CI 19.51, 24.87)] and acute digital ischaemia (DU and gangrene) [OR = 6.30 (95% CI 5.34, 7.42)]. This strongly supports that DPS are a cardinal component of the spectrum of digital vasculopathy in SSc. Patients with DPS were more likely to be prescribed both 'vasodilatory' and 'vasoactive' therapies, although the absolute numerical difference was small. This is presumably because these patients have a more severe 'vascular' phenotype including digital vascular disease (e.g. DUs), and potentially visceral vascular manifestations (e.g. pulmonary hypertension).

Our findings provide further support to the idea that ischaemia drives the pathogenesis of DPS in SSc. Patients with DPS were more likely to have 'late' and less likely either 'early' or 'active' capillaroscopic abnormalities. Furthermore, DPS were associated with longer Raynaud's phenomenon and SSc disease duration. This may have important implications for treatment, including the development of *preventive* vascular strategies to avoid the development of later major vasculopathic complications. Of direct relevance, a unified, generalized vascular phenotype in SSc has been recently proposed, in which vascular-acting therapies could be deployed as disease-modifying agents [13]. A key aspect is that patients with early SSc are the most likely to derive benefit from such a treatment approach (i.e. before the accumulation of irreversible vascular damage and tissue fibrosis).

The patient experience of DPS must be investigated, including similarities and differences with DUs, including to provide novel insights into the pathogenesis of DPS in SSc [14]. For example, patients with SSc report that ulcer development is not considered a random event,

and many have explanations for (and can predict) DU development (e.g. from Raynaud's phenomenon or trauma) [15]. Likely, DPS (and sites of previous DUs) could represent potentially vulnerable ischaemic foci and that could be amenable to locally acting intervention [15]. Furthermore, a possible fibrotic nature of DPS could also be suggested, for example through the observed associations with the diffuse cutaneous subset of the disease and presence of interstitial lung disease.

As previously described, DPS have been little studied to date, but have received recent attention relating to DU definition [16, 17, 18]. In a study that included 87 patients with (progressive) SSc, DPS were observed in 39%, and were closely associated with Raynaud's phenomenon, skin thickening and articular involvement (including swelling). In a recent pilot study by Nolan *et al.* [7], which included 25 patients with and 25 without DPS, pitting scars were associated with DUs and higher patient-reported pain. Similar to our study, pitting scars were associated with impaired activities of daily living. Patients with DPS were also more likely to have 'grossly abnormal' and less likely to have 'no/mild' capillary changes. Unlike our study, the authors did not find any association with age, sex, Raynaud's phenomenon and SSc disease duration, SSc-subset or SSc-associated autoantibodies. However, it is important to highlight that there were significant differences between our two studies; in particular, the number of patients ($n = 9671$) that we included in our analysis. Of interest, the temperature gradients (as assessed by thermography) did not differ between those with or without pitting (on the patient or finger level). This is of interest because thermographic abnormalities have been reported to be associated with SSc-DUs (including severity) and death [19]. In their study, patients with DPS were also more likely to be prescribed treatment with calcium channel blockers, phosphodiesterase-type 5 inhibitors or endothelin receptor antagonists, although this did not reach statistical significance. The authors postulate whether this could explain why thermographic abnormalities were not associated with DPS (i.e. the fingers were warmer due to treatment).

The key strength of our study is the large number of patients that were included in the analysis with longitudinally prospectively collected data. However, there are a number of important considerations that relate to research that is undertaken using registries including (but not limited to) incomplete data and the potential for selection bias [20]. We adopted a pragmatic approach to maximize the number of included patients in our analysis and therefore took the patient's first visit where their DPS status was known. A statistical limitation of this study is that, due to the large sample size, some differences between the DPS and non-DPS groups appear statistically significant but, in reality, may be too small to be of any clinical importance. Future research should also determine the cause of death between patients without or without DPS (e.g. cardiovascular and interstitial lung disease/pulmonary hypertension). The international SSc community should also consider if prospective studies are currently feasible or ongoing to explore DPS within a unified vascular phenotype, including with the limitations of the COVID-19 pandemic [21, 22].

In conclusion, DPS are associated with a severe disease course including internal organ and digital-based complications and death. A key clinical message is that DPS are not 'benign' and signal to the clinician the high likelihood of major disease-related complications and progression, and the need to carefully reappraise the therapeutic strategy. Our data further support that ischaemia contributes to the pathogenesis of DPS. Future dedicated, prospective research is required to understand the central role of DPS in a unified, generalized vascular phenotype in SSc, including preventative strategies to avoid the development of irreversible ischaemic tissue loss and organ dysfunction.

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Data availability statement

The authors and EUSTAR would consider reasonable requests to access the study data.

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