

# 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 1) examine DPS prevalence, 2) whether DPS are associated with digital ulcers (DUs) and active digital ischaemia (DUs or gangrene), and 3) describe other associations with DPS including internal organ complications. Secondary objectives were whether DPS are associated with 1) functional impairment, 2) structural microvascular disease, 3) and 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.** 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  $P < 0.001$ ). DPS were associated with interstitial lung disease, pulmonary hypertension, conduction blocks, telangiectases, calcinosis (all  $P < 0.001$ ) 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 (OR) with DUs: 22.03 (19.51 to 24.87), active digital ischaemia: 6.30 (5.34 to 7.42), and death: 1.86 (1.48 to 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 optimise the therapeutic strategy.

**Key words:** Systemic sclerosis; Scleroderma; Digital pitting scars; Vasculopathy; Digital ischaemia; Death.

### 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 systemic sclerosis (SSc), with a reported prevalence of approximately 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 9) which are required to fulfil the American College of Rheumatology/European League Against Rheumatism (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:

1. Describe the prevalence of DPS in patients with SSc.
2. Examine whether DPS is associated with DUs and acute digital ischaemia (DUs or gangrene).
3. Describe other associations with DPS including internal organ complications.

Secondary objectives were, to assess whether DPS are associated with:

1. Structural microvascular disease (as assessed by capillaroscopy).
2. Functional impairment (as assessed by the Cochin Hand Function Scale ((CHFS)) and Health Assessment Questionnaire ((HAQ)).
3. 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 categorised 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 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 (ACE) 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 (WSF), which has patient representatives from the Federation of European Scleroderma Associations (FESCA) in its governing board. All of the patients included in our analysis agreed to participate in the EUSTAR cohort by signing informed consent forms which were approved by the local ethics committees.

### **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 utilised 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**

1) 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.

2) In separate analyses, we considered whether 1) DUs, and 2) 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: 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 (OR) and accompanying 95% confidence intervals (CI) are reported.

3) A Chi-square 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**

4-5) 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 and for the CHFS and HAQ, joint synovitis. As with 2) all of the patient's visits were included in the analysis.

6) 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

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3 vasodilatory therapy status. We did not include smoking status as it massively reduced (by  
4 half) the number of available observations for our analysis. For this analysis only the patient's  
5 last visit was used.  
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## 10 **Results**

### 11 **Primary objectives**

#### 12 **1) Patient population and prevalence of DPS**

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15 In our analysis, 9671 SSc patients from the EUSTAR database were included. Of these patients,  
16 4924 (51%) had either current or previous DPS at baseline (Table 1). The majority (84.4%) of  
17 patients were female and the mean (SD) age was 55.7 (13.8) years. Just under half of patients  
18 (48.3%) had the limited subset of the disease.  
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#### 24 **2) Association between DPS and DUs and active digital ischaemia**

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26 At baseline: DPS were significantly ( $P < 0.001$ ) associated with DUs (Table 2). Patients with (or  
27 have had) DPS were significantly more likely to have either current DUs (24.8% vs. 4.4%) or  
28 previous DU (52.3% vs. 9.3%) and less likely to have never developed DUs (22.9% vs. 86.3%)  
29 compared to those who never had DPS. DPS were also associated with gangrene (8.4% vs.  
30 1.5%). Multivariable analysis (Table 3) also showed that that DPS were significantly associated  
31 with DUs: OR = 22.03 (95% CI: 19.51 to 24.87) and active digital ischaemia (DU and gangrene):  
32 OR: 6.30 (95% CI: 5.34 to 7.42).  
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#### 42 **3a) Clinical associations of DPS**

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44 Patient characteristics associated with DPS are presented in Table 1. Patients with DPS were  
45 younger (55.2 vs. 56.2 years) and had longer SSc disease (9 vs. 4 years) and Raynaud's (9 vs. 6  
46 years) duration. DPS were less common in females (82.1% vs. 86.9%) and more common in  
47 smokers (37.4% vs. 36.0%). Patients with DPS (compared to never DPS) were significantly  
48 more likely to have the diffuse SSc subset than those without (42.1% vs. 27.5%), and less likely  
49 to have the limited subset (57.9% vs. 72.5%). DPS were associated with SSc-associated  
50 autoantibodies. Those with DPS had higher prevalence of anti-Scl-70 (42.6% vs. 26.8%) and  
51 ANA (97.0% vs. 96.2%) and lower prevalence of anticentromere (35.3% vs. 45.2%), anti-RNA  
52 polymerase III (6.1% vs. 8.8%). No association between DPS was observed with anti-SSA or  
53 anti-SSB (Table 1). Patients with DPS were more likely to be receiving treatment with  
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3 vasodilators (89.1% vs. 87.7%) including calcium channel blockers (88.9% vs. 87.3%) and  
4 vasoactive therapy (97.5% vs. 96.9%).  
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### 8 **3b) Disease associations with DPS**

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10 Disease characteristics associated with DPS are presented in Table 2. DPS were associated  
11 with pulmonary hypertension (based on echocardiography) (16.5% vs. 12.4%), interstitial lung  
12 disease (43.1% vs. 28.9%), conduction blocks (16.3% vs. 9.8%), and diastolic dysfunction  
13 (25.8% vs. 19.1%). No association with renal involvement was observed (1.8% vs. 1.7%). DPS  
14 were more prevalent with telangiectases (68.1% vs. 53.6%), calcinosis (21.2% vs. 5.1%), joint  
15 synovitis (13.1% vs. 11.5%) and c-reactive peptide (0.30 vs. 0.28) to varying degrees of  
16 significance. No association was observed between DPS and elevated CK.  
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### 25 **Secondary objectives**

#### 26 **4) Association between DPS and functional impairment**

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28 Increasing CHFS total was associated with increased odds of DPS (OR 1.02 [95% CI 1.01 to  
29 1.03]) but not HAQ (OR 1.14 [95% CI 0.81 to 1.60]) after accounting for confounding variables  
30 (Table 3).  
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#### 35 **5) Association between DPS and structural microvascular disease**

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37 As compared to 'active', those with early capillaroscopy were less likely to be associated with  
38 DPS (OR 0.59 [95% CI 0.50 to 0.71]) after accounting for confounding variables (Table 3).  
39 Those with 'late' capillaroscopy however were more likely to have DPS (OR 2.79 [95% 2.40 to  
40 3.24]).  
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#### 47 **6) Association between DPS and mortality**

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49 Patients with DPS were more likely to die than those who never had DPS (OR 1.87 95% CI  
50 (1.48 to 2.36)  $P < 0.001$ ) after accounting for the specified potential confounding variables.  
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### 54 **Conclusions**

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56 The key findings of our study are that DPS are common in patients with SSc affecting ~60% of  
57 patients and are associated with a severe disease course including internal organ and digital  
58 complications, function and death. To our knowledge, this is the largest study to  
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3 comprehensively examine the burden and impact of DPS in SSc including disease course and  
4 impact on mortality.  
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9 In SSc, DPS were associated with major cardiopulmonary complications namely pulmonary  
10 hypertension, interstitial lung disease and conduction blocks. Furthermore, DPS were  
11 associated with major musculoskeletal disease, specifically, telangiectases, calcinosis and  
12 synovitis. DPS were associated with functional impairment as assessed by CHFS, the  
13 association between impairment and the HAQ is unclear – likely owing to the much smaller  
14 sample size who completed this measure. These findings highlight the high potential clinical  
15 impact of DPS in SSc akin to (and may exceed) DU. Therefore, our data suggest that DPS could  
16 represent a valuable clinical sign which should alert the clinician to likely more severe disease  
17 phenotype course or organ involvement and the need to review the therapeutic strategy.  
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27 Another major clinical finding is that DPS were significantly associated with DU (OR = 22.03  
28 [95% CI 19.51 to 24.87]) and acute digital ischaemia (DU and gangrene) (OR = 6.30 [95% CI  
29 5.34 to 7.42]). This strongly supports that DPS are a cardinal component of the spectrum of  
30 digital vasculopathy in SSc. Patients with DPS were more likely to be prescribed both  
31 ‘vasodilatory’ and ‘vasoactive’ therapies, although the absolute numerical difference was  
32 small. This is presumably because these patients have a more severe ‘vascular’ phenotype  
33 including digital vascular disease (e.g., DUs), and potentially visceral vascular manifestations  
34 (e.g., pulmonary hypertension).  
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44 Our findings provide further support the idea that ischaemia drives the pathogenesis of DPS  
45 in SSc. Patients with DPS were more likely to have ‘late’ and less likely either ‘early’ or ‘active’  
46 capillaroscopic abnormalities. Furthermore, DPS were associated with longer Raynaud’s  
47 phenomenon and SSc disease duration. This may have important implications for treatment,  
48 including the development of *preventive* vascular strategies to avoid the development of later  
49 major vasculopathic complications. Of direct relevance, a unified, generalised vascular  
50 phenotype in SSc has been recently proposed, in which vascular-acting therapies could be  
51 deployed as disease-modifying agents (12). A key aspect is that patients with early SSc are the  
52 most likely to derive benefit from such a treatment approach (i.e., before the accumulation  
53 of irreversible vascular damage and tissue fibrosis).  
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5 The patient experience of DPS must be investigated including similarities and differences with  
6 DUs, including to provide novel insights into the pathogenesis of DPS in SSc (13). For example,  
7 patients with SSc report that ulcer development is not considered a random event, and many  
8 have explanations for (and can predict) DU development (e.g. from Raynaud's phenomenon  
9 or trauma). [15] Likely, DPS (and sites of previous DUs) could represent potentially vulnerable  
10 ischaemic foci and that could be amenable to locally acting intervention (14). Furthermore, a  
11 possible fibrotic nature of DPS could also suggested e.g., through the observed associations  
12 with the diffuse cutaneous subset of the disease and presence of interstitial lung disease.  
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21 As previously described, DPS have been little studied to date, but have received recent  
22 attention relating to DU definition (15–17). In a study, which included 87 patients with  
23 (progressive) SSc, DPS were observed in 39%, and were closely associated with Raynaud's  
24 phenomenon, skin thickening, and articular involvement (including swelling). In a recent pilot  
25 study by Nolan et al (7), which included 25 patients with and 25 without DPS; pitting scars  
26 were associated with DUs and higher patient reported pain. Similar to our study, pitting scars  
27 were associated with impaired activities of daily living. Patients with DPS were also more likely  
28 to have 'grossly abnormal' and less likely to have 'no/mild' capillary changes. Unlike our study,  
29 the authors did not find any association with age, sex, Raynaud's phenomenon and SSc  
30 disease duration, SSc-subset or SSc-associated autoantibodies. However, it is important to  
31 highlight that there were significant differences between our two studies, in particular, the  
32 number of patients (n=9671) which we included in our analysis. Of interest, the temperature  
33 gradients (as assessed by thermography) did not differ between those with or without pitting  
34 (on the patient or finger level). This is of interest, because thermographic abnormalities have  
35 been reported to be associated with SSc-DUs (including severity) and death (18). In their study  
36 patients with DPS were also more likely to be prescribed treatment with calcium channel  
37 blockers, phosphodiesterase-type 5 inhibitors or endothelin receptor antagonists, although  
38 this did not reach statistical significance. The authors postulate whether this could explain  
39 why thermographic abnormalities were not associated with DPS (i.e., the fingers were  
40 warmer due to treatment).  
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3 The key strength of our study is the large number of patients which were included in the  
4 analysis with longitudinally prospectively collected data. However, there are a number of  
5 important considerations which relate to research, which is undertaken using registries  
6 including (but not limited to) incomplete data and the potential for selection bias (19). We  
7 adopted a pragmatic approach to maximise the number of included patients in our analysis  
8 and therefore took patient's first visit where their DPS status was known. A statistical  
9 limitation of this study is that, due to the large sample size, some differences between the  
10 DPS and non-DPS groups appear statistically significant but in reality, maybe too small to be  
11 of any clinical importance. Future research should also determine the cause of death between  
12 patients without or without DPS (e.g., cardiovascular and interstitial lung disease/pulmonary  
13 hypertension). The international SSc community should also consider if prospective studies  
14 are currently feasible or ongoing to explore DPS within a unified vascular phenotype, including  
15 with the limitations of the Covid-19 pandemic (20,21).  
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29 In conclusion, DPS are associated with a severe disease course including internal organ and  
30 digital based complications and death. A key clinical message is that DPS are not 'benign' and  
31 signal to the clinician the high likelihood of major disease-related complications and  
32 progression, and the need to carefully reappraise the therapeutic strategy. Our data further  
33 support that ischaemia contributes to the pathogenesis of DPS. Future dedicated, prospective  
34 research is required to understand the central role of DPS in a unified, generalised vascular  
35 phenotype in SSc, including preventative strategies to avoid the development of irreversible  
36 ischaemic tissue loss and organ dysfunction.  
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21 **Data availability statement:** The authors and EUSTAR would consider reasonable requests to  
22 access the study data.  
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	<b>Never DPS (n=4747)</b>	<b>DPS current/previous (n=4924)</b>	<b>P-value</b>
Age (mean, SD)	56.2 (13.6)	55.2 (13.9)	0.001
Sex (female, %)	4123/4747 (86.9%)	4041/4924 (82.1%)	<0.001
Disease duration (years, median [IQR])	4 (1 to 9)	9 (4 to 16)	<0.001
Raynaud's duration (years, median [IQR])	6 (2 to 15)	9 (3 to 18)	<0.001
Smoking	1623/4507 (36.0%)	1747/4671 (37.4%)	0.167
Subtype			<0.001
<i>Diffuse</i>	947/3442 (27.5%)	1579/3752 (42.1%)	
<i>Limited</i>	2495/3442 (72.5%)	2173/3752 (57.9%)	
Capillaroscopy			<0.001
<i>Early</i>	6190/1996 (31.0%)	328/2008 (16.3%)	
<i>Active</i>	989/1996 (49.6%)	808/2008 (40.2%)	
<i>Late</i>	388/1996 (19.4%)	872/2008 (43.4%)	
Antibodies			
<i>Anti-Scl-70</i>	1164/4351 (26.8%)	1859/4368 (42.6%)	<0.001
<i>Anticentromere</i>	1949/4316 (45.2%)	1515/4297 (35.3%)	<0.001
<i>Anti-RNA-Pol-3</i>	221/2508 (8.8%)	163/2677 (6.1%)	<0.001
<i>Anti-SSA</i>	57/350 (16.3%)	59/337 (17.5%)	0.67
<i>Anti-SSB</i>	8/341 (2.4%)	15/340 (4.4%)	0.14
<i>ANA</i>	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

**Table 1: Patient characteristics associated with DPS in SSc at baseline.**

	<b>Never DPS (n=4747)</b>	<b>DPS (n=4924)</b>	<b>P-value</b>
Digital ulceration			<0.001
<i>Current</i>	146/3295 (4.4%)	1183/4778 (24.8%)	
<i>Previously</i>	305/3295 (9.3%)	2500/4778 (52.3%)	
<i>Never</i>	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 to 0.65)	0.30 (0.10 to 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 to 14)	9 (2 to 26)	<0.001
HAQ	0.63 (0.13 to 1.13)	0.75 (0.25 to 1.34)	0.013

**Table 2: Disease characteristics associated with DPS in SSc at baseline.** Manifestations defined according to EUSTAR definitions (11,22).

Outcome	Independent variable of interest	Odds ratio	95% CI	P-value	Variables accounted for	Number of observations	Number of patients
DPS	DU (current/previous)	22.03	19.51 to 24.87	<0.001	Age, sex, smoking ever, disease subtype*, Telangiectases, anti-Scl-70, Interstitial lung disease, pulmonary hypertension, Vasodilatory therapies	22069	8804
DPS	Active digital ischaemia (DUs and gangrene)	6.30	5.34 to 7.42	<0.001	Age, sex, smoking ever, disease subtype, Telangiectases, Interstitial lung disease, Pulmonary hypertension	18761	7775
DPS	Cochin hand function scale	1.02	1.01 to 1.03	<0.001	Age, sex, smoking ever, disease subtype, joint synovitis	2713	1376
DPS	HAQ	1.14	0.81 to 1.60	0.451	Age, sex, disease subtype, smoking ever, joint synovitis	501	499
DPS	Capillaroscopy Early	0.59	0.50 to 0.71	<0.001	Age, sex, smoking ever, disease subtype	8018	4332
	Late	2.79	2.40 to 3.24	<0.001			
Mortality	DPS status at last visit	1.87	1.48 to 2.36	<0.001	Age at last visit, sex, smoking ever, disease subtype, anti-Scl-70, Interstitial lung disease, pulmonary hypertension, vasodilatory therapies	6649	6649 (only last visit used)

**Table 3: Association between DPS and structural microvascular disease (as assessed by capillaroscopy), functional impairment (Cochin hand function scale and HAQ), and mortality.**

\*Disease subtype refers to diffuse vs limited vs unknown, any other subtypes excluded.