Advances in Rheumatology

RESEARCH Open Access

Risk of digital ulcers occurrence in systemic sclerosis: a cross-sectional study

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Abstract

Background/objective: Digital ulcers (DUs) represent a frequent complication of systemic sclerosis (SSc). The aim of this study was to evaluate clinical, serological and capillaroscopy features that are associated with DUs in patients with SSc.

Methods: In this bicentric cross-sectional study, 70 patients with SSc were consecutively selected from March 2016 to April 2017. Demographic and clinical features, including the presence of active DUs, were collected. Videocapillaroscopy was performed in all patients.

Results: Among the 70 patients included (mean age of 46.8 years, mean disease duration of 9.41 years), 14 (20%) had active DUs. Based on multivariate analysis, the presence of anti-Scl-70 antibodies, the HAQ-DI score, and the capillary loss score were independently associated with DUs with odds ratios of 7.96 (95% CI 1.32–47.99), 55.77 (95% CI 1.76–1764.28), and 16.66 (95% CI 2.07–133.81), respectively.

Conclusions: The presence of avascular areas in capillaroscopy, elevation of HAQ-DI score and anti-Scl-70 antibodies were independent factors associated with DUs in patients with SSc.

Keywords: Systemic sclerosis, Digital ulcers, Capillaroscopy, Autoantibodies

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease with heterogeneous clinical presentation and a variable and unpredictable course [1, 2]. The pathogenesis of SSc is characterized by a triad of distinct abnormalities: vascular injury, autoimmunity, and skin thickening and tissue fibrosis of internal organs, including the lungs, heart, and gastrointestinal tract [3, 4]. Endothelial dysfunction, dysregulation of the vascular tone, and insufficient neoangiogenesis are present in the earliest stages of the disease [5–7]. Raynaud's phenomenon (RP) is almost universal and frequently the first symptom of SSc [8]. With disease progression, fibrosis of the media and adventitia layers as well as obliteration of the small arteries and microvessels may lead to digital ulcerations [6].

Digital ulcers (DUs) are a frequent clinical complication in these patients and may occur in greater than half of patients at some point in the evolution of SSc. These ulcers are very painful and significantly impact patients' quality of life, leading to severe functional impairment and work disability [9, 10]. DUs are often infected, requiring systemic antibiotics, and may lead to gangrene and eventually amputation [11].

Several factors, including SSc-related autoantibodies, nailfold capillaroscopy abnormalities and endothelial activation biomarkers, have been associated with DUs in patients with SSc [12–17]. In particular, capillaroscopy, a noninvasive toll to assess the structural digital microvasculopathy, has been associated with an increase in DUs development in several studies [13, 16]. Nonetheless, the pathogenesis of DUs is complex, and many factors are involved in the development of this complication. Thus, the aim of this study was to evaluate risk factors associated with the development of active digital ulcers, including clinical features, capillaroscopy abnormalities, and serum levels of SSc-related autoantibodies, antiphospholipid antibodies, and endothelin-1 in SSc patients.

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Patients and methods

Study population

In this bicentric cross-sectional study, 70 patients with SSc attending the outpatient clinic of the Rheumatology Division of the University Hospital of the Federal University of Mato Grosso do Sul (UFMS) and of the Federal University of São Paulo (UNIFESP) were consecutively selected from March 2016 to April 2017. Patients should meet the ACR/EULAR 2013 classification criteria for SSc [18]. All subjects signed informed consent approved by the institutional ethical review board by both institutions. Exclusion criteria were overlap with other rheumatic autoimmune diseases, malignancies and current infectious diseases.

Data collection

Data regarding demographic and clinical features were collected, including information about age, gender, RP duration until diagnosis, and disease duration (defined as the onset of the first non-Raynaud's symptom). The presence of calcinosis, telangiectasias, arthritis, renal crisis and esophageal dysmotility were also collected from all subjects. Interstitial lung involvement was evaluated by means of pulmonary function tests and high-resolution computed tomography (CT). Presence of pulmonary arterial hypertension (PAH) was assessed according to current definitions using Doppler echocardiography and right-sided heart catheterization [19]. The presence of diastolic dysfunction was also assessed by Doppler echocardiography. Routine laboratory studies included Westergreen erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. The modified Rodnan skin score (mRSS) was evaluated in all patients by the same physician as previously described [20]. SSc patients were also classified into diffuse or limited cutaneous disease groups [21].

Patients were instructed to record each RP event and the duration of the RP attack using a diary card during the week before the evaluation. At the end of each day, patients were instructed to complete the Raynaud's Condition Score (RCS), a validated outcome measure in which the difficulty the patient experienced with RP in the last 24 h was estimated on a scale from 0 to 10 (0 = no difficulty; 10 = extremely difficulty) [22]. Disease severity was evaluated using the Medsger Disease Severity Scale (DSS) as previously described [23]. The summed DSS score was assessed. The Health Assessment Questionnaire Disability Index (HAQ-DI) that contains 20 items divided into 8 domains with each score ranging from 0 (no disability) to 3 (maximal disability) was also recorded [24]. The SHAQ visual analog scale (VAS) scores for RP and DUs were also recorded.

The presence and number of active DUs was also recorded. Active digital ulcers were defined as loss of epithelialization and tissues involving, in different degrees, the epidermis, the dermis, the subcutaneous tissue and occasionally the bone. The presence of fingertip pitting scars, gangrene or amputation was also recorded [25]. Patients were divided in two groups: patients with active DUs and patients without DUs.

Nailfold videocapillaroscopy (NVC)

Videocapillaroscopy was performed using an optical videocapillaroscopic probe under 200x magnification lens (Optilia Medical OP-120020, Sollentuna, Sweden). The images were captured and stored for further analysis. The following variables were assessed: number of capillaries/mm, number of enlarged capillaries (apical diameter > 20 μm), number of giant capillaries (apical diameter > 50 μm), and number of microhemorrhages. The average number for each capillaroscopic variable was calculated from the analysis of four consecutive fields (1 mm each) in eight digits, excluding the thumbs. The mean scores from the eight fingers were added, and the total value was divided by the number of fingers evaluated. For the assessment of the score of capillary loss, the normal range of 9 capillaries/mm was adopted [13, 14, 26]. To calculate the mean score of capillary loss, a semiquantitative rating scale (0 = no changes; 1 = < 33% of capillary reduction; 2 = 33–66% of capillary reduction; 3 = > 66% of capillary reduction per linear mm) was adopted according to previous studies [13–15]. The participants were also classified according to two patterns found: normal or SD pattern. Patients with the SD pattern were subdivided according to three NVC patterns (early, active, and late) as described previously [14]. The intra-observer reproducibility for all parameters evaluated by videocapillaroscopy was high as reported in a previous study of our group [26].

Autoantibodies and serum biomarkers

Peripheral venous blood was collected simultaneously with the clinical assessment of the patients. Sera were stored at − 20 °C until use. Anticentromere (ACA), anti-topoisomerase-I (anti-Scl-70) and anti-RNA polymerase III antibodies were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits (INOVA Diagnostics, San Diego, CA, USA) according to the manufacturers' instructions. Samples greater than the cut-off value of 20 units/mL were considered positive per the manufacturer's recommendation.

Serum endothelin-1 (ET-1) (QUANTIKINE ELISA Endothelin-1, R & D systems, Minneapolis, MN, USA) and anti-annexin V IgG and IgM (ORG 643 Anti-Annexin V IgG/IgM kit, ORGENTEC Diagnostika GmbH, Mainz, Germany) were also measured using ELISA following the

manufacturer's specifications. Values > 2.0 pg/ml and > 8.0 Units/mL were considered positive for ET-1 and anti-annexin V IgG and IgM, respectively.

ELISA was also used to measure anticardiolipin IgM/IgG (Sigma Laboratory, Darmstadt, Germany) and anti-beta 2 glycoprotein 1 (ORGENTEC Diagnostika GmbH, Mainz, Germany). Tests were considered positive if the titer was > 20.0 U/ml for IgG/IgM anticardiolipin and > 8.0 U/ml for IgG/IgM anti-beta 2 glycoprotein 1. Lupus anticoagulant was detected according to the recommendations of the International Society of Thrombosis and Hemostasis (ISTH) using tests to verify the prolongation of clotting assays, such as activated partial thromboplastin time (aPTT), kaolin clotting time, and dilute Russell viper venom time (DRVVT). Then, the presence of lupus anticoagulant was confirmed by mixing normal platelet-poor plasma with the patient's plasma.

Statistical analysis

Results are expressed as the mean ± standard deviation or frequency and/or percentages. Kolmogorov-Smirnov test was used to evaluate normality distribution. Differences between patients with and without active DUs were compared by univariate analysis using Student's t-test for continuous variables and the chi-square test or Fischer exact test for categorical variables. Multivariate analyses were performed, and odds ratio (OR) and the corresponding 95% confidence intervals (CI) were calculated to determine independent risk factors associated with DUs. All variables with *P*-values ≤0.10 on univariate analysis were selected for the multivariate analysis. Statistical analysis was performed using SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered to be significant [27].

Results

Demographic and clinical features of the patients are presented in Table 1. Among the 70 patients included, most were women (92.9%) with a mean age of 46.8 ± 12.5 years. Twenty-five patients (35.7%) exhibit the diffuse cutaneous form, and 45 patients (64.3%) exhibit the limited cutaneous form. Among them, 14 (20%) had active DU. The total number of DUs among those patients was 25. ACA antibodies were present in 40% of the patients, anti-Scl70 in 30% and anti-RNA polymerase III in 7.1% of the patients. None of the patients had positivity for IgG/IgM anticardiolipin, IgG/IgM anti-beta 2 glycoprotein 1, or lupus anticoagulant. IgG anti-annexin V and IgM anti-annexin V were present in 15.7 and 14.3% of the patients, respectively. The mean HAQ-DI score was 0.77 ± 0.05. The average summed Medsger severity score was 5.91 ± 3.09, and the RCS scale was 5.29 ± 2.27.

According to Table 2, univariate analysis revealed an increased frequency of males and diffuse cutaneous SSc

Table 1 Demographic and clinical features of the SSc patients

Variable	Patients with SSc (*n* 70)
Age (years), mean ± SD	46.78 ± 12.52
Gender (F/M), (%)	65/5 (92.9/7.1)
RP duration (years), mean ± SD	5.10 ± 6.15
Disease duration (years), mean ± SD	9.41 ± 6.26
Cutaneous subset (Diffuse/Limited), *n* (%)	25/45 (35.7/64.3)
Modified Rodnan cutaneous score, mean ± SD	13.11 ± 10.55
Clinical manifestations	
Calcinosis, *n* (%)	11 (15.7)
Puffy fingers, (%)	13 (18.6)
Digital pitting scars, *n* (%)	28 (40.0)
Active digital ulcers, *n* (%)	14 (20.0)
Necrosis or amputation of extremities, *n* (%)	4 (5.7)
Telangiectasia, *n* (%)	38 (54.3)
Arthritis, n (%)	20 (28.6)
Hand flexion contracture, *n* (%)	10 (14.3)
Tendon friction rubs, *n* (%)	4 (5.7)
Esophageal involvement, *n* (%)	53 (75.7)
FVC < 70% predicted, *n* (%)	19 (27.1)
Interstitial lung involvement on CT scan, *n* (%)	34 (48.6)
PAH, *n* (%)	7 (10.0)
Diastolic dysfunction, *n* (%)	17 (24.3)
Renal crisis, *n* (%)	3 (4.3)
Antibodies and serum markers	
ACA, *n* (%)	28 (40.0)
Anti-Scl-70, *n* (%)	21 (30.0)
Anti-RNA polymerase III, *n* (%)	5 (7.1)
IgG anti-annexin V, *n* (%)	11 (15.7)
IgM anti-annexin V, *n* (%)	10 (14.3)
Endothelin-1 (pg/ml)	2.04 ± 1.49
ESR (mmHg)	30.50 ± 19.09
C-reactive protein (mg/L)	8.81 ± 8.97
Summed Medsger Disease Severity Scale (MDSS) score (range 0–10)	5.91 ± 3.09
Raynaud Condition Score (RCS) (range 0–10)	5.29 ± 2.27
Duration of RP attacks (minutes)	23.54 ± 19.80
Number of RP attacks	2.87 ± 1.84
HAQ-DI (range 0–3)	0.77 ± 0.05
SHAQ VAS for RP	5.26 ± 2.25
SHAQ VAS for digital ulcers	3.41 ± 2.30

Results are presented as mean ± standard deviation or absolute frequency (relative frequency)
RP: Raynaud's phenomenon; FVC: forced vital capacity; CT: computed tomography; PAH: pulmonary arterial hypertension; ACA: anticentromere; ESR: erythrocyte sedimentation rate; HAQ-DI: Health assessment questionnaire disability index; SHAQ: Scleroderma Health assessment questionnaire; VAS: analogic visual scale

Table 2 Univariate and multivariate analysis for risk factors for the development of digital ulcers

Variable	Active ulcers		Univariate	Multivariate	
	Yes ($n = 14$)	No ($n = 56$)	*P* value	*P* value	Odds Ratio (95%CI)
Age (years), mean ± SD	41.21 ± 13.97	48.18 ± 11.86	0.078		
Gender (F/M), *n*	11/3	54/2	0.020		
RP duration (years)	3.86 ± 5.36	5.41 ± 6.34	0.533		
Disease duration	7.50 ± 6.29	9.89 ± 6.21	0.089		
Cutaneous subset (Diffuse/Limited), *n*	11/3	14/42	0.003		
Modified Rodnan score, mean ± SD	24.29 ± 11.44	10.32 ± 8.30	< 0.001		
Calcinosis, *n* (%)	2 (14.3)	11 (19.6)	0.004		
Puffy fingers, *n* (%)	2 (14.3)	11 (19.6)	0.645		
Digital pitting scars, *n* (%)	14 (100.0)	14 (25.0)	< 0.001		
Necrosis or amputation, *n* (%)	3 (21.4)	1 (1.8)	0.005		
Telangiectasia, *n* (%)	8 (57.1)	30 (53.6)	0.810		
Arthritis, n (%)	4 (28.6)	16 (28.6)	1.000		
Hand flexion contracture, *n* (%)	5 (35.7)	5 (8.9)	0.010		
Esophageal involvement, *n* (%)	11 (78.6)	42 (75.0)	0.780		
Interstitial lung involvement, *n* (%)	3 (21.4)	31 (55.4)	0.023		
PAH, *n* (%)	0 (0.0)	7 (12.5)	0.163		
Diastolic dysfunction, *n* (%)	7 (50.0)	10 (17.9)	0.012		
Renal crisis, *n* (%)	0 (0.0)	3 (5.4)	0.376		
ACA, n (%)	2 (14.3)	25 (44.6)	0.037		
Anti-Scl-70, *n* (%)	11 (78.6)	10 (17.9)	< 0.001	0.024	7.96 (1.32–47.99)
Anti-RNA polymerase III, *n* (%)	2 (14.3)	3 (5.4)	0.246		
IgG anti-annexin V, *n* (%)	3 (21.4)	8 (14.3)	0.669		
IgM anti-annexin V, *n* (%)	1 (7,1)	9 (16.1)	0.866		
Endothelin-1 serum levels (pg/ml)	2.56 ± 1.09	1.91 ± 1.89	0.003		
ESR (mmHg)	34.00 ± 14.16	29.63 ± 20.14	0.163		
C-reactive protein (mg/L)	10.53 ± 8.51	8.38 ± 9.10	0.209		
Summed MDSS score (range 0–10)	9.21 ± 2.00	5.09 ± 2.74	< 0.001		
RCS (score 0–10)	7.93 ± 0.62	4.61 ± 2.03	< 0.001		
Duration of RP attacks (minutes)	51.43 ± 25.19	16.57 ± 9.70	< 0.001		
Number of RP attacks	4.85 ± 1.88	2.21 ± 1.33	< 0.001		
HAQ-DI (score 0–3)	1.42 ± 0.34	0.61 ± 0.43	< 0.001	0.023	55.77 (1.76–1764.28)
SHAQ VAS for RP	7.93 ± 0.61	4.61 ± 0.62	< 0.001		
SHAQ VAS for digital ulcers	6.57 ± 0.85	2.63 ± 1.84	< 0.001		

Results are presented as mean ± standard deviation or absolute frequency (relative frequency)
RP: Raynaud's phenomenon; PAH: pulmonary arterial hypertension; ACA: anticentromere; ESR: erythrocyte sedimentation rate; MDSS: Medsger Disease Severity Scale; RCS: Raynaud Condition Score; HAQ-DI: Health assessment questionnaire disability index; SHAQ: Scleroderma Health assessment questionnaire; VAS: analogic visual scale

among patients with DUs compared with patients without DUs (21.4% versus 3.5%, $p = 0.020$; 78.6% versus 25%, $p = 0.003$, respectively). The mRSS was significantly increased in the groups of patients with DUs compared with those without DUs (24.29 ± 11.44 versus 10.32 ± 8.30, $p < 0.001$). In addition, patients with DUs presented a significantly increased frequency of calcinosis ($p = 0.004$), digital pitting scars ($p < 0.001$), necrosis or amputation of the extremities ($p = 0.005$), hand flexion contractures ($p = 0.01$), interstitial lung involvement ($p = 0.023$) and diastolic dysfunction ($p = 0.012$) compared with those without DUs. ET-1 serum levels ($p = 0.003$), HAQ-DI score ($p < 0.001$), SHAQ VAS for RP and DUs ($p < 0.001$), duration and number of RP attacks ($p < 0.001$), summed DSS score ($p < 0.001$), and RCS ($p < 0.001$) were also significantly higher among

patients with active DUs compared with those without DUs. The frequency of ACA antibodies was significantly reduced in patients with DUs ($p = 0.037$). On the other hand, the presence of anti-Scl70 was significantly increased in patients with DUs compared with those without DUs ($p < 0.001$) (Table 2). Multivariate analysis revealed that the presence of anti-Scl-70 antibodies and elevated HAQ-DI score were independent factors associated with DUs in patients with SSc with an OR of 7.96 (95% CI 1.32–47.99) and 55.77 (95% CI 1.76–1764.28), respectively.

Using videocapillaroscopy, univariate analysis revealed that patients with active DUs exhibited a significantly reduced number of capillaries/mm, an increased number of enlarged capillaries and microhaemorrhages, and a higher score of capillary loss compared with patients without DUs. A late pattern was more frequently observed among patients with active DUs compared with those without DUs (85.7% versus 26.8%, respectively, $p < 0.001$). Based on multivariate analysis, the score of capillary loss was independently associated with DUs with an OR of 16.66 (95% CI 2.07–133.81) ($p < 0.001$) (Table 3).

Discussion

DUs are a considerable burden among patients with SSc. Despite efforts to identify risk factors for the development of DUs in SSc patients, few studies have evaluate clinical aspects, serological biomarkers and capillaroscopy abnormalities in the same study. In this cross-sectional study, microvascular abnormalities evaluated using capillaroscopy, the HAQ-DI and anti-Scl-70 were significant independent factors associated with DUs.

Peripheral microvasculopathy is a hallmark of SSc and can be detected early by capillaroscopy. NVC has already been reported as an important method to identify patients at risk of developing DUs [13, 16, 28, 29]. Nonetheless, different parameters and scores have been described, and no consensus exists regarding which parameter is the most reliable and exhibits a stronger association with DUs. In our study, several capillaroscopy parameters were evaluated using NVC. Capillary loss score presented the highest independent risk for DUs in SSc patients, confirming that microvasculopathy exhibits a strong association with increased risk of DUs development. Similar to our study, Smith et al. [13] proposed the mean score of capillary loss over eight fingers as a prognostic index for present/future digital trophic lesions (including DUs). In this study, a mean score value of capillary loss of 1.67 was chosen as the cut-off value for the clinical prognostic index with a sensitivity and specificity of approximately 70%. In a multicenter, prospective cohort study, which included videocapillaroscopic evaluation of 623 patients with SSc, the mean number of capillaries/millimeters in the middle finger of the dominant hand, the number of DUs at enrollment, and the presence of critical digital ischemia were identified as risk factors for the development of new DUs [14]. The study developed an index based on these 3 variables. Laboratory biomarkers were not included in the study. Moreover, in a prospective study of Avouac et al. [15] evaluating NVC in patients with SSc, loss of capillaries over time was an independent marker of overall disease progression (HR = 4.35) and occurrence of new DU (HR = 5.33).

Composite scores were used in few studies. The Capillaroscopic Skin Ulcer Risk Index (CSURI) was proposed in 2009 [30] as a tool to predict the development of digital ulcers in patients with SSc. The combination of the total number of capillaries in the distal row (N), maximum loop diameter (D), and number of megacapillaries (M) were used to create a mathematical formula as follows: D x M:N^2. ROC curve analysis revealed an area of 0.926 for ulcer appearance with a sensitivity and specificity of 94.3 and 85.9%, respectively, at the cutoff value of 2.94. The CSURI was further validated in a multicenter study [31]. However, the index has some limitations, including the inclusion

Table 3 Videocapillaroscopy parameters according to the presence or absence of digital ulcers - univariate and multivariate analysis

Variable	Active DUs		*P* value		Odds (95%CI)
	Yes	No	Univariate	Multivariate	
Number of capillaries/mm	6.43 ± 0.36	7.55 ± 0.99	< 0.001		–
Microhaemorrhages	1.2 ± 0.75	0.49 ± 0.45	0.002		–
Enlarged capillaries	1.78 ± 0.23	0.95 ± 0.80	< 0.001		–
Giant capillaries	0.30 ± 0.25	0.20 ± 0.24	0.145		–
Score of capillary loss	1.77 ± 0.38	0.77 ± 0.64	< 0.001	0.008	16.66 (2.07–133.81)
Patterns			< 0.001		
Normal, *n* (%)	0 (0)	5 (8.9)			
Early, *n* (%)	0 (0)	18 (32.1)			
Active, *n* (%)	2 (14.3)	18 (32.1)			
Late, *n* (%)	12 (85.7)	15 (26.8)			

Results are presented as mean ± standard deviation of the mean or relative frequency (absolute frequency). DUs: Digital ulcers

only of capillaroscopic parameters, the mandatory presence of giant capillaries and the complexity of the formula. In addition, the index has not been routinely used in other studies. Interestingly, in 2015, the same group proposed a predictive risk chart, including male gender, DU history, altered CSURI and ESR, to stratify DU risk [16].

A core set of measures has been proposed to assess RP and DUs in SSc patients that includes RCS, patient and physician VAS ratings of RP activity, and measures of disability and pain [22]. The RCS is a validated daily self-assessment measure that includes frequency, duration, severity and impact of RP attacks. As shown in previous studies, we also found increased RCS, a higher disability evaluated by means of the HAQ-DI, and a higher disease severity score in patients with DUs. Nonetheless, only the HAQ-DI was associated with DUs by multivariate analysis with an OR of 55.77. Indeed, DUs are associated with significant functional disability, particularly with hand dysfunction, in SSc patients [22, 24, 32–34].

Moreover, previous studies have proposed several vascular biomarkers as useful tools for predicting DUs [35–37]. In our study, anti-Scl-70 was associated with DUs in both univariate and multivariate analyses. Anti-Scl-70 is associated with diffuse cutaneous SSc and more severe involvement as well as with the occurrence of DUs in previous studies [35, 36]. Other antibodies related to vascular damage, such as annexin V, anti-beta 2 glycoprotein 1, anticardiolipin and lupus anticoagulant, were not associated with DUs. In addition, in a recent study, increased serum levels of ET-1, symmetric dimethylarginine and vascular endothelial growth factor were strong predictors of new DUs in a 3-year follow-up [12]. In our study, ET-1 was significantly increased in patients with DUs in the univariate analysis, suggesting that endothelial dysfunction might be associated with more severe microangiopathy.

In our study, several risk factors that have been identified previously, such as male gender, diffuse cutaneous SSc, a higher mRSS, the presence of digital pitting scars, necrosis or digital amputation, flexion contracture of the hands, interstitial lung disease and diastolic heart dysfunction, were also associated with DUs by univariate analysis.

As in previous studies, we did not find a statistically significant relationship between the presence of antiphospholipid antibodies (aPLs) and the occurrence of scleroderma complications [38, 39]. Although a wide prevalence of aPLs in systemic sclerosis has been reported (between 0 and 57,5%), we did not find positivity of aPLs in our patients, even with digital ulcers. Regarding anti-annexin V antibodies they were also detected in a small proportion of our patients with SSc. However, in contrary to a previous report of an association between anti-annexin V and digital ulcer or ischemia, we did not observe a statistical association between anti-annexin V antibodies and DUs [40].

Limitations of this study include the low sample number evaluated, and the lack of prospective data evaluating the occurrence of new DUs in these subjects.

Conclusion

In conclusion, in this bicentric study, multivariate analysis revealed that the presence of avascular areas in capillaroscopy, the HAQ-DI and the presence of anti-Scl-70 antibody were independent risk factors associated with DUs. Prospective analyses are needed to assess the value of these variables in predicting the occurrence of new DUs in SSc patients.

Acknowledgements
Not applicable.

Funding
The authors declare that they have used only private funds for research development.

Availability of data and materials
All data generated or analyzed during this study are included in this published article, and its supplementary information files.
The datasets generated and/or analyzed during the current study are not publicly available due to ethics policy of the institutions but are available from the corresponding author on reasonable request.

Authors' contributions
AMCH performed the nailfold videocapillaroscopy examination of all patients, and with CK was a major contributor in writing the manuscript. CK and ASS analyzed and interpreted the patient data regarding the statistical analysis. SHR performed with AMCH all autoantibodies and serum biomarkers tests. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The manuscript was approved by the institutional ethical review board by both institutions, in their respective ethics committees:
Federal University of São Paulo opinion number: 1.433.963 CAAE: 53429216.5.1001.5505.
Federal University of Mato Grosso do Sul: 1.300.296.
CAAE: 49087115.6.0000.0021.

Consent for publication
All subjects signed informed consent approved by the institutional ethical review board by both institutions.

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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Received: 20 November 2018 Accepted: 14 March 2019
Published online: 28 March 2019

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