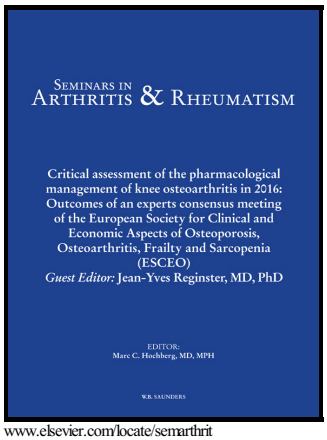

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Digital ulcers and cutaneous subsets of systemic sclerosis: Clinical, immunological, nailfold capillaroscopy, and survival differences in the spanish rescle registryDigital ulcers in systemic sclerosis and cutaneous subsets

Tolosa-Vilella Carles, Morera-Morales Maria Lluisa, Simeón-Aznar Carmen Pilar, Marí-Alfonso Begoña, Colunga-Arguelles Dolores, Callejas_Rubio José Luis, Rubio-Rivas Manuel, Freire-Dapena Maika, Guillén-del Castillo, Alfredo, Iniesta-Arandia Nerea, Castillo-Palma Maria Jesús, Egurbide-Arberas Marivi, Trapiellla-Martínez Luis, Vargas-Hitos José A, Todolí-Parra José Antonio, Rodriguez-Carballeira Mónica, Marin-Ballvé Adela, Pla-Salas Xavier, Rios-Blanco Juan José, Fonollosa-Pla Vicent

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Title: DIGITAL ULCERS AND CUTANEOUS SUBSETS OF SYSTEMIC SCLEROSIS: CLINICAL, IMMUNOLOGICAL, NAILFOLD CAPILLAROSCOPY, AND SURVIVAL DIFFERENCES IN THE SPANISH RESCLE REGISTRY.

Authors: Tolosa-Vilella, Carles, MD, PhD (1), Morera-Morales, Maria Lluisa, MD (1), Simeón-Aznar, Carmen Pilar, MD, PhD (2), Marí-Alfonso, Begoña, MD (1), Colunga-Arguelles, Dolores, MD (3), Callejas_Rubio, José Luis, MD, PhD (4), Rubio-Rivas, Manuel, MD, PhD (5), Freire-Dapena Maika, MD, PhD (6), Guillén-del Castillo, Alfredo, MD (2), Iniesta-Arandia, Nerea, MD (7), Castillo-Palma, Maria Jesús, MD, PhD (8), Egurbide-Arberas Marivi, MD, PhD (9), Trapiellla-Martínez Luis, MD (10), Vargas-Hitos, José A, MD (11), Todolí-Parra, José Antonio, MD (12), Rodriguez-Carballeira Mónica, MD (13), Marin-Ballvé Adela, MD (14), Pla-Salas, Xavier, MD (15), Rios-Blanco, Juan José, MD, PhD (16), Fonollosa-Pla, Vicent, MD, PhD (2), on behalf of RESCLE investigators, Autoimmune Diseases Study Group (GEAS).

(1) Department of Internal Medicine, Corporació Sanitària Universitària Parc Taulí, Sabadell, Barcelona, Universidad Autónoma de Barcelona; (2) Department of Internal Medicine, Hospital Valld´Hebron, Barcelona; (3) Department of Internal Medicine, Hospital Universitario Central de Asturias; (4) Unit of Autoimmune Systemic Diseases, Department of Internal Medicine, Hospital Clínico San Cecilio, Granada; (5) Department of Internal Medicine, Hospital Universitario de Bellvitge; (6) Department of Internal Medicine, Complejo Hospitalario Universitario de Vigo; (7) Department of Autoimmune Systemic Diseases, Hospital Clinic, Barcelona; (8) Unit of Connective Tissue Diseases, Department of Internal Medicine, Hospital Virgen del Rocio, Sevilla; (9) Department of Internal Medicine, Hospital de Cruces, Barakaldo, Vizcaya; (10) Department of Internal Medicine, Hospital de Cabueñes, Gijón; (11) Department of Internal Medicine, Hospital Virgen de las Nieves, Granada; (12) Department of Internal Medicine, Hospital La Fe, Valencia; (13) Department of Internal Medicine, Hospital Universitari Mútua Terrassa, Barcelona; (14) Department of Internal Medicine, Hospital Clínico Universitario Lozano Blesa, Zaragoza; (15) Consorci Hospitalari de Vic, Barcelona; (16) Department of Internal Medicine, Hospital La Paz, Madrid.

Corresponding author: Tolosa-Vilella, Carles, Internal Medicine Department. Corporació Sanitària Universitària Parc Taulí. Hospital of Sabadell. Universidad Autónoma de Barcelona.

e-mail: ctolosa@tauli.cat

Short title: Digital ulcers in systemic sclerosis and cutaneous subsets.

Keywords*:* systemic sclerosis, limited cutaneous SSc; diffuse cutaneous SSc; SSc sine scleroderma; digital ulcers, anticentromere antibodies; anti-topoisomerase I antibodies, nailfold capillaroscopy, survival.

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*See Appendix for members of the RESCLE Registry

ABSTRACT

Objective.

Digital ulcers (DU) are the most common vascular complication of systemic sclerosis (SSc). We compared the characteristics between patients with prior or current DU with those never affected and evaluated whether a history of DU may be a predictor of vascular, organ involvement and/or death in patients with SSc.

Methods.

Data from SSc patients with or without prior or current DU were collected by 14 referral centers in an ongoing registry of Spanish SSc patients, named Registro de ESCLErodermia (RESCLE). Demographics, organ involvement, autoimmunity features, nailfold capillary pattern, survival time, and causes of death were analyzed to identify DU related characteristics and survival of the entire series and according to the following cutaneous subsets: diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc), and SSc sine scleroderma (ssSSc).

Results.

552 out of 1326 patients enrolled in the RESCLE registry had prior or current DU, 88% were women, the mean age was 50±16 years, and the mean disease duration from first SSc symptom was 7.6±9.6 years. Many significant differences were observed in the univariate analysis between patients with and without prior/current DU. Multivariate analysis identified that history of prior/current DU in patients with SSc was independently associated to younger age at SSc diagnosis, diffuse cutaneous SSc, peripheral vascular manifestations such Raynaud's phenomenon, telangiectasia, and acro-osteolysis but not other vascular features such as pulmonary arterial hypertension or scleroderma renal crisis. DU were also associated to calcinosis cutis, interstitial lung disease, as well as worse survival. Multivariate analysis performed in the cutaneous subsets showed that prior/current DU were independently associated: 1) in dcSSc, to younger age at SSc diagnosis, presence of telangiectasia and calcinosis and rarely a non-SSc pattern on nailfold capillaroscopy; 2) in lcSSc, to younger age at SSc diagnosis, presence of Raynaud's phenomenon as well as calcinosis cutis, interstitial lung disease, and higher incidence of death from all causes; 3) in ssSSc, to younger age at first SSc symptom and greater incidence of death from all causes.

Conclusions.

Digital ulcers develop in patients with SSc younger at diagnosis, mainly in patients with dcSSc and lcSSc, and they are associated to other peripheral vascular manifestations such as Raynaud's phenomenon, telangiectasia, and acro-osteolysis but also to calcinosis, and interstitial lung disease. History of DU in SSc leads to worse survival, also noticeable for lcSSc and ssSSc subsets but not for dcSSc patients.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune systemic disease characterized by skin and visceral fibrosis with a proliferative and obstructive vasculopathy of small blood vessels. A growing body of evidence supports the role of the microvasculopathy as the primary pathogenetic event mediated by autoimmunity [1-3]. Raynaud's phenomenon (RP) is a reversible vascular hyperreactivity that affects early and almost universally SSc patients. Unlike primary RP, vascular dysfunction that characterizes SSc includes capillary loss, vascular remodeling and progressive narrowing of the lumen of small arteries evolving to skin ischemia [3, 4]. Persistent digital ischemia may lead to digital ulcers (DU) that occur rather early in the course of the illness [5, 6] and thus they may be a good candidate as predictor of clinical evolution. Up to 63% of SSc patients develop DU, depending on the clinical subtype, and its occurrence has been identified as predictor of organ involvements and disease worsening [5, 7-10]. However, despite its great incidence, information about clinical, immunological and capillaroscopic features, as well as survival of SSc patients who experienced at least one digital ulcer during the course of the disease is heterogeneous.

The present report is a cross-sectional analysis of SSc patients enrolled in the first ongoing nationwide registry by the RESCLE investigators. The objectives of our study were to compare the clinical characteristics and prognosis of SSc patients with prior or current digital ulcers with those never affected by digital ulcers and to compare both groups of patients according their cutaneous subsets. By understanding the SSc features associated with digital ulcers, clinicians may be better able to stratify risk patients and understand the burden of digital ulcers in this disease. We used a modification of the classification proposed by LeRoy and Medsger [11] on 3 subsets but patients with SSc sine scleroderma (ssSSc) were considered separately because ssSSc patients have lesser incidence of DU than lcSSc patients, as shown in previous studies [8, 12, 13]. No data

are currently available on the characteristics of patients with or without history of DU of these 4 differentiated SSc subsets in a large population of patients.

Patients and methods

The Spanish Scleroderma Study Group (SSSG) was created by the Spanish Internal Medicine Society in 2006 with the aim of compiling a large series of patients with SSc in a registry named RESCLE (Registro de ESCLErodermia as Spanish nomenclature). Nineteen Spanish centers with substantial experience in the management of these patients participated in the recruitment of 1326 SSc patients up to September, 2013. All participating centers obtained the Ethics Committee approval. To avoid excluding patients with clear diagnosis of SSc who did not fulfill the American College of Rheumatology (ACR) preliminary classification criteria for SSc [14], we also considered that diagnosis following a modification of the classification proposed by LeRoy and Medsger [11]. Further, we also evaluated how many patients fulfilled the recent published 2013 ACR/EULAR criteria for SSc [15]. Demographic, clinical, immunological, and nailfold capillaroscopic data encompassing 90 variables were collected according to a standard protocol and then entered into a SPSS database.

Variable Definitions

We used the following definitions:

Cutaneous subsets:

Four groups of SSc patients were established according to the extent of skin sclerosis, following a modification of the classification proposed by LeRoy and Medsger [11]:

1. Limited cutaneous SSc (*lcSSc)*, when skin sclerosis was confined distally to the elbows and knees or the face,
2. Diffuse cutaneous SSc (*dcSSc)*, when skin thickening extended proximally to the elbows and knees or affected the trunk.
3. *pre-SSc*, defined by the presence of RP, characteristic SSc nailfold capillaroscopic changes, and/or disease specific autoantibodies but no skin thickening, and
4. SSc sine scleroderma (*ssSSc)*, defined by the presence of RP or a peripheral vascular equivalent (digital pitting scars, fingertip ulcers, SSc-type nailfold capillary pattern), scleroderma clinical features (gastrointestinal hypomotility, interstitial lung disease,

pulmonary arterial hypertension, typical cardiac involvement, or scleroderma renal crisis), and positive antinuclear antibodies but no skin sclerosis.

Clinical features

Prior or current digital ulcers: presence of active DU or a history of DU related to digital ischemia. Ulcers overlying bony prominence secondary to trauma at the site of joint contractions, areas of calcium extrusion and skin fissures were not included.

SSc onset (first symptom): the date of the first self-reported symptom (Raynaud's phenomenon in the majority of patients).

SSc diagnosis: the date when the patient fulfilled the 1980 ACR preliminary classification criteria [14] or the modified classification proposed by LeRoy and Medsger [11].

Peripheral vascular manifestations: defined by the presence of RP with or without ischemic digital ulcers. Acro-osteolysis (bony resorption of the terminal digital tufts secondary to ischemia) and telangiectasia were also recorded under this category.

Digestive tract involvement: included any of the following diagnoses considered related to SSc: esophageal involvement, when hypomotility of the lower two-thirds of the esophagus and/or decreased peristalsis were confirmed by manometry or cineradiographic study; gastric involvement, when gastric hypomotility was detected by radiographic or radionuclide study or when gastric antral vascular ectasia was identified by endoscopy; intestinal involvement, when an intestinal motility disturbance was confirmed by manometry or cine-radiographic study, when malabsorption syndrome was diagnosed by breath test, or when intestinal pseudoobstruction was identified by simple radiology or computerized tomography scan. Diagnoses of primary biliary cirrhosis, autoimmune hepatitis, or nodular regenerative hyperplasia of the liver were encompassed under the term hepatic involvement.

Pulmonary involvement: defined by the presence of interstitial lung disease (ILD) or pulmonary hypertension (PH). The former was established if evidence consistent with pulmonary fibrosis was present in chest radiograph or high-resolution computed tomography (HRCT), regardless of forced vital capacity (FVC). FVC predicted threshold of 70% was selected because of lower levels were associated to poorer prognosis in SSc patients [16]. PH was considered when systolic pulmonary arterial pressure (PAP) was estimated to be >40 mm Hg by Doppler echocardiogram or when mean PAP was found to be equal or higher than 25 mm Hg at rest by right-sided heart

catheterization (RHC). PH was classified as pulmonary arterial hypertension when the pulmonary capillary wedge pressure was < 15 mmHg by RSHC, with no ILD or ILD and FVC percent predicted > 60% [17, 18].

Heart involvement: established by 1 or more of the following: pericarditis, ischemic cardiomyopathy with no known cause, reversible thallium perfusion defects after cold stimulation, any disturbance on color-Doppler echocardiography, electrocardiographic abnormalities with no other cause, or left ventricular ejection fraction lower than 50%.

Musculoskeletal involvement: myopathy was established by the presence of proximal muscle weakness or myalgias and serum creatine kinase levels over the normal value or presence of myopathic pattern on electromyography (EMG). Calcinosis cutis was defined as widespread or localized soft-tissue calcification Arthritis, tendon friction rubs, and flexion contractures were also considered.

Scleroderma renal crisis: defined by the presence of a rapid deterioration of renal function (with concomitant normal urine sediment) within a period of less than 1 month in the absence of previous evidence of significant kidney disease or by the combination of abrupt onset or aggravation of moderate to severe arterial hypertension (>160/90 mm Hg) accompanied by manifestations of malignant hypertension (hypertensive grade III or IV retinopathy, pulmonary edema and/or hypertensive encephalopathy) and elevation of peripheral renin activity to at least twice the upper limit of normal [19].

Sicca syndrome: defined when ocular and oral dryness, and ocular signs and abnormal salivary gland function tests were present.

Nailfold capillaroscopy:

Nailfold capillaroscopy was carried out in each participating center following the recommendations of the Working Group for the Study of Capillaroscopy (GREC), sponsored by the Autoimmune Diseases Study Group (GEAS), available from http://www.capilaroscopia.es/#/. Capillaroscopy images of the nailfold bed of the second to fifth fingers of both hands were obtained by 80-200 × magnification lenses. Nailfold beds presenting trauma, microtrauma, or severe digital ischemia phenomena were disregarded. Nailfold beds that did not provide a correct display for image interpretation were also disregarded.

Two main capillaroscopic patterns were distinguished according to the study of Maricq and coworkers [20]: 1) active pattern characterized by predominant capillary loss and 2) slow pattern characterized by the presence of megacapillaries but no significant

capillary loss. Tortuous capillaries, thrombosis, and other minor capillaroscopic changes were defined as a non-SSc pattern.

Immunological features:

Antinuclear antibodies (ANA) were identified by indirect immunofluorescence (IIF) assay using Hep-2 cell lines or by IIF using triple tissue cryostat section (liver-stomach-kidney). Anti-Centromere antibodies (ACA), anti-PM-Scl, anti-Ku, anti-RNA-polimerase III, anti-U1 RNP, anticardiolipin antibodies, and antibodies to extractable nuclear antigens (SSA/Ro, SSB/La, Sm, RNP, and topoisomerase I, were also determined.

Statistical analysis

Statistical evaluation was performed using a contingency table test (χ^2 test or Fisher's exact *t* test) to identify significant differences or associations between SSc patients with or without prior/current DU, in the whole cohort and in patients with the SSc cutaneous subsets, dcSSc, lcSSc, and ssSSc. Differences between continuous variables (mean ± standard deviation) were determined using the t-student test. Survival curves were calculated using the Kaplan-Meier method, and the logrank ratio was used to identify differences. Significant differences in disease presentation on univariate comparisons were then retested by forward multivariate logistic regression. A *p*-value lesser than 0.05 was considered significant. All statistical analyses were carried out with the statistics software SPSS V.18.0 for Windows (SPSS, Chicago, IL).

RESULTS

Characteristics of SSc patients with and without prior/current digital ulcers

Baseline demographic and clinical characteristics for the entire SSc group (n=1326), according to the presence (n=552, 41.6%) and absence (n=774, 58.4%) of prior/current of DU are shown in Table 1. Digital ulcers history was more frequent in dcSSc than in lcSSc patients, and in both subsets more frequent than in ssSSc patients, as shown in figure 1. In addition, the elapsed time from first SSc symptom to the DU appearance and SSc diagnosis was lesser in dcSSc patients compared to lcSSc and ssSSc but it was

not different between the last subsets. The majority of patients were classified as lcSSc (60%) subset, followed by dcSSc (25%), ssSSc (8.9%) and pre-SSc (6.1%) subsets. One thousand and seventy-eight out of 1198 (90%) evaluated patients fulfilled the 2013 ACR/EULAR SSc criteria. The follow-up for the entire cohort was 14±12 years and mean survival time from the first SSc symptom was 40 years. Up to September 2013, 225 (17%) patients died and the cause of death could be identified in 212 patients that was SSc-related in 102 cases (48.1%). Immunological features, nailfold capillaroscopy patterns, causes of death and survival from both groups are shown in table 2. Then, associations with digital ulcers were calculated for dcSSc, lcSSc, and ssSSc subsets and results are shown in the supplementary tables S1 and S2, S3 and S4, and S5 and S6, respectively. Pre-SSc patients were not compared because of the small number of patients and the absence of organ involvement. Multivariate analysis and Kaplan-Meier cumulative survival for the entire SSc group and its subsets, according to the presence or absence of prior/current DU, are shown in table 3 and figure 2, respectively.

Associations with digital ulcers in patients with SSc.

Four hundred and eighty-three out of 552 (88%) patients with prior/current DU were female, with a mean age at DU appearance of 50±16 years. All comparisons between SSc patients with or without history of DU are summarized in tables 1 and 2. Both the 1980 preliminary ACR criteria and the 2013 ACR/EULAR criteria for SSc were more frequently fulfilled by patients with DU history compared to patients never affected by DU with a similar follow-up period for both groups. The prevalence of dcSSc subset was higher in patients with prior/current DU and lower for lcSSc, ssSSc, and pre-SSc subsets. By univariate analysis, a history of DU was significantly associated with the following demographic factors and clinical features: younger age at first SSc symptom and SSc diagnosis, with no significant delay in SSc diagnosis when DU were absent. Peripheral vascular manifestations such Raynaud's phenomenon, telangiectasia, and acro-osteolysis were also more frequent in patients with prior/current DU as well as the following organ involvements: Esophageal and gastrointestinal involvement; lung involvement with higher prevalence of ILD and DLCO/VA<70%, as well as reduced mean percent predicted FVC, mean percent predicted DLCO/VA, and presence of PH but a trend to lesser occurrence of PAH. Interestingly, 44% of patients with DU history were chronically treated with some of the potent vasodilators

(endothelin receptor antagonists, phosphodiesterase 5 inhibitors and/or prostaglandin analogues) versus 11% of the patients never affected ($p<0.001$); heart involvement, with lesser mean percent of LVEF; musculoskeletal involvement with more frequent presence of calcinosis cutis, arthritis, myopathy, and flexion contractures as well as more frequent scleroderma renal crisis, and nervous system involvement, but lesser systemic arterial hypertension. Patients with history of DU had higher prevalence of anti-Topoisomerase I antibodies and lesser prevalence of anti-centromere antibodies as well as higher prevalence of active pattern and lesser occurrence of non-SSc pattern on nailfold capillaroscopy. Mortality rate was higher in patients with DU–but it was not significantly related to SSc except for death by PH related-ILD. Mean survival time from the first symptom was less prolonged in patients with history of DU than patients without prior/current DU. Survival rates from the first SSc symptom at 5, 10, 20 and 30 years were 95.2% vs 95.9%, 90% vs 92.4%, 77% vs 81.5% and 57.7% vs 73.5%, respectively.

Associations with digital ulcers in patients with dcSSc subset.

Three hundred and thirty-one out of 1326 patients (25%) were classified as dcSSc and history of DU was recorded in 208 (62.2%) of them. One hundred and seventy-eight patients (86%) with prior/current DU were female with a female:male ratio significantly higher than patients with no history of DU. By definition, all patients with dcSSc, with or without history of DU fulfilled both the 1980 preliminary ACR criteria and the 2013 ACR/EULAR criteria for SSc. The mean age at DU appearance was 45±15 years, with a similar follow-up period for dcSSc patients with or without prior/current DU. By univariate analysis, a history of DU was associated with the following demographic factors and clinical features: younger age at first SSc symptom and SSc diagnosis, with no delay of SSc diagnosis when DU were absent. Peripheral vascular manifestations such Raynaud's phenomenon, telangiectasia, and acro-osteolysis as well as the presence of calcinosis cutis, and flexion contractures were also more frequent in patients with prior/current DU. Arterial hypertension was less frequent in patients with DU history. No significant differences were identified in the internal organ involvements. Patients with history of DU had higher prevalence of antinuclear antibodies but not in their specificities. On nailfold capillaroscopy, there was a higher prevalence of active pattern and lesser occurrence of non-SSc pattern. Mortality, causes of death and mean survival

time from the first symptom (25 vs 24 years) were similar in dcSSc patients with or without history of DU. Survival rates from the first SSc symptom at 5, 10, 20 and 30 years were 91.1% vs 90.9%, 83.4% vs 82.5%, 66.7% vs 45.1% and 31% vs 39.5%, respectively. All data are summarized in the supplementary tables S1 and S4.

Associations with digital ulcers in patients with lcSSc subset.

Seven hundred and ninety-three out of 1326 patients (60%) were classified as lcSSc and history of DU was recorded in 307 (38.7%) of them. Two hundred and seventy-three patients (89%) with prior/current DU were female, with similar gender ratio between both groups. The 1980 preliminary ACR criteria were fulfilled by 267 and 217 patients (87% vs 45%, $p<0.001$) with or without previous/current DU, respectively and the recent 2013 SSc ACR/EULAR criteria were fulfilled by 100% of both groups taking into account 721 assessed patients. The mean age at DU appearance was 54±15 years, and the follow-up period was longer for patients with DU history. By univariate analysis, a history of DU was associated with the following demographic factors and clinical features: Raynaud's phenomenon as first manifestation, younger age at first SSc symptom and SSc diagnosis, with no delay of SSc diagnosis when DU were absent. Peripheral vascular manifestations such Raynaud's phenomenon, telangiectasia, and acro-osteolysis were also more frequent in patients with prior/current DU as well as the following organ involvements: Oesophageal involvement; lung involvement with higher prevalence of ILD, and PH, higher sPAP and higher prevalence of sPAP>40 mm Hg; heart involvement, with higher prevalence of ischemic heart disease; musculoskeletal involvement with calcinosis cutis, and flexion contractures, and other manifestations such nervous system involvement and lesser prevalence of arterial hypertension. Patients with history of DU had higher prevalence of active pattern and lesser occurrence of non-SSc pattern on nailfold capillaroscopy. There was neither difference in the prevalence of antinuclear antibodies nor in the determined antigenic specificities. Mortality was higher in patients with history of DU but only had a trend to be related to SSc. Mean survival time from the first symptom was similar in lcSSc patients with or without history of DU (40 vs 48 years). Survival rates from the first SSc symptom at 5, 10, 20 and 30 years were 97.8% vs 96.3%, 93.4% vs 94.3%, 82.4% vs 87.7% and 65.6% vs 78.5%, respectively. All data are summarized in the supplementary tables S3 and S4.

Associations with digital ulcers in patients with ssSSc subset.

One hundred and eighteen out of 1326 patients (8.9%) were classified as ssSSc and history of DU was recorded in 19 (16.1%) of them. Sixteen patients (84%) with prior/current DU were female, with no significant differences in gender ratio between both groups. The 1980 preliminary ACR criteria were fulfilled by 6 and 7 patients with or without previous/current DU (33% vs 7.2%, p=0.006), respectively but the 2013 ACR/EULAR SSc criteria were fulfilled by 7 and 14 patients (41% vs 22%), respectively, and the differences vanished. The mean age at DU appearance was 49±22 years, with a similar follow-up period for ssSSc patients with or without prior/current DU. By univariate analysis, a history of prior/current DU was only associated with lesser incidence of sicca syndrome. No significant differences were identified in organ involvements, autoantibodies' profile, nailfold capillaroscopy pattern, mortality, causes of death and mean survival time from the first symptom in patients with or without history of DU. Survival rates from the first SSc symptom at 5, 10, 20 and 30 years were not different in both groups of patients. All data are summarized in the supplementary tables S5 and S6.

Multivariate associations with digital ulcers.

A logistic regression model including significant associations in univariate analysis was performed for the entire SSc cohort and the cutaneous subsets. Only variables with >75% of the data were included in multivariate analysis, which are summarized in table 3. The independent variables of the SSc series as a whole associated to prior/current digital ulcers were younger age at SSc diagnosis, dcSSc subset, Raynaud's phenomenon, telangiectasia, acro-osteolysis, calcinosis cutis, ILD, and higher mortality from all causes. The multivariate analysis of the three cutaneous subsets, independent variables associated to prior/current DU were as follows: *1) in dcSSc subset*, patients were younger at SSc diagnosis with more prevalence of telangietasies and calcinosis cutis, and lesser occurrence of non-SSc pattern on nailfold capillaroscopy; *2) in lcSSc subset*, patients were younger at SSc diagnosis, Raynaud's phenomenon, calcinosis cutis, ILD, and higher mortality from all causes; and *3) in ssSSc subset*, patients were younger at first SSc symptom with higher mortality from all causes.

DISCUSION

In this cross-sectional analysis of 1326 SSc patients recruited in a large ongoing Spanish multicenter registry named RESCLE, prior or current DU were recorded in 41.6% of the series. By univariate analysis of the database, many differences have been identified between patients with or without history of DU including peripheral and visceral vascular manifestations, organ involvements, immunologic profile, capillaroscopy patterns and prognosis. However, multivariate analysis only confirmed that prior/current DU in SSc patients were associated to younger age at SSc diagnosis, higher prevalence of dcSSc subset, development of peripheral vascular manifestations such Raynaud phenomenon, telangiectasia and acro-osteolysis as well as development of calcinosis cutis and ILD. The elapsed time from first SSc symptom to the DU appearance and SSc diagnosis was lesser in dcSSc compared to lcSSc and ssSSc patients but it was not different between the last subsets, in accordance with some studies [8, 12]. History of DU was an independent predictor of poorer survival related to higher risk of death from all causes, SSc and non-SSc related.

The prevalence of prior/current DU observed in this study was high and consistent with that reported in previous studies [5, 10, 21-26]. At SSc diagnosis, patients with prior/current DU were younger than patients never affected, regardless of whether they were affected by dcSSc or lcSSc. ssSSc patients were younger at first SSc symptom but not significantly younger at SSc diagnosis, a finding probably related to the small number of ssSSc patients with DU included in our series as occurs in others [12, 13]. There was no difference in the mean time from the first SSc symptom to diagnosis. Thus, the absence of DU in patients suspected to have SSc did not delay that diagnosis. Women were predominant in the entire series of SSc and also in the assessed cutaneous subsets, regardless of the history of DU. In this sense, we did not find difference in the incidence of males in patients with prior/current DU, neither in the series as a whole, suggested by some authors, nor in the cutaneous subsets [10, 22]. History of DU was more frequent in dcSSc than in lcSSc patients, in agreement with many studies [5, 8, 21-23, 27, 28], and more frequent in both subsets than in ssSSc patients [figure 1]. Probably, it reflects that the extension of the cutaneous sclerosis is an important factor leading to the peripheral ischemic vascular complications [5, 22]. Smoking status and systemic arterial hypertension are arterial risk factors that were not significantly associated to the occurrence of DU in our study. It remains possible that their presence

is not able to promote digital ulcers in SSc patients but it may aggravate outcomes. Interestingly, patients with prior/current DU had lesser prevalence of systemic arterial hypertension, probably because these patients were chronically treated 4 more times with some of the potent vasodilators (endothelin receptor antagonists, phosphodiesterase type 5 inhibitors and/or prostaglandin analogs).

DU have been considered as a possible marker of vascular damage [3, 29]. As expected, our study showed that the presence of prior/current DU in SSc patients was associated to some peripheral vascular manifestations such as Raynaud's phenomenon, telangiectasia, and acro-osteolysis even though they were not associated to any visceral vasculopathy. Thus, although univariate analysis identified a higher incidence of PH, ischemic myocardiopathy, and scleroderma renal crisis, these differences vanished in the multivariate analysis, in accordance with some studies [22, 30]. It is stated that the reduction of the nailfold capillary density is correlated with the severity of PAH [31, 32] and the diminution of the capillary density that exceeds the threshold of a validated capillaroscopy risk index is able to identify patients at risk of developing DU [26]. Both findings suggest an association between the peripheral and systemic microvascular changes [3]. However, although PH has been associated to the presence of DU in some clinical studies [10, 21] it was not confirmed in others [5, 22, 24, 30]. Surprisingly, we observed in our study a trend to lower incidence of PAH in patients with SSc and DU that was also identified in the dSSc and lcSSc subsets. One could argue that it may be related to the higher rate of treatment with potent vasodilators recorded in patients with DU which could delay and/or ameliorate the pulmonary vasculopathy, as suggested by preliminary data [33]. In that series, the only musculoskeletal manifestation independently associated to DU in SSc patients was calcinosis cutis, in accordance with the results by Avouac et al [34]. Moreover, this association was also found in patients classified as dcSS and lcSSc but not in ssSSc patients supporting the hypothesis that digital ulcers in SSc are associated to the extent of the skin sclerosis as well as the appearance and progression of calcinosis. It highlights a potential role of the vascular ischemia and injury in the pathogenesis of calcinosis [8, 34].

Some authors reported that DU are associated to some organ involvements along the course of SSc, in particular pulmonary and gastrointestinal systems [6, 10, 21, 24, 30]. Moreover, a recent study reported that visceral dysfunction may appear very early in the disease related to the DU occurrence [6]. Our results are in agreement with the reported data and show that SSc patients with prior/current DU, and particularly patients with

lcSSc subset, have more prevalence of ILD. This organ involvement could have an impact on prognosis.

In agreement with other series, anti-Topoisomerase I antibodies were more frequent in patients with prior/current DU [8, 21, 22, 24, 27, 28, 30, 35] and the detection of a worse scleroderma pattern on nailfold capillaroscopy was associated to severe ischemic peripheral vascular disease [25, 26] in the univariate analysis. Notwithstanding, both findings were not found as independent factors in the multivariate analysis, probably because the prevalence of dcSSc subset was significantly higher in patients with ulcerative digital vasculopathy and this fact may encompass by itself many clinical, immunological, and capillaroscopy features identified in the univariate analysis. A non-SSc pattern was found a rare event in SSc patients with history of DU in our study, in accordance with the literature [25, 26, 36]. Curiously, some authors have described a relationship between the presence of antiphospholipid antibodies and digital ulcers as well as other vascular manifestations [37] but this statement was not confirmed by our large series.

It is well recognized that mortality is increased in patients with SSc and some clinical manifestations have acquired a significant impact on it, mainly pulmonary involvement [38]. Nowadays, DU have also been identified as an independent predictor of mortality [10, 39]. Noteworthy, results from our large database confirm that DU occurrence in SSc patients is a predictor of a poorer survival with 1.85-fold more deaths from all causes in comparison of patients without history of DU. This increased mortality was also observed in patients classified as lcSSc and ssSSc but not in the dcSSc subset. When detailed data on causes of death were stratified as SSc-related and non-SSc related, no significant difference was observed in mortality between patients with or without history of DU despite a wide mean follow-up that seems enough to allow an accurate detection of predictive factors of death. Cumulative survival from the first SSc symptom has been estimated by Kaplan-Meyer in the entire series and according to the cutaneous subsets. Mean survival time of the entire SSc cohort with history of DU at 30-year was 57.7%, significantly lower than 73.5% of those never affected, as reflected in table 2 and figure 2a but we could not found differences in survival among the cutaneous subsets.

Strengths of the present study include that this series is a large multicentre cohort of Spanish SSc patients derived from the same geographic location, and the long term follow-up period, given the relative low prevalence of that illness. Cohort studies allow

easier identification of disease related manifestations and predictors of developing a determinate course of the illness, supplying data that allows studying outcomes for each exposure. However, such cohorts usually have some limitations such as missing data, loss to follow-up and inability to distinguish the categories of DU in the database as occurred in the RESCLE registry and others.

In spite of these limitations, our data demonstrate that DU develop in patients with SSc younger at diagnosis, mainly in patients with diffuse cutaneous sclerosis and they are associated to other peripheral vascular manifestations such Raynaud's phenomenon, telangiectasia, and acro-osteolysis but also to calcinosis, and interstitial lung disease. DU occurrence in SSc patients predicts worse survival from all causes of death, also noticeable for lcSSc and ssSSc subsets. Therefore, early identification of the peripheral ischemic vasculopathy is essential in order to initiate an appropriate treatment of this painful and disabling clinical manifestation and also to carefully assess any organ involvement that could be implicated in disease prognosis.

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Table 1. Demographic and clinical characteristics of 1326 SSc patients, with or without prior/current digital ulcers*.

Demographic data and clinical characteristics n (%)	**SSc patients entire series** 1326 (100%)	**Never digital ulcers** 774 (58.4%)	**Prior or current digital ulcers** 552 (41.6%)	**Univariate analysis O.R (95% C.I.)**	**p**
Female gender, n (%)	1181 (89%)	698 (90%)	483 (88%)	0.76 (0.54-1.08)	0.12
Criteria fulfillment for SSc:					
1980 preliminary ACR (N= 1315)	832 (63%)	350 (46%)	482 (88%)	8.55 (6.38-11.5)	<0.001
2013ACR/EULAR (N= 1198)	1078 (90%)	554 (85%)	524 (96%)	4.21 (2.61-6.79)	<0.001
SSc subtypes: (N= 1322)					
Diffuse cutaneous SSc, n (%)	331 (25%)	123 (16%)	208 (38%)	3.21 (2.48-4.16)	<0.001
Limited cutaneous SSc, n (%)	793 (60%)	486 (63%)	307 (56%)	0.74 (0.59-0.93)	0.009
SSc sine scleroderma, n (%)	118 (8.9%)	99 (13%)	19 (3.3%)	0.24 (0.15-0.40)	<0.001
pre-SSc, n (%)	80 (6.1%)	64 (8%)	16 (2.7%)	0.33 (0.19-0.58)	<0.001
Time of follow-up, mean ± SD, years	14±12	13 ± 12	15 ± 12		0.007
Age at digital ulcer, mean ± SD, years	50 ± 16	---	50 ± 16		
Age at first SSc symptom, mean ± SD, years	45 ± 16	48 ± 16	42 ± 16		<0.001
Age at SSc diagnosis, mean ± SD, years	52 ± 15	54 ± 14	49 ± 16		<0.001
Time from first SSc symptom to SSc diagnosis ± SD, years	6.4 ± 9.0	6.6 ± 9.1	6.2 ± 8.8		0.488
Raynaud's phenomenon as first manifestation, n (%) (N= 1214)	998 (82%)	588 (81%)	410 (84%)	1.30 (0.96-1.77)	0.089
Smoking history					
Current smoker, n (%) (N= 900)	104 (12%)	63 (12%)	41 (11%)	0.88 (0.78-1.33)	0.539
Smoked ever, n (%) (N= 900)	161 (18%)	89 (17%)	72 (19%)	1.13 (0.80-1.60)	0.479
Never smoked, n (%) (N= 900)	635 (71%)	368 (71%)	267 (70%)	0.98 (0.73-1.30)	0.869
Systemic arterial hypertension, n (%) (N= 909)	300 (33%)	192 (36%)	108 (28%)	0.70 (0.52-0.93)	0.013
Peripheral vascular manifestations:					
Raynaud's phenomenon, n (%) (N= 1319)	1260 (96%)	722 (94%)	538 (98%)	4.14 (2.02-8.49)	<0.001
Telangiectasies, n (%) (N= 1321)	794 (60%)	403 (52%)	391 (71%)	2.25 (1.78-2.83)	<0.001
Acro-osteolysis, n (%) (N= 1061)	94 (8.9%)	24 (4.1%)	70 (15%)	4.12 (2.55-6.66)	<0.001
Digestive involvement:					
Esophagus, n (%) (N= 1307)	794 (61%)	425 (56%)	369 (68%)	1.66 (1.32-2.09)	<0.001
Gastrointestinal, n (%) (N= 1307)	267 (20%)	141 (19%)	126 (23%)	1.32 (1.01-1.74)	0.041
Hepatic, n (%) (N= 1301)	94 (7.2%)	56 (7.4%)	38 (7.0%)	0.95 (0.62-1.46)	0.825
Lung involvement					
Interstitial lung disease, n (%) (N= 1323)	573 (43%)	278 (36%)	295 (54%)	2.05 (1.64-2.56)	<0.001
FVC, %, mean ± SD (N= 1094)	85 ± 22	87 ± 22	82 ± 23		<0.001
FVC < 70%, n (%) (N= 1094)	273 (25%)	135 (22%)	138 (29%)	1.44 (1.09-1.89)	0.009
DLCO/VA, %, mean ± SD (N= 975)	71± 23	73 ± 22	69 ± 24		0.007
DLCO/VA <70%, n (%) (N= 975)	433 (44%)	224 (41%)	209 (48%)	1.34 (1.04-1.72)	0.026
Pulmonary hypertension, n (%) (N= 1121)	259 (23%)	132 (21%)	127 (26%)	1.35 (1.02-1.78)	0.035
Pulmonary arterial hypertension, n (%) (N= 1139)	72 (6.3%)	47 (7.3%)	25 (5.1%)	0.68 (0.41-1.12)	0.126
sPAP, mm Hg, mean ± SD (N= 791)#	37 ± 18	36 ± 18	39 ± 19		0.081
sPAP>40 mm Hg, n (%) (N= 791)#	224 (28%)	109 (26%)	115 (32%)	1.36 (0.99-1.85)	0.053
Heart involvement:					
Pericarditis, n (%) (N= 843)	60 (7.1%)	34 (7.1%)	26 (7.2%)	1.01 (0.60-1.72)	0.965
Ischemia, n (%) (N= 844)	108 (13%)	51 (11%)	57 (16%)	1.56 (1.04-2.34)	0.030
Conduction alteration, n (%) (N=841)	145 (17%)	80 (17%)	65 (18%)	1.01 (0.76-1.57)	0.633

LVEF, %, mean ± SD (N= 882)	64 ± 10	65 ± 10	63 ± 10		0.018
Musculoskeletal involvement:					
Calcinosis cutis, n (%) (N= 1319)	275 (21%)	96 (13%)	179 (33%)	3.40 (2.57-4.49)	<0.001
Arthritis, n (%) (N= 1065)	199 (19%)	98 (17%)	101 (21%)	1.36 (1.00-1.86)	0.049
Miopathy, n (%) (N= 1065)	136 (13%)	63 (11%)	73 (15%)	1.53 (1.06-2.19)	0.021
Tendon friction rubs, n (%) (N= 1063)	61 (5.7%)	27 (4.6%)	34 (7.2%)	1.63 (0.97-2.74)	0.064
Flexion contractures, n (%) (N= 825)	177 (22%)	45 (9.4%)	132 (38%)	5.87 (4.03-8.54)	<0.001
Renal involvement:					
Scleroderma renal crisis, n (%) (N= 913)	34 (3.7%)	11 (2.2%)	23 (5.5%)	2.59 (1.25-5.37)	0.008
Sicca syndrome, n (%) (N=1317)	426 (32%)	247 (32%)	179 (33%)	1.03 (0.82-1.30)	0.805

OR (95% CI): odds ratio, and 2-sided 95% confidence interval of the mean, SSc: systemic sclerosis; FVC, forced vital capacity; DLCO/VA, diffusing capacity for carbon monoxide corrected by alveolar volume. sPAP: systolic pulmonary arterial pressure; LVEF: left ventricular ejection fraction.

*: All data derived from 1326 patients except when indicated (N=). #: total of echocardiograms with estimated sPAP.

Table 2. Immunological features, nailfold capillaroscopy characteristics, cause of death and survival of 1326 SSc patients, with or without prior/current digital ulcers*.

Autoantibodies, nailfold capillaroscopy, and survival n (%)	**SSc patients** 1326 (100%)	**Never digital ulcers** 774 (58.4%)	**Prior or current digital ulcers** 552 (41.6%)	**Univariate analysis O.R (95% C.I.)**	**p**
Autoantibodies:					
ANA positive (N= 1324)	1203 (91%)	692 (90%)	511 (93%)	1.44 (0.97-2.14)	0.068
ACA positive (N= 1179)	532 (45%)	341 (51%)	191 (38%)	0.59 (0.46-0.74)	<0.001
Anti-Topoisomerase positive (N= 1197)	266 (22%)	130 (19%)	136 (27%)	1.53 (1.16-2.01)	0.002
Anti-RNA polimerase III positive (N= 161)	26 (16%)	10 (11%)	16 (22%)	2.26 (0.95-5.34)	0.060
Anti-Ku positive, (N= 222)	10 (4.5%)	8 (6.7%)	2 (2.0%)	0.28 (0.06-1.35)	0.092
Anti-Pm-Scl positive (N= 651)	48 (7.4%)	22 (6.1%)	26 (8.9%)	1.51 (0.86-2.72)	0.170
Anti-U1 RNP positive (N= 1161)	67 (5.8%)	40 (6.0%)	27 (5.5%)	0.91 (0.55-1.50)	0.701
Anti-Ro positive (N= 1181)	159 (14%)	91 (13%)	68 (14%)	1.03 (0.74-1.45)	0.851
Anti-La positive (N= 1174)	36 (3.1%)	23 (3.4%)	13 (2.6%)	0.77 (0.39-1.54)	0.461
Anti-cardiolipin positive (N= 788)	78 (9.9%)	51 (11%)	27 (8.1%)	0.69 (0.42-1.13)	0.137
Nailfold capillaroscopy performed, n (%)	998 (91%)	593 (93%)	405 (88%)		
Slow pattern, n (%)	499 (51%)	302 (51%)	197 (49%)	0.91 (0.70-1.17)	0.450
Active pattern, n (%)	343 (35%)	165 (28%)	178 (44%)	2.03 (1.56-2.65)	<0.001
Non-SSc pattern, n (%)	147 (15%)	120 (20%)	27 (6.7%)	0.28 (0.18-0.44)	<0.001
Death from all causes	225 (17%)	103 (13%)	122 (22%)	1.85 (1.39-2.47)	<0.001
Causes of death:					
Interstitial lung disease	25 (11.1%)	13 (12.6%)	12 (9.8%)	0.76 (0.33-1.74)	0.508
Pulmonary hypertension	36 (16.0%)	16 (15.5%)	20 (16.4%)	1.07 (0.52-2.18)	0.861
Interstitial lung disease and pulmonary hypertension	21 (9.3%)	5 (4.9%)	16 (13.1%)	2.96 (1.05-8.38)	0.034
Scleroderma renal crisis	17 (7.6%)	8 (7.8%)	9 (7.4%)	0.95 (0.35-2.55)	0.912
Ischemic cardiopathy	6 (2.7%)	1 (1.0%)	5 (4.1%)	4.36 (0.50-38)	0.223
Other causes not related to SSc	114 (51%)	53 (52%)	61 (50%)	0.94 (0.56-1.59)	0.828
Unknown	13 (5.8%)	9 (8.7%)	4 (3.3%)	0.35 (0.11-1.19)	0.080
Deaths related to SSc, n (%) (N= 212)	106 (50.0%)	44 (47%)	60 (56%)	1.40 (0.73-2.17)	0.407
Mean survival time from first SSc symptom, (95% C.I.), years	42 (39-45)	46 (42-51)	37 (33-40)		0.007
Median survival time from first SSc symptom, (95% C.I.), yea	40 (35-46)	46 (38-54)	36 (32-40)		0.007
5 years	0.955	0.959	0.952	-	0.656
10 years	0.912	0.924	0.900	-	0.220
20 years	0.792	0.815	0.770	-	0.167
30 years	0.653	0.735	0.577	-	0.013

ANA: antinuclear antibodies; ACA: anticentromere antibodies; SSc: systemic sclerosis

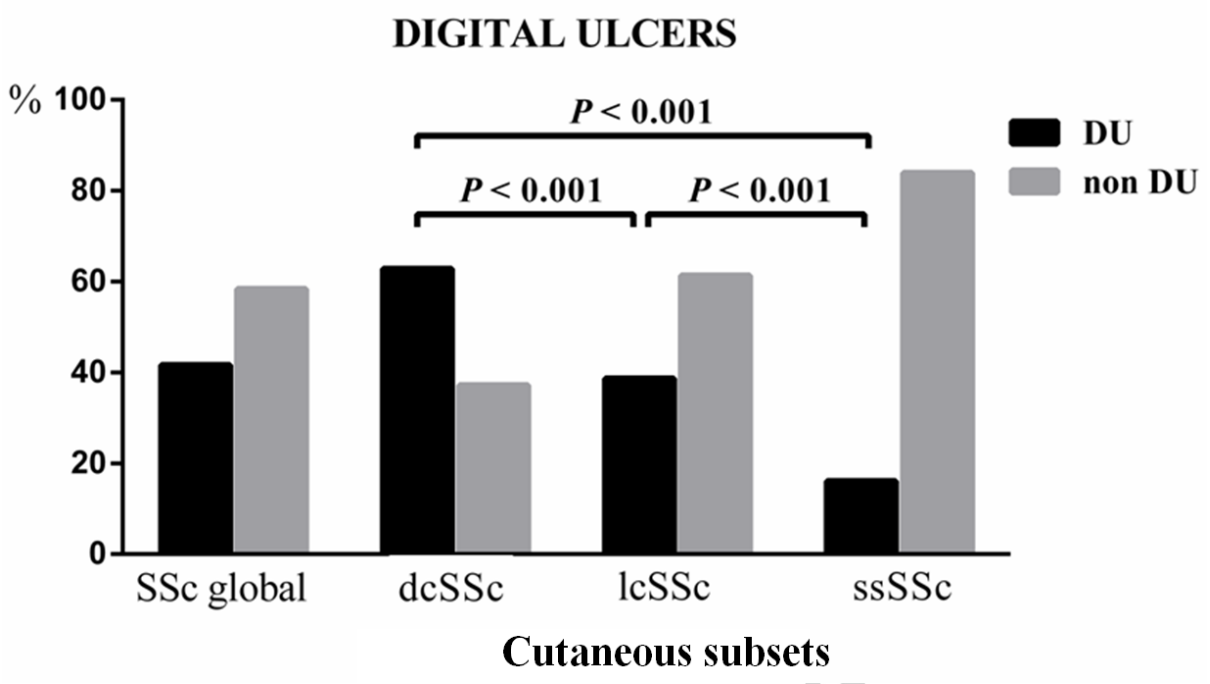
*: All data derived from 1326 patients except when indicated (N=).

Table 3. Multivariate analysis of SSc patients and the cutaneous subsets, according to the presence or absence of prior/current digital ulcers. Only variables with >75% of the data were included in the model.

SSc patients, patients evaluated (%)	**O.R (95% C.I.)**	**p**
SSc patients, n: 940 (71%):		
Age at SSc diagnosis	0.97 (0.96-0.98)	<0.001
Diffuse cutaneous SSc	3.27 (2.20-4.85)	<0.001
Raynaud's phenomenon	4.61 (1.78-11.96)	0.002
Telangiectasies	1.90 (1.39-2.60)	<0.001
Acro-osteolysis	4.17 (2.04-8.54)	<0.001
Calcinosis cutis	2.89 (1.99-4.20)	<0.001
Interstitial lung disease	1.74 (1.27-2.39)	0.001
Death from all causes	1.80 (1.20-2.70)	0.004
dcSSc patients, n: 211 (63.7%):		
Age at SSc diagnosis	0.97 (0.95-0.99)	0.003
Telangiectasies	3.43 (1.78-6.62)	<0.001
Calcinosis cutis	3.99 (1.61-9.89)	0.003
Non SSc Pattern	0.15 (0.04-0.58)	0.006
lcSSc patients, n: 769 (97%):		
Age at SSc diagnosis	0.98 (0.97-0.99)	<0.001
Raynaud's phenomenon	7.18 (2.04-25.2)	0.002
Calcinosis cutis	2.68 (1.88-3.84)	<0.001
Interstitial lung disease	1.63 (1.18-2.25)	0.003
Death from all causes	2.13 (1.38-3.28)	0.001
ssSSc patients, n: 106 (87.6%):		
Age at first SSc symptom	0.96 (0.93-0.99)	0.15
Death from all causes	9.67 (2.02-46.28)	0.005

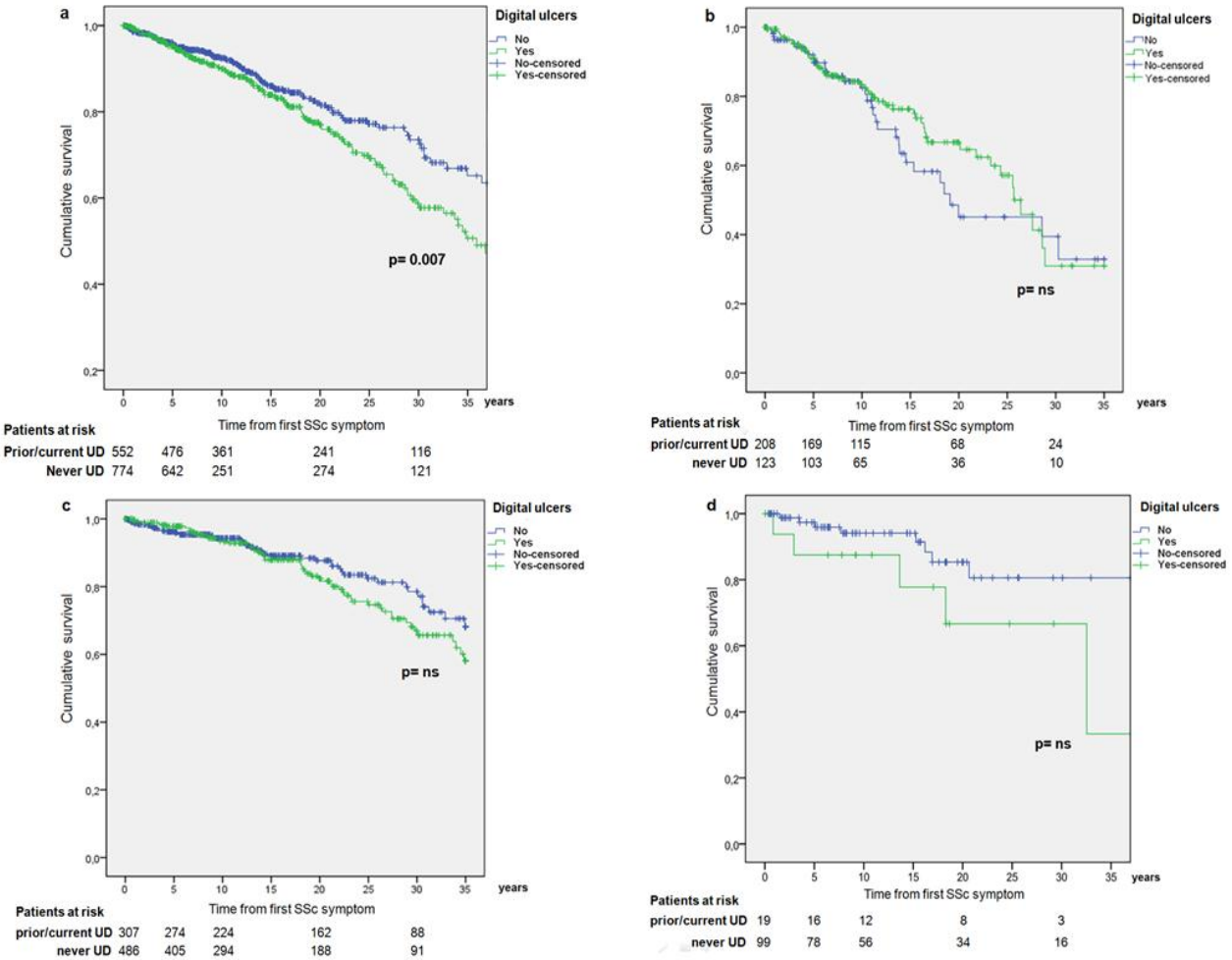
SSc: systemic sclerosis; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; ssSSc: SSc sine scleroderma.

Figure 1. Incidence of previous/current digital ulcers in patients with systemic sclerosis and the cutaneous subsets.



SSc: systemic sclerosis; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; ssSSc: SSc sine scleroderma.

Figure 2. Kaplan–Meier survival for patients with or without previous/current digital ulcers in (a) the entire SSc series and the following cutaneous subsets: (b) diffuse cutaneous SSc (c) limited cutaneous SSc, and (d) SSc sine scleroderma.



***Appendix**:*

RESCLE Registry members:

Boldova R, Callejas JL, Castillo MJ, Castro A, Colunga D, Egurbide MV, de Escalante B, de la Colina G, Espinosa G, Fernández de la Puebla RA, Fonollosa V, Freire M, García-Hernández F, Guillén A, Hurtado R, Iniesta N, Madroñero AB, Marí B, Marín A, Márquez-Fernández V, Morales M, Morera ML, Muela A, Ortego-Centeno N, Pla X, Pons I, Ríos-Blanco JJ, Rodríguez-Carballeira M, Rubio M, Ruiz M, Sáez L, Salvador G, Sánchez S, Simeón CP, Soto A, Sousa A, Todolí JA, Tolosa C, Trapiella L, Vargas JA.

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