
An observational cohort study of patients with newly diagnosed digital ulcer disease secondary to systemic sclerosis registered in the EUSTAR database

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ABSTRACT

Objective. *This study describes clinical characteristics, prognostic factors, and quality of life in patients with newly diagnosed (incident) digital ulcers (DU).*

Methods. *Observational cohort study of 189 consecutive SSc patients with incident DU diagnosis identified from the EUSTAR database (22 centres in 10 countries). Data were collected from medical charts and during one prospective visit between 01/2004 and 09/2010.*

Results. *Median age at DU diagnosis was 51 years, majority of patients were female (88%), and limited cutaneous SSc was the most common subtype (61%). At incident DU diagnosis, 41% of patients had one DU and 59% had ≥ 2 DU; at the prospective visit 52% had DU. Pulmonary arterial hypertension (PAH) and multiple DU at diagnosis were associated with presence of any DU at the prospective visit (odds ratios: 4.34 and 1.32). During the observation period (median follow-up was 2 years) 127 patients had ≥ 1 hospitalisation. The event rate of new DU per person-year was 0.66, of DU-associated complications was 0.10, and of surgical or diagnostic procedures was 0.12. At the prospective visit, patients with ≥ 1 DU reported impairment in daily activities by 57%, those with 0 DU by 37%. The mean difference between patients with or without DU in the SF-36 physical component was 2.2, and in the mental component 1.4. DU patients were not routinely prescribed endothelin receptor antagonists or prostanoids.*

Conclusion. *This real world cohort demonstrates that DU require hospital admission, and impair daily activity. PAH and multiple DU at diagnosis were associated with future occurrence of DU.*

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease characterised by an occlusive vasculopathy of small arteries with intimal hyperplasia and endothelial dysfunction (1). Patients with SSc develop digital ulcers (DU) as a clinical correlate of this macroangiopathy, although repetitive microtrauma, pressure, and calcinosis have been also implicated (2). DU are painful, necrotic lesions located at the distal tips of digits or overlying bony prominences, are typically slow to heal and are often complicated by infections (3, 4). Up to one-half of patients with SSc will develop DU at some time during their disease (5) and among these almost three-quarters will have developed their first ulcer within 5 years of SSc diagnosis (6). Severe digital vasculopathy contributes significantly to the morbidity of SSc patients (7).

Therapeutic options are limited in DU. Calcium channel blockers form the mainstay of vasodilator therapy, while intravenous prostacyclin, specifically intravenous iloprost, and phosphodiesterase-5 (PDE-5) inhibitors are currently used empirically as treatment or for prophylaxis (8–10). Bosentan, an endothelin receptor antagonist (ERA), is indicated to reduce the number of new DU in patients with SSc and ongoing DU disease and its efficacy and safety have been demonstrated in 2 randomised controlled trials (11, 12). Further management of DU often results in the chronic use of analgesics and antibiotics, as at least 50% of DU become superficially infected (4). A small but significant number of patients will develop more serious complications such

as gangrene or osteomyelitis, and ultimately require hospitalisation and possibly surgery (including digital amputation) (2, 13). Thus, DU and their complications may lead to significant utilisation of healthcare and non-healthcare resources and heavily impact on the patient's quality of life.

Studies in a number of SSc patient cohorts have identified common risk factors for the presence of DU (*e.g.* DU prevalence) (14), including early onset of Raynaud's phenomenon (15, 16) or SSc (6, 17, 18), high modified Rodnan skin score (mRSS) (6, 17, 18) and presence of anti-scleroderma-70 (SCL-70) antibodies (13, 15-18). To date, however, there have been no published analyses on a cohort of patients with newly diagnosed DU (*i.e.* incident DU), and multinational data on the burden of DU and associated healthcare resource utilisation are scarce.

The aim of this multinational cohort study was to describe the clinical characteristics, treatment patterns, healthcare resource utilisation, quality of life, and functional status of patients with newly diagnosed DU. Clinical risk factors associated with future occurrence of DU were also investigated.

Patients and methods

Study design and patients

This observational multinational cohort study included SSc patients from the Minimal Essential Data Set (MEDS) owned by the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) group (15). Patients in the EUSTAR database newly diagnosed by a physician with a first DU (incident DU diagnosis), defined as loss of epithelialisation (3), were potentially eligible. Between January 1, 2004 and November 30, 2009 patients were enrolled in the study if they also had at least two of the following criteria: positive antinuclear antibody (ANA) (EUSTAR definition: above upper limit of normal), Raynaud's phenomenon, abnormal capillaroscopy pattern, or puffy fingers. Ethics approval and patient informed consent were covered by the umbrella EUSTAR ethics approval (15).

In consecutive patients, data were col-

lected from time of incident DU diagnosis until the last visit recorded in the medical charts, up to January 30, 2010. Each patient was invited to attend a single prospective visit at least 3 months after the last visit recorded in the medical chart, to capture the most current disease status and to perform quality of life and functional assessments. The last prospective visit was recorded on September 28, 2010; this date was the end of the variable observation time; observation time per patient was the time from incident DU diagnosis to the single prospective visit. Disease characteristics at incident DU diagnosis were recorded from medical chart information using a specifically designed web-based Case Report Form as close as possible to the date of incident DU diagnosis within a 6-month window (from 4 months prior, to 2 months after DU diagnosis). Data recorded outside of this window were deemed missing.

Data collection

Data collection included patient demographics and SSc disease characteristics, employment status, smoking behaviour, DU characteristics, DU associated events (*e.g.* gangrene, autoamputation, soft tissue infection), and interventions (*e.g.* diagnostic procedure, surgical amputation, sympathectomy, debridement), therapies, and hospitalisations. Information on SSc disease manifestations such as internal organ involvement, or pulmonary arterial hypertension (PAH) (defined as per EUSTAR requirements (15) as an estimated pulmonary arterial systolic pressure equal to or above 40 mmHg by Doppler echocardiography), and pulmonary function tests (forced vital capacity; FVC) were also collected. Information on whether a PAH diagnosis was confirmed by right heart catheterisation was not requested.

Quality of life and functional assessment

Patients were asked to complete the 36-item Short Form Health Survey version 2 (SF-36) (19) and a Functional Assessment Questionnaire (15) at the prospective visit.

The SF-36 self-administered question-

naire covers 8 domains: physical functioning, physical role, bodily pain, general health perception, mental health, vitality, emotional role, and societal functioning. For each domain, the score ranges from 0 (worst health status) to 100 (best health status). The scores are also summarised in 2 component scores: the physical component (PCS) and the mental component score (MCS) (20).

In the Functional Assessment Questionnaire, the patients were asked about their employment status (employed, self-employed, unemployed), the impact of DU on work status (missed work, normal working hours per week, the hours missed due to DU), the impairment of productivity at work due to DU, as well as daily activity (non-work) impairment due to DU during the previous month. Patients were also asked to report if they needed help from others due to their DU during the previous month and, if yes, the hours of help needed and whether it was paid or unpaid help. The impairment was scored on a semi-quantitative scale from 0 (had no effect on work/daily activities) to 100 (completely prevented from working/ daily activities). Overall work impairment was based on the numbers of hours the patient normally works.

Statistics

Only patients who attended a prospective visit were included in the analyses. The analyses of the SF-36 or Functional Assessment Questionnaire only included patients who completed these assessments. All data analyses were exploratory. Continuous variables were summarised using the mean, standard deviation (SD), median, 95% confidence interval (CI), and range. Categorical variables were described as counts and percentages, with the percentage denominator being the number of patients with information available for the respective variable.

Outcome data collected at the prospective visit were attributable to the time between the last visit recorded in the medical charts to the date of the prospective visit. To account for variable observation times, outcomes were also expressed as rates per patient-year.

Univariable logistic regression models were conducted to determine factors that were associated with the risk of developing DU at their prospective visit, including 95% Wald CI for the odds ratio for each factor. SF-36 descriptive statistics were calculated using scores normalised to a mean of 50, SD, and 95% CI of the mean.

A post-hoc comparison of demographic and disease characteristics between eligible patients who were enrolled and analysed in this study *versus* patients from the EUSTAR database who were eligible but were not enrolled was also conducted to determine whether patients enrolled and analysed in this study were a representative population of all SSc patients with newly diagnosed DU in the EUSTAR database. For categorical as well as continuous data, differences in proportions and means (including 95% CI) were estimated using Wald's method under the assumption of approximation to the normal distribution. DU characteristics at the prospective visit were described and stratified by the presence of 1 DU or ≥ 2 DU at incident DU diagnosis. Other results were presented stratified by the presence of 0 DU or ≥ 1 DU at the prospective visit. Mean differences (95% CI) between groups were estimated using the approximation to the normal distribution.

Results

Patient disposition

Twenty-two EUSTAR centres in 10 countries (Egypt, France, Germany, Hungary, Italy, Romania, Serbia, Spain, South Africa, and Switzerland) participated in this study. Between January 1, 2004 and November 30, 2009, 867 patients were newly diagnosed with a first DU and were eligible for inclusion. Of these 867 patients, 207 were enrolled, and 189 (Italian centres, n=121) attended a prospective visit and were therefore included in the analyses.

Demographics and disease characteristics

Post-hoc analysis showed similar demographics and disease characteristics among eligible patients who were not enrolled (n=660) and those who were analysed (n=189; Table I).

Table I. Patient demographics and disease characteristics of the study population analysed and potentially eligible patients who were not enrolled.

Characteristics	Potentially eligible patients n=867*		Difference between groups (95% CI)
	Enrolled and analysed n=189	Not enrolled n=660	
Female, n (%)	167 (88)	575 (87)	0.01 (-0.04, 0.07)
Diffuse SSc, n (%)	68 (36)	275 (42)	
Limited SSc, n (%)	115 (61)	354 (54)	0.07 (-0.01, 0.15)
Other SSc [†] , n (%)	5 (3)	23 (4)	
ACA positive, n (%)	79 (45)	232 (36)	0.08 (0.002, 0.17)
SCL-70 positive, n (%)	79 (44)	299 (46)	-0.21 (-0.11, 0.06)
Mean (SD) age at first DU diagnosis, years	50 (14)	Not available	
Mean (SD) age at onset of Raynaud's, years	40 (15)	40 (15)	0.71 (-1.70, 3.13)
Mean (SD) age at first non-Raynaud's [‡] , years	43 (15)	45 (14)	1.64 (-0.86, 4.14)

The information provided in this table is based on data from the EUSTAR database, for patients identified with an incident DU diagnosis between January 1, 2004 and November 30, 2009.

*Eighteen patients were enrolled but not analysed as they did not complete a prospective visit.

[†]Other SSc = skin sclerosis distal of metacarpophalangeal joints.

[‡]First non-Raynaud's manifestation is considered to be age of onset of SSc.

SSc: systemic sclerosis; ACA: anticentromere autoantibody; SCL-70: antiscleroderma 70 antibody; DU: digital ulcers; SD: standard deviation.

Table II. DU characteristics at prospective visit stratified by the number of DU at diagnosis.

DU characteristics at prospective visit	Patients with 1 DU at diagnosis n=77	Patients with ≥ 2 DU at diagnosis n=112	Difference between groups (95% CI)
Patients with 0 DU, n (%)	46 (60)	45 (40)	19.6 (5.3, 33.8)
Patients with ≥ 1 DU, n (%)	31 (40)	67 (60)	Not applicable
Median (range) of total number of DU	0 (0–12)	1 (0–36)	1.0 (0.0, 2.0)
Median (range) of new DU per patient	0 (0–8)	0 (0–7)	Not applicable
Total number of new DU (all patients)	50	62	Not applicable
New DU event rate per person-year	0.8	0.6	Not applicable

DU: digital ulcers; SD: standard deviation; CI: confidence interval.

For the patients included in this study, at the time of incident DU diagnosis, the median body mass index was 24 (range 15, 38) kg/m²; 31 (16%) patients were current smokers, 28 (15%) were former smokers and 125 (66%) had never smoked. No occupational risk factors were documented in 161 (99%) patients; one patient was exposed to solvents and one to glue. PAH was recorded in 29/189 (15%) patients. Only 3/189 patients (2%) had a history of renal crisis at incident DU diagnosis. Other internal organ disease was documented in 127/189 (67%) patients: of these, 91 (72%) had gastrointestinal tract involvement, 23 (18%) had myocardial involvement and 73 (58%) had lung fibrosis. The median FVC at incident DU diagnosis was 92 (range 48, 147, n=143) percent of predicted

and mean was 92 (SD 19.7) percent of predicted. The median mRSS was 10 (range 0, 44, n=156) and the mean was 12.3 (SD 8.6).

DU characteristics at incident DU diagnosis and occurrence of DU at prospective visit

At time of incident DU diagnosis, of the 189 patients, 77 (41%) had 1 DU and 112 (59%) had ≥ 2 DU recorded. The median number of DU (finger and toe) at diagnosis was 2 (range 1–29) and the mean was 2.8 (SD 3.0). One hundred and fifty-one (80%) patients were reported to have only finger DU and 12 (6%) to have only toe DU; 26 patients (14%) had both finger and toe DU at diagnosis. The most common origin of finger DU was classified as ischaemic in 157 (88%) patients, as pressure related

in three (2%), and as calcinosis related in 14 (8%); in three patients the origin was not classified. Among the toe DU, 34 (90%) were classified as ischaemic and as pressure related in 4 (10%).

The median observation period from incident DU diagnosis to the prospective visit was 2 (range 0.4, 6.7) years and the mean was 2.6 (SD 1.85) years.

At the prospective visit, 91 (48%) patients had no DU and 98 (52%) had ≥ 1 DU. The median number of DU (finger and toe) was 1 (range 0–36) and the mean was 1.8 (SD 3.5). The mean annualised change in number of DU from time of incident diagnosis to the prospective visit was -0.9 (95%CI -1.2, -0.6). The median number of new DU at the prospective visit was 0 (range 0–8) and the mean was 0.6, translating into an event rate of 0.66 per person-year. The occurrence of DU at the prospective visit stratified by patients with 1 DU, or ≥ 2 DU at diagnosis is presented in Table II.

Determinants associated with the presence of DU at the prospective visit

Table III displays the demographics and disease characteristics at time of incident DU disease diagnosis of patients with DU present at the prospective visit (n=98) compared with those who had no DU at the prospective visit (n=91). In the univariable logistic regression model, the diagnosis of PAH was associated with the presence of any DU at the prospective visit: odds ratio (95% CI) of 4.34 (1.68, 11.24). A 10% reduction of the FVC predicted was associated with an occurrence of DU at the prospective visit: odds ratio of 1.03 (95% CI 1.01, 1.05). Every additional DU present at diagnosis was also associated with an occurrence of DU at the prospective visit: odds ratio 1.25 (95% CI 1.07, 1.46) (Table III). Smoking, irrespective of former or current smoker status, was not found to be associated with the future occurrence of DU.

DU-associated events, treatment pattern, and hospitalisation
Forty-four (23%) of the 189 patients developed DU-related complications during the observation period, which translates into 0.10 events per person-year of observation. Gangrene was

Table III. Descriptive statistics of patient demographics and disease characteristics at first/ incident DU diagnosis and observation period stratified by the absence or presence of DU at the prospective visit and which were included in the univariable logistic regression modelling to determine their prognostic relevance, displayed as odds ratios (95% CI).

Parameters	Patients with no DU at prospective visit n=91*	Patients with ≥ 1 DU at prospective visit n=98*	Odds ratio (95% CI)
Female, n (%)	77 (85)	90 (92)	2.05 (0.82, 5.14)
Diffuse SSc, n (%)	35 (39)	44 (45)	1.30 (0.73, 2.34)
Limited SSc, n (%)	55 (60)	53 (54)	
Other SSc*, n (%)	1 (1)	1 (1)	Not included in the logistic regression
ACA positive, n (%)	16 (18)	15 (15)	0.73 (0.30, 1.81)
SCL-70 positive, n (%)	13 (14)	23 (24)	2.23 (0.90, 5.54)
Mean (SD) age at onset of Raynaud's, years	40 (15.0)	40 (15.1)	1.00 (0.98, 1.02)
Mean (SD) age at first non-Raynaud's, years	43 (15.4)	43 (14.7)	1.00 (0.98, 1.02)
Mean (SD) age at first DU diagnosis, years	49 (15.2)	51 (13.6)	1.01 (0.99, 1.03)
Mean (SD) time from Raynaud's onset to first DU diagnosis, years	10 (11.3)	11 (9.7)	1.01 (0.98, 1.04)
Mean (SD) time from first non-Raynaud's onset to first DU diagnosis, years	6 (8.9)	7 (6.1)	1.01 (0.97, 1.05)
Mean (SD) observation time, years	2.6 (1.8)	2.6 (1.9)	1.00 (0.85, 1.16)
<i>DU location</i>			
Fingers and toes, n (%)	8 (9)	18 (18)	
Fingers only, n (%)	78 (86)	73 (75)	0.42 (0.17, 1.02)
Toes only, n (%)	5 (6)	7 (7)	0.62 (0.15, 2.57)
Median (range) of total number of DU at first diagnosis	1 (1–10)	2 (1–29)	1 (0.1, 2.1)
<i>Smoking behaviour</i>			
Current, n (%)	16 (17.6)	10 (10.2)	0.51 (0.22, 1.21)
Former, n (%)	17 (18.7)	17 (17.3)	0.82 (0.38, 1.74)
Never, n (%)	58 (63.7)	71 (72.5)	Not applicable
PAH, n (%)	6 (7)	23 (24)	4.34 (1.68, 11.24)
Mean (SD) FVC at incident DU diagnosis, percent of predicted	98 (19.9)	88 (18.3)	1.03 (1.01, 1.05)
Renal crisis, n (%) [†]	0	3 (3)	Unable to calculate

The information provided in the table is based on medical chart data entered into the EUSTAR-DU database; patients with information available were considered.

*Other SSc: skin sclerosis distal of metacarpophalangeal joints.

[†]The validity of the model is questionable due to the small number of patients with a history of renal crisis.

DU: digital ulcers; CI: confidence interval; SSc: systemic sclerosis; ACA: anticentromere autoantibody; SCL-70: antiscleroderma 70 antibody; SD: standard deviation; PAH: pulmonary arterial hypertension; FVC: forced vital capacity.

recorded in 11, autoamputation in 13, and infections requiring systemic antibiotics in 36 patients. Fifty-one (27%) patients required ≥ 1 DU procedure (19 diagnostic procedures, six surgical amputations, 36 debridements), which translates to 0.12 events per person-year of observation.

A substantial proportion of patients received systemic antibiotics, immunosuppressants calcium channel blockers, analgesic/antiinflammatory treatments, or anticoagulants/platelet aggregation inhibitors at incident DU diagnosis and during the observation period (Fig. 1).

With the exception of systemic antibiotics, which tended to be mainly related to DU, these agents were widely prescribed for other reasons in addition to specifically being prescribed for DU. The use of prostanoids, prescribed for DU or other reasons, at incident DU diagnosis and during the observation period was higher than the usage of ERAs (Fig. 1). The use of PDE-5 inhibitors at less than 10% was lower than for prostanoids and ERAs. The usage of ERAs, PDE-5 inhibitors, and prostanoids for DU increased during the observation period.

At the time of incident DU diagnosis, 111 patients required ≥ 1 hospitalisation. The reasons (multiple reasons were possible) were (*n*, %): DU-associated (89, 80%), or associated with other SSc complications (75, 67%). DU-associated procedures at first hospitalisation were recorded in 108 (97%) of the 111 patients: diagnostic procedures (64, 58%); inpatient medical therapy (94, 85%); and surgical procedures (22, 20%). During the observation period, 127, (67%) patients had ≥ 1 hospitalisation (multiple reasons possible), 72% were attributable to DU and 65% to SSc. All 127 patients had DU-associated interventions (multiple reasons possible) during hospitalisation: diagnostic procedures (59, 47%); inpatient medical therapy (119, 94%); and surgical procedures (13, 10%). Of the 127 patients with ≥ 1 (inpatient or ambulatory care or both) hospitalisation, 85 (67%) were hospitalised for >1 day and 62 (49%) had ambulatory care (day case hospitalisations). In both cases the most frequent reasons were DU or SSc associated.

Impact of DU on quality of life

Of the 189 patients, 162 (86%) completed the SF-36 questionnaire. Of the 91 patients with no DU at the prospective visit, 72 (79%) replied, as did 90 (92%) of the 98 patients with ≥ 1 DU. Patients with ≥ 1 DU at the prospective visit showed a decrease on the SF-36 norm-based score in both the PCS, mean difference 2.2 (95% CI -0.6, 5.1), as well as the MCS, mean difference 1.4 (95% CI -2.1, 5.0) compared with those without DU at the prospective visit (Table IV). The largest mean differences (95% CI) in the eight domains were observed in physical 3.9 (0.3–7.5) and social functioning 3.7 (0.6–6.8).

Impact of DU on daily activities and work impairment

Of the 116 patients who completed or partially completed the Functional Assessment Questionnaire at the prospective visit, 114 indicated that their daily activities were impaired by 47% (95% CI 41, 53). Patients with ≥ 1 DU present at the prospective visit reported a higher rate of daily activity impairment

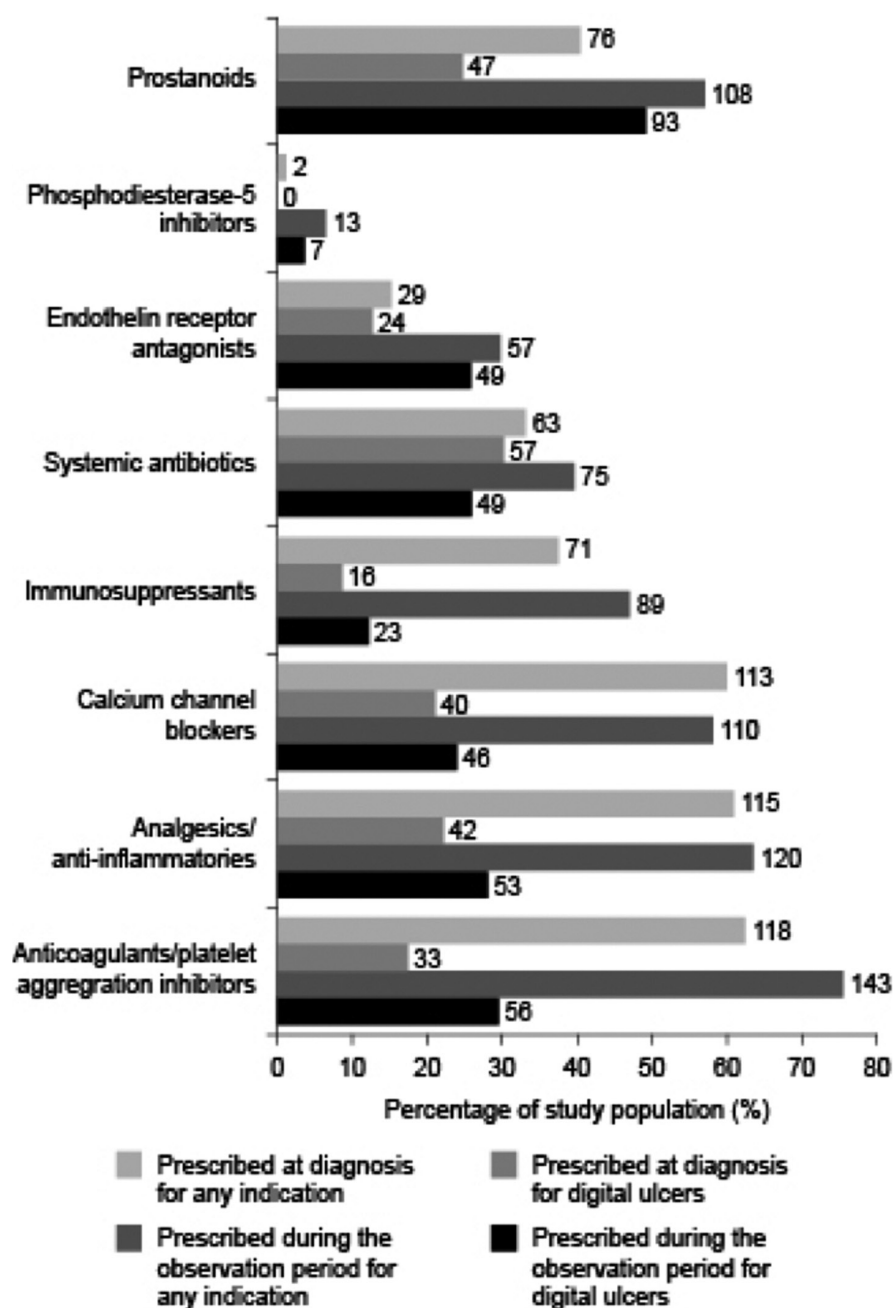


Fig. 1. Drugs most commonly used at digital ulcer diagnosis and during the observation period. The numbers on the top of each bar indicate the absolute numbers of observations.

(58%) than patients with no DU present (34%) (Fig. 2). Need for help in the completion of daily activities was recorded by 33 (53%) patients with ≥ 1 DU at the prospective visit and 18 (34%) patients with no DU at the prospective visit. Among patients with ≥ 1 DU at the prospective visit requiring help, 13 required a mean of 31 hours' paid help in the previous month, and five patients with no DU at the prospective visit required a mean of 19 hours' paid help.

A total of 92 (79%) of the 116 patients who completed or partially completed the Functional Assessment Questionnaire, indicated they were unemployed at the prospective visit while 24 (21%) patients in the workforce reported a mean of 35 working hours (95% CI 30, 40) per week. Seven (29%) of the 24 missed work due to their DU and the mean proportion of missed working time was 43% (95% CI 18, 68). The mean productivity impairment due to DU of these 24 patients was 31% (95%

Table IV. SF-36 norm-based scores summary.

	Patients with no DU at prospective visit n=91	Patients with ≥1 DU at prospective visit n=98	Difference between groups (95% CI)
Physical component	38.6 (36.1, 41.1) n=61	36.4 (34.7, 38.1) n=83	2.2 (-0.6, 5.1) n=144
Mental component	35.5 (32.7, 38.3) n=61	34.1 (31.8, 36.4) n=83	1.4 (-2.1, 5.0) n=144
Physical functioning	38.9 (36.0, 41.9) n=72	35.0 (32.9, 37.2) n=88	3.9 (0.3, 7.5) n=160
Role-physical	34.8 (32.2, 37.5) n=72	33.1 (31.1, 35.1) n=88	1.7 (-1.6, 5.0) n=160
Bodily pain	41.3 (38.9, 43.7) n=72	38.1 (36.2, 40.0) n=90	3.2 (0.2, 6.2) n=162
General health	33.9 (31.7, 36.1) n=61	30.9 (29.3, 32.4) n=87	3.0 (0.4, 5.6) n=148
Vitality	41.0 (38.8, 43.3) n=72	39.1 (37.3, 40.9) n=89	2.0 (-0.9, 4.8) n=161
Social functioning	37.8 (35.3, 40.2) n=72	34.1 (32.1, 36.1) n=90	3.7 (0.6, 6.8) n=162
Role-emotional	32.8 (29.6, 36.0) n=72	30.9 (28.3, 33.4) n=87	2.0 (-2.0, 6.0) n=159
Mental health	37.6 (34.8, 40.4) n=72	34.1 (31.9, 36.2) n=89	3.5 (0.0, 6.9) n=161

All variables are presented as mean (95% confidence interval). DU: digital ulcers.

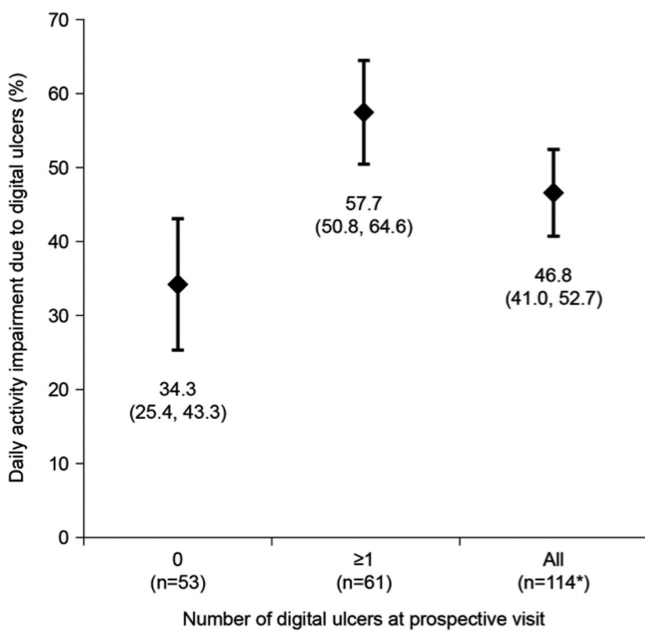


Fig. 2. Mean percent of daily activity impairment due to digital ulcers and by number of digital ulcers at the prospective visit. Error bars indicate 95% confidence interval.

*Of the 116 patients who completed or partially completed the Functional Assessment Questionnaire at the prospective visit, 114 indicated that their daily activities were impaired.

CI 19, 43) and the overall work impairment was 35% (95% CI 21, 49).

Discussion

This study of a cohort of patients from the EUSTAR registry reflects the real-world situation. An important aspect of this study is that, unlike other DU cohorts (13–17) only patients with incident DU disease were included. Thus, our findings expand upon previous work by identifying factors associated with the development of new DU in patients with existing DU secondary to SSc. Our data show that once DU disease manifests, it can reoccur and/or persist over a considerable period of time. The DU event rate of 0.66 per person-year indicates that about

two-thirds of newly diagnosed patients will go on to develop new DU within 1 year. This rate is within the range of 31.4–71.5% found in a systematic review of SSc patients with recurrent digital tip ulceration (21). Furthermore, large randomised, placebo-controlled studies which included over 300 patients suggest that about two-thirds of patients with existing DU develop new DU within 16 to 24 weeks (11, 12). Our cohort study is unique in that it investigated factors associated with the presence of DU at a prospective visit in 189 patients newly diagnosed with DU. In this incident DU cohort the univariable logistic regression model showed that the presence of PAH, and a 10% FVC reduction and additional DU at diagno-

sis were associated with future occurrence of DU. Microvasculopathy is a common factor of DU and PAH which may provide a pathophysiological rationale for this association. In a multivariable analysis, PAH has been shown to be a risk factor in DU development in the German Network for Systemic Scleroderma registry amongst the 1881 SSc patients included in this national registry (16). Although this was not the case in the Canadian Scleroderma Research Group registry which included 938 SSc patients at the time of the analysis (17). Associations with DU and other organ manifestations of SSc, particularly the involvement of the gastrointestinal tract including the oesophagus and mouth, have been reported in other studies (16, 17). However, data on the involvement of the oesophagus were not collected in our study and so an association with DU development could not be evaluated.

Our study did not show SSc subtype or autoantibody status to be associated with a future DU occurrence. The distribution of diffuse SSc and limited SSc subtypes was similar in patients with or without DU at the prospective visit. Previous DU cohorts from national registries which included between 100–2439 patients (3, 13, 14, 16, 17) and international initiatives such as EUSTAR which included 3656 patients reported a higher frequency of DU diagnosis in diffuse SSc (3, 13–17). While most other registries have found in their SSc cohorts an association of SCL-70 positivity with DU development in univariable (17) and multivariable analyses (15, 16, 18), our study shows that in a cohort of patients with incident DU, SCL-70 is not associated with the occurrence of future DU. Young age at the onset of Raynaud’s phenomenon is frequently identified in multivariable analyses as a predictor of new DU occurrence in other studies (15–18), but no association was evident in our study. Together these results suggest that factors associated with the development of DU in patients with SSc may be different to those factors associated with a risk of further DU development in patients once an initial diagnosis of DU has been made.

National studies have retrospectively described the natural history of DU (6). Our combined retrospective and prospective study augments these data into an era during which medications have become available which have the possibility to change the natural course of DU (11, 12). Similar to one national cohort (16), the present study observed that a large proportion of patients do not receive DU-specific medications. Further research may be warranted to better understand physician and patients' use of DU medicines.

Our data found higher hospitalisation rates and lower employment rates compared with previous studies in tertiary care centres. This may be due to varied country practices (6, 7, 22) and demonstrates that SSc patients with DU require frequent hospitalisation and day care. These data extend previous observations which showed that patients with DU need more external home help and more paid and unpaid household help than patients without DU (23). Increasing reliance on others and reduced independence may contribute to the low mental component score of the SF-36 found in patients with DU (23, 24). A previous post-hoc analysis of two prospective studies has demonstrated stable Health Assessment Questionnaire (HAQ) scores if there is no change in DU status and an improved HAQ score in patients with SSc without DU, compared with those with DU, although the changes may not have reached the minimally important difference for the HAQ (25).

Our cohort is multicentred and multinational, includes a prospective visit, focuses on newly diagnosed DU, and the data collection on patient and disease characteristics is very detailed. Therefore, the study design differs from most previous published observations. Nevertheless, data collected from medical charts is subject to recall bias and thus limited interpretation. Minor episodes could have been forgotten by patients between visits, as patients may have seen other physicians in-between visits, or physicians may have inadequately recorded data. The prospective visit attempted to overcome this limitation. Recall bias is, however, likely to un-

derestimate disease burden. Although this cohort has a wide geographical range, the large proportion of Italian patients needs to be considered when interpreting the results. Differences in patient referral and care patterns may account for variability in patient presentation and healthcare resource utilisation (26). We also cannot exclude a centre-specific ascertainment bias due to differences in case documentation. Over one-fifth of potential eligible patients from the EUSTAR database were enrolled and completed the study. However, the similarities between the two groups suggests that the analysed cohort was representative of the larger population, making the data broadly applicable. PAH was confirmed by right heart catheterisation in only a very small proportion of patients in whom PAH was suspected. Additionally, unmeasured confounders may explain SF-36 mean differences observed between patients with and without DU. In conclusion, we have demonstrated that DU is a serious complication of SSc that frequently requires hospital admission, reoccurs, and impairs daily activity. Pulmonary organ involvement and additional DU at diagnosis are associated with the future occurrence of DU.

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