EXTENDED REPORT

Digital ulcers predict a worse disease course in patients with systemic sclerosis

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Handling editor Tore K Kvien

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Received 10 May 2014
Revised 4 November 2014
Accepted 25 January 2015
Published Online First 16 February 2015

ABSTRACT

Objective Systemic sclerosis (SSc) is a systemic autoimmune disease with high morbidity and significant mortality. There is a great need of predictors that would allow risk stratification of patients with SSc and ultimately initiation of treatment early enough to ensure optimal clinical results. In this study, we evaluated whether a history of digital ulcers (HDU) at presentation may be a predictor of vascular outcomes and of overall clinical worsening and death in patients with SSc.

Methods Patients from the EULAR Scleroderma Trials and Research (EUSTAR) database, satisfying at inclusion the 1980 American College of Rheumatology classification criteria for SSc, who had a follow-up of at least 3 years since baseline or who have died, were included in the analysis. HDU at presentation as a predictor of disease worsening or death was evaluated by Cox proportional hazards regression analysis.

Results 3196 patients matched the inclusion criteria (male sex 13.2%, 33.4% diffuse subset). At presentation, 1092/3196 patients had an HDU (34.1%). In multivariable analysis adjusting for age, gender and all parameters considered potentially significant, HDU was predictive for the presence of active digital ulcers (DUs) at prospective visits (HR (95% CI)): 2.41 (1.91 to 3.03), p<0.001, for an elevated systolic pulmonary arterial pressure on heart ultrasound (US-PAPs):1.36 (1.03 to 1.80), p=0.032, for any cardiovascular event (new DUs, elevated US-PAPs or LV failure): 3.56 (2.26 to 5.62), p<0.001, and for death (1.53 (1.16 to 2.02), p=0.003).

Conclusions In patients with SSc, HDU at presentation predicts the occurrence of DUs at follow-up and is associated with cardiovascular worsening and decreased survival.

INTRODUCTION

Systemic sclerosis (SSc) is characterised by skin and internal organ fibrosis, in association with small vessel dysfunction and obliterative changes. While fibrosis is the hallmark of SSc, growing evidence supports the role of the microvasculopathy as the primary pathogenetic event.[1] It has been shown that SSc is the connective tissue disease with the highest mortality.[2] In fact, patients with SSc are at risk for developing life-threatening internal organ involvement such as interstitial lung disease (ILD), pulmonary hypertension, heart failure, severe gastrointestinal involvement and scleroderma renal crisis.[3] Therefore, it is imperative to diagnose and to treat the disease and the involvement of internal organs as early as possible. However, in clinical practice this is a difficult task, in particular because reliable predictors or biomarkers of outcome are still missing. At present, the main strategy is to screen regularly for internal organ involvement, with a frequency that has not been standardised yet. Early aggressive treatment may be of crucial importance, but because of toxicity it is currently restricted to patients in whom clinically significant visceral involvement, in most cases with irreversible damage, has already been documented. For this reason, in SSc, there is an urgent need to identify and validate predictors of disease worsening.

Digital ulcers (DUs) occur rather early in the course of SSc[4 5] and are a good candidate as clinical predictor of disease evolution. In SSc, several cross-sectional studies have found an association between the presence of DUs and more severe disease, as defined by the following: more extensive skin involvement in the SSc diffuse cutaneous subset (dc-SSc),[4 6 7] the presence of pulmonary arterial hypertension,[7] and of ILD.[6 8] Another prospective study showed that patients with SSc with DUs developed organ involvement approximately 2–3 years earlier than patients without DUs.[7] Recently, it has been shown that DUs may herald internal organ involvement also in patients with very early SSc.[5]

These interesting results need to be confirmed in larger cohorts. The EULAR Scleroderma Trials and Research (EUSTAR) cohort is currently the largest prospective SSc cohort in the world.[9 10] The aim of the present work was to use the EUSTAR database to test the hypothesis that a history of DUs (HDU) at the patient's first presentation may predict a worse prognosis characterised by a worse disease course and death.

METHODS

All patients satisfying at inclusion the 1980 American Rheumatology Association classification criteria for SSc[11] and with a follow-up of at least 3 years since inclusion, or who died (the baseline visit being registered before 1 January 2009), were extracted from the EUSTAR database. The following outcomes have been defined as indicating a severe course of the disease: active DUs observed at

To cite: Mihai C, Landewé R, van der Heijde D, *et al*. *Ann Rheum Dis* 2016;**75**:681–686.

prospective visits; recent DUs, defined as DUs reported by the patient at prospective visits as having occurred since the last visit; skin involvement worsening, defined as an increase of the modified Rodnan skin score (mRSS)[12] with at least five points and at least 20% compared with baseline; severe ILD, defined by a forced vital capacity (FVC) <50% of the predicted value, at any visit; severely decreased alveolo-capillary diffusion of carbon monoxide (DLCO) of any cause, defined as a DLCO <40% of the predicted value, at any visit; elevated systolic pulmonary arterial pressure >40 mm Hg as assessed by power Doppler heart ultrasound examination (US-PAPs), at any visit; heart failure, defined by an LVEF <50%, at any visit; scleroderma renal crisis (excluding the patients in which there is a history of SSc renal crisis at baseline); and overall cardiovascular events, defined as the occurrence of any of the following: recent DUs (as already specified), US-PAPs >40 mm Hg or LVEF <50%. All cause-mortality has also been investigated as an outcome.

Statistical analysis

The analysis was carried out with the statistics softwares IBM SPSS V.20.0 and SAS V.9.2. A p value <0.05 was considered as statistically significant. Comparisons between groups were performed with the χ^2 test (for categorical variables) or with the independent samples t test (for numeric variables).

HDU at presentation and all baseline parameters recorded in the EUSTAR minimal, essential data set (MEDS), potentially influencing each of the outcomes described above, were evaluated by Kaplan–Meier survival plots and by age-adjusted and gender-adjusted Cox proportional hazards regression analysis (as categorical, dichotomous variables). Further, HDU at inclusion, age, gender and all baseline MEDS parameters considered potentially significant predictors were introduced in the multivariable analysis.

RESULTS

Following the inclusion criteria, 3207 patients were selected from the EUSTAR database. Of these, we had baseline data about the presence or absence of HDU in 3196 patients, of which 1092 (34.1%) were positive for HDU. The demographic and clinical features of the study cohort are shown in table 1.

The follow-up for the entire cohort was 5.0±2.2 years and 451 deaths of all causes were recorded up to February 2012. The time to death since the onset of Raynaud's phenomenon (RP) was 17.3±11.3 years and since the first non-Raynaud symptom 8.9±8.6 years. Death due to SSc was mentioned in 288 cases, non-SSc related death—in 85 cases while 78 deaths remained unclassified.

Patients with HDU at baseline (HDU-positive) were further compared by χ^2 test with patients negative for HDU at inclusion (HDU-negative) in regard to baseline variables as well as to outcomes (table 1). HDU-positive patients had a significantly more frequent occurrence of both active DUs and recent DUs at prospective visits, as defined in the Methods section. Also, deterioration of FVC, DLCO and LVEF, as well as elevated US-PAPs, overall cardiovascular events, and death, were more frequent outcomes in HDU-positive patients. There was no difference in occurrence of skin involvement worsening and of scleroderma renal crisis between groups.

Cox proportional hazards analysis of HDU as a predictor of the selected outcomes, adjusted for age and gender

In age-adjusted and gender-adjusted analysis, HDU at inclusion in the cohort was predictive for both active and recent DUs at prospective visits (table 2), also for elevated US-PAPs, overall cardiovascular events and death of all causes (tables 3–5). We have not explored pulmonary arterial hypertension defined by right heart catheterisation as an outcome, because of the small number of patients who had performed this investigation (96 of

Table 1 Demographic data and outcomes in patients with and without a history of digital ulcers (DUs) at inclusion (n=3196)

Demographic data	HDU+ (n=1092)	HDU− (n=2104)	All patients (n=3196)	p Value*
Female sex	83.8%	88.3%	86.8%	0.002
Age (years), mean±SD	52.5±14.0	55.6±13.2	54.6±13.6	<0.001
Disease duration (years)				
Since first non-Raynaud symptom, mean±SD	8.8±8.0	7.7±7.4	8.1±7.7	<0.001
Since onset of Raynaud's, mean±SD	12.4±11.0	12.2±11.3	12.3±11.2	0.564
Diffuse cutaneous subset	41.7%	29.1%	33.4%	<0.001
Anti-centromere positive	28.0%	38.0%	34.6%	<0.001
Anti-topoisomerase I positive	42.4%	28.9%	33.5%	<0.001
Raynaud's phenomenon present	98.2%	95.7%	96.5%	<0.001
Outcomes				
DUs reported since last visit	77.2%	34.1%	48.3%	<0.001
Active DUs at prospective visits	34.6%	14.0%	20.6%	<0.001
Skin involvement worsening	40.1%	41.5%	41.0%	0.508
FVC <50% predicted	5.4%	3.0%	3.8%	0.004
DLCO<40% predicted	20.1%	15.4%	17.0%	0.001
LVEF<50%	5.5%	3.6%	4.2%	0.073
Elevated US-PAPs	39.7%	34.5%	36.2%	0.004
Scleroderma renal crisis	1.7%	1.6%	1.6%	0.887
Death	19.7%	11.4%	14.1%	<0.001

See the Methods section for definition of outcomes.
HDU+/HDU−, patients positive/negative for a history of DUs at baseline.
FVC <50% predicted, lung forced vital capacity <50% of the predicted value; DLCO<40% predicted, lung CO diffusion <40% of the predicted value; Elevated US-PAPs, a systolic pulmonary arterial pressure >40 mm Hg as measured by power Doppler heart ultrasound examination. For all these parameters values are considered at any visit including baseline.
*Significance of the difference between HDU+ and HDU− patients, by χ^2 test (for categorical variables) or independent samples t test (for numeric variables).

Table 2 Predictors of observed active digital ulcers (DUs) and of reported recent DUs (since previous visit) at prospective visits

	Active DUs				Reported recent DUs			
Covariate (at baseline)	HR (95% CI) Analysis adjusted only for age and gender	p Value	HR (95% CI) Analysis adjusted for age, gender and all listed covariates	p Value	HR (95% CI) Analysis adjusted only for age and gender	p Value	HR (95% CI) Analysis adjusted for age, gender and all listed covariates	p Value
HDU	**2.60 (2.19 to 3.08)**	**<0.001**	**2.41 (1.91 to 3.03)**	**<0.001**	**3.59 (3.23 to 3.99)**	**<0.001**	**3.23 (2.78 to 3.74)**	**<0.001**
Anti-topo I antibodies	2.09 (1.76 to 2.48)	<0.001	1.78 (1.39 to 2.28)	<0.001	1.81 (1.62 to 2.01)	<0.001	1.41 (1.20 to 1.66)	<0.001
Joint contractures	2.15 (1.81 to 2.56)	<0.001	1.53 (1.20 to 1.94)	<0.001	2.04 (1.83 to 2.27)	<0.001	1.38 (1.18 to 1.61)	<0.001
Elevated US-PAPs	1.52 (1.22 to 1.86)	<0.001	1.37 (1.05 to 1.81)	0.023	1.49 (1.30 to 1.70)	<0.001	1.41 (1.17 to 1.69)	<0.001
DLCO<80% predicted	1.61 (1.26 to 2.06)	<0.001	1.29 (1.00 to 1.66)	0.055	1.66 (1.48 to 1.85)	<0.001	1.08 (0.92 to 1.27)	0.349
Diffuse cutaneous subset	1.65 (1.38 to 1.97)	<0.001	1.15 (0.89 to 1.49)	0.282	1.61 (1.26 to 2.06)	<0.001	1.22 (1.02 to 1.44)	0.024

Bold typeface highlights the baseline covariate of interest, HDU.
Cox proportional hazards analysis adjusted only for age and gender (left column for each outcome) and for age, gender and all clinically important covariates (right column for each outcome).
DLCO, lung CO diffusion; Elevated US-PAPs, a systolic pulmonary arterial pressure >40 mm Hg as measured by power Doppler heart ultrasound examinationl; HDU, history of digital ulcers at baseline.

3196). Figure 1 illustrates by Kaplan–Meier survival plots the relationship between HDU at presentation and these outcomes.

Furthermore, HDU at baseline was found to be predictive for severe ILD with an HR and 95% CI of 1.71 (1.13 to 2.59), p=0.011 and for severely decreased DLCO with an HR (95% CI) of 1.42 (1.19 to 1.70), p<0.001. HDU was not predictive for worsening of skin involvement, scleroderma renal crisis and cardiac worsening defined as an LVEF of <50%. In all models, both adjusting for disease duration since first non-Raynaud's symptom, or since RP onset, instead of age, led to similar results (data not shown).

Cox proportional hazards analysis of HDU as a predictor of the selected outcomes, adjusted for age, gender and all clinically significant baseline covariates

The results of the Cox proportional hazards regression analysis adjusted for age, gender and all potentially significant predictors of each outcome are shown in tables 2–5. HDU at baseline was predictive for active and for recent DUs, also for elevated US-PAPs, for overall cardiovascular events and for death. In this multivariable analysis, the relationship between HDU at baseline and the outcomes 'severe ILD' and 'severely decreased DLCO' was not statistically significant.

DISCUSSION

Our data, derived from the largest prospective SSc cohort, show that patients with HDU are prone to develop not only more new DUs, but an elevated US-PAPs and overall cardiovascular events as well, and are characterised by a decreased survival.

As expected, HDU at the first visit was found to be the strongest predictor for the occurrence/reoccurrence of DUs at prospective visits, with the highest HR among all covariates in the multivariable Cox proportional hazards models. We have been able to include as covariates several other baseline parameters that have been shown in other studies to be predictive for DUs, such as male gender, dcSSc subset, elevated US-PAPs, and anti-topoisomerase I antibodies (ATA), thus demonstrating that HDU is a stronger predictor for new DUs than any other of these.[6 7] Recently, biomarkers such as increased serum placental growth factor (PlGF) levels and low circulating endothelial progenitor cells (EPCs) levels have been shown to predict the subsequent development of DUs in patients with SSc.[13] Noteworthy, in the multivariable model which also included high PlGF, low EPCs and high erythrocyte sedimentation rate (ESR) as independent predictors of new DUs, HDU was the predictor with the highest HR.[13] The results of our multivariable analysis confirm once more that for clinical trials aiming at DU prevention, HDU is the

Table 3 Predictors of elevated pulmonary arterial pressure of all causes, estimated by power Doppler heart ultrasound examination (systolic pulmonary arterial pressure >40 mm Hg)

Covariate (at baseline)	HR (95% CI) Analysis adjusted only for age and gender	p Value	HR (95% CI) Analysis adjusted for age, gender and all listed covariates	p Value
HDU	**1.32 (1.17 to 1.49)**	**<0.001**	**1.36 (1.03 to 1.80)**	**0.032**
Dyspnoea (clinically significant)	2.19 (1.25 to 2.47)	<0.001	1.85 (1.32 to 2.58)	<0.001
Lung function restrictive defect	2.19 (1.95 to 2.47)	<0.001	1.89 (1.38 to 2.60)	<0.001
DLCO<80% predicted	2.08 (1.72 to 2.53)	<0.001	1.88 (1.32 to 2.66)	<0.001
Diastolic heart dysfunction	1.63 (1.42 to 1.88)	<0.001	1.47 (1.07 to 2.03)	0.018
Lung fibrosis (X-ray or HRCT)	2.03 (1.80 to 2.28)	<0.001	1.27 (0.93 to 1.74)	0.138
Anti-topo I antibodies	1.43 (1.24 to 1.58)	<0.001	1.11 (0.82 to 1.51)	0.509
Diffuse cutaneous subset	1.40 (1.24 to 1.58)	<0.001	0.88 (0.64 to 1.21)	0.432

Bold typeface highlights the baseline covariate of interest, HDU.
Cox proportional hazards analysis adjusted only for age and gender (left) and for age, gender and all clinically important covariates (right).
DLCO<80%, lung CO diffusion <80% predicted; HDU, history of digital ulcers at baseline; HRCT, high resolution CT.

Table 4 Predictors of overall cardiovascular events, defined as a composite outcome resulting of the occurrence of any of the following: reported HDU occurring after any previous visit, systolic pulmonary arterial pressure >40 mm Hg by power Doppler heart ultrasound, or an LVEF<50%

Covariate (at baseline)	HR (95% CI) Analysis adjusted only for age and gender	p Value	HR (95% CI) Analysis adjusted for age, gender and all listed covariates	p Value
HDU	**2.12 (1.48 to 3.03)**	**<0.001**	**3.56 (2.26 to 5.62)**	**<0.001**
Joint contractures	2.96 (2.09 to 4.20)	<0.001	1.82 (1.10 to 3.00)	0.019
Dyspnoea (clinically significant)	2.06 (1.24 to 3.41)	0.005	2.02 (0.93 to 4.38)	0.076
Diastolic heart dysfunction	2.06 (1.26 to 3.39)	0.004	1.53 (0.88 to 2.65)	0.133
Lung function restrictive defect	1.89 (1.25 to 2.84)	0.002	1.30 (0.72 to 2.35)	0.386
DLCO <80% predicted	1.42 (0.95 to 2.12)	0.085	1.64 (1.04 to 2.58)	0.033
Lung fibrosis (X-ray or HRCT)	1.45 (0.98 to 2.15)	0.061	0.72 (0.41 to 1.25)	0.240
Anti-topo I antibodies	1.56 (1.07 to 2.27)	0.021	1.34 (0.77 to 2.34)	0.302
Diffuse cutaneous subset	1.89 (1.33 to 2.70)	<0.001	1.08 (0.62 to 1.87)	0.791

Bold typeface highlights the baseline covariate of interest, HDU.
Cox proportional hazards analysis adjusted only for age and gender (left) and for age, gender and all clinically important covariates (right).
HDU, history of digital ulcers.

most important and the most easily evaluable inclusion criterion to define high risk of DUs during follow-up. Another conclusion is that HDU-positive patients would benefit of vasoactive treatment such as prostanoids and endothelin receptor blockers as prevention for DUs reoccurrence, especially in the cold season, while HDU-negative patients would have less benefit.

Our results also show that HDU is predictive for overall cardiovascular events including new DUs, elevated US-PAPs and decreased LVEF, thus highlighting the severe prognosis indicated by HDU. As recently shown by Bruni *et al*,[5] DUs appear to be a sentinel sign for internal organ involvement and as such for a worse disease course even in very early SSc. These findings strengthen the concept of a vascular phenotype of SSc, encompassing peripheral vasculature and organ microcirculation involvement.[13] It may seem surprising that in multivariable analysis HDU was not predictive for severely decreased DLCO, while being a predictor of elevated US-PAPs; the most likely explanation is that we have used a rather strict definition for the severely decreased DLCO (<40% than predicted), while the definition for increased US-PAPs set a more lenient threshold for abnormal PAP.

Finally, our study found that HDU is an independent predictor of a poorer survival. There are several studies on predictors of death in patients with SSc, but only a single-centre cohort study found that DUs were associated with a poorer prognosis in terms of survival.[14] Noteworthy, our model includes as independent covariates next to HDU the baseline parameters DLCO and proteinuria, demonstrated by Bryan *et al*[15] to be, next to age, gender and ESR, the most important predictors on survival.[16] The Bryan model was intended as a clinical tool to predict survival and therefore is as simple as possible, while our model was focused on HDU and therefore we included all the covariates that were potentially significant (on clinical judgement). Similarly, Tyndall *et al* analysed the mortality of patients with SSc in the EUSTAR cohort and identified the following independent risk factors for death: proteinuria, an elevated US-PAPs, FVC <80% of normal, the presence of dyspnoea on exertion, a reduced DLCO, an elevated age at SSc onset and a high mRSS. The statistical analysis of this study used the same methods as in our present article, and although in univariable analysis a HDU at inclusion was associated with decreased survival (HR 1.61, p<0.001), this was no longer

Table 5 Predictors of death of all causes

Covariate (at baseline)	HR (95% CI) Analysis adjusted only for age and gender	p Value	HR (95% CI) Analysis adjusted for age, gender and all listed covariates	p Value
HDU	**2.02 (1.67 to 2.43)**	**<0.001**	**1.53 (1.16 to 2.02)**	**0.003**
Dyspnoea (clinically significant)	3.25 (2.68 to 3.96)	<0.001	1.59 (1.17 to 2.15)	0.003
Lung function restrictive defect	3.39 (2.78 to 4.11)	<0.001	1.59 (1.13 to 2.23)	0.008
DLCO <80% predicted	3.76 (2.50 to 5.65)	<0.001	2.07 (1.31 to 3.28)	0.002
Elevated US-PAPs	3.54 (2.92 to 4.30)	<0.001	2.21 (1.65 to 2.96)	<0.001
Diastolic heart dysfunction	2.03 (1.65 to 2.51)	<0.001	1.34 (1.00 to 1.79)	0.052
Lung fibrosis (X-ray or HRCT)	2.69 (2.21 to 3.28)	<0.001	0.92 (0.65 to 1.29)	0.612
Renal crisis history	2.90 (1.87 to 4.50)	<0.001	2.03 (1.13 to 3.65)	0.018
Proteinuria	3.50 (2.69 to 4.54)	<0.001	2.09 (1.44 to 3.04)	<0.001
Diffuse cutaneous subset	2.48 (2.05 to 3.00)	<0.001	1.64 (1.19 to 2.25)	0.002
Anti-topo I antibodies	2.19 (1.81 to 2.66)	<0.001	1.26 (0.93 to 1.70)	0.139

Bold typeface highlights the baseline covariate of interest, HDU.
Cox proportional hazards analysis adjusted only for age and gender (left) and for age, gender and all clinically significant covariates (right).
Elevated US-PAPs, a systolic pulmonary arterial pressure >40 mm Hg defined by power Doppler heart ultrasound examination.
DLCO <80%, lung CO diffusion <80% predicted; HDU, history of digital ulcers at baseline; HRCT, high resolution CT.

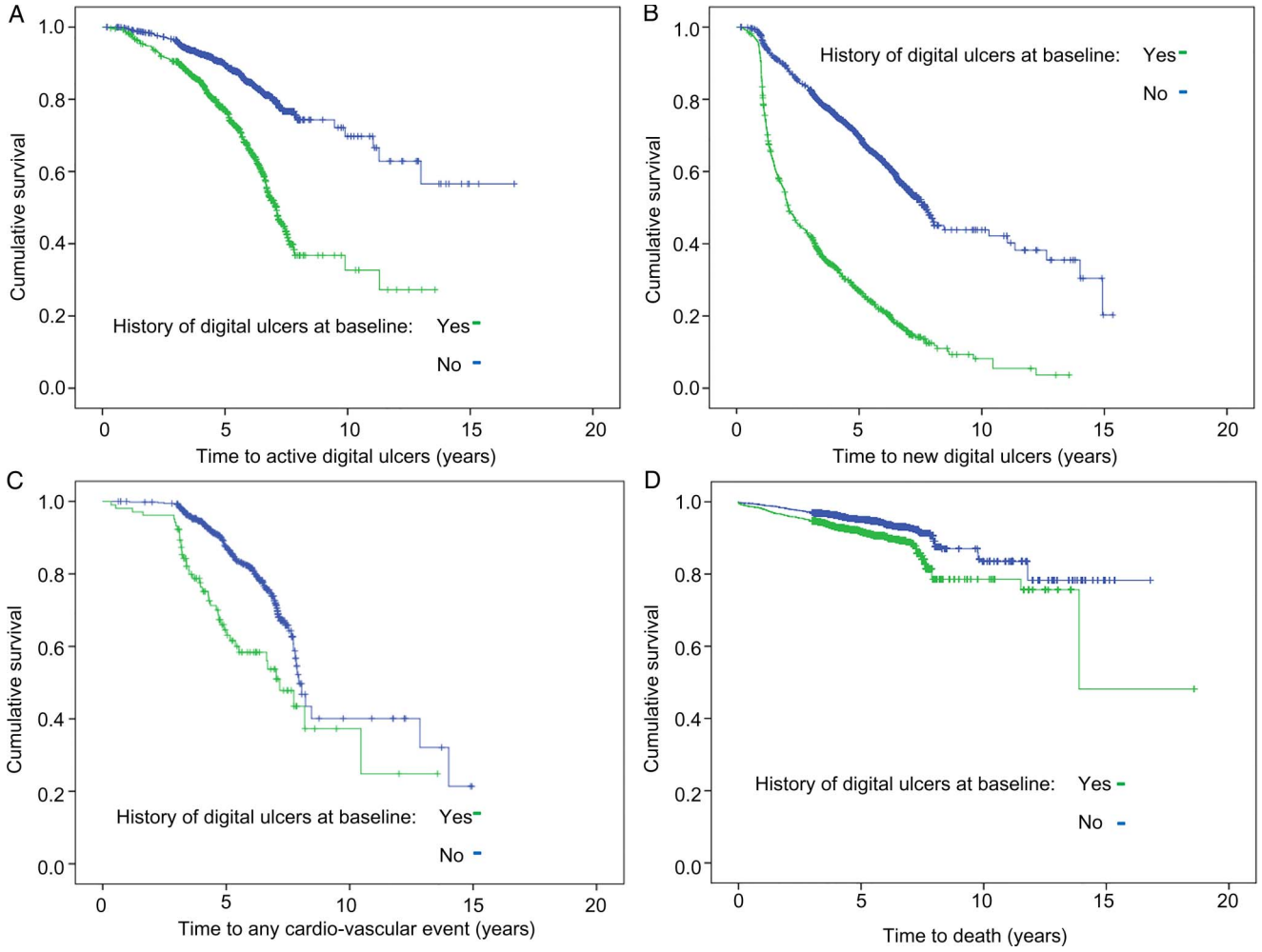

Figure 1 The influence of a history of digital ulcers (DUs) at presentation on several outcomes: (A) presence of active DUs at prospective visits; (B) reported recent DUs (since previous visit) at prospective visits; (C) overall cardiovascular events, defined as a composite outcome resulting of the occurrence of any of the following: reported history of DUs occurring after any previous visit, systolic pulmonary arterial pressure >40 mm Hg by power Doppler heart ultrasound, or an LVEF <50%; and (D) all-cause mortality (n=3196 patients with SSc). Kaplan–Meier survival plots, all p<0.001 by the log-rank test.

significant in the multivariable model.[10] However, it is not surprising that our study, with a larger population and a threefold longer follow-up, could identify more risk factors for death. Comparing the HRs of the various predictors of death in the multivariable model, it is of interest that an HDU has a prognostic value in regard to survival similar with that of dcSSc subset and of a decreased FVC and stronger than that of ATA.

The EUSTAR cohort is impressively large and there is no doubt that cohort studies have significant strengths: they can be used to study high-risk patients even before they develop certain manifestations, several outcomes can be studied for each exposure, and statistical modelling can be applied. But such cohorts also have limitations like missing data and loss to follow-up.[17] In our study, for example, many missing values for baseline ESR (>50% of the patients) made us decide to not include ESR as a covariate in the Cox models.

Furthermore, in order to allow for a minimum of 3 years of follow-up, we have selected from the EUSTAR cohort only patients enrolled before 1 January 2009 and therefore the baseline data are derived from the original MEDS and not from MEDS online data. For this reason, as original MEDS include only few numerical variables (such as the mRSS and DLCO as a percentage of the predicted value), and do not record medication, we have not been able to define outcomes by a variation from baseline (with the exception of skin worsening), nor could we adjust for treatment. We have tried to overcome this issue by defining 'strong' outcomes that are independent of the baseline value of the respective parameter—for example, FVC <50% of the predicted value, at any visit.

Another limitation is the fact that in the EUSTAR database the presence of 'baseline HDU' has been based on patient-reported data only, and there is no distinct recording for different categories of DUs (ischaemic, traumatic or related to calcinosis). Recently, a clinical evidence-based classification of DUs has been proposed but our baseline data, recorded before 2009, are not detailed accordingly.[18] Also, we would have found useful to include nailfold capillaroscopic pattern at baseline as a covariate in the multivariable models for new DUs, as it has been recently shown that a decreased capillary density is predictive for DUs,[19] but for the majority of the patients baseline capillaroscopy data were not available.

In our cohort, average disease duration at baseline is over 8 years, showing that the majority of cases are not early. However, this is what we frequently encounter in clinical practice, so reported HDU remains an important item not to be forgotten in history taking, and useful in decision making in regard to treatment.

The number of patients who developed US-PAPs >40 mm Hg or LV dysfunction was much lower than that of patients with recent or active DUs at prospective visits, and the multivariable Cox model on cardiovascular outcomes, including contractures as an independent covariate, suggests that new DUs are what this model mainly predicts. Further studies with more detailed baseline and follow-up data on cardiovascular outcomes are thus warranted to assess the predictive value of HDU for the development of cardiac and vascular complications.

The relationship between HDU at presentation and decreased survival, as suggested by our results, remains to be confirmed in studies with more detailed data on mortality. As we lacked information on the cause of death and this was not defined as SSc-related or non-SSc related in a large percentage of cases, we have not attempted to develop this analysis here.

In conclusion, our data demonstrate that in patients with SSc, HDU is a risk factor for more severe disease, predicting the occurrence of new DUs, new cardiovascular events and even a poorer survival. Reported HDU should prompt the physician to a careful clinical assessment, management and follow-up of the patient.

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Acknowledgements The authors and all EUSTAR centres are grateful for the support of the European League Against Rheumatism (EULAR).

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Contributors All authors contributed to one or more of the following aspects of the manuscript: conception and design, acquisition, analysis and interpretation of data, drafting and revising the article.

Funding EUSTAR is supported by EULAR.

Competing interests None.

Patient consent Obtained.

Ethics approval All contributing EUSTAR centres have obtained approval from their respective ethics committee for including a patient's data in the EUSTAR database after the patient has given written informed consent.

Provenance and peer review Not commissioned, externally peer reviewed.

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Ann Rheum Dis 2016 75: 681-686 originally published online February 16, 2015
doi: 10.1136/annrheumdis-2014-205897