Clinical characteristics and predictors of gangrene in patients with systemic sclerosis and digital ulcers in the Digital Ulcer Outcome Registry: a prospective, observational cohort

Digital vasculopathy in systemic sclerosis (SSc) consists of a spectrum of Raynaud's phenomenon (RP), digital ulcers (DUs), critical digital ischaemia and escalation to gangrene. The complications of severe digital vasculopathy often require hospital-based management with intravenous therapies and surgery.[1–3] Although gangrene is not infrequent in the clinic, data on the prevalence and

implications of gangrene in patients with SSc are scarce.[3–7] The DU Outcomes (DUO) Registry is a European, prospective, multicentre, observational cohort of patients with SSc and past and/or current DUs at enrolment.[8–10] The aims of the current study were (i) to describe the characteristics of an SSc–DU population according to the presence/history of gangrene and (ii) to identify the risk factors for the development of incident gangrene.

All patients in the participating centres with SSc and a history or presence of DUs are eligible for inclusion in the DUO Registry, irrespective of their treatment regimen. At enrolment, data were collected on demographic and clinical variables. Patients were categorised into three groups according to their past history of gangrene and current gangrene status at enrolment: 'never gangrene': no past and no current gangrene; 'ever gangrene': past and/or current gangrene; and 'current gangrene': gangrene reported at enrolment, irrespective of gangrene history (a subset of the 'ever gangrene' group).

Categorical variables were analysed using descriptive statistics. Potential risk factors for the development of incident gangrene in patients with ≥1 follow-up visit and no current gangrene at enrolment were analysed using univariable logistic regression (ULR) conducted on demographics, clinical variables and autoantibody measurements collected at enrolment. Multivariable logistic regression (MLR) using forward selection was conducted on patients with complete covariate information using those variables with a p value <0.15 and sample size >3000 from the ULR models, considering interdependency among similar factors.

Among the 4944 patients enrolled in the DUO Registry from April 2008 to November 2014, 4642 had information recorded on their gangrene status: 81.6% (n=3787) were categorised as 'never gangrene', 18.4% (n=855) as 'ever gangrene' and 5.6% (n=258) as 'current gangrene'. The three groups were generally similar regarding demographics and SSc characteristics, although

Table 1 Enrolment characteristics and patient demographics according to gangrene status*

	Never† gangrene (n=3787)	Ever‡ gangrene (n=855)	Current gangrene (n=258)§
Gender			
Female, %	82.1	77.7	77.5
Age at enrolment			
Mean (95% CI), years	54.4 (53.9 to 54.8)	54.8 (53.9 to 55.8)	52.8 (50.9 to 54.7)
Smoking status			
n	3386	757	233
Current, %	14.4	17.6	24.0
Former, %	23.3	25.6	17.6
Never, %	62.3	56.8	58.4
Pack-years of smoking			
n	868	206	73
Mean (95% CI)	37.8 (31.3 to 44.3)	37.9 (27.5 to 48.4)	44.9 (24.9 to 64.9)
Age at first RP			
n	3409	752	229
Mean (95% CI), years	41.3 (40.8 to 41.8)	40.7 (39.6 to 41.8)	41.2 (39.0 to 43.3)
Age at first DU			
n	3000	700	218
Mean (95% CI), years	47.6 (47.1 to 48.2)	47.1 (45.9 to 48.2)	48.3 (46.1 to 50.5)
SSc cutaneous subset			
n	3774	850	256
Diffuse SSc, %	37.7	32.0	33.6
Limited SSc, %	52.3	58.2	54.3
Overlap, %	6.5	6.0	7.8
Other, %	3.6	3.8	4.3
Organ manifestations			
n	3787	855	258
GI tract, %	54.0	56.8	46.5
Lung fibrosis, %	40.4	40.1	38.0
PAH, %	12.1	15.2	13.2
Heart, %	9.9	10.9	12.4
Kidney, %	4.1	6.0	5.8
Time from first RP to enrolment visit			
n	3409	752	229
Mean (95% CI), years	13.1 (12.8 to 13.5)	14.4 (13.6 to 15.3)	11.9 (10.4 to 13.5)
Time from first DU to enrolment visit			
n	3000	700	218
Mean (95% CI), years	5.9 (5.7 to 6.2)	7.4 (6.8 to 8.0)	4.6 (3.8 to 5.5)

Continued

Table 1 Continued

	Never† gangrene (n=3787)	Ever‡ gangrene (n=855)	Current gangrene (n=258)§
Antibodies, n^1/n^2 (%)			
ACA	1184/2942 (40.2)	303/668 (45.4)	88/216 (40.7)
ANA	3307/3511 (94.2)	750/785 (95.5)	226/238 (95.0)
Anti-Scl 70	1397/3145 (44.4)	282/690 (40.9)	87/218 (39.9)
Anti-U1 RNP	170/2158 (7.9)	52/470 (11.1)	17/151 (11.3)
Anti-U3 RNP	59/1534 (3.8)	19/300 (6.3)	4/104 (3.8)
RNA polymerase III	127/1584 (8.0)	25/323 (7.7)	6/103 (5.8)
Employed/self-employed, n (%)	983/2674 (36.8)	167/564 (29.6)	75/207 (36.2)
History of complications/interventions, % (95% CI)¶			
Critical digital ischaemia	30.1 (28.5 to 31.8)	82.2 (78.6 to 85.4)	69.4 (61.6 to 76.4)
Gangrene	–	91.7 (89.7 to 93.5)	71.9 (65.9 to 77.4)
Autoamputation	3.1 (2.6 to 3.7)	24.1 (21.2 to 27.2)	15.9 (11.6 to 21.1)
Soft-tissue infection requiring systemic antibiotics	23.9 (22.5 to 25.3)	53.5 (49.9 to 57.0)	44.5 (38.1 to 51.1)
Osteomyelitis	1.3 (0.9 to 1.7)	11.9 (9.7 to 14.3)	7.4 (4.4 to 11.4)
Hospitalisations for DUs	32.7 (31.2 to 34.2)	70.1 (66.9 to 73.2)	58.9 (52.5 to 65.2)
Upper limb sympathectomy	2.2 (1.8 to 2.7)	8.8 (6.9 to 10.9)	7.2 (4.2 to 11.2)
Digital sympathectomy	1.4 (1.0 to 1.8)	4.8 (3.4 to 6.5)	3.4 (1.5 to 6.6)
Arterial reconstruction	0.7 (0.5 to 1.0)	2.1 (1.3 to 3.4)	4.3 (2.1 to 7.7)
Arthrodesis	1.4 (1.0 to 1.9)	5.7 (4.1 to 7.6)	2.0 (0.5 to 4.9)
Debridement	7.5 (6.6 to 8.4)	25.7 (22.5 to 29.1)	21.0 (15.6 to 27.2)
Surgical amputation	2.4 (1.9 to 3.0)	34.0 (30.5 to 37.5)	18.9 (13.8 to 24.8)
Use of parenteral prostanoids	51.6 (49.9 to 53.2)	74.4 (71.2 to 77.4)	74.4 (68.3 to 79.8)
Prior DUs, n^1/n^2 (%)	3759/3787 (99.3)	852/855 (99.6)	255/258 (98.8)
Ongoing medications, %			
n	3787	855	258
Analgesics and anti-inflammatories	52.4	60.6	65.1
Immunosuppressants	33.5	28.2	29.5
Systemic antibiotics	13.3	19.6	36.0
ERAs	39.9	52.0	50.4
CCBs	46.0	52.5	53.1
Prostacyclins	35.0	36.5	51.9
PDE-5i	5.9	7.6	5.8
Topical DU treatments	19.1	24.4	36.8
Other medications	64.8	74.2	67.1
ERA+PDE-5i	2.2	3.3	2.7
ERA+prostacyclin	14.3	18.5	24.4
PDE-5i+prostacyclin	1.7	2.8	3.1
ERA+PDE-5i+prostacyclin	0.8	1.5	1.6
ERA only**	24.1	31.8	24.8

*Only patients who provided information on gangrene status (n=4642/4944) were categorised.
†Patients with no past and no current gangrene.
‡Patients with past and/or current gangrene.
§Patients with current gangrene at enrolment. The current gangrene group is a subset of the 'ever gangrene' group.
¶Data include only patients who provided information on the given item.
**Out of ERA, PDE-5i and prostacyclins, only ERA is ticked.
ACA, anticentromere antibody; ANA, antinuclear antibody; CCB, calcium channel blocker; DU, digital ulcer; ERA, endothelin receptor antagonist; GI, gastrointestinal; n^1/n^2, n patients tested positive/n patients who had the test done; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase-type 5 inhibitor; RNP, ribonucleic protein; RP, Raynaud's phenomenon; SSc, systemic sclerosis.

more current smokers at enrolment were in the 'ever gangrene' and 'current gangrene' groups than in the 'never gangrene' group, and the 'current gangrene' group had the shortest time between first RP and enrolment (table 1). The proportion of patients with a history of DU-associated complications, interventions and hospitalisations was greater in the 'ever gangrene' group compared with the 'never gangrene' group.

Overall, 3809 patients were eligible for inclusion in the ULR analysis; the final number of patients included in each ULR model varied depending on missing data (table 2A). On MLR analysis, being a current/former smoker, having ≥3 finger DUs, previous gangrene and previous upper limb sympathectomy were independent risk factors at enrolment for development of incident gangrene (table 2B).

This analysis was the largest to date describing an SSc–DU population according to the presence/history of gangrene at enrolment and risk factors for incident gangrene during follow-up. It has demonstrated that, in current practice, gangrene

Table 2 Risk factors associated with the development of incident gangrene during the observation period

Risk factor	Incident gangrene n/N (%)	No incident gangrene, n/N (%)	OR (95% CI)	p Value*
(A) *ULR (N=3809)*[†]	*N=243*	*N=3566*		
Female gender	189/243 (77.8)	2938/3566 (82.4)	0.73 (0.53 to 1.01)	0.055
Smoking status				
Current	45/205 (22.0)	438/3102 (14.1)	1.91 (1.32 to 2.76)	<0.001
Former	58/205 (28.3)	728/3102 (23.5)	1.46 (1.04 to 2.04)	0.028
Number of finger DUs at enrolment				
1–2	89/236 (37.7)	1315/3546 (37.1)	1.27 (0.93 to 1.72)	0.132
3+	58/236 (24.6)	666/3546 (18.8)	1.54 (1.09 to 2.17)	0.015
Anti-Scl 70	103/196 (52.6)	1279/2872 (44.5)	1.39 (1.04 to 1.87)	0.027
Previous gangrene	96/229 (41.9)	404/3378 (12.0)	4.75 (3.57 to 6.34)	<0.0001
Previous autoamputation	32/231 (13.9)	188/3386 (5.6)	2.69 (1.78 to 4.04)	<0.0001
Previous soft-tissue infection requiring systemic antibiotics	94/222 (42.3)	933/3253 (28.7)	1.76 (1.33 to 2.32)	<0.0001
Previous osteomyelitis	19/232 (8.2)	84/3367 (2.5)	3.24 (1.19 to 5.47)	<0.0001
Ongoing autoamputation	6/242 (2.5)	46/3552 (1.3)	2.32 (0.97 to 5.57)	0.059
Ongoing osteomyelitis	4/243 (1.6)	24/3558 (0.7)	2.36 (0.80 to 6.99)	0.121
Previous hospitalisation(s) for DUs (at least 1 day)	144/231 (62.3)	1290/3385 (38.1)	2.49 (1.89 to 3.29)	<0.0001
Previous upper limb sympathectomy	20/228 (8.8)	100/3345 (3.0)	3.24 (1.94 to 5.40)	<0.0001
Previous digital sympathectomy	11/228 (4.8)	58/3341 (1.7)	2.70 (1.38 to 5.31)	0.004
Previous arterial reconstruction	5/227 (2.2)	21/3336 (0.6)	3.43 (1.25 to 9.44)	0.017
Not employed/self-employed	205/243 (84.4)	2687/3566 (75.4)	1.78 (1.22 to 2.61)	0.003
(B) *MLR*[‡] *(N=2479)*	*N=157*	*N=2322*		
Observation time, mean (SD), weeks	174.7 (78.7)	126.2 (78.9)	1.03 (1.02 to 1.04)	<0.0001
Smoking status				
Current	27/157 (17.2)	311/2322 (13.4)	1.72 (1.07 to 2.77)	0.025
Former	47/157 (29.9)	509/2322 (21.9)	1.69 (1.14 to 2.51)	0.009
Number of finger DUs at enrolment				
1–2	60/157 (38.2)	951/2322 (41.0)	1.35 (0.90 to 2.03)	0.144
3+	46/157 (29.3)	491/2322 (21.1)	1.69 (1.09 to 2.62)	0.020
Anti-Scl 70	79/157 (50.3)	1031/2322 (44.4)	1.39 (0.99 to 1.96)	0.058
Previous gangrene	63/157 (40.1)	244/2322 (10.5)	4.67 (3.24 to 6.73)	<0.0001
Previous upper limb sympathectomy	15/157 (9.6)	67/2322 (2.9)	2.21 (1.15 to 4.27)	0.018

*Wald χ^2 test.
[†]For the ULR analysis, observation time was a fixed covariate in the model. Data are shown for variables having p<0.15 and n>3000 for the patients for whom information is available).
[‡]For the MLR analysis, observation time was forced into the model as a fixed covariate and not included by the forward selection procedure; variables were selected with a selection criterion of p=0.15. Data are shown for the subset of patients making up the final models (n=2479) to allow comparison with the full cohort.
ACA, anticentromere antibody; ANA, antinuclear antibody; DU, digital ulcer; MLR, multivariable logistic regression; PAH, pulmonary arterial hypertension; RNP, ribonucleic protein; ULR, univariable logistic regression.

is still a common event occurring in 18% of patients with SSc–DUs. Participating centres involved in the DUO Registry are specialist centres for the management of SSc–DUs; this may be selective for patients with more severe vascular disease, and therefore more prevalent gangrene. Multivariate analyses indicated that, in patients with no current gangrene, along with previous gangrene, being a current/former smoker, having ≥3 DUs and previous upper limb sympathectomy were independent risk factors at enrolment for developing incident gangrene. These results will help to risk-stratify patients with SSc–DUs and to evaluate preventive gangrene management strategies.

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Collaborators List of DUO investigators in online supplementary appendix.

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