Nailfold videocapillaroscopy patterns in systemic sclerosis: implications for cutaneous subsets, disease features and prognostic value for survival

C. Tolosa-Vilella[1], M. del Mar Rodero-Roldán[2], A. Guillen-del-Castillo[3], A. Marín Ballvé[2], R. Boldova-Aguar[2], B. Marí-Alfonso[1], C. Feijoo-Massó[1], D. Colunga-Argüelles[4], M. Rubio-Rivas[5], L. Trapiella-Martínez[6], N. Iniesta-Arandia[7], E. Callejas-Moraga[1], F.J. García-Hernández[8], L. Sáez-Comet[9], C. González-Echávarri[10], N. Ortego-Centeno[11], M. Freire[12], J.A. Vargas-Hitos[13], J.J. Ríos-Blanco[14], J.A. Todolí-Parra[15], I. Rodríguez-Pintó[16], A.-J. Chamorro[17], X. Pla-Salas[18], A.B. Madroñero-Vuelta[19], M. Ruiz-Muñoz[20], V. Fonollosa-Pla[3], C.P. Simeón-Aznar[3] and the RESCLE Investigators

[1]Systemic Autoimmune Diseases Unit, Dept. of Internal Medicine, Parc Taulí, Hospital Universitari, Sabadell, Barcelona, and Universitat Autònoma de Barcelona; [2]Systemic Autoimmune Diseases Unit, Dept. of Internal Medicine, Hospital Clínico Universitario Lozano Blesa, Zaragoza; [3]Systemic Autoimmune Diseases Unit, Dept. of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, and Universitat Autònoma de Barcelona; [4]Dept. of Internal Medicine, Hospital Universitario Central de Asturias, Oviedo; [5]Autoimmune Diseases Unit, Dept.of Internal Medicine, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona; [6]Systemic Autoimmune Diseases Unit, Dept. of Internal Medicine, Hospital Universitario de Cabueñes, Gijón; [7]Dept. of Systemic Autoimmune Diseases, Institut Clinic de Medicina i Dermatología, Hospital Universitario Clínic, Barcelona; [8]Dept. of Internal Medicine, Hospital Universitario Virgen del Rocío, Sevilla; [9]Dept. of Internal Medicine, Hospital Universitario Miguel Servet, Zaragoza; [10]Autoimmune Diseases Research Unit, Dept. of Internal Medicine, Biocruces Bizkaia Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo; [11]Dept. of Internal Medicine, Unit of Systemic Autoimmune Diseases, Hospital Universitario San Cecilio, Instituto de Investigación Biosanitaria Ibs Granada, Facultad de Medicina Granada; [12]Unit of Autoimmune Diseases, Dept. of Internal Medicine, Hospital Clínico Universitario de Santiago, Santiago de Compostela, A Coruña; [13]Dept. of Internal Medicine, Hospital Universitario Virgen de las Nieves, Granada; [14]Department of Internal Medicine, Hospital Universitario La Paz, Madrid; [15]Dept. of Internal Medicine, Hospital Universitario y Politécnico La Fe, Valencia; [16]Dept. of Internal Medicine, Hospital Clinic, Barcelona; [17]Dept. of Internal Medicine, Hospital Clínico Universitario de Salamanca, Universidad de Salamanca-IBSAL, Salamanca; [18]Systemic Autoimmune Diseases Unit, Dept. of Internal Medicine, Consorci Hospitalari de Vic, Vic, Barcelona; [19]Dept. of Internal Medicine, Hospital General San Jorge, Huesca; [20]Dept. of Internal Medicine, Hospital Universitario Fundación Alcorcón, Madrid, Spain.

Abstract

Objective

To assess the associations and prognostic value of scleroderma patterns by nailfold videocapillaroscopy (NVC) in patients with systemic sclerosis (SSc) and cutaneous subsets.

Methods

At baseline, 1356 SSc patients from the RESCLE registry were compared according to the scleroderma pattern as Late pattern and non-Late pattern, which included Early and Active patterns. Patient characteristics, disease features, survival time and causes of death were analysed.

Results

Late pattern was identified in 540 (39.8%), and non-Late pattern in 816 (60.2%) patients (88% women; 987 lcSSc/251 dcSSc). Late pattern was associated to dcSSc (OR=1.96; p<0.001), interstitial lung disease (ILD) (OR=1.29; p=0.031), and scleroderma renal crisis (OR=3.46; p<0.001). Once the cutaneous subset was disregarded in an alternative analysis, both digital ulcers (DU) (OR=1.29; p<0.037) and anti-topoisomerase I antibodies (OR=1.39; p< 0.036) emerged associated with the Late pattern. By cutaneous subsets, associations with Late pattern were: (1) in dcSSc, acro-osteolysis (OR=2.13; p=0.022), and systolic pulmonary artery pressure >40 mmHg by Doppler echocardiogram (OR=2.24; p<0.001); and (2) in lcSSc, ILD (OR=1.38; p=0.028). Survival was reduced in dcSSc with Late pattern compared to non-Late pattern (p=0.049). Risk factors for SSc mortality in multivariate regression Cox analysis were age at diagnosis (HR=1.03; p<0.001), dcSSc (HR=2.48; p<0.001), DU (HR=1.38; p=0.046), ILD (HR=2.81; p<0.001), and pulmonary arterial hypertension (HR=1.99; p<0.001).

Conclusion

SSc patients with Late pattern more frequently present dcSSc and develop more fibrotic and vascular manifestations. Advanced microangiopathy by NVC identifies dcSSc patients at risk of reduced survival due to SSc-related causes.

Key words

systemic sclerosis, nailfold videocapillaroscopy, limited cutaneous SSc, diffuse cutaneous SSc, organ involvement, survival

Carles Tolosa-Vilella, MD, PhD
Mª del Mar Rodero-Roldán, MD
Alfredo Guillen-del-Castillo, MD, PhD
Adela Marín Ballvé, MD, PhD
Rafael Boldova-Aguar, MD, PhD
Begoña Marí-Alfonso, MD, PhD
Carlos Feijoo-Massó, MD
Dolores Colunga-Argüelles, MD
Manuel Rubio-Rivas, MD, PhD
Luis Trapiella-Martínez, MD, PhD
Nerea Iniesta-Arandia, MD, PhD
Eduardo Callejas-Moraga, MD, PhD
Francisco José García-Hernández, MD, PhD
Luis Sáez-Comet, MD, PhD
Cristina González-Echávarri, MD
Norberto Ortego-Centeno, MD, PhD
Mayka Freire, MD, PhD
Jose Antonio Vargas-Hitos, MD, PhD
Juan José Ríos-Blanco, MD, PhD
Jose Antonio Todolí-Parra, MD
Ignasi Rodríguez-Pintó, MD, PhD
Antonio-J. Chamorro, MD, PhD
Xavier Pla-Salas, MD, PhD
Ana Belén Madroñero-Vuelta, MD, PhD
Manuel Ruiz-Muñoz, MD
Vicent Fonollosa-Pla, MD, PhD
Carmen Pilar Simeón-Aznar, MD, PhD

A full list of the RESCLE investigators is given on page 1702.

Please address correspondence to:
Alfredo Guillen-del-Castillo,
Systemic Autoimmune Diseases Unit,
Department of Internal Medicine,
Hospital Universitario Vall d'Hebron,
Universitat Autònoma de Barcelona,
08208 Barcelona, Spain.
E-mail: alfredo.guillen@vallhebron.cat
ORCID ID: 0000-0003-0626-507X

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Introduction

Systemic sclerosis (SSc) is a chronic autoimmune systemic disease characterised by early hyperreactive and proliferative microvasculopathy, and chronic progressive fibrosis of skin and internal organs. A growing body of evidence supports the role of the scleroderma microvasculopathy as the primary pathogenic event mediated by autoimmunity (1-3). Structural and functional capillary alterations initially include dilated or giant capillaries and microhaemorrhages that may evolve to a progressive reduction of capillary density and vascular remodelling. These capillary changes are denominated "scleroderma pattern", which can be easily identified by nailfold videocapillaroscopy (NVC) in over 90% of SSc patients (4, 5). The scleroderma pattern has been categorised from initial to more advanced microvascular changes by Cutolo into three patterns: Early, Active and Late (4). Furthermore, capillary loss both at baseline and over time may predict future organ damage (6).

Some authors have described an association between advanced SSc patterns, in particular the Late pattern and different clinical manifestations such as digital ulcers (DU) (7, 8), telangiectasis, calcinosis, cutaneous sclerosis, pulmonary involvement and future cardiovascular events, as recently reviewed (9, 10). Furthermore, they suggested that the more severe the capillary abnormalities, the more severe the organ involvement.

Other studies have considered the association of NVC alterations with mortality in a secondary analysis (6, 11-18) but only a few relatively small cohorts have addressed the association of NVC patterns with mortality in SSc as a primary endpoint (14-17).

The present study is an analysis of a large cohort of SSc patients enrolled in the Spanish nationwide registry by RESCLE investigators. The objectives were to describe the disease characteristics associated with the most severe videocapillaroscopic features defined by the Late pattern, to assess whether this advanced pattern is a prognostic factor, and to evaluate the influence of the capillaroscopic pattern on survival and causes of death in the entire SSc cohort independent of previous poor prognostic factors. As not previously reported, these objectives were also investigated in SSc patients according to the cutaneous subsets.

Methods

Thirty-six Spanish centres participated in the recruitment of 1356 SSc patients up to December 2018 in the Spanish registry of SSc named RESCLE (Registro de ESCLErodermia), of the Autoimmune Diseases Study Group (GEAS) and the Spanish Society of Internal Medicine (SEMI). All participating centres obtained the local Ethical Committee approval, and all patients signed the informed consent. We considered SSc diagnosis when patients fulfilled criteria of the classification proposed by LeRoy *et al*. (19) and/or the 2013 ACR/EULAR criteria for SSc (20). Demographic, clinical, immunological, and qualitative NVC data encompassing 260 variables were collected prospectively from 2006 onwards, but retrospectively recorded formerly, in a multicentre approach following a standardised protocol, and then entered into the RESCLE database.

SSc patients were categorised following LeRoy *et al*. classification (19) into limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), and SSc sine scleroderma (ssSSc). Detailed definitions of clinical features, organ involvements, immunological features, and SSc and non SSc-related causes of death have been published elsewhere (21).

Baseline NVC was carried out in each participating centre following recommendations by the Working Group for the Study of Capillaroscopy (GREC), endorsed by the Autoimmune Diseases Study Group (GEAS). Fourteen members created the GREC and started regular meetings in 2006 with the aim of improving the knowledge of the capillaroscopic technique of all RESCLE researchers. Capillaroscopic 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, severe digital ischaemia phenomena or do not provide a correct display for

Table I. Demographic and clinical characteristics of 1356 SSc patients according to the SSc pattern by nailfold videocapillaroscopy.

Demographic and clinical characteristics, n (%) [a]	Overall SSc 1356 (100%)	Late pattern 540 (39.8%)	Non-Late pattern 816 (60.2%)	Univariate analysis OR (95% CI)	*p*
Age at first SSc symptom, mean ± SD, y	45.9 ± 16.3	46.1 ± 16.7	44.2 ± 15.9	-	0.443
Age at SSc diagnosis, mean ± SD, y	52.8 ± 15.4	52.8 ± 16.1	53.8 ± 15.0	-	0.951
Time from first symptom to SSc diagnosis, mean ± SD, y	7.2 ± 10.0	6.7 ± 9.9	7.8 ± 10.1	-	0.209
Female gender (%)	1196 (88%)	471 (87%)	725 (89%)	0.86 (0.61-1.20)	0.390
Time of follow-up, mean ± SD, y	15.2 ± 12.1	14.4 ± 11.4	15.8 ± 12.5	-	0.077
SSc subset on follow-up (n= 1356)					
Diffuse cutaneous SSc (%)	251 (19%)	141 (26%)	110 (13%)	2.27 (1.72-2.99)	<0.001
Limited cutaneous SSc (%)	987 (73%)	367 (68%)	620 (76%)	0.67 (0.53-0.85)	0.001
Peripheral vascular manifestations					
Raynaud's phenomenon as first symptom, (n=1334)	1115 (84%)	428 (82%)	687 (85%)	0.80 (0.60-1.07)	0.150
Raynaud's phenomenon (n=1355)	1312 (97%)	521 (96%)	791 (97%)	0.83 (0.45-1.53)	0.635
Telangiectasia (n=1351)	812 (60%)	338 (63%)	474 (58%)	1.21 (0.97-1.51)	0.100
Acro-osteolysis (n=874)	63 (7.2%)	42 (12%)	21 (4.0%)	3.30 (1.92-5.68)	<0.001
Digital ulcers (n=1354)	540 (40%)	241 (45%)	299 (37%)	1.39 (1.11-1.73)	0.004
Digestive involvement					
Oesophageal (n=1346)	771 (57%)	301 (56%)	470 (58%)	0.92 (0.74-1.15)	0.465
Gastric and/or intestinal (n=1346)	270 (20%)	101 (19%)	169 (21%)	0.88 (0.67-1.15)	0.367
Liver (n=1351)	118 (8.7%)	45 (8.4%)	73 (9.0%)	0.93 (0.63-1.36)	0.768
Pulmonary involvement:					
Interstitial lung disease (n=1352)	541 (40%)	248 (46%)	293 (36%)	1.53 (1.22-1.91)	<0.001
FVC < 70% (n=1213)	214 (18%)	103 (21%)	111 (15%)	1.49 (1.11-2.01)	0.009
DLCO/VA (% of expected) (n=1114)	80.5 ± 44.6	78.2 ± 37.8	82.1 ± 48.4	-	0.157
Pulmonary hypertension (n=1071)	272 (25%)	117 (27%)	155 (24%)	1.15 (0.87-1.52)	0.353
Pulmonary arterial hypertension (n=1080)	89 (8.2%)	29 (6.6%)	60 (9.3%)	0.69 (0.44-1.10)	0.142
sPAP mmHg, mean ± SD (n=1212)	519 (43%)	221 (45%)	298 (41%)	1.17 (0.93-1.47)	0.193
Heart involvement					
Pericarditis (n=602)	58 (9.6%)	35 (14%)	23 (6.7%)	2.21 (1.27-3.84)	0.005
Ischemic cardiopathy (n=605)	93 (15%)	33 (13%)	60 (17%)	0.70 (0.44-1.11)	0.139
Conduction alteration (n=606)	169 (28%)	65 (25%)	104 (30%)	0.79 (0.55-1.14)	0.234
Left ventricle diastolic dysfunction (n=1131)	281 (25%)	112 (25%)	169 (25%)	1.02 (0.78-1.35)	0.888
Scleroderma renal crisis (n=1353)	26 (1.9%)	20 (3.7%)	6 (0.74%)	5.19 (2.07-13.01)	<0.001
Osteomuscular involvement					
Arthritis (n=878)	185 (21%)	72 (21%)	113 (21%)	0.95 (0.68-1.33)	0.800
Myositis (n=879)	113 (13%)	44 (13%)	69 (13%)	0.96 (0.64-1.44)	0.918
Tendon friction rubs (n=876)	54 (6.2%)	30 (8.6%)	24 (4.6%)	1.97 (1.13-3.43)	0.021
Calcinosis (n=1352)	293 (22%)	144 (27%)	149 (18%)	1.62 (1.25-2.11)	<0.001
Flexion contractures (n=555)	108 (19%)	63 (31%)	45 (13%)	3.07 (1.99-4.73)	<0.001
Peripheral nervous system involvement (n=1215)	99 (8.1%)	31 (6.8%)	68 (9.0%)	0.74 (0.48-1.15)	0.195
Malignancy (n=1352)	150 (11%)	56 (10%)	94 (12%)	0.89 (0.63-1.26)	0.537

DLCO/VA: diffusing capacity for carbon monoxide corrected by alveolar volume; FVC: forced vital capacity; odds ratio, and 2-sided 95% confidence interval of the mean; sPAP: estimated systolic pulmonary artery pressure; SSc: systemic sclerosis; OR (95% CI).
[a]All data derived from 1356 patients except when indicated (n=).

image interpretation were disregarded. Patients with non-SSc pattern were excluded from the study. To avoid misclassification into less severe patterns, the Late pattern described by Cutolo was compared with the more preserved microvascular patterns (Early and Active) defined as the non-Late pattern (4).

Statistical analysis

Comparison between groups was performed using Student's *t*-test or Mann-Whitney test for continuous variables and chi-square test or Fisher's exact test for categorical data. A statistical evaluation was performed to identify significant differences and associations between both groups of patients, the entire SSc cohort and according to the cutaneous subsets: lcSSc, and dcSSc. A multivariate logistic regression analysis was performed to stablish the clinical associations with the Late pattern. To analyse the risk factors of death in SSc patients, some relevant variables (age at diagnosis, dcSSc, digital ulcers, interstitial lung disease [ILD], pulmonary arterial hypertension [PAH], scleroderma renal crisis [SRC], Late pattern, and presence of anti-topoisomerase antibodies [ATA]) were assessed using univariate and multivariate Cox proportional hazards models. Differences in variables with a *p*-value below 0.10 in univariate comparisons were retested by forward multivariate logistic regression. Only variables with >75% of the data were included in the multivariate analysis. Significance was defined as a *p*-value<0.05.

Survival curves from onset of symptoms were calculated using the Kaplan-Meier method, and differences were identified by log-rank test ratio. All statistical analyses were performed using the SPSS statistics version 24.0 for Windows (IBM SPSS Inc, Chicago, IL, USA).

Table II. Immunological features, causes of death and survival of 1356 SSc patients, according to the SSc pattern by nailfold video-capillaroscopy.

Autoantibodies, causes of death, and survival, n (%) [a]	SSc patients 1356 (100%)	Late pattern 540 (39.8%)	Non-late pattern 816 (60.2%)	Univariate analysis OR (95% CI)	*p*
Autoantibodies					
Anti-nuclear antibodies (n=1353)	1277 (94%)	512 (95%)	765 (94%)	1.15 (0.71-1.85)	0.630
Anti-centromere antibodies (n=1230)	631 (51%)	233 (48%)	398 (54%)	0.78 (0.62-0.99)	0.041
Anti-Topoisomerase I (n=1214)	218 (18%)	107 (23%)	111 (15%)	1.70 (1.26-2.28)	<0.001
Anti-RNA polymerase III (n=319)	36 (11%)	15 (15%)	21 (9.7%)	1.58 (0.78-3.22)	0.256
Anti-PM-Scl (n=751)	54 (7.2%)	23 (8.2%)	31 (6.6%)	1.26 (0.72-2.21)	0.466
Death from all causes, n (%)	225 (17%)	98 (18%)	127 (16%)	1.20 (0.90-1.61)	0.233
Causes of death					
Interstitial lung disease	23 (10%)	13 (13%)	10 (7.9%)	1.79 (0.75-4.27)	0.193
Pulmonary arterial hypertension	36 (16%)	18 (18%)	18 (14%)	1.36 (0.67-2.78)	0.464
ILD related pulmonary hypertension	18 (8.0%)	6 (6.1%)	12 (9.4%)	0.63 (0.23-1.73)	0.460
Scleroderma renal crisis	11 (4.9%)	8 (8.2%)	3 (2.4%)	3.67 (0.95-14.23)	0.061
Malignancy	32 (14%)	8 (8.2%)	24 (19%)	0.38 (0.16-0.89)	0.033
Ischaemic cardiopathy	7 (3.1%)	3 (3.1%)	4 (3.1%)	0.97 (0.21-4.44)	1.000
Stroke	4 (1.8%)	2 (2.0%)	2 (1.6%)	1.30 (0.18-9.41)	1.000
Chronic renal failure	2 (0.89%)	0 (0.0%)	2 (1.6%)	-	0.506
Sepsis	16 (7.1%)	8 (8.2%)	8 (6.3%)	1.32 (0.48-3.66)	0.610
Pulmonary embolism	2 (0.89%)	1 (1.0%)	1 (0.79%)	1.30 (0.08-21.03)	1000
Other causes	63 (28%)	23 (23%)	40 (31%)	0.67 (0.37-1.21)	0.231
Not specified	6 (2.7%)	4 (4.1%)	2 (1.6%)	2.66 (0.48-14.83)	0.408
SSc-related causes of death, n (%) (n=219)	111 (51%)	56 (60%)	55 (44%)	1.88 (1.09-3.23)	0.029
Median survival time since first symptom, y (IQR)	43.8 (39.4-48.2)	47.2 (38.7-55.7)	43.8 (39.3-48.3)	-	0.138
Cumulative survival rates since disease onset					
At 5 years	0.966	0.948	0.977	-	0.008
At 10 years	0.932	0.904	0.951	-	0.003
At 20 years	0.824	0.812	0.831	-	0.105
At 30 years	0.702	0.675	0.720	-	0.057

[a]All data derived from 1356 patients except when indicated (n=). ILD: interstitial lung disease; IQR: interquartile range; SSc: systemic sclerosis.

Results

Characteristics of SSc patients with scleroderma pattern

Demographic and clinical characteristics for the entire SSc cohort (n=1356), according to the presence of Late pattern (n=540, 39.8%) or non-Late pattern (n=816, 60.2%) are shown in Table I. Out of 1356, 1328 (98%) evaluated patients fulfilled the 2013 ACR/EULAR SSc criteria. The mean follow-up time was 15.2±12.1 years. Most patients were female (88%) and were classified as lcSSc (n=987, 73%) followed by dcSSc (n=251, 19%), and SSc sine scleroderma (ssSSc) (n=118, 8%). The mean age at the first SSc symptom and SSc diagnosis was 45.9±16.3 and 52.8±15.4 years old, respectively. The time elapsed from the first symptom to SSc diagnosis was similar for both NVC groups.

Associations according to the scleroderma pattern in the entire SSc cohort

Patients with Late pattern showed higher frequency of dcSSc (26% *vs*. 13%, $p<0.001$) and lower of lcSSc (68% *vs*. 76%, $p=0.001$) (Table I). Conversely, the prevalence of Late pattern was higher in dcSSc than in lcSSc patients (56% *vs*. 37.2%, $p<0.001$). The Late pattern was also associated with a higher prevalence of acro-osteolysis, DU, ILD with a more severe lung restrictive pattern, pericarditis, SRC, calcinosis, flexion contractures, and anti-topoisomerase I antibodies compared to patients with non-Late pattern (Table I and II). Otherwise, non-Late pattern was associated more frequently to lcSSc, and anti-centromere antibodies (ACA). Of note, SRC was more present in patients with Late pattern and dcSSc than lcSSc (11% *vs*. 1.1%, respectively; $p<0.001$). Immunological features, causes of death, and cumulative survival rates of the entire SSc cohort according to NVC patterns are summarised in Table II. Two hundred and twenty-five (17%) patients died, and the cause of death could be identified in 219 which were SSc-related in 111 (51%) cases. Mortality rate was similar for both NVC groups with a median survival time from first SSc symptom of 43.8 years (range: 39.4–48.2) for the entire SSc cohort (Fig. 1a). However, patients with Late pattern died more frequently from SSc-related causes than patients with non-Late pattern (60% *vs*. 44%, $p=0.029$). Non-SSc-related causes of death prevailed in patients with non-Late pattern, mainly related to malignancies (Table II).

Associations according to the scleroderma pattern in dcSSc

Out of 1356 SSc patients, 251 (19%) were classified as dcSSc. Late pattern was recorded in 141 (56%), and non-Late pattern in 110 (44 %). The mean age at the first symptom and SSc diagnosis as well as the elapsed time from first symptom to SSc diagnosis was similar for both NVC patterns. Late pattern was associated with a higher prevalence of patients with estimated systolic pulmonary artery pressure (sPAP)>40 mm Hg by Doppler echo-

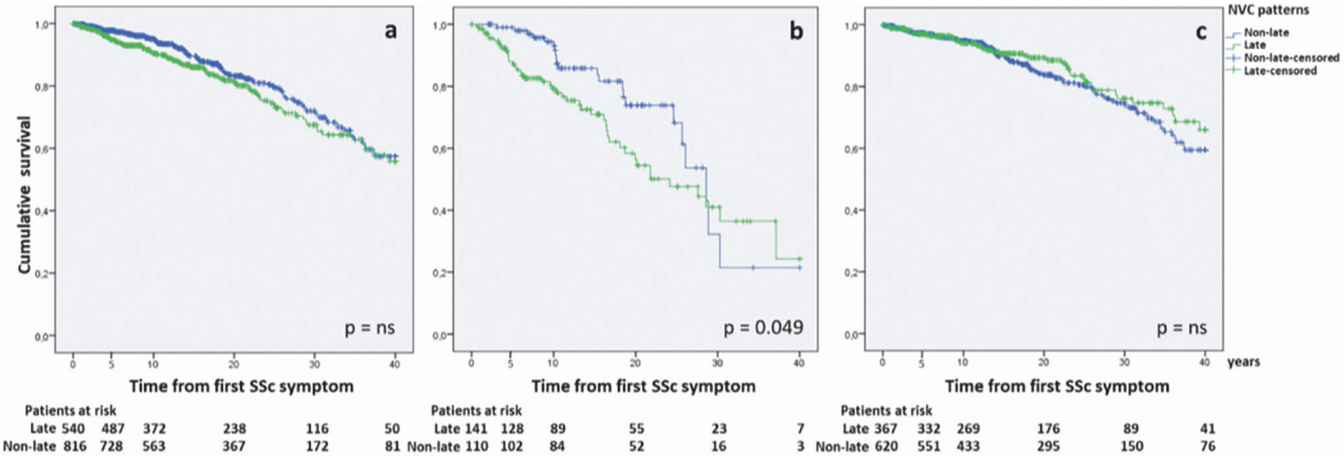

Fig. 1. Kaplan-Meier survival curves for SSc patients comparing Late pattern and non-Late pattern from the first SSc symptom: (a) entire SSc cohort, (b) diffuse cutaneous SSc subset, and (c) limited cutaneous SSc subset.

cardiography (52% *vs*. *35%*; *p*=0.008), SRC (11% *vs*. 2.8%; *p*=0.014), and flexion contractures (57% *vs*. 36%; *p*=0.023). No significant differences in immunological features were identified (Supplementary Tables S1 and S2).

Mortality rate was similar for dcSSc patients and either pattern, but SSc-related causes of death were more common in patients with the Late pattern than patients with the non-Late pattern (73% *vs*. 38%; *p*=0.005), mainly related to ILD (24% *vs*. 4%; *p*=0.046). In contrast, non-SSc-related causes of death were more frequent in patients with the non-Late pattern, mainly related to malignancies (40% *vs*. 4.3%; *p*<0.001). The median survival time from the first SSc symptom was shorter in patients with Late pattern than those with non-Late pattern (24.1 *vs*. 28.6 years, respectively), with a poorer survival according to the survival analysis (log-rank test *p*=0.049) (Suppl. Table S2, Fig. 1b).

Associations according to the scleroderma pattern in lcSSc

Out of 1356 SSc patients, 987 (73%) were classified as lcSSc. A Late pattern was identified in 367, and a non-Late pattern in 620 patients (37% *vs*. 63%, respectively; *p*=0.001). No differences were identified either in the mean age at the first SSc symptom and SSc diagnosis or in the elapsed time from first symptom to SSc diagnosis. Late pattern was more frequently associated with acro-osteolysis (12% *vs*. 3.4%; *p*<0.001), pericarditis (13% *vs*. 6.7%; *p*=0.038), flexion contractures (19% *vs*. 8.1%; *p*=0.005), and ATA (13% *vs*. 8.5%; *p*=0.046). Nevertheless, non-Late pattern showed more prevalence of cardiac conduction disturbances (32% *vs*. 22%; *p*=0.037), and peripheral nervous system involvement (9.4% *vs*. 5.1%; *p*=0.026) (Suppl. Tables S3 and S4).

Mortality rate and causes of death were similar for lcSSc patients in both NVC groups, with no differences in SSc-related or non-SSc-related causes. Median survival time from the first SSc symptom was similar for lcSSc patients in both patterns, with no differences in survival analysis (Suppl. Table S4, Fig. 1c).

Table III. Multivariate analysis according to the SSc pattern (Late *vs*. non-Late) by nailfold videocapillaroscopy of the entire SSc cohort and according to the cutaneous subsets. Only variables with > 75% of the data were included in the model.

SSc patients evaluated, n (%)	Late pattern OR (95% CI)	*p*
SSc, 1351 (99.6%)		
dcSSc	1.96 (1.46-2.63)	<0.001
Interstitial lung disease	1.29 (1.02-1.63)	0.031
Scleroderma renal crisis	3.46 (1.35-8.82)	<0.001
SSc, once disregarded the cutaneous subset, 1211 (89.3%)		
Interstitial lung disease	1.58 (1.23-2.02)	<0.001
Scleroderma renal crisis	3.38 (1.29-8.82)	0.013
Digital ulcers	1.29 (1.02-1.65)	0.037
Anti-topoisomerase I antibodies	1.39 (1.02-1.90)	0.036
dcSSc, 228 (90.8%)		
Acro-osteolysis	2.13 (1.12-4.05)	0.022
sPAP > 40 mm Hg	2.24 (1.30-3.87)	<0.001
lcSSc, 893 (90.5%)		
Interstitial lung disease	1.38 (1.04-1.84)	0.028

sPAP: estimated systolic pulmonary artery pressure; SSc: systemic sclerosis; dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc.

Multivariate logistic regression analysis according to the scleroderma pattern in SSc and cutaneous subsets

Variables in the entire SSc cohort independently associated with the presence of Late pattern by NVC were dcSSc subset, ILD, and SRC (Table III). To identify whether other clinical manifestations were associated with the advanced capillaroscopic pattern that might be hidden by the cutaneous sclerosis extent, an alternative logistic regression model was performed once this variable was disregarded. Results of this alternative model confirmed the association of both ILD and SRC with the Late pattern but revealed that DU and ATA were also associated. Accord-

ing to the cutaneous subsets, the variables associated to Late pattern were: (1) in dcSSc, acro-osteolysis and estimated sPAP>40 mmHg; and (2) in lcSSc, ILD.

Predictors of death in SSc patients

By univariate Cox regression analysis, age at diagnosis, dcSSc, DU, ILD, PAH, SRC (HR: 2.97; $p<0.001$), and ATA (HR: 1.56; $p=0.008$) showed an increased risk of death (data not shown). However, neither the Late pattern by NVC nor the presence of ATA were found to be predictors of death. In the multivariate Cox regression model, age at diagnosis (HR: 1.03; 95% CI: 1.02-1.04; $p<0.001$), dcSSc (HR: 2.48; 95% CI: 1.65-3.74; $p<0.001$), DU (HR: 1.38; 95% CI: 1.01-1.88; $p=0.046$), ILD (HR: 2.81; 95% CI: 1.91-4.14; $p<0.001$), and PAH (HR: 1.99; 95% CI: 1.47-2.69; $p<0.001$) were confirmed as independent risk factors for mortality.

Discussion

In this cross-sectional study from the Spanish RESCLE registry, 1356 SSc patients were clustered according to the capillaroscopic pattern by NVC. To our knowledge, this is the largest study to estimate the direct impact of NVC patterns on organ involvement and survival, considering the entire SSc cohort, the cutaneous subsets, and baseline disease features.

Associations between NVC patterns and internal organ involvement represent a shift of interest from diagnostic to prognostic usefulness of this technique in SSc. Thus, the presence of avascular areas on NVC examination has been associated with a worse prognosis related to the occurrence of clinical manifestations, including proximal extension of cutaneous sclerosis and the development of both vascular and fibrotic manifestations, in agreement with our results (8, 14-16, 22-26).

Our data show that Late pattern was associated with the dcSSc subset, ILD, and SRC but also with DU and ATA when the cutaneous subset variable was not taken into account in an alternative logistic regression analysis. According to cutaneous subset, the presence of Late pattern in dcSSc patients was associated with acro-osteolysis and an estimated sPAP >40 mmHg. However, Late pattern in lcSSc patients was only associated with ILD.

In the present study, a Late pattern was identified in 39.8% and non-Late pattern in 60.2% of the SSc cohort. Patients with Late pattern developed dcSSc twice as often as patients with non-Late pattern in agreement with other studies, Similarly, previous investigations reported that the Late pattern was the most frequent scleroderma pattern in dcSSc patients. This bidirectional relationship reflects the parallelism between advanced microvascular changes and the severity of skin involvement, as well as its association with some clinical manifestations (6-9, 13, 22, 23, 25, 27-34).

An association between advanced capillaroscopic abnormalities in SSc and the presence of peripheral vasculopathy has been suggested (6-8, 27, 28, 35, 36). Our data show that DU are present more frequently in patients with the Late pattern by univariate analysis, but not in the multivariate analysis. Interestingly, once diffuse cutaneous extent was disregarded in an alternative logistic regression analysis, DU emerged as associated with the Late pattern. This suggests that the cutaneous sclerosis extent itself encompasses some clinical manifestations that appear when it is excluded from the analysis.

Acro-osteolysis is a rare peripheral vasculopathy in SSc. Although it was recognised more frequently in patients with Late pattern, regardless of the cutaneous subset, it was only independently associated with capillary loss in dcSSc patients. We confirmed this association (37) suggesting that impaired blood flow related to capillary loss may lead to bone resorption and then stimulate neoangiogenesis in an attempt of vascular recovery. The high degree of digital tissue fibrosis present in dcSSc patients probably limits the process of angiogenesis which may become insufficient to repair vascular damage.

SRC was detected in 1.5% of the SSc cohort. This life-threatening organ involvement was more than threefold independently associated with the Late pattern. Interestingly, although this renal microangiopathy is usually associated with diffuse subset, our data show that SRC continued to be associated with the Late pattern once diffuse cutaneous subset was ruled out in the alternative analysis. This suggests that the advanced capillary changes observed by NVC may also indicate the possible coexistence of renal endothelial damage leading to SRC. Previously, a large EUSTAR study observed that SSc patients with Late pattern only had a trend to higher prevalence of SRC compared to Early and Active patterns (25).

The course and prognosis of SSc are mainly determined by the extent and severity of internal organ involvement, in particular cardiopulmonary manifestations, the main causes of death in this population (13, 38). In the entire SSc cohort, we detected no difference in the prevalence of PAH by right heart catheterisation or in the prevalence of sPAP>40 mmHg estimated by Doppler echocardiography according to NVC patterns. However, the Late pattern in dcSSc patients was associated with a higher prevalence of patients with estimated sPAP>40 mmHg, in agreement with other studies (29, 33), suggesting that the capillary derangement may be a risk factor for pulmonary hypertension. Although some cross-sectional and longitudinal studies have highlighted an association between lower capillary density and PAH suggesting that it reflects what is going on in the pulmonary circulation (6, 8, 24-26, 34, 39) other studies differ on this issue (29, 40). Discrepancies may be related to different methodological approaches and PAH assessment tools.

ILD is the most common lung involvement in SSc and is a major cause of reduced survival (1, 13). According to our data, SSc patients with Late pattern developed ILD more frequently and this association was maintained in lcSSc patients but not in the dcSSc subset. In a remarkable investigation, Markusse *et al*. concluded that the presence of a specific autoantibody is independent of the development of microangiopathy (33). Furthermore, the severity of the NVC pattern may reveal an increased risk of cardiopulmonary manifestations even when the autoantibody profile was con-

sidered low risk. Thus, the association of ILD with the capillaroscopic patterns was independent of the presence of any of the autoantibodies tested, which included ACA, ATA, and RNA polymerase III antibodies (33). It is noteworthy in our series that ILD was associated with a Late pattern in SSc patients, particularly in lcSSc, suggesting that advanced microvascular changes may be indicative of the presence of this pulmonary complication regardless of cutaneous extension and autoantibody profile. It is in agreement with some previous studies, which also associated ILD or worse FVC and DLCO values with the presence of avascular areas, reduced capillary density or Late pattern (29, 33, 41, 42). Moreover, other investigations also correlated capillary drop out with lung involvement both at baseline and during follow-up, suggesting a common pathophysiological mechanism for ILD based on vascular damage (16, 23, 26, 27, 29, 31-33, 42, 43). In this regard, our group highlighted that ILD was independently associated with the presence of DU in SSc (21). Thus, capillary loss is associated with a wide spectrum of clinical manifestations, emphasising the significant role of microangiopathy in the SSc outcome, especially in relation to the lung. Most evidence suggests that NVC may be useful as a complementary test to predict cardiopulmonary complications, in the same way as the skin sclerosis extension or the autoantibody profile (19, 44-47).

SSc-specific antibodies are useful for diagnosing, classifying and predicting the natural course of SSc (46). A correlation between capillaroscopic patterns and some autoantibodies has been reported, suggesting a relationship between autoimmunity and vasculopathy (16, 25, 26, 32, 40, 48). Our data showed that ATA emerged as associated with an advanced NVC pattern when the extent of cutaneous sclerosis was not taken into account. In contrast, the relationship between ACA and non-Late pattern was not statistically significant. In this regard, Cutolo *et al*. confirmed that patients with an Active or Late pattern were more likely to be ATA-positive than patients with an Early pattern (48). More recently, Van Leeuwen *et al*. also observed that ATA-positive SSc patients developed severe microangiopathy more frequently compared to ACA-positive patients (26). Therefore, the evidence points to an association between a specific antibody response and the severity of microangiopathy.

Our data showed that mortality was not influenced by NVC patterns in the entire SSc cohort, but survival was significantly shortened for dcSSc patients with Late pattern**.** Some previous studies also reported shorter survival associated to a higher degree of capillary drop out (13-15, 17). Nevertheless, NVC patterns were non-independent risk factors for a worse prognosis, in agreement with the present study (6, 11-18).

The challenge in managing scleroderma is to define the disease course of each patient as early as possible, predict the clinical outcome and determine the appropriate intervention. In this sense, the autoantibody profile is increasingly proposed to subcategorise SSc patients, although it is not always consistent with the cutaneous sclerosis extent (12, 49). Nowadays, NVC is also recognised as the most practical technique to instantly visualise skin capillaries and could therefore help predict future organ involvement and survival (6, 8, 9, 50-52). If the prognostic role of NVC is confirmed, it could be used to identify more homogeneous SSc phenotypes, based on the cutaneous sclerosis extent, serological profile, and NVC pattern which would allow modification of the disease course.

Our study has several strengths. First, this series is a large Spanish multicentre cohort of SSc patients and therefore derived from the same geographical location. Secondly, the long-term follow-up period allows us to better establish the relationship between baseline NVC changes and associations with organ involvement and survival for the entire SSc series but also according to cutaneous subsets. Third, although longitudinal NVC examinations may provide more accurate prognostic data, this study reinforces the hypothesis of the association between baseline NVC changes and future organ involvement and therefore encourages its incorporation as a useful tool for better phenotyping SSc patients. Limitations of this research include the missingness of some data and the loss to follow-up inherent in observational studies. Patients with non-scleroderma patterns such as normal or unspecific patterns were excluded from the study to avoid the overestimation of Late pattern associations or SSc patients with milder disease. To avoid misclassification between Early and Active SSc patterns, we analysed both patterns together as a non-Late pattern. However, this does not allow us to determine the associations or prognosis separately.

In conclusion, our results highlight the usefulness of baseline NVC in defining a subgroup of patients who may be associated with severe organ involvement and worse prognosis. Thus, the Late pattern was independently associated with dcSSc subset, ILD, and SRC but also with DU and ATA once the cutaneous sclerosis extent was disregarded in an alternative analysis. According to the cutaneous subset, the Late pattern was associated to acro-osteolysis and sPAP >40 mmHg by Doppler echocardiography in dcSSc patients but also with poorer survival. In lcSSc, Late pattern was associated with ILD. SSc-related causes of death were more frequent in patients with advanced capillary abnormalities. Thus, NVC may be a practical technique to instantly predict future organ damage and prognosis in some SSc subgroups and may therefore be useful in disease phenotyping.

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Appendix

Spanish RESCLE Registry Investigators (in alphabetical order)

R. Boldova, E. Callejas-Moraga, C. Carbonell, M.J. Castillo, A.J. Chamorro, D. Colunga, B. de Escalante, M.V. Egurbide, G. Espinosa, C. Feijoo, R.A. Fernández de-la-Puebla, V. Fonollosa, M. Freire, F.J. García Hernández, C. González-Echávarri, A. Guillén-del-Castillo, N. Iniesta, A.B. Madroñero, B. Marí, A. Marín, N. Ortego-Centeno, I. Perales, M. Pestaña, X. Pla-Salas, I. Pons, J.J. Ríos Blanco, M.M. Rodero, M. Rodríguez-Carballeira, I. Rodríguez Pintó, M. Rubio Rivas, M. Ruiz Muñoz, L. Sáez-Comet, P. Segovia, C.P. Simeón-Aznar, J.A. Todolí, C. Tolosa-Vilella, L. Trapiella, J.A. Vargas-Hitos.

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