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Nailfold capillaroscopy in systemic sclerosis: Data from the EULAR scleroderma trials and research (EUSTAR) database

Francesca Ingegnoli [a,*], Ilaria Ardoino [b], Patrizia Boracchi [b], Maurizio Cutolo [c], EUSTAR co-authors Paolo Airò [3], Lidia P. Ananieva [4], Codrina Ancuta [5], Luis Eduardo Andrade [6], Radim Becvar [7], Alessia Benenati [8], Paola Caramaschi [9], Patricia E. Carreira [10], Giovanna Cuomo [11], Nemanja Damjanov [12], Oliver Distler [13], Rosario Foti [8], Serena Guiducci [14], Eric Hachulla [15], John Highton [16], Cristiane Kayser [6], Chiara Lubatti [1], Marco Matucci Cerinic [14], Florian Meier [17], Pier Luigi Meroni [1], Carmen Marina Mihai [18], Ewa Morgiel [19], Ulf Müller-Ladner [17], Esthela Loyo [20], Vera Ortiz [21], Valeria Riccieri [22], Agneta Scheja [23], Simona Skacelova [7], Vanessa Smith [24], Bojana Stamenkovic [25], Simon Stebbings [16], Viktor Stoica [18], Alberto Sulli [2], Jacek Szechinski [19], Alan Tyndall [26], Gabriele Valentini [11], Ulrich Walker [26], Silvana Zeni [1], Maja Zlatanovic [12]

[1] *Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical Sciences & Community Health, University of Milano, Milano, Italy*
[2] *Research Laboratory and Academic Unit of Clinical Rheumatology, University of Genova, Genova, Italy*
[3] *Spedali Civili di Brescia Servizio di Reumatologia Allergologia e Immunologia Clinica, Spedali Civili, Brescia, Italy*
[4] *Institute of Rheumatology, Russian Academy of Medical Science, Moscow, Russia*
[5] *Rheumatology Department, Rehabilitation Hospital, Iasi, Romania*
[6] *Universidade Federal de São Paulo - Disciplina de Reumatologia, São Paulo, SP, Brazil*
[7] *Institute of Rheumatology, 1st Medical School, Charles University, Praha, Czech Republic*
[8] *U.O. di Reumatologia, A.O.U. Policlinico Vittorio Emanuele Università di Catania, Catania, Italy*
[9] *Università degli Studi di Verona, Dipartimento di Medicina Clinica e Sperimentale Reumatologia-Medicina Interna B, Verona, Italy*
[10] *Servicio de Reumatología Hospital 1De Córdoba, Madrid, Spain*
[11] *Dipartimento Medicina Clinica e Sperimentale "F-Magrassi" II Policlinico U.O. Reumatologia, Napoli, Italy*
[12] *Institute of Rheumatology Belgrade, Serbia*
[13] *Department of Rheumatology, University Hospital Zürich, Zürich, Switzerland*
[14] *University of Florence, Department of Bio-Medicine, Division of Rheumatology, Florence, Italy*
[15] *Department of Internal Medicine Hôpital Claude Huriez, Lille cedex, France*
[16] *Dunedin School of Medicine, Dunedin, New Zealand*
[17] *Lehrstuhl für Innere Medizin mit Schwerpunkt Rheumatologie der Justus-Liebig-Universität Giessen Abteilung für Rheumatologie und Klinische Immunologie, Kerckhoff-Klinik, Bad Nauheim, Germany*
[18] *Department of Internal Medicine and Rheumatology ClinicIon Cantacuzino Clinical Hospital Bucharest, Romania*
[19] *Department of Rheumatology and Internal Diseases, Wroclaw University of Medicine, Wroclaw, Poland*
[20] *Reumatologia e Inmunologia Clinica, Hospital Regional Universitario Jose Ma Cabral y Baez Clinica Corominas Restauracion Santiago, Dominican Republic*
[21] *Santamaria Rheumatology Granollers General Hospital, Granollers, Spain*
[22] *Divisione di Reumatologia, Università di Roma La Sapienza Dipartimento di Clinica e Terapia medica applicata, Policlinico Umberto I, Roma, Italy*
[23] *Department of Rheumatology, Lund University Hospital, Lund, Sweden*
[24] *University of Ghent, Department of Rheumatology, Gent, Belgium*
[25] *Institute for prevention, treatment and rehabilitation rheumatic and cardiovascular disease Niska Banja, Serbia*
[26] *Rheumatologische Universitätsklinik Felix Platter Spital, Basel, Switzerland*

[a] *Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical Sciences & Community Health, University of Milano, Milano, Italy*
[b] *Medical Statistics and Biometry, Department of Clinical Sciences & Community Health, University of Milano, Milano, Italy*
[c] *Research Laboratory and Academic Unit of Clinical Rheumatology, University of Genova, Genova, Italy*

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ABSTRACT

Objective: The aims of this study were to obtain cross-sectional data on capillaroscopy in an international multi-center cohort of Systemic Sclerosis (SSc) and to investigate the frequency of the capillaroscopic patterns and their disease-phenotype associations.
Methods: Data collected between June 2004 and October 2011 in the EULAR Scleroderma Trials and Research (EUSTAR) registry were examined. Patients' profiles based on clinical and laboratory data were obtained by

* Corresponding author at: Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical & Community Sciences, University of Milano, Piazza Cardinal Ferrari 1, 20122 Milano, Italy. Fax: +39 0258296315.
E-mail address: francesca.ingegnoli@unimi.it (F. Ingegnoli).

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cluster analysis and the association between profiles and capillaroscopy was investigated by multinomial logistic regression.
Results: 62 of the 110 EUSTAR centers entered data on capillaroscopy in the EUSTAR database. 376 of the 2754 patients (13.65%) were classified as scleroderma pattern absent, but non-specific capillary abnormalities were noted in 55.48% of the cases. Four major patients' profiles were identified characterized by a progressive severity for skin involvement, as well as an increased number of systemic manifestations. The "early" and "active" scleroderma patterns were generally observed in patients with mild/moderate skin involvement and a low number of disease manifestations, while the "late" scleroderma pattern was found more frequently in the more severe forms of the disease.
Conclusion: These data indicate the importance of capillaroscopy in SSc management and that capillaroscopic patterns are directly related to the extent of organ involvement.

Introduction

Systemic sclerosis (SSc) is a severe connective tissue disease in which vascular dysfunction, tissue fibrosis and immune dysregulation are key events. SSc has a heterogeneous clinical presentation, but skin and vascular changes are the hallmark of the disease (Geyer and Muller-Ladner, 2011; Herrick, 2012). Pathological microvascular findings in SSc document a significant loss of the peripheral vascular network, with loss of capillaries, deficient vascular repair and the absence of new vessel growth, and subsequent tissue ischemia and fibrosis (Brown and O'Leary, 1925; Herrick and Cutolo, 2010; Kuwana et al., 2004).

The sequence of these alterations in the microcirculation can be observed using a reliable, rapid, non-invasive examination such as nailfold capillaroscopy, which can be regarded as the most valuable technique for assisting the early diagnosis of SSc and monitoring the evolution of microangiopathy in overt SSc (Avouac et al., 2011; Cutolo et al., 2010). Capillaroscopy is a powerful *in vivo* tool not only in screening patients with Raynaud's phenomenon for underlying scleroderma spectrum disorders (Ingegnoli et al., 2008, 2010; Nagy and Czirjak, 2004; Vayssairat et al., 1982), but also in detecting the progressive microvascular damage during the course of SSc (Herrick and Cutolo, 2010).

The distinctive and identifiable morphological nailfold changes observed in patients with SSc have been extensively studied; they include enlarged loops, giant capillaries, neovascularization, capillary loss, and disrupted architecture of the nailfold microvascular network (Bukhari et al., 1996; Herrick and Cutolo, 2010; Herrick et al., 2010; Maricq and LeRoy, 1973; Maricq et al., 1980, 1983). These microvascular scleroderma specific capillaroscopy abnormalities were initially described by Maricq (Maricq et al., 1980, 1983) and called "scleroderma patterns"; subsequently they were classified into 3 different patterns, which include an "early" pattern (*i.e.* few enlarged/giant capillaries, few capillary hemorrhages, no evident loss of capillaries), an "active" pattern (*i.e.* frequent giant capillaries, frequent capillary hemorrhages, mild disorganization of the capillary network), and a "late" pattern (*i.e.* irregular enlargement of the capillaries, few or absent giant capillaries, hemorrhages, and extensive avascular areas) (Cutolo et al., 2000).

In order to clarify with further aspects the reported associations between nailfold capillary abnormalities and clinical and/or laboratory features (Bredemeier et al., 2004; Caramaschi et al., 2007; Chen et al., 1984; Cutolo et al., 2004; Hofstee et al., 2009; Lovy et al., 1985; Smith et al., 2012; Sulli et al., 2012) it was decided to evaluate a large multinational group of patients with SSc such as the international multicenter cohort of the EULAR Scleroderma Trials And Research (EUSTAR) registry.

Therefore, the steps of this cross-sectional study were:

- To ascertain the use of capillaroscopy in everyday practice in the EUSTAR centers. Due to the fact that data on capillaroscopy were not mandatory points in the database, a lot of missing data on this topic were present. Therefore, EUSTAR centers were invited to give additional information by a short survey for assessing whether and how capillaroscopy is performed.
- To define a proper target population and to evaluate if the sample of patients in the study was representative of the population. After completing as much as possible the missing information, the target population was identified with inclusion and exclusion criteria. The representativity of the sample studied was evaluated comparing the characteristics of patients with and without information on capillaroscopy.
- To determine the frequency of capillaroscopic patterns (*i.e.* scleroderma pattern vs non-scleroderma pattern) in adult SSc patients, and to identify disease-phenotype associations. For this purpose clinical and demographic characteristics of patients with and without scleroderma pattern were compared.
- To examine the prevalence of the three different scleroderma patterns (*i.e.* early, active or late) and to better characterize these patterns in terms of their association with disease measurements, clinical and laboratory features. With this aim clinical and demographic characteristics of patients with early, active or late scleroderma pattern were compared.
- To evaluate jointly the association between clinical/laboratory information and capillaroscopic patterns. For this purpose, firstly groups (profiles) of patients which were homogeneous for their clinical/laboratory characteristics were obtained by cluster analysis; thus, these patients' profiles were related with capillaroscopy data.

Materials and methods

The EUSTAR database

This EUSTAR study on capillaroscopy is based on data collected from the SSc patients entered in the EUSTAR registry. This database was launched in June 2004 and documents a multi-national, prospective and open SSc cohort. Participating medical centers have entered the data of consecutive patients into a specific database, which was definitely locked for this study in October 2011. The structure and minimal essential dataset (MEDS) of the EUSTAR database have been previously described (Tyndall et al., 2005; Walker et al., 2007). The MEDS was constructed with the consensus of EUSTAR members, and includes demographic and laboratory data, disease duration and organ involvement.

To guarantee the quality and the standardization of the clinical and capillaroscopic assessments, EUSTAR and EULAR regularly held courses to coach, update and standardize the assessment of SSc patients. In every course there is a coaching session specifically devoted to capillaroscopy. Moreover additional coaching materials are available on the EUSTAR website.

As shown in Fig. 1, the data on capillaroscopy are assessed in the following manner: a) scleroderma pattern as "present" or "absent"; and b) in its presence, specification of its type (*i.e.* early, active or late). These 2 points are not mandatory. Capillaroscopy examination was performed generally on eight digits (excluded thumbs) using the technical equipment available in each EUSTAR center, ranging from videocapillaroscope to dermatoscope with magnification from 20× to 200×.

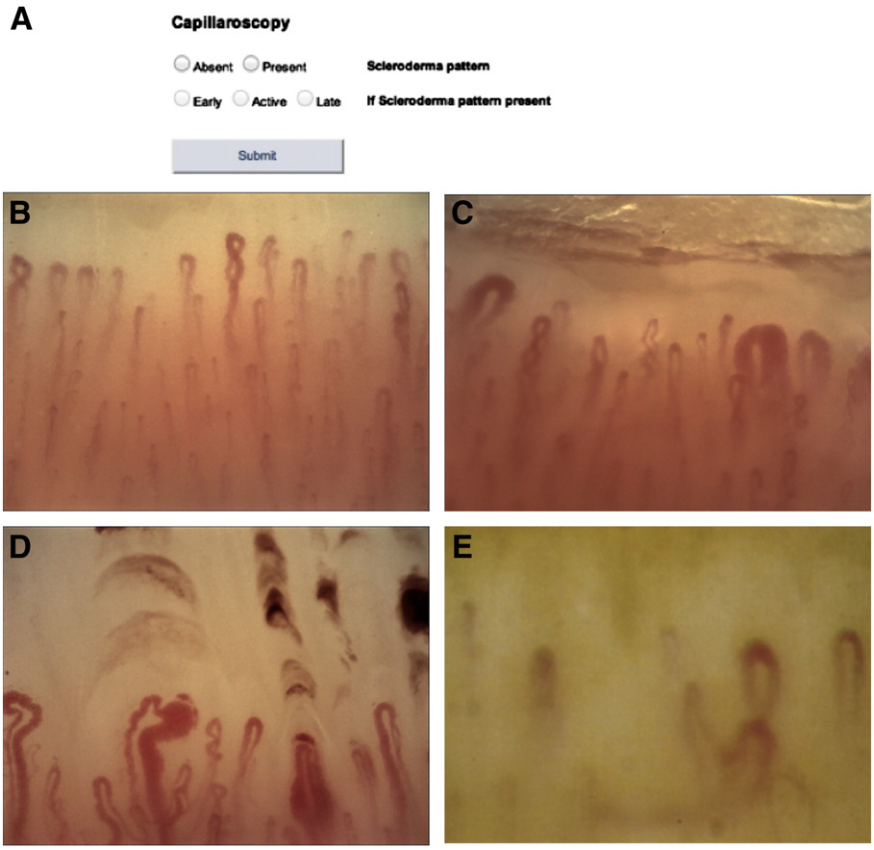

Fig. 1. Items on capillaroscopy of the Minimal Essential Dataset (MEDS) in the EUSTAR registry (A). The data are assessed as scleroderma patter "absent" (B) or "present"; and in its presence, specification of its type: early (C), active (D) or late (E). Magnification 200×.

The use of different instruments has been allowed based on the results of previous studies on the agreement between capillaroscopic methods (Anders et al., 2001; Wildt et al., 1999, 2012), and because data collected in the EUSTAR registry are based on an overall capillaroscopic pattern characterized only by morphological capillary abnormalities easily identifiable with all the tools employed.

All of the patients included in the database gave their informed consent, and the study was approved by the various institutional Ethics Committees.

Study design

For the first purpose of this study, EUSTAR centers were invited to fill out a specifically designed questionnaire, which required them to give the reason for any incomplete capillaroscopic information (*i.e.* capillaroscopy not routinely assessed, performed only when specifically requested, assessed but not recorded in the database, or recently introduced) and to specify the instrument used (*i.e.* video-capillaroscope, microscope, dermatoscope or other). To ensure security and confidentiality, each participant received a personal e-mail invitation with individual access to an attached standardized questionnaire; the same form was also distributed and collected during a EUSTAR meeting.

In the following parts of this study, eligible patients were adult SSc of EUSTAR centers in which capillaroscopy exam was routinely performed. Therefore, data from the EUSTAR database were analyzed by excluding: a) patients with juvenile SSc (Zulian et al., 2007) and, b) EUSTAR centers without any data on capillaroscopy or with less than 15% of capillaroscopic reports or with less than 5 capillaroscopies were excluded.

The MEDS data closest to the date of capillaroscopy were used in the analysis. From the collected MEDS data is not possible to describe the capillary abnormalities when scleroderma pattern is absent. In its absence, EUSTAR participants were invited to fill out a standardized form, which required them to specify the capillary pattern (normal or capillary abnormalities other than a scleroderma pattern).

For all patients with SSc, disease activity was assessed using the activity indices described by the European Scleroderma Study Group (Valentini et al., 2001, 2003). According to these criteria, SSc was considered active if the overall score was ≥ 3. Disease stages were defined as: early limited cutaneous (lc)-SSc (disease duration <5 years), intermediate/late lcSSc (disease duration ≥ 5 years), early diffuse cutaneous (dc)-SSc (disease duration <3 years), and intermediate/late dcSSc (disease duration ≥ 3 years) (Medsger and Steen, 1996). Modified Rodnan skin score (mRSS) has been classified as: normal $= 0$, mild between 1 and 14, moderate between 15 and 29, severe between 30 and 39, endstage >40 (Medsger et al., 2003).

Statistical analysis

The Chi Squared Test with Bonferroni correction for multiple comparisons was used to investigate differences in distribution of disease manifestation between: patients included, with and without scleroderma pattern; and patients with specified scleroderma pattern: early, active and late.

Aiming to identify patients' profiles based on clinical manifestations, agglomerative hierarchical cluster analysis was performed. Clustering is a technique that allows the classification of patients within homogeneous subsets (cluster), by the definition of a "distance" measure between subjects on the basis of their characteristics. A subgroup of variables including clinical manifestations such as esophageal, stomach, intestinal, renal, Raynaud's phenomenon, active digital ulcers, scleredema, mRSS, synovitis, contractures, tendon friction rubs (TFR), muscle weakness and atrophy, heart conduction block, pericardial effusion, lung fibrosis, pulmonary arterial hypertension (PAH) and diffusing lung capacity of

the lung for carbon monoxide (DLCO), and autoantibodies such as antinuclear antibodies (ANA), anticentromere antibodies (ACA), and antitopoisomerase I antibodies (Scl70) were considered. U1RNP and RNA were excluded due to the large number of missing values.

In order to facilitate the calculation of the distance among subjects, Multiple Correspondence Analysis (MCA) (Greenacre, 1993) was preliminarily performed. MCA extracts relevant information from a large amount of data by reducing a starting set of correlated variables into a smaller set of uncorrelated ones (namely factor or axis), ordered on the basis of the amount of data variability they explain. Each individual can be represented by its coordinates on the newly identified factorial axis; thus patients with similar coordinates' values share similar characteristics. Disease subsets and capillaroscopy patterns were used as supplementary passive variables (*i.e.* these variables did not contribute to the identification of the clusters among other variables).

The stability of cluster assignment (*i.e.* internal validation) was also investigated. Resampling methods were utilized to face this issue during two steps separately; firstly to determine the number of clusters and secondly to assess the reliability of each cluster by conditioning to a fixed number of clusters. Then the agreement (similarity) between each clustering run on the perturbed data and the clustering on original data set were assessed *via* the Jaccard's coefficient (Hennig, 2007). In both steps, 1500 bootstrap resamples with replacement were randomly generated from the original data set.

Finally, multinomial logistic regression analysis was used to evaluate the association among the identified clusters and the capillaroscopy patterns.

Statistical analysis was carried out using software R (R Development Core Team, 2006), with FactoMineR and ca packages added.

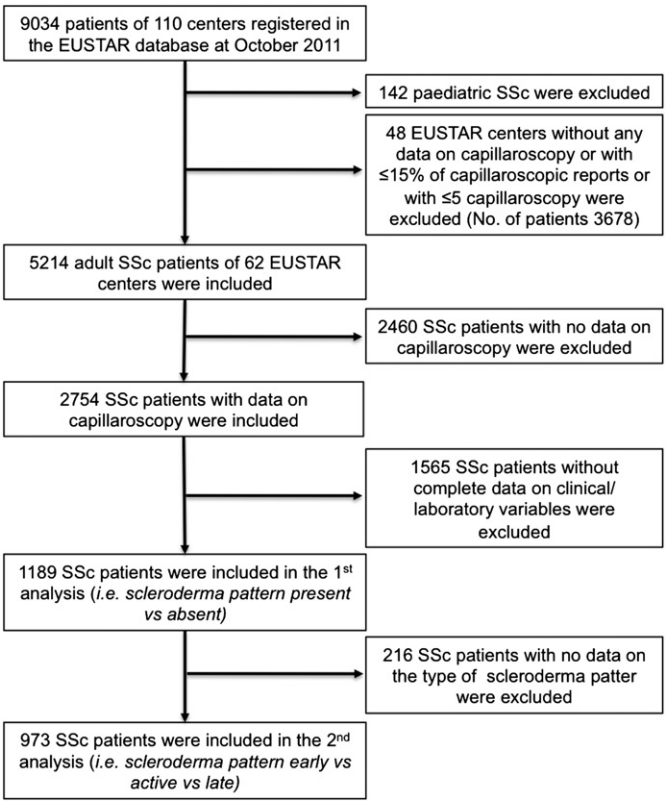

Fig. 2. Flowchart of the study.

Results

Use of nailfold capillaroscopy

A short survey was undertaken to collect information on capillaroscopy and response rate was 33.6% (37 of 110 centers), of whom 91.4% are European centers. In 18.9% (7 of 37) capillaroscopy was not routinely assessed, whereas in the 67.6% (25 of 37) of cases capillaroscopy was performed but data were not reported in the EUSTAR database. In 10 of 37 (27.0%) centers, capillaroscopy technique had been recently introduced and a videocapillaroscopic equipment was available only in 26 of 37 (70.3%) centers, otherwise microscope (24.3%) and dermatoscope (5.4%) were used.

SSc patients with scleroderma pattern vs SSc patients without scleroderma pattern

Firstly, the impact of exclusion criteria and the impact of missingness with regard to capillaroscopy data were evaluated. In Fig. 2 the main steps for selecting patients are described. A total of 9034 patients from 110 centers were recorded in the EUSTAR database locked for this study in October 2011. 5214 adult SSc patients within 62 out of 110 centers were eligible for the study. Among these, 1189 patients who had at least one capillaroscopy examination reported in the database and complete information on clinical/laboratory features were studied.

Characteristics of the study population are reported in Table 1. There were no relevant clinical and demographic differences between these groups.

Complete data on the presence or absence of a scleroderma pattern were available for 2754 SSc patients, whose main characteristics are shown in Table 2. The following characteristics were more frequently observed in patients with scleroderma pattern: dcSSc, active disease, digital ulcers, joint contractures, ANA and Scl-70 positive.

In 376 of 2754 (13.65%) patients the capillaroscopy pattern was not classified as scleroderma pattern. A detailed description of these capillaroscopy patterns was obtained in 256 of 376 (68.09%) of the cases. The capillaroscopy pattern was classified as normal in 70 of 256 (27.34%). However, non-specific capillary abnormalities were reported in 142 of 256 (55.48%), and otherwise the capillaroscopy pattern was not of clear interpretation because of the poor quality of images in 44 of 256 (17.18%). Non-specific capillary abnormalities were defined as enlarged and tortuous loops with hemorrhages. With regard to the characteristics of SSc patients without scleroderma pattern, dcSSc subtype, ANA positive, Scl-70 positive, digital ulcers and joint contractures were less frequent.

Scleroderma pattern "early" vs "active" vs "late" pattern

Data on the subtype of scleroderma pattern were available for 1870 out of 2754 patients. The disease characteristics of patients with different scleroderma patterns are shown in Table 3. It can be noted that patients with "late" scleroderma pattern are more frequently dcSSc with Scl-70 positive. Moreover, regarding clinical manifestations, an increased frequency of digital ulcers, and of lung, heart and musculoskeletal involvement is noted from patients with "early" pattern as compared to those with "late" pattern.

The further step was the cluster analysis performed on a complete case basis, including only the 1189 among 1870 patients, those with complete information on clinical symptoms, disease manifestation and autoantibodies profile.

The first three factorial axis generated by MCA analysis explained near the 80% of the overall variability in the data and were used to perform the subsequent cluster analysis on patient coordinates. The cluster analysis suggests the presence of four major patients' profiles, whose characteristics about the distribution of disease manifestations are shown Table 4.

The first cluster mainly refers to subjects without Raynaud's phenomenon, with autoantibodies negative and without organ involvement and without a capillaroscopic scleroderma pattern. The second cluster mainly identifies patients with lcSSc with normal/mild mRSS,

Table 1
Characteristics of the study population of the EUSTAR database up to October 2011.

	EUSTAR centers (no. 110)		
	Included (no. 62)		Excluded (no. 48)
	With data on capillaroscopy	Without data on capillaroscopy	No data on capillaroscopy
No. of patients	2754	2460	3678
Female	2400 (87.15%)	2096 (85.20%)	3220 (87.54%)
Age, mean ± SD years	54.97 ± 13.6	56.16 ± 13.5	55 ± 13.5
Disease duration, mean ± SD years	7.62 ± 7.38	8.26 ± 8.03	8.32 ± 8. 06
Cutaneous subtype, no. %			
Limited	1622 (58.9%)	1377 (55.97%)	1982 (53.89%)
Diffuse	803 (29.15%)	841 (34.19%)	1159 (31.51%)
Other	328 (11.91%)	215 (8.74%)	492 (13.38%)
Not classified	1 (0.04%)	27 (1.1%)	45 (1.22%)
Raynaud's phen., no. %	2615 (97.15%)	2360 (97,00%)	3405 (92.57%)
Digital ulcers, no. %	934 (33.91%)	769 (31.26%)	1123 (30.53%)
Pulmonary fibrosis, no. %	716 (30.08%)	946 (42.77%)	1117 (32.58%)
PAH, no. %	477 (17.32%)	583 (23.69%)	1020 (27.95%)
Muscle weakness, no. %	489 (18.07%)	625 (25.88%)	1020 (29.88%)
Joint contractures, no. %	711 (26.02%)	711 (29.49%)	1099 (30.06%)
Synovitis, no. %	370 (13.43%)	381 (15.48%)	570 (15.49%)
Tendon friction rubs, no. %	218 (7.75%)	208 (8.66%)	376 (10.36%)
Renal crisis, no. %	42 (1.52%)	51 (2.07%)	92 (2.50%)
Conduction blocks, no. %	310 (11.25%)	327 (13.29%)	266 (7.23%)
Positive ANA, no. %	2583 (94.79%)	2213 (92.29%)	3308 (92.09%)
Positive Scl-70, no. %	878 (32.88%)	765 (32.09%)	1121 (32.00%)
Positive ACA, no. %	1068 (39.77%)	794 (34.27%)	1222 (35.22%)
Active disease according to European score, no. %	337 (1344 missing)	111 (2057 missing)	107 (3414 missing)

SD: standard deviation; PAH: pulmonary arterial hypertension; ANA: antinuclear antibodies; Scl-70: antitopoisomerase-1 antibodies; ACA: anticentromere antibodies.

Table 2
Disease characteristics of systemic sclerosis patients with and without a scleroderma pattern by nailfold capillaroscopy.

	EUSTAR centers included (no. 62)		
	With data on capillaroscopy (no. 2754)		
	Without scleroderma pattern	With scleroderma pattern	p
No. of patients	376	2378	NS
Female	310 (82.45%)	2091 (87.93%)	NS
Age, mean ± SD years	56.10 ± 13.4	54.81 ± 13.7	NS
Disease duration, mean ± SD years	7.18 ± 7.24	7.69 ± 7.40	NS
Cutaneous subtype, no. %			*
Limited	225 (59.84%)	1398 (58.79%)	
Diffuse	74 (19.68%)	729 (30.66%)	
Other	75 (19.95%)	250 (10.51%)	
Not classified	2 (0.53%)	1 (0.04%)	
Raynaud's phen., no. %	329 (92.20%)	2286 (97.69%)	*
Digital ulcers, no. %	70 (18.61%)	864 (36.33%)	*
Pulmonary fibrosis, no. %	78 (24.74%)	638 (30.82%)	NS
PAH, no. %	48 (14.20%)	429 (19.40%)	NS
Muscle weakness, no. %	51 (13.56%)	438 (18.41%)	NS
Joint contractures, no. %	52 (14.82%)	659 (27.71%)	*
Synovitis, no. %	41 (10.90%)	329 (13.83%)	NS
Tendon friction rubs, no. %	23 (6.11%)	195 (8.20%)	NS
Renal crisis, no. %	7 (1.86%)	35 (1.47%)	NS
Conduction blocks, no. %	43 (12.13%)	267 (11.83%)	NS
Positive ANA, no. %	330 (89.76%)	2253 (95.55%)	*
Positive Scl-70, no. %	91 (25.20%)	787 (34.09%)	*
Positive ACA, no. %	140 (38.26%)	929 (39.76%)	NS
Active disease according to European score, no. %	23 (13.86%)	314 (25.22%)	*

SD: standard deviation; PAH: pulmonary arterial hypertension; ANA: antinuclear antibodies; Scl-70: antitopoisomerase-1 antibodies; ACA: anticentromere antibodies; NS: not significant; *: $p < 0.05$.

Table 3
Disease characteristics of patients with scleroderma pattern early, active or late by nailfold capillaroscopy.

	EUSTAR centers included (no. 62)			
	With scleroderma pattern (no. 1870)			
	Scleroderma pattern early	Scleroderma pattern active	Scleroderma pattern late	p
No. of patients	494	778	598	NS
Female	454 (91.90%)	673 (86.5%)	522 (87.29%)	NS
Age, mean ± SD years	53.53 ± 13.93	54.24 ± 13.44	56.62 ± 13.03	NS
Disease duration, mean ± SD years	6.23 ± 6.47	7.48 ± 6.98	9.95 ± 8.08	NS
Cutaneous subtype, no. %				*
Limited	307 (62.14%)	457 (58.74%)	288 (48.16%)	
Diffuse	105 (21.26%)	222 (28.53%)	278 (46.49%)	
Other	82 (16.60%)	98 (12.6%)	32 (5.35%)	
Not classified	0	1 (0.13%)	0	
Raynaud's phen., no. %	473 (96.75%)	761 (97.81%)	576 (96.32%)	NS
Digital ulcers, no. %	121 (24.49%)	287 (36.88%)	292 (48.83%)	*
Pulmonary fibrosis, no. %	120 (27.03%)	221 (31.13%)	227 (43.29%)	*
PAH, no. %	51 (14.41%)	151 (20.60%)	152 (27.94%)	*
Muscle weakness, no. %	78 (17.58%)	137 (17.60%)	157 (26.25%)	*
Joint contractures, no. %	74 (14.98%)	214 (27.50%)	276 (46.39%)	*
Synovitis, no. %	51 (10.32%)	118 (15.16%)	109 (18.22%)	*
Tendon friction rubs, no. %	18 (3.64%)	76 (9.77%)	83 (13.88%)	*
Renal crisis, no. %	2 (0.40%)	10 (1.29%)	13 (2.17%)	NS
Conduction blocks, no. %	37 (7.99%)	96 (13.34%)	97 (17.41%)	*
Positive ANA, no. %	472 (96.74%)	747 (96.61%)	555 (94.07%)	NS
Positive Scl-70, no. %	136 (28.53%)	254 (32.64%)	275 (47.33%)	*
Positive ACA, no. %	219 (45.15%)	332 (43.37%)	160 (27.56%)	*
Active disease according to European score, no. %	43 (13.87%)	114 (23.65%)	130 (37.14%)	*

PAH: pulmonary arterial hypertension; ANA: antinuclear antibodies; Scl-70: antitopoisomerase-1 antibodies; ACA: anticentromere antibodies; NS: not significant; *: $p < 0.05$.

ANA positive without lung, articular, renal and heart involvement, and with no active digital ulcers. The third cluster is mainly characterized by patients with dcSSc or intermediate/late lcSSc with moderate mRSS, with ANA positive and organ involvement (*i.e.* joint contractures, TFR, synovitis and lung fibrosis). The forth cluster mainly refers to patients with dcSSc with more severe mRSS and with multiple organ involvement (*i.e.* gastro/intestinal, muscle, renal and heart involvement, joint contractures and TFR). The scleroderma pattern was mainly present in the second, third and fourth group, whereas patients with absent scleroderma pattern were mainly classified in cluster 1 (24.41%) and in cluster 2 (48.03%).

The internal validation process identified only two clusters. Cluster A (that included cluster 1, 2 and part of cluster 3) was characterized by less severe clinical manifestations, while cluster B (that included cluster 4 and part of cluster 3) grouped patients with more severe disease and with a heterogeneous pattern of clinical symptoms.

The strength of association between the above-mentioned four clusters of patients' profiles and the scleroderma patterns were also studied. The odds of the scleroderma pattern “active” or “late” vs the “early” pattern in each cluster were evaluated. The “active” pattern was more likely to be observed in clusters three and four with respect to cluster 1 (OR 1.7, 95% CI 0.89–2.27 and OR 4.07, 95% CI 1.95–8.49 respectively); as much as the “late” pattern was more likely to be reported in clusters three and four (OR 2.7, 95% CI 1.58–4.79 and OR 6.92, 95% CI 3.26–14.69) with respect to cluster 1.

Discussion

In the context of a constant chase for identifying a useful non-invasive tool to monitor SSc, the results of this large study on capillaroscopy add important information concerning the actual role of capillaroscopy.

Table 4
Disease characteristics of patients in the four major patients' profiles obtained from systemic sclerosis in the EUSTAR database by cluster analysis.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
No. of patients	168	548	318	155
Raynaud's phen., no. %	147 (87.5%)	546 (99.6%)	315 (99.05%)	154 (99.35%)
Active digital ulcers, no. %	4 (2.4%)	46 (8.4%)	71 (22.3%)	59 (38.06%)
Scleredema, no. %	35 (20.8%)	237 (43.2%)	152 (47.8%)	60 (38.7%)
mRSS, no. %				
□ Normal	18 (10.7%)	87 (15.9%)	3 (0.9%)	5 (3.2%)
□ Mild	132 (78.6%)	438 (79.9%)	208 (65.4%)	69 (44.5%)
□ Moderate	13 (7.7%)	23 (4.2%)	104 (32.8%)	61 (39.4%)
□ Severe	5 (3%)	0	3 (0.9%)	16 (10.3%)
□ Endstage	0	0	0	4 (2.6%)
Esophageal involvement, no. %	68 (40.5%)	339 (61.9%)	203 (63.8%)	138 (89.03%)
Stomach involvement, no. %	8 (4.8%)	99 (18.06%)	46 (14.5%)	113 (72.9%)
Intestinal involvement, no. %	23 (13.7%)	134 (24.4%)	29 (9.1%)	83 (53.5%)
Pulmonary fibrosis, no. %	63 (37.5%)	40 (7.3%)	175 (55%)	91 (58.7%)
DLCO <70 no. %	111 (66.1%)	275 (50.2%)	278 (87.4%)	134 (86.45%)
PAH, no. %	26 (15.5%)	77 (14.05%)	101 (31.8%)	59 (38.06%)
Muscle weakness, no. %	25 (14.9%)	55 (10%)	50 (15.7%)	108 (69.7%)
Muscle atrophy, no. %	6 (3.6%)	5 (0.9%)	4 (1.25%)	81 (52.25%)
Joint contractures, no. %	41 (24.4%)	50 (9.1%)	148 (46.5%)	112 (72.25%)
Synovitis, no. %	18 (10.7%)	27 (4.9%)	82 (25.8%)	48 (31%)
Tendon friction rubs, no. %	3 (1.8%)	5 (0.9%)	51 (16%)	46 (29.7%)
Renal crisis, no. %	4 (2.4%)	1 (0.2%)	0	10 (6.45%)
Pericardial effusion	4 (2.4%)	15 (2.8%)	31 (9.7%)	20 (12.9%)
Conduction blocks, no. %	11 (6.5%)	43 (7.8%)	46 (14.5%)	41 (26.45%)
Positive ANA, no. %	119 (70.8%)	548 (100%)	318 (100%)	152 (98%)
Positive Scl-70, no. %	7 (4.2%)	101 (18.4%)	240 (75.5%)	83 (53.5%)
Positive ACA, no. %	2 (1.2%)	378 (69%)	33 (10.4%)	35 (22.6%)

mRSS: modified Rodnan skin score; DLCO: diffusing lung capacity of the lung for carbon monoxide; PAH: pulmonary arterial hypertension; ANA: antinuclear antibodies; Scl-70: antitopoisomerase-1 antibodies; ACA: anticentromere antibodies.

The first part of this study aimed to depict the use of capillaroscopy in clinical practice. A low adherence to the survey was observed, but the collected data confirm that this technique is particularly used in European countries. This diagnostic tool was only recently introduced in clinical practice in 27% of centers, thus suggesting an increased interest in capillaroscopy. It is a matter of fact that different devices (*e.g.* videocapillaroscope, microscope, or dermatocope) are used to perform the exam. The variability in the way capillaroscopy is employed and performed by clinicians could be related to different aspects of everyday practice such as: health-care system access and utilization, reimbursement policy and physician experience.

In this study the potential heterogeneity related to the analysis of capillaroscopic images has been overcome by continuous EUSTAR/EULAR effort to coach, update and standardize the assessment of SSc patients.

In addition, the data collected in the EUSTAR registry are based on an overall capillaroscopic pattern characterized only by morphological capillary abnormalities easily identifiable with all the tools as previously demonstrated (Anders et al., 2001; Baron et al., 2007; Beltran et al., 2007; Bukhari et al., 2000; Hudson et al., 2010; Wildt et al., 1999, 2012).

In the EUSTAR registry, capillaroscopy scleroderma pattern was observed in more than 86% of SSc subjects, while in the other patients capillaroscopy pattern was characterized by non-specific capillary abnormalities other than scleroderma pattern, and in a minority of patients capillaroscopy was within the normal range. Patients within this group generally do not have organ involvement, Raynaud's phenomenon and also have negative antibodies; these data may suggest that even though they are classified as SSc probably they do not have an overt disease, and that non-specific capillary abnormalities may precede a full-blown scleroderma pattern. This subgroup has been recently studied in depth by other EUSTAR members (Schneeberger et al., 2013).

On the other hand, the patients' profiles identified by the cluster analysis were in a progressive order of severity for skin as well as organ involvement. In patients with overt SSc, capillaroscopy scleroderma pattern is almost always present. Particularly, in the initial stages of the disease or when the organ involvement is less severe the "early" (or "active") scleroderma patterns may be observed, while in the more severe forms of the disease the capillaroscopic scleroderma pattern "late" becomes more frequent. These results advocate the important role of capillaroscopy images as a mirror of internal organ involvement progression.

In fact, it has long been known that the damaged capillary network in SSc results in micro-vessel abnormalities that can worsen during disease progression (Caramaschi et al., 2007; Cutolo et al., 2004). These observations confirm the results of a recent longitudinal study that reported a dynamic transition of microvascular damage through different capillaroscopy patterns in nearly 50% of SSc patients (Smith et al., 2012; Sulli et al., 2012).

It has been argued that widespread use of appropriately developed capillaroscopy technique can be of a great value for an early diagnosis of SSc and in monitoring the disease course, even if the majority of published data regarding capillaroscopy are derived from limited number of patients. This study can be considered a first effort to ascertain the use of capillaroscopy because this data are extrapolated from the EUSTAR registry that is conducted in a multicenter real world setting.

Limitations of this study include the missing information concerning some clinical, laboratory and particularly full capillaroscopy data. On the one hand, these latter information were often missed in the database since were not mandatory, and it was difficult to obtain new data which were previously not recorded. However patients included and/or excluded from the analysis had similar characteristics thus a relevant selection bias was not suspected. Due to the fact that capillaroscopy is an operator dependent method, the inter-individual and intra-center variability might also influence the results. This potential confounder may be reduced by the inclusion of a large number of centers contributing to MEDS. Even if a consistent number of patients needed to be excluded from the analysis, this is the largest multicenter international cohort of SSc patients in which capillaroscopy was studied.

In conclusion, capillaroscopy should be part of the screening and monitoring process of SSc, because it is directly related to the extent of organ involvement. These data also indicate the large use of capillaroscopy internationally and that the variability with which a seemingly straightforward technique such as capillaroscopy is used in everyday practice (Cutolo et al., 2012; De Angelis et al., 2009).

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László Czirják Department of Immunology and Rheumatology, Faculty of Medicine, University of Pécs, Akác u.l., Hungary; Montecucco, Unita' Operativa e Cattedra di Reumatologia IRCCS Policlinico S Matteo, Pavia, Italy; Eugene J. Kucharz Department of Internal Medicine and Rheumatology, Medical University of Silesia, Katowice, Poland; Blaz Rozman University Medical Center Ljublijana, Division of Internal Medicine, Department of Rheumatology, Ljubliana, Slovenia; Armando Gabrielli Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica, Università Politecnica delle Marche, University of Ancona, Ancona, Italy; Dominique Farge Bancel, Department of Internal Medicine Hopital Saint-Louis, Paris, France; Ina Kötter, Universitätsklinikum Tübingen, Medizinische Klinik und Poliklinik, Internal Medicine/Rheumatology/Haematology/Oncology, Tübingen, Germany; Stefan Heitmann, Department of Rheumatology, Marienhospital Stuttgart, Germany; Matthias Seidel, Medizinische Universitäts-Poliklinik, Dep. of Rheumatology, Bonn, Germany; José Antonio Pereira Da Silva, Reumatologia, Hospitais da Universidade Coimbra, Portugal; Bianca Marasini, Rheumatology Unit – Humanitas Clinical Institute, Rozzano, Milano, Italy; Francesco Indiveri, Clinica di Medicina Interna ad orientamento immunologico, Università di Genova, Azienda Ospedale - Università San Martino,

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