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Reproducibility of capillaroscopic classifications of systemic sclerosis: results from the SCLEROCAP study

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Abstract

Objectives. Subgroups of capillaroscopic scleroderma landscape have been correlated with stages of SSc: two groups for Maricq's classification (slow and active), and three for Cutolo's classification (early, active and late). We report inter- and intra-observer agreement for these classifications as a preliminary step in the multicentre prospective SCLEROCAP study, which aims to assess the classification and single capillaroscopic items as prognostic tools for SSc.

Methods. SCLEROCAP included 385 patients. Agreement was studied in the first 100 patients, who were independently rated twice by two observers, blind to patients' characteristics; 30 of the patients were rated once by six observers. After consensus meetings, these ratings were held again. Kappa and intra-class correlation coefficients were used to assess agreement.

Results. Interobserver agreement on 100 patients was moderate for Maricq and Cutolo classifications [κ 0.47 (0.28, 0.66) and 0.49 (0.33, 0.65), respectively], and became substantial after consensus meetings [0.64 (0.50, 0.77) and 0.69 (0.56, 0.81)]. Intra-observer agreement between two observers was moderate to substantial: κ 0.54 (0.33, 0.75) and 0.70 (0.57, 0.83) for Maricq's classification; 0.57 (0.38, 0.77) and 0.76 (0.65, 0.87) for Cutolo's. Thirty patients were rated once by each of six observers, and agreement was moderate to substantial: κ 0.57 ± 0.10 (Maricq) and 0.61 ± 0.12 (Cutolo). Agreement was substantial for bushy, giant capillaries and microhaemorrhages, moderate for capillary density and low for oedema, disorganization and avascular areas.

Conclusion. The moderate reproducibility of Maricq and Cutolo classifications might hamper their prognostic value in SSc patients. Consensus meetings improve reliability, a prerequisite for better prognostic performances. A focus on giant capillaries, haemorrhages and capillary density might be more reliable.

Key words: systemic sclerosis, capillaroscopy, prognosis, classification, agreement

CLINICAL SCIENCE

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Rheumatology key messages

- Inter and intra-observer agreements are not substantial for the prognostic classifications of SSc by capillaroscopy.
- Reproducibility of these classifications is improved after consensus meetings, which seem mandatory in clinical trials using these classifications.
- Some primary capillaroscopic abnormalities observed in SSc are reproducible, such as giant or bushy capillaries and microhaemorrages; others are not.

Introduction

SSc primarily involves the microcirculation, leading to the early occurrence of specific capillary abnormalities that can be assessed by videocapillaroscopy. The scleroderma pattern is characterized by capillary angiogenesis (giant and bushy capillaries) and capillary destruction (decrease in capillary density, avascular areas, disorganization of capillary bed) [1]. Capillary abnormalities are heterogeneous among patients, some having numerous giant capillaries, while others have rare giant capillaries but mainly capillary loss. An evolution of the capillary bed from giant capillaries to capillary loss has been shown [2], but some patients seem to progress rapidly to capillary destruction [3]. Thus, some authors have proposed a classification of capillary abnormalities in two stages (slow: many giant capillaries and haemorrhages; and active: diffuse capillary loss and disorganization) that might predict the clinical prognosis of SSc [4]. First, Maricq found that patients at the slow stage had less systemic organ involvement during SSc follow-up than those at the active stage (1 out of 11 *vs* 5 out of 8) [3]. In a retrospective study including 68 SSc patients, Chen *et al.* [5] showed that the active stage was associated with skin fibrosis, pulmonary hypertension and renal involvement. More recently, Cutolo proposed a classification in three stages (early: rare giant capillaries and haemorrhages; active: many giant capillaries and haemorrhages; and late: diffuse capillary loss, disorganization and bushy capillaries) [6]. The relationship between these stages and the occurrence of complications has been addressed in retrospective and transversal studies [3, 6, 7, 8]. The late stage has been correlated with age; duration of disease; and cardiac, pulmonary and renal complications [3, 6, 7, 8]. The only validation study for Cutolo's classification was a prospective pilot study in 66 Belgian and 82 Italian SSc patients, and it showed an increased risk of peripheral vascular or lung involvement with the late nailfold videocapillaroscopy pattern [9]. Another transversal study showed that microhaemorrhages and giant capillary counting were associated with disease activity as measured by the European Scleroderma Study Group Index [10].

The SCLEROCAP study is a multicentre prospective study with a follow-up of 3 years. Its main objective was to determine the predictive value of Maricq's and Cutolo's capillaroscopic classifications for the prognosis of SSc. The secondary objectives were to study the reproducibility of the capillaroscopic classifications and to describe capillary bed modifications over 3 years in SSc patients. In the case of bad performance of these classifications, we intend to build a new prognostic score combining the most reproducible and predictive single items. Here we present the results of the assessment of the intra- and interobserver reproducibility of these classifications at study inclusion.

Methods

Study design

SCLEROCAP is a French prospective, observational, multicentre study that is ongoing and complies with good clinical practices and the Declaration of Helsinki. Patients were enrolled between March 2014 and August 2015. The end of the study is planned for August 2018 after 3 years of follow-up. Formal ethics committee approval was obtained on 7 March 2014. The patients gave informed signed consent. The present study used the capillaroscopic descriptive data obtained at inclusion from the first 100 patients enrolled.

Setting and participants

A total of 373 consecutive patients were included from 10 French medical departments (vascular medicine, rheumatology, internal medicine and dermatology). Inclusion criteria were age above 18 years and diagnosis of SSc according to LeRoy and Medsger's definition in order to be able to include early SSc and SSc without skin sclerosis [11]. Criteria of non-inclusion were: other associated CTD, severe complication of SSc (renal crisis, pulmonary hypertension or respiratory insufficiency). Data obtained from the first 100 patients included were analysed in the present study.

Study procedures

Demographic data, general medical history, SSc subtype and clinical and biological SSc characteristics were collected at inclusion. Nailfold capillaroscopic data and finger systolic pressure measurements were determined at inclusion and at each annual visit during the study follow-up. SSc progression after 3 years was considered as severe in the event of heart, lung, pulmonary artery or kidney involvement, as defined previously and validated by an event validation committee [12]. For each patient, capillaroscopic images were analysed for qualitative and quantitative abnormalities using the same tool at each visit: first in the clinical centre by the investigator, second by another investigator blind to the first assessment, and then by a third investigator in the event of discordance. The images from four fingers of each hand

(total of eight fingers) were classified according to Maricq's and Cutolo's scoring systems [4, 6, 13].

For Maricq's classification, two patterns were considered [4]. The slow one consisted of extremely enlarged capillaries with no or minimal avascular area. The active one consisted of moderate-to-extensive avascular areas without extremely enlarged capillaries.

For Cutolo's classification, three patterns were considered [6]. The early pattern was made of few giant capillaries, few haemorrhages, relatively preserved capillary distribution and no evident loss of capillaries. The active pattern was made of frequent giant capillaries, frequent capillary haemorrhages, moderate loss of capillaries with some avascular areas, mild disorganization of the capillary architecture, and absent or some ramified capillaries. The late pattern consisted of irregular enlargement of capillaries, few or absent giant capillaries, absence of haemorrhages, severe loss of capillaries with large avascular areas, severe disorganization of normal capillary array, and frequent ramified or bushy capillaries.

Acquisition of nailfold capillaroscopic images

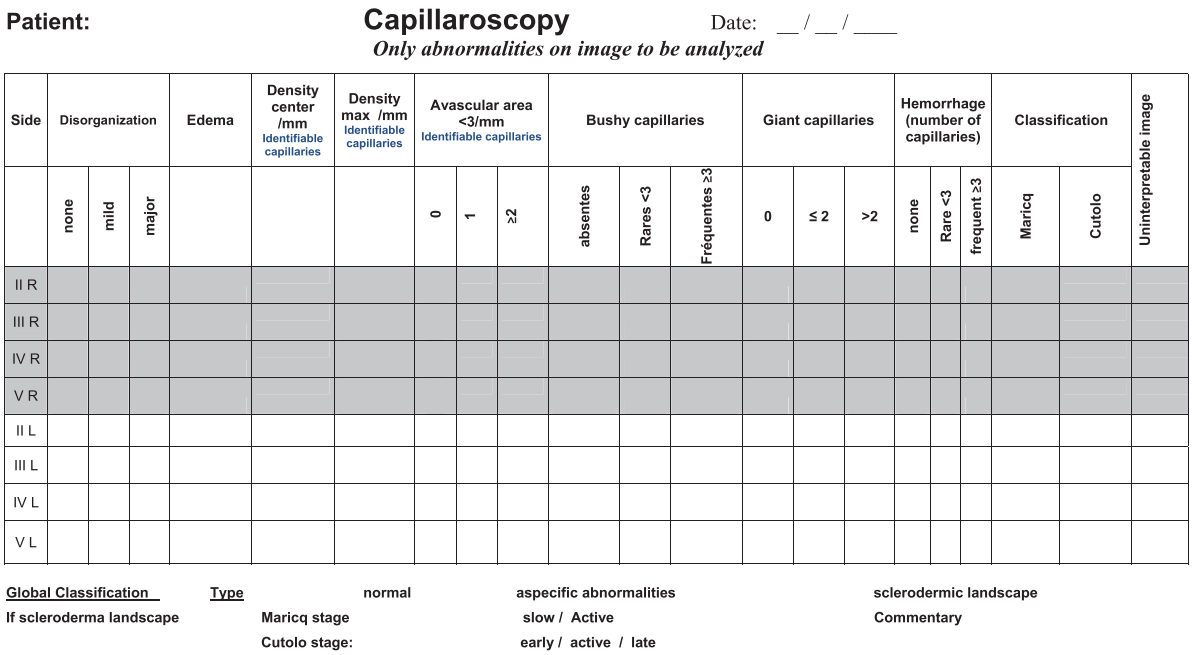
Images were acquired at inclusion and during the follow-up visits on eight fingers (all fingers except thumbs) by using the same wide-field videocapillaroscopy device in all of the centres (×50 to ×100 magnification, Perimed, Järfälla, Sweden). The images were recorded on a disk, which was then blinded by a research assistant and provided to experimental investigators not aware of the patient's identity or status for assessment/classification. During the first meeting, the investigators agreed on a sheet for recording elementary capillaroscopic abnormalities and Maricq's and Cutolo's classifications. For each patient, evaluation was first performed on each finger and then as a whole, taking into account the landscape observed in most of the patient's fingers (Fig. 1). The abnormalities were analysed from the first row of capillaries.

Outcomes and measurements

In the present study, quantitative and qualitative data of a set of capillaroscopic images were assessed by investigators. Two other meetings were then held in order to analyse discordant findings and to improve agreement about the definition of abnormalities. It was found that there was a need to define more precisely each elementary abnormality, and consensus definitions were determined (Table 1).

Several analyses were performed: assessment of intra-observer and interobserver agreement for qualitative and quantitative capillaroscopic abnormalities observed on the fourth left finger in 100 patients rated by two experienced investigators A and B, independently performing two ratings with a 6 months' interval, the second rating being blind to the first one. Cutolo and Maricq stages were assessed both from the fourth finger of the left hand and globally from the eight fingers. Agreement for elementary parameters was only studied on one finger because statistical analysis would have been hampered by correlated data if eight fingers were pooled for each patient. We chose the fourth finger because we think that this finger usually has the most abnormalities, and the left finger because the majority of patients have a right dominant side (the fingers of the dominant side may be more

Fig. 1 Form filled out by the observers of capillaroscopies



Patient:

Capillaroscopy Date: __ / __ / ____

Only abnormalities on image to be analyzed

Side	Disorganization			Edema	Density center /mm Identifiable capillaries	Density max /mm Identifiable capillaries	Avascular area <3/mm Identifiable capillaries			Bushy capillaries			Giant capillaries			Hemorrhage (number of capillaries)			Classification		Uninterpretable image
	none	mild	major				0	1	≥2	absentes	Rares <3	Fréquentes ≥3	0	≤ 2	>2	none	Rare <3	frequent ≥3	Maricq	Cutolo	
II R																					
III R																					
IV R																					
V R																					
II L																					
III L																					
IV L																					
V L																					

Global Classification Type normal aspecific abnormalities sclerodermic landscape

If scleroderma landscape Maricq stage slow / Active Commentary

Cutolo stage: early / active / late

difficult to examine because of more numerous traumatic lesions).

Assessment of interobserver agreement was also analysed in six observers rating 30 patients once independently. Assessment of the impact of consensus meetings was performed by comparing capillaroscopic data obtained by the rating of 30 patients by three experienced investigators before any consensus meeting, after a first meeting, and then after a second meeting. The flow chart for these analyses is shown in Fig. 2.

Table 1 Definitions of elementary abnormalities

Architectural disorganization	Lack of parallelism of capillaries (mild: some capillaries, extensive: global lack of parallelism, suggesting anarchy)
Capillary rarefaction	Capillary density $\leqslant$7/mm (measured on lowest part of first row)
Avascular area	Area at least 1 mm long, with capillary density $<$3/mm
Giant capillary	Capillary whose two branches are enlarged, at least one having a diameter $>$50 μm
Bushy capillary	Capillary with ramifications (different from tortuous capillaries branched on venules)
Haemorrhage	Red spot migrating toward edge of nail
Oedema	Globally blurred image

Statistical analysis

Agreement was calculated for qualitative data by simple Kappa coefficients for items with two response classes and by weighted Fleiss–Cohen Kappa coefficients for items with three response classes [14]. The 95% CIs were calculated from the normal distribution approximation. The Landis and Koch interpretation of kappa values was used [15]: 0.2–0.4: fair; 0.4–0.6: moderate; 0.6–0.8: substantial; $>$0.8: almost perfect. The observed proportion of concordant observations (p0) was also calculated. For quantitative variables (capillary density in the middle of nailfold or in the area of maximal density), agreement was expressed by intraclass correlation coefficients and their 95% CIs [16]. Statistical analysis system software version 9.2 was used to compute the statistical analyses (SAS France, Brie Comte Robert).

Results

The 100 patients included in these studies included 14 males and 86 females, and their mean age was 59 (13) years. According to Le Roy and Medsger's classification, 30 patients had limited SSc, 61 lcSSc and 8 dcSSc. ANAs were found in 98 patients, ACAs in 64 patients, anti-topo-isomerase I antibodies in 17 patients and anti-RNA polymerase III antibodies in 5 patients.

Elementary abnormalities and Maricq and Cutolo classifications: agreement between readers A and B

Agreement was assessed twice between readers A and B for 100 patients (Table 2).

Fig. 2 Flow-chart of capillaroscopy reading by observers

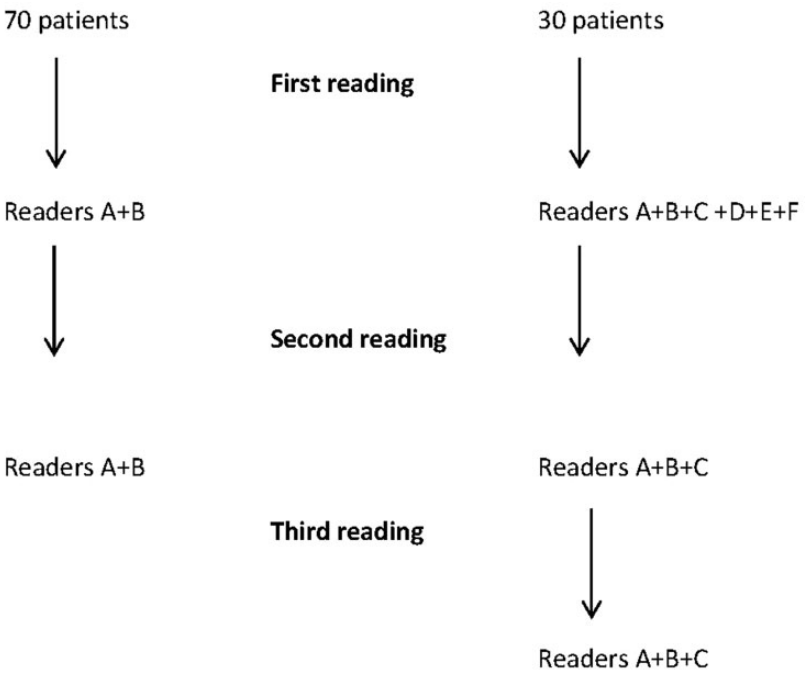


Table 2 Inter-observer agreement between two investigators (A and B) for capillaroscopic reading of images in 100 patients

Agreement of capillaroscopic reading						
Parameters Fourth left finger	1st reading			2nd reading		
	κ (95% CI)	P0	*n*	κ (95% CI)	P0	*n*
Disorganization	0.19 (0, 0.40)	0.76	95	0.55 (0.34, 0.75)	0.84	93
Oedema	0.48 (0.26, 0.72)	0.84	94	0.27 (0, 0.56)	0.88	93
Avascular areas	0.53 (0.35, 0.70)	0.78	95	0.58 (0.40, 0.76)	0.82	93
Bushy capillaries	0.62 (0.49, 0.74)	0.61	95	0.52 (0.35, 0.68)	0.61	93
Giant capillaries	0.72 (0.59, 0.84)	0.72	95	0.70 (0.56, 0.83)	0.72	93
Micro, haemorrhages	0.78 (0.67, 0.95)	0.77	95	0.70 (0.56, 0.83)	0.69	93
Maricq's classification	0.44 (0.24, 0.63)	0.69	95	0.66 (0.52, 0.80)	0.69	93
Cutolo's classification	0.39 (0.22, 0.57)	0.48	95	0.66 (0.53, 0.80)	0.56	93
	ICC (95%)	–	*n*	ICC (95%)	–	*n*
Moderate density	0.59 (0.18, 0.91)	–	91	0.51 (0.10, 0.89)	–	90
Maximal density	0.58 (0.17, 0.91)	–	91	0.54 (0.13, 0.90)	–	90
Global classification for patient	**κ (95% CI)**	**P0**	***n***	**κ (95% CI)**	**P0**	***n***
Maricq's classification	0.47 (0.28, 0.66)	0.70	100	0.64 (0.50, 0.77)	0.70	100
Cutolo's classification	0.49 (0.33, 0.65)	0.43	100	0.69 (0.56, 0.81)	0.55	100

κ: kappa coefficient; ICC: intraclass correlation; P0: percentage of concordant observations; *n*: number of observations.

Table 3 Intra-observer agreement for two investigators (A and B) for capillaroscopic reading of images in 100 patients

Intra-observer agreement of capillaroscopic reading						
Parameters Fourth left finger	Investigator A			Investigator B		
	κ (95% CI)	P0	*n*	κ (95% CI)	P0	*n*
Disorganization	0.46 (0.25, 0.48)	0.81	93	0.39 (0.17, 0.61)	0.83	93
Oedema	0.20 (0, 0.47)	0.84	92	0.30 (0.06, 0.54)	0.81	93
Avascular areas	0.56 (0.38, 0.74)	0.81	93	0.68 (0.52, 0.83)	0.85	93
Bushy capillaries	0.72 (0.61, 0.83)	0.70	93	0.49 (0.32, 0.66)	0.57	93
Giant capillaries	0.79 (0.70, 0.88)	0.74	93	0.88 (0.80, 0.96)	0.86	93
Microhaemorrhages	0.64 (0.68, 0.80)	0.75	93	0.73 (0.60, 0.86)	0.76	93
Maricq's classification	0.70 (0.55, 0.84)	0.77	93	0.71 (0.57, 0.85)	0.77	93
Cutolo's classification	0.73 (0.59, 0.97)	0.68	93	0.72 (0.58, 0.87)	0.72	93
	ICC (95%)	–	*n*	ICC (95%)	–	*n*
Middle density	0.72 (0.36, 0.95)	–	89	0.52 (0.11, 0.89)	–	93
Maximal density	0.81 (0.50, 0.97)	–	89	0.58 (0.17, 0.91)	–	93
Global classification for patient	**κ (95% CI)**	**P0**	***n***	**κ (95% CI)**	**P0**	***n***
Maricq's classification	0.54 (0.33, 0.75)	0.78	100	0.70 (0.57, 0.83)	0.75	100
Cutolo's classification	0.57 (0.38, 0.77)	0.70	100	0.76 (0.65, 0.87)	0.65	100

κ: kappa coefficient; ICC: intraclass correlation; P0: percentage of concordant observations; *n*: number of observations.

For elementary abnormalities, agreement was substantial for giant capillaries, bushy capillaries and microhaemorrhages, moderate for avascular areas and capillary density, and fair for oedema and disorganization. Agreement was moderate for Maricq and Cutolo classifications on first reading, but became substantial on

second reading, when considering all the patients' fingers as a whole and only the fourth left finger (Table 2). No difference was found between these means of rating.

Intra-observer agreement was studied in the 100 patients for readers A and B (Table 3). It was fair for disorganization and oedema, moderate for avascular areas, moderate or substantial for bushy capillaries, and substantial for giant capillaries and microhaemorrhages. Agreement for capillary density was moderate for one observer and substantial for the other one. Agreement was good for Maricq and Cutolo classifications, but for one of the readers it was better when defined from the fourth left finger than from all the fingers.

Elementary abnormalities, Maricq and Cutolo classification in 30 patients: agreement between six observers

Inter-observer agreement was fair for disorganization, oedema and avascular areas among the six observers (Table 4). For bushy capillaries, giant capillaries, haemorrhages and capillary density, agreement between observers was substantial. Agreement for Maricq and Cutolo classifications was moderate or substantial, and there was no difference between the fourth left finger and all the fingers for establishing the classification.

Elementary abnormalities, Maricq and Cutolo classification: agreement between three observers on three readings (before and after two consensus meetings)

Agreement was studied between three readers for three readings. For disorganization and oedema, agreement was fair and did not improve to an acceptable level. For avascular areas and bushy capillaries, agreement was fair among the three pairs of readers, but improved over time [third rating: κ 0.41 (0.20, 0.61) to 0.68 (0.44, 0.93)]. For giant capillaries and microhaemorrhages, agreement was substantial and did not significantly improve from the first to the third reading [third rating: κ 0.61 (0.36, 0.86) to 0.85 (0.67, 1) and 0.75 (0.55, 0.95) to 0.81 (0.62, 1), respectively]. Agreement was substantial for capillary density, except for one pair of readers who improved from the first to the third reading [third rating: κ 0.64 (0.24, 0.93) to 0.73 (0.37, 0.95)]. There was no difference between capillary density measured in the middle of the nailfold or in the area of maximal capillary density.

The agreement was fair for Maricq and Cutolo classifications at first reading. Improvement was obtained after consensus meetings, although CIs of kappa coefficients were still large. For the eight fingers overall, the κ coefficients were 0.25 (0, 0.68) to 0.47 (0.13, 0.82) (Maricq classification) and 0.34 (0, 0.77) to 0.49 (0.17, 0.81) (Cutolo classification). For the fourth left finger, the κ coefficients were 0.44 (0.08, 0.81) to 0.84 (0.70, 0.98) (Maricq classification) and 0.42 (0.08, 0.76) to 0.77 (0.55, 1) (Cutolo classification). There was no clear difference in agreement between determining these classifications only on the fourth left finger or on the eight fingers.

Table 4 Inter-observer agreement: rating of 30 patients by six observers

Qualitative parameters	Kappa coefficients (by pairs of observers)	
Fourth left finger	**Mean (S.D.)**	**Median**
Disorganization	0.381 (0.207)	0.426
Oedema	0.362 (0.215)	0.395
Avascular areas	0.353 (0.243)	0.267
Bushy capillaries	0.716 (0.082)	0.711
Giant capillaries	0.713 (0.065)	0.709
Haemorrhages	0.724 (0.058)	0.733
Maricq	0.576 (0.145)	0.595
Cutolo	0.623 (0.157)	0.630
Global classification		
Maricq	0.575 (0.105)	0.595
Cutolo	0.612 (0.122)	0.617
Qualitative parameters	**Intraclass correlation coefficients (by pairs of observers)**	
Middle density	0.601 (0.114)	0.522
Maximal density	0.609 (0.112)	0.519

Discussion

With regard to elementary abnormalities, agreement was good for giant capillaries, microhaemorrhages and capillary density. Oedema and architectural disorganization were poorly reproducible, while vascular areas and bushy capillaries were moderately reproducible. There was no difference in the assessment of capillary density between measuring in the middle or in the place where the capillary concentration was maximal. There was no difference between Cutolo and Maricq classifications for reproducibility. The percentages of concordant values were higher for Maricq's classification than for Cutolo's, owing to the different number of variables (2 *vs* 3). There was no difference in agreement when determining the stage on the fourth left finger or on the eight fingers. The agreement between the readers for these classifications was better after the assessment procedure, but could still be improved.

Good inter-observer reproducibility has been reported for the diagnosis of scleroderma landscape in patients suffering from RP, with a 90% agreement and a κ coefficient of 0.60 [17]. As far as elementary abnormalities are concerned, parameters such as giant capillaries, capillary density and microhaemorrhages seem to be reproducible, with a κ coefficient above 0.80 [17], while others are not, such as tortuous or bizarre capillaries [17, 18]. We found similar results in the present study. Ingegnoli *et al.* [19] found very good agreement for avascularity and disorganization, but they studied 216 Raynaud's patients of whom only 24 had SSc, so their results may not be transposable to SSc patients. In a recent EULAR study, morphological abnormalities of capillaries were not reproducible, either

by experienced observers or novices, resulting in a κ coefficient below 0.50 [20]. Capillary density may be assessed as the maximal density observed on a finger as well as the density measured in the middle of the finger, because the reproducibility is similar.

The interpretation of images is not the only potential problem for the reproducibility of capillaroscopy; image acquisition may also lead to variations in interpretation. Nycthemeral nailfold capillary density has been shown to vary from morning to afternoon [20], but we did not assess this because it is not our current practice to do so. Another cause of variation may be the site where the image is recorded in the capillary bed, a problem that may be even more acute if the recorded area is smaller, especially when magnification is higher [21]. This is one reason why ×50 or ×100 magnification is preferred by many teams, since it provides a more accurate interpretation of the landscape as a whole [22].

The reproducibility of Maricq's classification has not been explored to date. The reproducibility of Cutolo's classification was moderate when assessed by two experts who read the images of 71 patients (κ 0.52, 90% agreement) [17]. In our study, interobserver reproducibility was fair or moderate for Maricq's and Cutolo's classifications, respectively, at the first reading. Consensus meetings improved their reproducibility, and training is probably of paramount importance before they can be used reliably. Intra-observer variability was good, with a κ coefficient of ∼0.70. The SCLEROCAP investigators needed to specify definitions in order to increase reliability. However, some points remained unclear, such as whether the classifications should be applied globally on the capillary beds of all the fingers or whether a single finger should be analysed, for example, the fourth left one. Our results suggest that both methods give similar results.

Finally, both classifications raise problems of reproducibility. To be used in clinical trials, these classifications need to be assessed systematically by at least two experts. Their usefulness will be analysed at the end of the SCLEROCAP study, whose results should be available by the end of 2018. It is even possible that another scoring system might prove to be better. In any case, a highly reproducible score is a prerequisite if either of these classification systems is to be deemed to have a good prognostic performance.

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