



Fast track algorithm: How to differentiate a “scleroderma pattern” from a “non-scleroderma pattern”

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ABSTRACT

Objectives: This study was designed to propose a simple “Fast Track algorithm” for capillaroscopists of any level of experience to differentiate “scleroderma patterns” from “non-scleroderma patterns” on capillaroscopy and to assess its inter-rater reliability.

Methods: Based on existing definitions to categorise capillaroscopic images as “scleroderma patterns” and taking into account the real life variability of capillaroscopic images described standardly according to the European League Against Rheumatism (EULAR) Study Group on Microcirculation in Rheumatic Diseases, a fast track

Abbreviations: ACR, American College of Rheumatology; CI, Confidence Interval; EULAR, European League Against Rheumatism; EULAR SG MC/RD, EULAR Study Group on Microcirculation in Rheumatic Diseases; EUSTAR, European Scleroderma Trials and Research group; NVC, nailfold videocapillaroscopy; SSc, systemic sclerosis

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Experts
Algorithm

decision tree, the “Fast Track algorithm” was created by the principal expert (VS) to facilitate swift categorisation of an image as “non-scleroderma pattern (category 1)” or “scleroderma pattern (category 2)”. Mean inter-rater reliability between all raters (experts/attendees) of the 8th EULAR course on capillaroscopy in Rheumatic Diseases (Genoa, 2018) and, as external validation, of the 8th European Scleroderma Trials and Research group (EUSTAR) course on systemic sclerosis (SSc) (Nijmegen, 2019) versus the principal expert, as well as reliability between the rater pairs themselves was assessed by mean Cohen's and Light's kappa coefficients.

Results: Mean Cohen's kappa was 1/0.96 (95% CI 0.95–0.98) for the 6 experts/135 attendees of the 8th EULAR capillaroscopy course and 1/0.94 (95% CI 0.92–0.96) for the 3 experts/85 attendees of the 8th EUSTAR SSc course. Light's kappa was 1/0.92 at the 8th EULAR capillaroscopy course, and 1/0.87 at the 8th EUSTAR SSc course.

Conclusion: For the first time, a clinical expert based fast track decision algorithm has been developed to differentiate a “non-scleroderma” from a “scleroderma pattern” on capillaroscopic images, demonstrating excellent reliability when applied by capillaroscopists with varying levels of expertise versus the principal expert and corroborated with external validation.

1. Introduction

The “scleroderma pattern” on capillaroscopy has been incorporated into the 2013 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria, as well as in criteria to facilitate a (very) early diagnosis of systemic sclerosis (SSc) [1–3]. Its importance is based on the fact that the combination of a “scleroderma pattern” and SSc specific antibodies has the highest performance characteristics to discern in a Raynaud's phenomenon population who will and who will not develop SSc [4].

In 1973 and more detailed in 1981, Maricq et al. was the first to describe key capillary abnormalities of a “scleroderma pattern” using “wide-field” capillary microscopy as “enlargement of capillary loops, loss of capillaries (‘loop drop-out’), disruption of the normal capillary architecture and haemorrhages” [5,6]. Moreover, in her seminal quantitative study she measured with the stereomicroscopic technique the apical diameter of “definitely enlarged” capillaries, and found a mean apical diameter of $47.7 \mu\text{m} \pm 5.8$ to be specific for scleroderma spectrum diseases [7]. This finding was adopted and further developed by Cutolo et al. who likewise defined “giant capillaries” with the

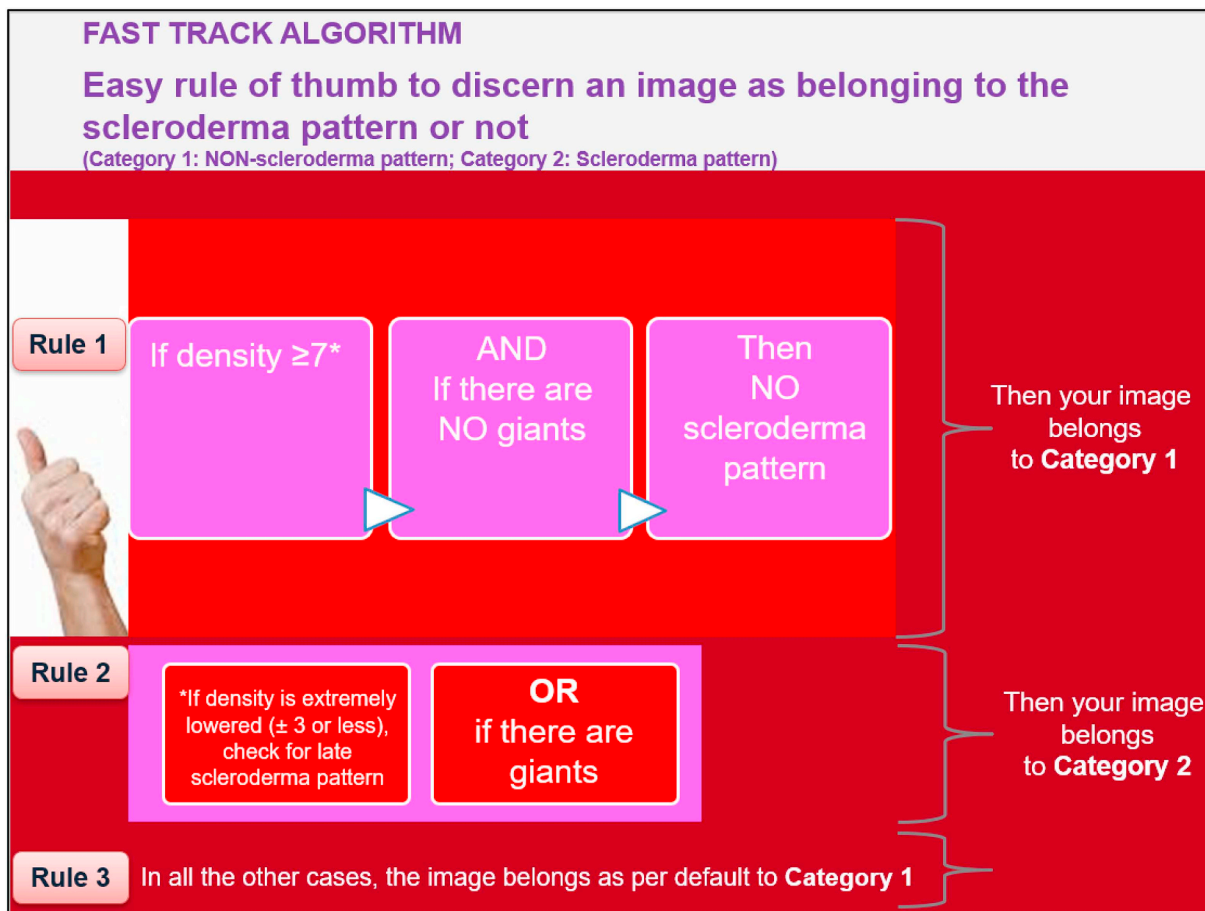


Fig. 1. The “Fast Track algorithm”.

The “Fast Track algorithm” consists of three easy rules: 1) **Rule 1:** a capillary density ≥ 7 capillaries AND the absence of giant capillaries allows the rater to call the capillaroscopic image a “non-scleroderma pattern (category 1)”; 2) **Rule 2:** an extremely lowered capillary density (≤ 3 capillaries) in combination with abnormal shapes (i.e. “late scleroderma pattern”) OR the presence of giant capillaries allows the capillaroscopist to call the capillaroscopic image “a scleroderma pattern (category 2)”; 3) **Rule 3:** if the image does not meet rule number 1 or rule number 2 then the image is automatically classified as a “non-scleroderma pattern (category 1)”.

Table 1

Mean Cohen's kappa (95% CI) and Light's kappa for the groups of raters at the 8th EULAR course on capillaroscopy in Rheumatic Diseases (Genoa 2018).

Group of raters	Mean Cohen's kappa (95% CI)	Light's kappa
Expert raters (n = 6)	1	1
Attendees (n = 135)	0.96 (0.95–0.98)	0.92
“Novices” (n = 68)	0.98 (0.96–0.99)	0.95
“Moderately experienced” (n = 53)	0.96 (0.93–0.99)	0.91
“Experienced” (n = 14)	0.93 (0.85–1)	0.84

CI: Confidence Interval.

naifold videocapillaroscopic (NVC) technique as homogeneously enlarged capillaries with a normal shape and apical diameter over 50 μm [8]. The presence of these giant capillaries on NVC is interesting, as it allows distinction between SSc and non-SSc with over 95.6% specificity [9,10]. Of note, giant capillaries are the hallmark of the “early” and “active” scleroderma patterns, whilst the “late” scleroderma pattern is characterised by the combination of severe loss of capillaries combined with abnormal shapes (“[neo-] angiogenesis”) [7,8].

Even though the classification of a capillaroscopic image as “scleroderma pattern” or not has a high inter-rater reliability between trained capillaroscopists, to the untrained rheumatologist this classification may be very challenging [11–13]. One of the reasons may be the vast variety of non-specific abnormalities of capillaroscopic characteristics (i.e. of capillary density, capillary dimension, capillary morphology and haemorrhages) that may be found in the general population (see below and in Supplementary File 1).

To facilitate the non-trained capillaroscopist in easily classifying an image as “scleroderma pattern” or “non-scleroderma pattern”, the EULAR Study Group on Microcirculation in Rheumatic Diseases (EULAR SG MC/RD), a non-profit international network of expert centres established in 2014 which has as its main (research) focus to facilitate standardization of different non-invasive techniques, decided to create a swiftly trainable decision tree, the “Fast Track algorithm”, based on existing definitions to categorise capillaroscopic

images into the category of “scleroderma patterns” or into the category of “non-scleroderma patterns”. Additionally, the EULAR SG MC/RD decided to assess the reliability of raters using this decision tree to classify capillaroscopic images. The key advantage of a fastly trainable, reliable decision tree would be that any capillaroscopist of any level of experience would be able to use this, knowing that he/she would rate likewise to a principal capillaroscopy expert, without the need to evaluate each single capillaroscopic characteristic that can be evaluated in capillaroscopy for research aims (see below and Supplementary File 1).

2. Methods

2.1. “Fast Track algorithm”

Based on the standard interpretation of capillaroscopic images by the EULAR SG MC/RD, more specifically of the following capillaroscopic characteristics: capillary density, capillary dimension, presence of abnormal capillary shapes and presence of haemorrhages (see Supplementary File 1) and based on the key elements of the “scleroderma pattern”, a decision tree (i.e. the “Fast Track algorithm”) was consented by two founding members of the EULAR SG MC/RD (VS, MC) (see Fig. 1). The “Fast Track algorithm” consists of three easy rules: 1) Rule number 1: the presence of ≥ 7 capillaries (capillary density) AND the absence of giant capillaries (capillary dimension) allows the rater to call the capillaroscopic image a “non-scleroderma pattern (category 1)”; 2) Rule number 2: the presence of giant capillaries or the presence of an extremely lowered capillary density (≤ 3 capillaries) in combination with abnormal shapes (= “late” scleroderma pattern) allows the capillaroscopist to call the capillaroscopic image a “scleroderma pattern (category 2)”; 3) Rule number 3: if the image does not meet rule number 1 or rule number 2 then the image is automatically classified as a “non-scleroderma pattern (category 1)” (see Fig. 1).

2.2. Capillaroscopic images

Thirty representative NVC images (i.e. 14 images with “scleroderma pattern” and 16 with “non-scleroderma pattern”) with good visibility,

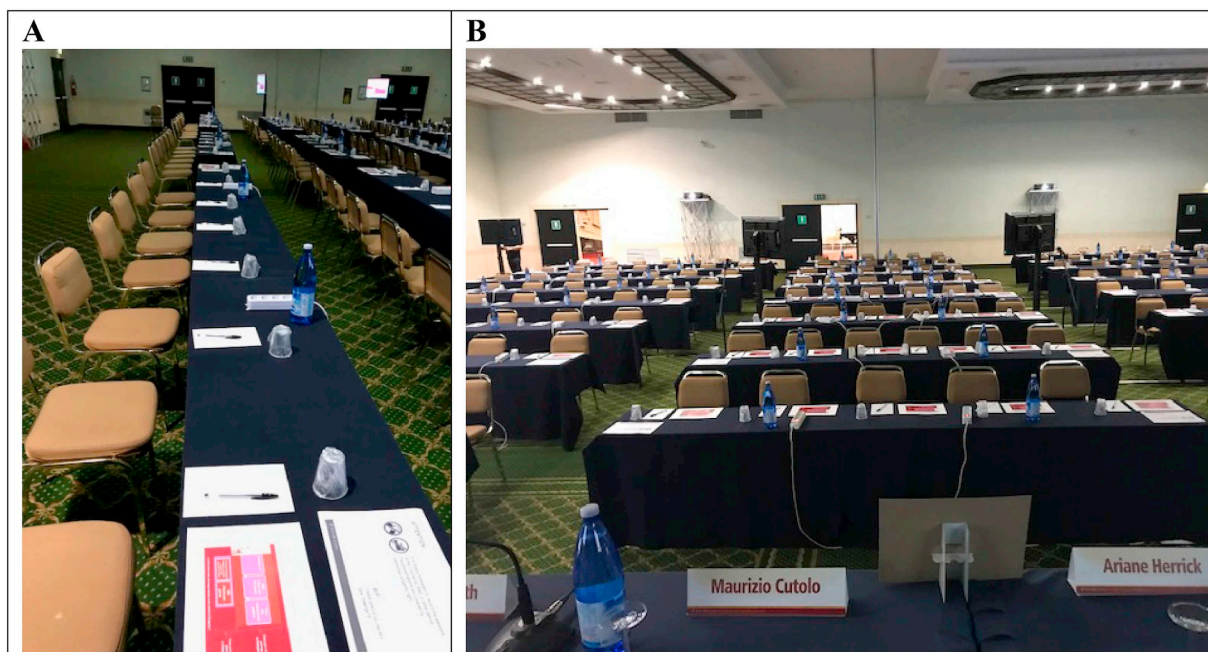


Fig. 2. Examination setting.

After the teaching lecture, the PowerPoint slide of the “Fast Track algorithm” was projected in the room during the whole examination (A) and the attendees had the picture of the “Fast Track algorithm” at hand during the examination (B).

acquired by an optical probe videocapillaroscope equipped with a 200× magnification contact lens, were randomly selected from all NVC examinations of patients referred to the Ghent University Scleroderma Unit between December 2017 and June 2018 (see Supplementary File 2 for the examination set with all capillaroscopic images). In the distal row, the apical diameter of dilated capillaries was reported by a trainee (MG), who had been trained by the principal expert (VS). All images were proofread by the principal expert (VS). Categorisation of images as “scleroderma pattern” or “non-scleroderma pattern” had been executed by the principal expert (VS).

2.3. Procedure of teaching the “Fast Track algorithm” and examining the raters

In the first part of this international multicentre study, a 45 min lasting lecture (“Capillaroscopy in daily practice”) was given at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa (September 2018) to 141 attendees, more specifically 6 experts in capillaroscopy and 135 attendees with varying levels of experience in capillaroscopy: 68 “novices”, 53 “moderately experienced” and 14 “experienced” (see Table 1). In this lecture the EULAR SG MC/RD standardly assessed capillaroscopic characteristics (capillary density, capillary dimension, abnormal morphology and haemorrhages) were explained step by step by the principal expert (VS) and for the attendees’ information an overview of all possible combinations of each of the capillaroscopic characteristics resulting into either “scleroderma patterns” or oppositely “non-scleroderma patterns” was taught both theoretically and applied to exemplary images (see Supplementary File 1 and 3). The “Fast Track algorithm” was applied to each capillaroscopic image and explained by the teacher, the principal expert (VS). Hence, in this interactive way, the audience was stimulated to actively learn the “Fast Track algorithm” (see Fig. 1). After the teaching lecture, the attendees had the picture of the “Fast Track algorithm” at hand during the examination (see Fig. 1). In addition, the PowerPoint slide of the “Fast Track algorithm” had also been projected in the room during the whole examination (see Fig. 2A and B). The exams consisted of 16 pages, containing two capillaroscopic images per page (see Supplementary File 2). Next to an image the attendee was asked to choose between two options by applying a cross, i.e. more specifically category 1 (“non-scleroderma pattern”) or category 2 (“scleroderma pattern”) (see Supplementary File 2). Collaboration between attendees to execute the exam was not allowed. Two trainees (AV, MG) of the principal expert (VS) as well as the principal expert (VS) and the senior author (MC) supervised the room to avoid any collaboration between attendees in taking the exam. Of note, the raters (experts and attendees) were asked to attest their levels of expertise in capillaroscopy into one of the following categories: “novices” (no experience), “moderately experienced” (< 5 years of experience with capillaroscopy) and “experienced” raters (> 5 years of experience with capillaroscopy).

In a second time, as an external validation, this procedure was repeated during the 8th European Scleroderma Trials and Research group (EUSTAR) course on SSc in Nijmegen (February 2019) on 88 attendees, more specifically 3 experts and 85 attendees with varying levels of knowledge of capillaroscopy: 47 “novices”, 29 “moderately experienced” and 9 “experienced” (see Table 2).

2.4. Statistical analysis

Inter-rater agreement for each rater versus the principal expert (VS), i.e. “mean index of reliability”, was calculated for the group of experts, “novices”, “moderately experienced” raters and “experienced” raters, both at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and for reasons of external validation, as well at the 8th EUSTAR course on SSc. To this end, the mean Cohen’s kappa value was reported, which is estimated by taking the mean of all Cohen’s kappa statistic scores between raters and the principal expert (VS) (see Fig. 3A) [14].

Additionally, the agreement between all possible rater pairs, irrespective of the principal expert (VS), was reflected through reporting the Light’s kappa. Hence, conceivably, if the algorithms should be representative for the experts (other than the principal expert) then the Light’s kappa should be high in between the experts (see Fig. 3B) [14].

Thirdly, to get an idea of the percentage of raters at both courses which had a nearly perfect agreement, which is a kappa of > 0.8 versus the principal expert (VS), the distribution of the individual kappa’s was calculated [15].

3. Results

3.1. Raters

Six expert raters (MC, AH, FI, VR, AS, VS [principal expert]) and 135 attendees (68 “novices”, 53 “moderately experienced” and 14 “experienced” raters, from 43 different countries) participated at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 3 expert raters (MC, MV, VS [principal expert]) and 85 attendees (47 novices, 29 moderately experienced and 9 experienced raters, from 22 different countries) participated at the 8th EUSTAR course on SSc.

3.2. Inter-rater reliability

The mean index of reliability (i.e. mean Cohen’s kappa) based on 30 images was 1 for the expert raters present at the 8th EULAR course on capillaroscopy in Rheumatic Diseases ($n = 6$) and 1 for the expert raters present at the 8th EUSTAR course on SSc ($n = 3$). The mean index of reliability was 0.96 (95% Confidence Interval [CI] 0.95–0.98) for the attendees of the 8th EULAR course on capillaroscopy in Rheumatic Diseases ($n = 135$) and 0.94 (95% CI 0.92–0.96) for the attendees of the 8th EUSTAR course on SSc ($n = 85$). Subgroup analysis according to the level of experience of the attendees, demonstrated a mean Cohen’s kappa of 0.98 (95% CI 0.96–0.99) and 0.93 (95% CI 0.90–0.96) for “novices” (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively), 0.96 (95% CI 0.93–0.99) and 0.94 (95% CI 0.89–0.98) for “moderately experienced” raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively) and 0.93 (95% CI 0.85–1) and 0.97 (95% CI 0.92–1) for “experienced” raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively).

Inter-rater agreement for each possible combination of rater pairs (i.e. Light’s kappa), irrespective of the principal expert (VS), based on the 30 images was 1 for the expert raters present at the 8th EULAR course on capillaroscopy in Rheumatic Diseases ($n = 6$) and 1 for the expert raters present at the 8th EUSTAR course on SSc ($n = 3$). The inter-rater agreement for each possible combination of rater pairs, irrespective of the principal expert was 0.92 for the attendees of the 8th EULAR course on capillaroscopy in Rheumatic Diseases ($n = 135$) and 0.87 for the attendees of the 8th EUSTAR course on SSc ($n = 85$). Subgroup analysis demonstrated a Light’s kappa of 0.95 and 0.87 for

Table 2

Mean Cohen’s kappa (95% CI) and Light’s kappa for the groups of raters at the 8th EUSTAR course on SSc (Nijmegen 2019).

Group of raters	Mean Cohen’s kappa (95% CI)	Light’s kappa
Expert raters ($n = 3$)	1	1
Attendees ($n = 85$)	0.94 (0.92–0.96)	0.87
“Novices” ($n = 47$)	0.93 (0.90–0.96)	0.85
“Moderately experienced” ($n = 29$)	0.94 (0.89–0.98)	0.88
“Experienced” ($n = 9$)	0.97 (0.92–1)	0.94

CI: Confidence Interval.

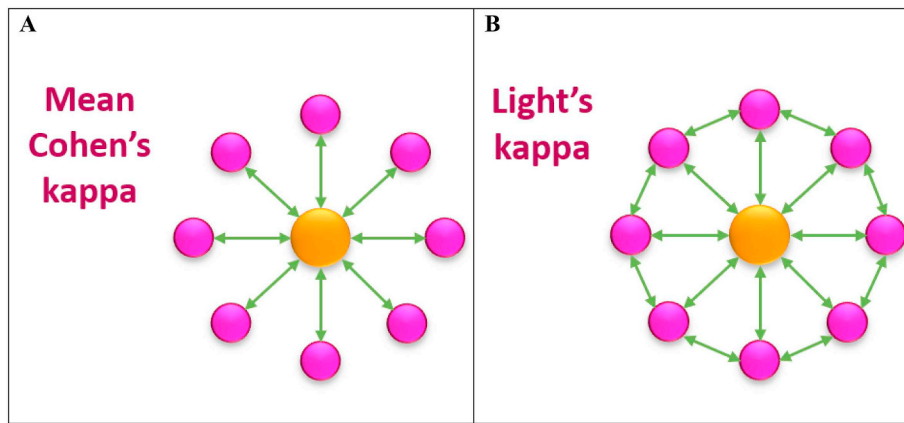


Fig. 3. Inter-rater agreement assessed by kappa coefficients.

Inter-rater agreement was assessed by calculating kappa coefficients, i.e. the mean Cohen's kappa (A) and Light's kappa (B). A) **Mean Cohen's kappa** was calculated to obtain the inter-rater agreement for each rater (expert/ attendees/ “novices”/ “moderately experienced”/ “experienced”) versus the principal expert (VS). B) **Light's kappa** was calculated to obtain the inter-rater agreement for each possible combination of agreement between raters and the principal expert (VS).

“novices” (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively), 0.91 and 0.88 for “moderately experienced” raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively) and 0.84 and 0.94 for “experienced” raters (at the 8th EULAR course on capillaroscopy in Rheumatic Diseases and 8th EUSTAR course on SSc respectively).

3.3. Percentage of raters with high agreement versus the principal expert

The distribution of the individual kappa's showed that 95% of raters at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa and 89% of raters at the 8th EUSTAR course on SSc in Nijmegen had a kappa of > 0.8 versus the principal expert (VS).

4. Discussion

This is the first international multicentre study to step forward to the need to find an easy rule of thumb decision tree (i.e. the “Fast Track algorithm”) to categorise capillaroscopic images as “scleroderma pattern” or “non-scleroderma pattern”. A principal expert (VS) had first classified 30 images, taken with a nailfold videocapillaroscope with a 200× magnification, as “scleroderma pattern” or “non-scleroderma pattern”, the latter comprising perfectly normal images but also images with non-specific abnormalities. Then, in two renowned international training courses (the 8th EULAR course on capillaroscopy in Rheumatic Diseases and the 8th EUSTAR course on SSc) course raters (experts and attendees of different level of experience [“novices”, “moderate experienced”, “experienced”]) had been trained in 45 min by the principal expert to categorise images in the exact same way as the principal expert through exemplary teaching the “Fast Track algorithm”. Subsequently, both in the pilot study at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa, as well as in the external validation study at the 8th EUSTAR course on SSc in Nijmegen, an excellent inter-rater reliability, not only versus the principal expert rater (mean Cohen's kappa) but also in between the raters themselves (Light's kappa) was found in categorizing capillaroscopic images as “scleroderma pattern” or as “non-scleroderma pattern”. Hence, we strongly feel that this “Fast Track algorithm” may be used safely as a teaching tool in daily practice to capillaroscopists with any level of experience, with the aim to have certainty to categorise a capillaroscopic image as a “scleroderma pattern” in the same way that an expert rater does.

This swiftly trainable and reliable decision tree is important, certainly as the “scleroderma pattern” is a criterion in the new 2013 ACR/EULAR classification criteria for systemic sclerosis [3]. Correct attribution (vis à vis a principal expert as repère point) of a capillaroscopic image to the “scleroderma pattern” category is key to correctly denote a patient to meet the criterion of “abnormal capillaroscopy” of the 2013

ACR/EULAR criteria [3].

One of the advantages of the “Fast Track algorithm” is that only simple capillaroscopic characteristics were needed to teach the raters, more specifically, capillaroscopic characteristics that have attested through literature to have a high inter-rater reliability: “capillary density” (number of capillaries), “giant capillaries” (capillaries with an apical diameter $\geq 50 \mu\text{m}$) and “abnormal shapes” [13,16–24]. Rather than trying to train the eye of the rater to interpret capillaroscopic images according to any combination of all existing capillaroscopic characteristics that are being used nowadays in research which may be quite challenging to the untrained capillaroscopists (see Supplementary File 1), with the “Fast Track algorithm” the capillaroscopist only has to check three rules which automatically lead him/her to a correct categorisation, more specifically into a “scleroderma pattern or “non-scleroderma pattern”.

Additionally, we want to draw attention to the fact that the aim of this study was not to assess discriminatory characteristics of capillaroscopy to differentiate between healthy controls, primary Raynaud's patients and patients with secondary Raynaud's phenomenon due to SSc. Landmark work on this issue has already been done [4,25,26]. Moreover, such a research question would have needed a totally different statistical approach with calculation of receiver operating curves and calculation of sensitivity and specificity of capillaroscopy to discriminate healthy controls and primary from secondary Raynaud's phenomenon due to SSc. In contrast, our intention was to assess an expert designed decision tree, the “Fast Track algorithm”, with the aim to enable every capillaroscopist of any level of experience to differentiate within groups of clinically relevant capillaroscopic patterns, more specifically between “the scleroderma patterns” versus the “non-scleroderma patterns”.

5. Conclusion

For the first time, a clinical expert based fast track decision algorithm has been developed to differentiate a “non-scleroderma” from a “scleroderma pattern” on capillaroscopic images. This algorithm demonstrated an excellent reliability when applied by capillaroscopists with varying levels of expertise versus the principal expert, at the 8th EULAR course on capillaroscopy in Rheumatic Diseases in Genoa and corroborated with external validation at the 8th EUSTAR course on SSc in Nijmegen.

Contributors

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Vanessa Smith: Ideation of the study, substantial contributions to the design of the study, acquisition of data, analysis and interpretation of data, drafting of the article, critical revision of the intellectual content, final approval of the version to be published.

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Ariane L. Herrick: Analysis and interpretation of data, drafting of the article, critical revision of the intellectual content, final approval of the version to be published.

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