External clinical validation of automated software to identify structural abnormalities and microhaemorrhages in nailfold videocapillaroscopy images

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Abstract

Objective

Automated systems to analyse nailfold videocapillaroscopy (NVC) images are needed to promptly and comprehensively characterise patients with systemic sclerosis (SSc) or Raynaud's phenomenon (RP). We previously developed, and validated in-house, a deep convolutional neural network-based algorithm to classify NVC-captured images according to the presence/absence of structural abnormalities and/or microhaemorrhages. We present its external clinical validation.

Methods

A total of 1,164 NVC images of RP patients were annotated by 5 trained capillaroscopists according to the following categories: normal capillary; dilation; giant capillary; abnormal shape; tortuosity; microhaemorrhage. The images were also presented to the algorithm. Matches and discrepancies between algorithm predictions and those annotations obtained by consensus of ≥3 or ≥4 interobservers were analysed.

Results

Consensus among ≥3 capillaroscopists was achieved in 86.9% of images, 75.8% of which were correctly predicted by the algorithm. Consensus among ≥4 experts occurred in 52.0% of cases, in which 87.1% of the algorithm's results matched with those of the expert panel. The algorithm's positive predictive value was >80% for microhaemorrhages and unaltered, giant or abnormal capillaries. Sensitivity was >75% for dilations and tortuosities. Negative predictive value and specificity were >89% for all categories.

Conclusion

This external clinical validation suggests that this algorithm is useful to assist in the diagnosis and follow-up of SSc or RP patients in a timely manner. It may also be helpful in the management of patients with any pathology presenting with microvascular changes, as the algorithm has been designed to also be useful for research aiming at extending the usage of nailfold capillaroscopy to more conditions.

Key words

nailfold videocapillaroscopy, deep learning, machine learning, systemic sclerosis, Raynaud's phenomenon, algorithm, quantitative

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Introduction

Nailfold videocapillaroscopy (NVC) allows the assessment of microvascular damage or dysfunction in patients with suspected or confirmed connective tissue diseases. NVC images play an important role in properly stratifying patients with early systemic sclerosis (SSc) (1) and enabling us to differentiate between primary and secondary Raynaud's phenomenon (RP) (2). The easy training, low cost and non-invasiveness of this procedure mean that it is used worldwide.

There is no general consensus on what the specific criteria to stratify capillary types and functionality should be, and the Maricq and Cutolo classifications have been reported to have moderate reproducibility (3). Furthermore, the lack of widely available automated systems to study capillaroscopy images means that physicians need to examine each videocapture manually, in a time-consuming procedure. As a result, detailed analyses and measurements to distinguish between dilated and giant capillaries, or identify abnormal shapes, are often not performed. Indeed, this manual procedure leads to biases, caused not only by the inspection of arbitrary nailfold sections of arbitrarily chosen fingers, but also by the unavoidable interobserver variability (4).

In order to overcome these shortcomings, research is now being performed to develop methods able to measure capillary parameters automatically (5-13). Nevertheless, some of these require additional procedures such as optoacoustic imaging or Doppler laser, which limits their availability (5, 6). We recently described a deep learning, data-driven approach to NVC practice, facilitated by an interactive web-based tool. An exploratory image dataset consisting of 18,000 measurements in more than 2,700 images was used to design an automated software containing an algorithm. This software is able not only to determine the number and density of nailfold capillaries, but also to assess parameters associated with vessel dysfunction such as microhaemorrhages, abnormal shapes (formerly referred to as *ramifications*) or capillary enlargement leading to the development of dilated or giant capillaries (also known as *megacapillaries*). In the first step, the reliability of the algorithm was positively evaluated after comparing manual and automatic examination of NVC images according to standard metrics used in the machine learning field for object detection tasks (14). In order to ascertain whether this system might be useful in routine clinical practice to diagnose or follow-up patients with scleroderma, RP or other connective pathologies, we have now studied the concordance between the algorithm and a gold standard consisting of the consensus reached by a group of experienced capillaroscopists. For this purpose, more than 1,000 images were examined by both procedures, and the number of matches for the identification of each capillary type or abnormality was assessed.

Materials and methods

Ethical approval

The software and its database, as well as the current project to test the reliability of the software-based algorithm, were approved by the Clinical Research Ethics Committee of Aragón, Spain. All patients whose images were analysed by both the software and the trained physicians signed an informed consent form indicating that they agreed to participate.

NVC images

A total of 1,164 NVC images taken during routine explorations of patients with RP in 5 Spanish hospitals were randomly chosen from a collection of more than 10,000 images to be examined by 5 capillaroscopists and the software-based algorithm.

Automated software

The development and features of the automated software designed to count and classify nailfold capillaries have been comprehensively described elsewhere (14). In brief, it consists of a database to store information concerning NVC examinations of patients organised by finger and nailfold sector, as well as other image collections useful for research and dataset elaboration; a web application to manage NVC data;

a desktop application to allow users to capture NVC images with any appropriate device and upload the information to the database.

Deep learning data-driven models

Several deep learning models were built. On the one hand, a first-phase model was set up to locate and count capillaries and microhaemorrhages, and classify the capillaries into normal, giant, abnormal or tortuous shapes.

Note that, although tortuosities are now considered unspecific capillary changes, our algorithm was also taught to identify them, as this might be useful for research or future clinical applications. Our algorithm has been designed to produce detailed analysis of capillaroscopy images (both individual images and complete capillaroscopies) that later can be used by the physician or researcher in any desired way. NVC is a field where new advances are still happening, therefore, even though tortuosities are not currently known to be associated with any disease, we cannot be sure that they are useless in new ongoing research that tries to apply NVC to other diseases than SSc or RP.

On the other hand, a second-phase model was developed to produce measurements for the apical diameter and width of limbs, and thus determine whether a capillary is normal, dilated or giant capillary. Finally, an auxiliary model was constructed to identify dilated/giant capillaries according to their visual appearance only, to be used if no physical size calibration is available.

Our goal is to make our algorithm beneficial for all medical professionals and researchers working with NVC, not just those determining the capillaroscopic pattern in RP patients. Therefore, we aim to detect capillaroscopic parameters in the most comprehensive way possible to produce objective quantitative metrics for any situation.

Dataset

The updated version of the dataset used to generate the algorithm applied in the current study consisted of 2,713 manually annotated and subsequently validated NVC images of primary and secondary RP patients from five Spanish tertiary hospitals. Most images were at 200x magnification level.

None of the images for training the algorithm were later used to carry out this external validation, since the images examined for consensus were randomly extracted from a separate dataset of NVC images in order to reduce biases. The images in the dataset were obtained with a wide range of high resolution capillaroscopy devices (portable capillaroscopes of popular brands and some stereo microscopes), and from different hospitals. The external validation dataset was formed by images from patient capillaroscopies of all the participating hospitals.

Criteria to classify capillaries by the algorithm

A capillary was considered normal, dilated or giant by the algorithm when its apical diameter length or arterial and venous limb width were <20 μm, 20–50 μm or >50 μm, respectively (15). Since the algorithm may not be able to measure the apical width of all capillaries (sometimes it is not clear enough even for humans), the algorithm uses the limb measurements to overcome this limit when trying to apply measurements for objective capillary size classification. Tortuosities were also identified according to the prespecified criteria (16).

Automated analysis performed for the current study

The bounding box annotations to mark on each one of the 1,164 images included in the current analysis were: normal capillary; dilated capillary; tortuous capillary; abnormal shape; microhaemorrhage; giant capillary. Personal information allowing patient identification was never uploaded.

Consensus among capillaroscopists

Five internists from 5 Spanish tertiary hospitals, all with experience of more than 500 capillaroscopies certified by the Spanish Autoimmune Systemic Diseases Group (GEAS), were recruited to analyse manually the same anonymized NVC images that would also be analysed by the software. Bounding box annotation categories were common for both the experts and the algorithm, namely normal capillary, dilated capillary, microhaemorrhage, giant capillary, abnormal shape, tortuous capillary. Consensus was considered to be achieved for each of the 1,164 examined capillaries when at least three of the physicians agreed in their judgement.

Statistical analyses

Consensus among capillaroscopists was considered the gold standard against which the reliability of the algorithm would be tested. The cut-off to consider that consensus had been achieved was an agreement of ≥3 experts in the annotation of each image analysed. Interobserver consensus was calculated at two different levels, when ≥3 and ≥4 capillaroscopists agreed in their judgment. Subsequently, the overall and type-by-type match between each gold standard (consensus of ≥3 and ≥4 experts) and the algorithm prediction was determined. Confusion matrices were built, and the reliability of the algorithm was assessed by calculating its positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity, according to gold standard verdicts. SPSS 22.0 and EPIDAT 3.0 (Xunta de Galicia, Spain) softwares were used for these purposes.

Results

After examining 1,164 images, agreement among ≥3 expert capillaroscopists, the minimum consensus established, was achieved in 1,012 cases (86.9%). Consensus was reached in 52.0% of images when ≥4 experts concurred in their judgment. Unaltered/normal capillary accounted for roughly 40% of the consensus annotations, irrespective of the extent of interobserver agreement (Table I). Almost 70% of images identified as normal capillaries by ≥3 capillaroscopists were also classified as normal by ≥4 interobservers. Among pathological hallmarks, microhaemorrhages and giant capillaries were still well identified when the conditions to achieve consensus became more rigorous (>95% and >75% of microhaemorrhages and giant capillaries according to ≥3 capillaroscopists were identically labelled by ≥4 of them).

Table I. Consensus reached among capillaroscopists after examination of NVC images.

	Capillary type (n=1,164)	Number of capillaroscopists agreeing in their assessment
	≥3	≥4
Normal, n	397	264
Dilated, n	275	119
Microhaemorrhage, n	76	73
Giant, n	119	92
Abnormal, n	29	12
Tortuous, n	116	45
N.C., n	152	559
Overall agreement, n/N (%)	1.012/1.164 (86.9%)	605/1.164 (52.0%)

Five physicians experienced in the management of nailfold capillaroscopy blindly analysed 1,164 capillaries, and the consensus reached for each type of capillary according to the number of operators agreeing, was assessed.
N.C.: no consensus among capillaroscopists reached; NVC: nailfold videocapillaroscopy.

Table II. Metrics to assess the ability of the algorithm designed to categorise nailfold capillaries to match with the consensus reached among capillaroscopists.

Capillary type*	Number of capillaroscopists agreeing in their assessment	
	≥3	≥4
Normal		
PPV	92.7 (89.6-95.8)	97.4 (95.0-99.7)
NPV	89.4 (87.6-91.3)	93.3 (91.2-95.3)
Sensitivity	70.3 (65.7-74.9)	83.7 (79.1-88.4)
Specificity	97.8 (96.9-98.8)	99.0 (98.1-99.9)
Dilated		
PPV	67.2 (61.8-72.6)	76.9 (69.3-84.5)
NPV	93.7 (92.2-95.2)	96.9 (95.5-98.4)
Sensitivity	75.3 (70.0-80.5)	84.0 (77.0-91.0)
Specificity	90.9 (89.1-92.6)	95.2 (93.5-97.0)
Microhaemorrhage		
PPV	98.6 (95.1-100)	98.5 (95.0-100)
NPV	99.3 (98.7-99.9)	99.2 (98.4-100)
Sensitivity	90.8 (83.6-97.9)	93.1 (86.7-99.6)
Specificity	99.9 (99.7-100)	99.8 (99.4-100)
Giant		
PPV	80.9 (73.8-88.0)	91.7 (85.8-97.7)
NPV	98.7 (98.0-99.5)	99.5 (98.9-100)
Sensitivity	89.1 (83.0-95.1)	96.7 (92.6-100)
Specificity	97.6 (96.6-98.6)	98.7 (97.7-99.7)
Abnormal		
PPV	100 (96.1-100)	100 (92.9-100)
NPV	98.4 (97.6-99.2)	99.2 (98.4-100)
Sensitivity	44.8 (25.0-64.5)	58.3 (26.3-90.4)
Specificity	100 (99.9-100)	100 (99.9-100)
Tortuous		
PPV	60.0 (52.0-68.0)	80.8 (69.1-92.4)
NPV	97.8 (96.8-98.7)	99.5 (98.9-100)
Sensitivity	80.2 (72.5-87.9)	93.3 (84.9-100)
Specificity	94.2 (92.8-95.6)	98.4 (97.3-99.4)

Statistical indicators were calculated to estimate the ability of the software to match with the expert consensus panel in categorising 1,164 capillaries. Values are percentages, with 95% confidence intervals in parenthesis. Annotations where agreement among capillaroscopists was not achieved were not considered for calculations. *According to the consensus reached by capillaroscopists.
NPV: negative predictive value; PPV: positive predictive value.

Roughly 40% of dilated, abnormal, and tortuous capillaries at ≥3 expert consensus were also included in these categories when agreement among ≥4 interobservers was set for consensus (Supplementary Table S1).

The overall concordance between the annotations reported by both the expert consensus and the software is shown in Figure 1A. The algorithm's predictions matched 75.8% of those annotations agreed by ≥3 interobservers. Matching increased to 87.1% when ≥4 experts had to concur in their judgment to consider consensus. A detailed description of matches and discrepancies between both methods to categorise capillary types according to the pre-set level of consensus among interobservers is shown in Supplementary Tables S2 and S3. Figure 1B summarises this information. The algorithm's predictions always matched in more than 70% of cases with the expert panel when this identified either microhaemorrhages or normal, dilated, giant or tortuous capillaries. Concordance was lower for abnormal shapes, although the number of cases classified into this category by the interobservers, 29 and 12 in ≥3 and ≥4 expert consensus, respectively, was not large enough to perform reliable comparisons between manual and automatic analysis.

In order to further evaluate matching between experts and the algorithm, PPVs, NPVs, sensitivities and specificities were calculated for each category (Table II). All of these variables were >90% for microhaemorrhages. When either ≥3 or ≥4 interobservers identified normal capillaries, the PPV for the algorithm was >90%. PPVs were >75% for giant and abnormal capillaries regardless of expert consensus level, and for dilations and tortuosities when matching between the automated and manual system was assayed considering consensus when agreement was achieved among ≥4 interobservers. NPVs were in the range of 90-100% for all categories at any expert consensus level. Sensitivities and specificities were in the line of PPVs and NPVs, respectively. Sensitivities were always above 70% for all categories except for abnormal capillaries, and specificities were always >90% (Table II).

Discussion

The incorporation of capillaroscopy to the classification criteria for SSc together with its usefulness to monitor disease progression has made this procedure a widely used tool to assess

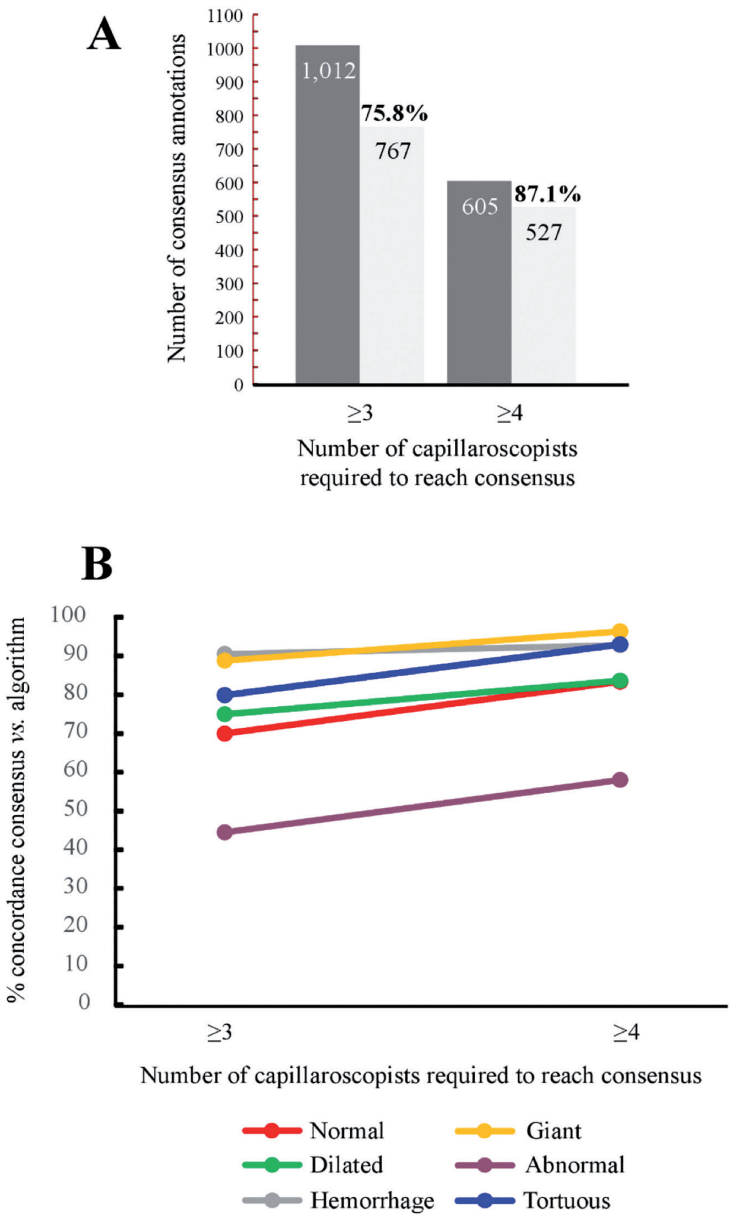

Fig. 1. Concordance between the expert consensus panel and the algorithm designed to categorise nailfold capillaries.
A total of 1,164 capillaries were analysed by 5 blinded physicians experienced in the management of nailfold capillaroscopy, and by the software-based algorithm designed to categorize nailfold capillaries. The concordance between the annotations of the expert panel when consensus was achieved and the annotations generated by the algorithm, was calculated for each degree of interobserver agreement. The total amount of experts' consensual annotations was considered 100%. Annotations where consensus among capillaroscopists was not achieved were not considered for calculations.
A. Overall concordance. Dark grey bars, number of annotations whose categorization was agreed consensually by the group of capillaroscopists. Light grey bars, number of categorisations performed by the algorithm that matched with the expert consensus panel. The concordance (%) is indicated in bold text for each degree of expert consensus.
B. Concordance for each one of the 6 categories established to classify capillaries.

organ involvement/progression in connective tissue disorders (17-18). However, challenges remain that prevent us from extracting the maximum benefit from this method. A comprehensive analysis, if manually performed, may be extremely time-consuming (19). Furthermore, biases may arise due to variability in image interpretation among interexaminers (20). We developed an easy-to-learn web-based automated system that takes advantage of a series of neural networks to assist in the diagnosis of scleroderma and RP, as well as NVC research, by assessing the amount and density of capillaries, measure their apical diameter and limbs, classify them by shape and size and detect the presence of microhaemorrhages. In a first in-house validation, the system showed a high level of precision and recall after comparing automatic counting with manual counting on 2,713 NVC images of RP patients (14). Here, we present the external clinical validation of the software-based algorithm by comparing its analyses with those performed by five experienced capillaroscopists on 1,164 images.

Manual analysis is limited by interobserver variability, even among trained physicians (20). In our case, the fact that agreement among ≥3 experts was achieved in almost 90% of images was encouraging. However, almost 50% of these could not be classified when agreement among at least 4 interobservers was mandated to achieve consensus. This finding is in the line of those of previous work examining concordance among expert capillaroscopists when identifying structural abnormalities or pathological patterns (20-23), and thus highlights the need for alternative assessment methods. In this sense, the high percentage of matches found between automated and manual annotations suggests that the algorithm may be reliable enough to be used in the clinical setting for diagnosis purposes. The fact that matching increases as the conditions set to consider consensus among experts become more stringent further validates the accuracy of the software. This notion is further substantiated by the good PPVs, NPVs, sensitivities and specificities obtained, except in the case of abnormal shapes. In this situation, the small amount of capillaries classified within this category by the experts may have precluded reliable analysis of the ability of the algorithm to predict its occurrence.

Despite the existing pre-set size-based criteria to identify dilated capillaries (15), there was a decrease in consensus among physicians when it comes to classifying these, with a drop from 275 to 119 annotations when consensus was set at ≥3 or ≥4 interobservers,

respectively. The wide range of sizes considered for this category might have increased subjectivity. Since the software was designed to assess sizes objectively, algorithm predictions may be superior to manual examinations when identifying capillary dilations. In any case, the sensitivity of the automated system to identify dilated capillaries was in the range of 75-85%, which means that most of those images annotated as dilations by the expert panel would also be located within such a category by the algorithm.

To the best of our knowledge, ours is the first automated system for identifying capillary abnormalities whose usefulness has been borne out in the clinical setting, taking advantage of a collection of more than 2,700 images of RP patients. These are a good representation of those commonly found in the day-to-day clinical workflow. On the other hand, the comparison between the software's predictions and the manual annotations performed by up to 5 trained specialists constituted a demanding test of the algorithm's accuracy. Our findings may be relevant for clinical practice. By relying on a large bank of images, the software assesses not only the number and density of capillaries but also anomalies such as microhaemorrhages or giant capillaries. Its reliability may help physicians to diagnose or follow-up their patients in a straightforward way, and thus take clinical decisions promptly. Deep convolutional neural networks (CNN) have been successfully applied to many image processing problems in recent work (24), and other automated or semi-automated systems to analyse nailfold capillaries have been reported. One of them was designed to predict nailfold capillary number and density, and was validated by comparing its predictions against the annotations performed by four independent observers on 80 NVC images of patients with SSc or primary RP, and healthy controls (7). Other systems have been reported to improve capillary analysis in preliminary stages (25). One of them, which was also CNN-based, focused on searching for differences among capillary beds of normal subjects, diabetic and hypertensive patients, but did not delve into structural abnormalities (9). Another one also followed a layered machine learning approach and relied on a set of 455 images to identify patterns distinctive of primary RP patients, potentially life-threatening SSc patients, and healthy controls. The program did not provide information regarding each individual image (8). Others aimed to obtain fully automated measurements based on high-quality captures to assess capillary number, density and identification of morphological changes, although without the support of an image bank-based prediction algorithm (10-13). Finally, most recently the development of a vision transformer-based deep-learning model has been reported which may be useful to assess patterns of microangiopathy (26, 27), although quantitative metrics are not produced at all.

Our study has some limitations. Firstly, consensus among interobservers was not achieved in a non-negligible number of images, and the algorithm's precision could therefore not be assessed in such cases. Nevertheless, the good match observed between those manual annotations achieving stringent consensus and the automatic ones, substantiates the clinical reliability of the software. Furthermore, patient diagnosis relies on large pools of images, which considerably reduces the risk of errors. Finally, the low number of abnormal capillaries identified by the experts, as was the case in our previous study (14), precluded robust analysis to assess the accuracy of the algorithm for identifying this abnormality.

In summary, we provide the external clinical validation of a previously reported automated system for the routine assessment of nailfold capillaries that can be applied to NVC images obtained with any microscope. Regular updating of the training dataset with images of varied origin is continuously improving the precision of the algorithm. We are currently working on examining the accuracy of this tool to identify morphological patterns consistent with RP or SSc and improving the global precision and recall of the system by extending the training dataset.

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