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ORIGINAL ARTICLE

Towards a consensus on the clinical applications and interpretations of the nailfold capillaroscopy standards in clinical practice: An initiative by the Egyptian Society of Microcirculation

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ABSTRACT

Objectives: Based on the mainstream adoption of nailfold capillaroscopy as an investigative tool for rheumatologists, this work was carried out by a panel of experts in the field of capillaroscopy and microcirculation to issue a consensus view on capillaroscopic image acquisition and analysis standardization.

Materials and methods: After the key clinical questions were identified by the core team, a systematic review of the published research was carried out focusing on variable capillaroscopic techniques, definitions, and characteristics, including capillary density (number of capillaries), capillary morphology (shape of each capillary), capillary dimensions (width of apical, arterial, and venous limb of the capillary), and the presence of hemorrhages. The expert panel attained a consensus and developed recommendations for the standardization of capillaroscopy in clinical practice. These included recommendations for normality and abnormality and the different capillaroscopic patterns. It also involved recommendations for scoring systems, reliability, and reporting.

Results: A panel of 11 experts participated in the two rounds with a response rate of 100%. A total of nine recommendations were obtained. The agreement with the recommendations (a score of 7-9) ranged from 81.8 to 90.9%. A consensus (i.e., ≥75% of respondents strongly agreed or agreed) was reached on all the clinical standards.

Conclusion: This work highlighted the main NFC indications, the technical equipment that should be used, how to carry out the procedure, standardization of the terminology of the parameters, and the interpretation of NFC findings. An evidence-based consensus incorporating the advice and experience of a diverse international expert panel was reached.

Keywords: Clinical practice, microcirculation, nailfold capillaroscopy, recommendations.

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The capillary exchange function of microcirculation is to provide oxygen and nutrients to tissues while removing carbon dioxide and waste products. Capillaries in most parts of the fingers are perpendicular to the skin surface, making visibility difficult. However, they become parallel to the skin surface in the nailfold zones.[1] Nailfold capillaroscopy (NFC) is a noninvasive, highly sensitive, easy, safe, and low-cost imaging technique,[2] and since 1990, significant attempts have been made to improve and standardize the NFC protocol. The earlier wide-field microscopy technique (low magnification 12) was replaced with a typical 200-fold magnification.[3] Further research demonstrated that autoantibodies and capillaroscopic results, when used together, are commonly acknowledged as a powerful diagnostic tool for diagnosing developing connective tissue disorders in patients with Raynaud's phenomenon.[4,5]

Although NFC has been recognized as a mainstream assessment tool for rheumatologists and the procedure has established its value in early diagnosis and prediction for clinical complications in patients with systemic sclerosis, capillaroscopy remains an underutilized technique in clinical practice. This has been attributed to a lack of clarity regarding the validation, scoring, and classification of capillaroscopic patterns.[6] The EULAR study group recently issued a study that clarified the importance of NFC and produced an agreement on the standardization of NFC for the evaluation of patients with Raynaud's phenomenon and systemic sclerosis.[7] Clarity on image acquisition, optimum capillaroscopic technique, the terminology, and what is normal or abnormal, as well as the reliability of image analysis, are vital for NFC to establish its place in day-to-day practice.

The unceasingly developing role of NFC in inflammatory rheumatic disorders prompts us to continue pursuing new updates, recommendations, and expert sentiments in this field. This study aimed to carry out a comprehensive expansion based on the review published in 2020[7] and provide consensus-based recommendations for clinical applications and interpretations of the NFC, as well as a complete strategy for incorporating NFC into conventional rheumatology practices.

MATERIALS AND METHODS

The study design was developed using qualitative scientific evidence and consensus based on existing scientific evidence as well as clinical experience. This was a multistep procedure that followed the clinical evidence-based guidelines initiative methodology with the aim of implementing an actionable clinical gold standard for inflammatory arthritis. The evidence-based component of the composition followed the favored announcing items for systematic reviews and meta-analyses criteria for precise survey distribution.[8,9]

Development stages

The core team was formed of three experts with recognized experience in NFC. The core team supervised and coordinated the teamwork, assisted with developing the scope of the project and clinical questions, reached a consensus on the key questions, nominated the expert panel, and drafted the manuscript. The key clinical questions were formulated following the PICO (patient, intervention, control, and outcome) strategy.

Following the core team's identification of the key questions, a dedicated team conducted a systematic review of studies, focusing on the most appropriate NFC techniques, capillaroscopic characteristics and definitions, scoring systems, and image acquisition and interpretation reliability, as well as reporting. The search approach followed the preferred standards for systematic reviews and meta-analyses.[10] The Oxford Centre for Evidence-Based Medicine (OCEBM) approach was used to establish the level of evidence for each component (Table 1).

Inclusion criteria

Articles included were systematic reviews, randomized controlled trials, uncontrolled trials, observational studies including cohort, case-control, and cross-sectional studies. Editorials, commentaries, conference abstracts, and nonevidence-based narrative/personal reviews were excluded. The core leadership team nominated 11 participants. The criteria for their selection included professional knowledge and experience in the field of NFC and active participation in scientific research on NFC.

Developing the clinical care standards framework

A structured template was designed to assist consistent identification of the model components based on the answers to the structured key questions and the literature review. The format in which the recommendations/information are delivered and extracted has been identified for each component.

Delphi Rounds

The Delphi rounds were based on an online survey. In the first round, established between March 26 and March 31, 2022, participants were asked to consider the key clinical questions identified by the systemic literature review, identify any new items that may have been overlooked, and clarify any items that were unclear. The second round was based on the first round's results and conducted between April 6 and April 11, 2022. In this round, participants were asked to assess each item on a scale of 1 to 9 (1=completely inappropriate, 9=completely appropriate) and provide comments.

Definition of consensus

The definition of consensus was established before data analyses. It was determined that consensus would be achieved if at least 75% of participants reached an agreement (a score of 7-9) or disagreement (a score of 1-3).[11] If a statement received a mean vote of <3 or a low level of agreement, it was retired. In view of the comments, statements with a score of 4-6, which exhibited uncertainty, were changed. The levels of agreement on each statement of recommendation were regarded as high if all votes on a statement fell into the agreement bracket (7-9) following the second round of votes.[12,13] If the differences between round group responses were less than 10%, the consensus was termed stable.[14]

RESULTS

Literature research and evidence selection

By using a search strategy, 1,377 possibly relevant studies were found during the research selection phase. By screening the titles and abstracts, 1,281 were ruled out (duplicate studies, studies that did not match the study design of interest, studies that did not examine the patient of interest or did not report the outcome measures of interest). As a result, 18 studies that were relevant were included in the complete article review (Figure 1). To establish the degree of evidence in each area, the OCEBM approach was utilized (Table 1).

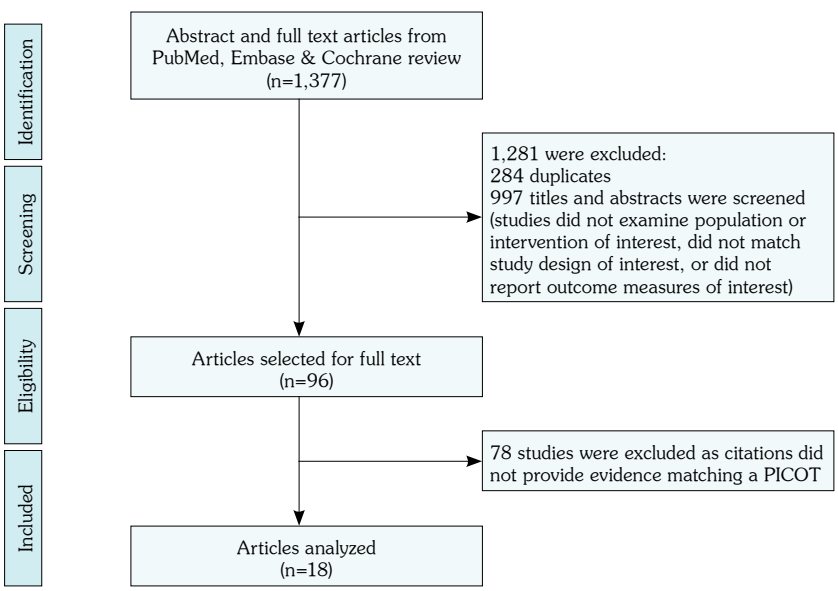

Figure 1. Flow chart for the study selection process.
PICOT: Patient, intervention, control, and outcome.

Table 1. Levels of evidence

Level of evidence	
1	Systematic review of all relevant randomized clinical trials or n-of-1 trials
2	Randomized trial or observational study with dramatic effect
3	Non-randomized controlled cohort/follow-up study (observational)
4	Case series, case-control study, or historically controlled study
5	Mechanism-based reasoning (expert opinion, based on physiology, animal or laboratory studies)
Grades of recommendation	
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies, or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troubling, inconsistent or inconclusive studies of any level

Expert panel characteristics

The Delphi form was sent to the expert panel (n=11) who participated in the two rounds. Of the respondents, two (18.2%) were Italian, two (18.2%) were German, and one (9.1%) was from the UK . The remaining six experts were gathered from different governorates and health centers across Egypt, with one from each of the following: Cairo University, Ain Shams University, Tanta University, Fayoum University, Assiut University, and National Research Center.

Delphi round 1

The clinical questions that formed the foundation for this work, as well as the titles of the items in the guidelines, were introduced during this phase (Table 2). For the first round, the response rate was 100% (11/11). On 90% of the topics, there was agreement on the key clinical questions (≥75% of respondents strongly agreed or agreed). There were no comments on the first round.

Delphi round 2

The second round received 100% (11/11) of the responses (Table 3). On 86.0% of the questions, there was agreement on the inclusion of clinical standards (≥75% of respondents strongly agreed or agreed). The wording of some of the recommendations drew some comments. For

Table 2. Key questions used to develop the recommendations

Question	Mean±SD	Percent of agreement	Level of agreement
What are the indications of nailfold capillaroscopy?	8.2±2.5	90	H
What is the most appropriate NFC device?	7.6±2.7	80	H
Who are the targeted patients?	7.7±2.6	80	H
Who to perform NFC?	7.4±2.7	80	H
What are the recommendations for standardization and terminology in nailfold capillaroscopy?	8.1±2.5	90	H
What are the recommendations for capillaroscopy procedure?	8.2±2.0	90	H
What is the value relevance of capillaroscopy for assessment of patients with Raynaud's phenomenon?	8.2±2.5	90	H
Is there a link between capillaroscopic and serological findings?	7.9±2.1	80	H
How to optimize reporting of the capillaroscopic findings?	8.0±2.0	80	H

SD: Standard deviation; NFC: Nailfold capillaroscopy.

Table 3. Summary of recommendations of on the clinical applications and interpretations of the NFC

Statement	Level of evidence	Mean±SD	Percent of agreement	Level of agreement
Indications of NFC: 1. Differentiating between primary and secondary Raynaud's 2. Monitoring the transition from primary to secondary RP; 3. Early diagnosis of SSc; 4. Differential diagnosis of SSc-related conditions, such as localized SSc and eosinophilic fasciitis, which usually have a normal capillaroscopic pattern; 5. Detection of severe microangiopathy and prognostic evaluation in SSc; 6. Monitoring treatment and disease activity in dermatomyositis. 7. Evaluating cases of idiopathic pulmonary fibrosis for possible underlying connective tissue diseases	2	7.8±2.9	90.9	H
Device: The gold standard device is the digital videocapillaroscope that combines a microscope with a digital video camera.	3	8.1±2.4	90.9	H
Targeted patients: NFC should be performed in almost all patients with RP even primary or secondary type.	4	7.6±2.4	90.9	H
Who should do the NFC procedure and interpret the results? Specialists who have the experience in NFC. These include: 1. Working in National/University Hospital/Ministry of Health hospital providing NFC service and having regular scientific meetings. 2. In solo practice: -if less than 3 years, a log book showing traceable record of NFC cases and diagnosis/management outcomes; and -if practice more than 3 years, the specialist should provide an audit comparing his/her service with gold standards as national guidelines showing the outcome of his service. 3. Preferable if healthcare professional have publications in peer-reviewed journal whether national or international	2	8.2±2.7	90.9	H
Terminology in NFC: **Counting** the capillaries number: All the capillaries present in the distal row are considered for counting, even if they are not at the same levels. **Capillary density** (the number of capillaries in the distal row of each finger or toe in a 1 mm length. **Low Capillary density:** Less than 9 capillaries per mm Intercapillary distance: defined as the longest distance that H exists between two neighboring capillary loops (Normal <110 µm) **Drop out zone** (Avascular Areas): Region with intercapillary distance over 500 µm with no apparent cause of visual field obstruction **Capillary dimension** The width and height of a capillary are the main parameters. Capillary width is the width of a capillary loop at its widest section Capillary length is the distance between the apex of a capillary loop and the point where the capillary loop is no longer visible **Cut off measures** ***Dilated Capillary:*** The arterial limb diameter larger than 15 µm or whose venous limb wider than 20 µm ***Giant Capillary:*** Capillaries with an apical diameter ≥50 µm (afferent, apical, efferent) **Capillary elongation:** Over 295 µm length **Capillary Morphology** (shape of individual capillaries): The shape of a regular capillary: like a hair pin or the letter "U" upside-down, with a slimmer arterial arm, an upper part, and a venous arm. Other shapes include: tortuous, branched, bushy, dilated, and giant capillaries. **Capillary direction** is the angle between a vertical line and the vector associated with the highest proper value **Capillary polarity** is the standard deviation of all the capillary directions in an image **Neo angiogenesis:** Newly formed irregular, branching capillaries usually in an avascular area replacing the older ones that were lost **Hemorrhage(s):** Extravascular deposits consisting of fresh, bright-red blood or old blood containing hemosiderin deposits (present/absent) **Microhemorrhage:** Reddish brown rounded well defined hemorrhage blotches outside the capillary	4	8.1±2.4	90.9	H

Table 3. Continued

Statement	Level of evidence	Mean±SD	Percent of agreement	Level of agreement
Relevance of capillaroscopy for assessment of patients with Raynaud's phenomenon: NFC findings are usually normal in primary RP, and abnormal in secondary RP (abnormal findings differ according to the underlying rheumatic disease).	4	8±2.4	90.9	H
In case of primary Raynaud`s It is recommended to perform capillaroscopy every 12-24 months in primary RP, since up to 10% of these patients will develop a connective tissue disease, sometimes after decades.	4	8±2.4	90.9	H
Abnormal NFC findings in primary RP have a positive predictive value for the development of systemic rheumatic disease.	4	8±2.4	90.9	H
Relevance of capillaroscopy for systemic sclerosis The pattern of NFC in SSC is specific and is characterized by presence of loss of capillaries, dilated capillaries, avascular areas, hemorrhages and neoangiogeneis.	4	8.2±2.4	90.9	H
There are three phases of capillaroscopic changes during the course of SSc: 1. An early phase: presence of few dilated and/or giant capillaries and few hemorrhages without loss of capillaries. 2. An active phase: (a marker of disease progression) presence of frequent giant capillaries, frequent (more than 6 per millimetre) capillary microhemorrhages, moderate (20-30%) capillary loss, absent or mild ramified capillaries and a mild disorganization of the capillary architecture. 3. A late phase: it is characterized by, irregular enlargement of the capillaries, severe (>50%) capillary loss with evident extensive avascular areas, ramified or bushy capillaries, severe disorganization of the capillary array, and almost absence of giant capillaries and microhemorrhages.	4	8.2±2.4	90.9	H
Diagnostic parameters: Capillaroscopy has diagnostic parameters (irregularly enlarged capillaries, giant capillaries, microhemorrhages) and progression parameters (reduced capillary number, capillary ramifications and capillary architectural disorganization	4	7.6±2.8	81.8	H
In a systemic disease in which vascular damage is one of the pathogenetic factors, abnormalities in capillary morphology can be observed long before the onset of clinical symptoms. In patients already diagnosed with a systemic disease, damage to the capillaries may reflect the involvement of internal organs and help determine the stage of the disease".	3	7.6±2.8	81.8	H
The link between Capillaroscopic and Serological Findings: There is association between NFC, disease specific autoantibodies and cardiopulmonary complications.	4	8±1.9	81.8	H
The combination of autoantibodies and NFC-defined microvascular lesions identified patients at higher risk for cardiopulmonary disease more accurately	4	8±1.9	81.8	H
NFC and comorbidities Loss of capillary density is linked with higher mortality rate in SSC patients.	3	7.8±2.1	81.8	H
Nailfold videocapillaroscopy has a relation with visceral organ involvement in SSc; especially PAH, digital ulcers & ILD.	4	7.8±2.1	81.8	H
Using NFC could be of value for the evaluation of treatment response.	4	7.8±2.1	81.8	H
Technique: The NVC technique with 200× magnification, capturing at least two adjacent fields of 1 mm in the middle of the nailfold finger, is the gold standard capillaroscopic technique to perform nailfold capillaroscopy	2	7.9±2.1	90.9	H
Preparation: 1. Patient preparation: Artificial nails and nail polish are contraindicated. Patients should have no history of recent (at least 2 weeks) trauma to the distal phalanges (including manicure), and the nail beds should appear normal with no evidence of recent or old infection, wound, etc. 2. Environment preparation: Room temperature should be between (22-25°C), and the patient should be present for at least 15 minutes before the examination so the nail fold capillary network can adapt to the room temperature	3	8.2±1.6	90.9	H

Table 3. Continued

Statement	Level of evidence	Mean±SD	Percent of agreement	Level of agreement
Procedure: 1. Nailfolds are prepared by rubbing on a thin layer of herbal oil, preferably cedar oil (olive oil and sesame oil can also be used). Emulsion oil used in microscopes is not recommended as it reduces the visual field. 2. All fingertips, except for the thumbs, should be studied. Thumbs often show irregularities in their capillary network due to repeated trauma in everyday task. The best fingers are often the 4th (ring), but it is better to study all eight fingers. 3. Three high quality pictures of each finger are taken from the medial and lateral corners of the nail bed and from the midpoint. These pictures increase the sensitivity of the diagnosis. A total of 24 images are recorded which is very important in scoring (quantitative assessment) and follow-up, but the average of the three readings for each nail is recorded in the table for the final report.	3	7.9±2.5	90.9	H
How to read NFC: 1. Transparency 2. Density 3. Dimension 4. Morphology 5. Hemorrhage 6. Angiogenesis 7. Venous plexus 8. Flow	3	7.8±2.6	81.8	H
Reporting: 1. Relevant patient's data (reason for referral, occupation, patient's habits e.g. smoking, comorbidities, medications, rheumatologic diagnosis, antibody positivity) 2. Description of patient preparation before NVC 3. Details of device description (make and model of the NFC, use of oil, PC software for image analysis, the use of automated grid.) 4. Description of examination: 5. Details of experience or qualifications of personnel responsible for image acquisition and interpretation should be reported 6. In case of more than one examiner, training for each examiner should be specified 7. The number of fingers examined should be reported 8. Which fingers have been examined 9. Each finger should be analyzed separately and reported separately or together 10. Reasons for finger exclusion should be reported 11. Number of images collected at each nailfold should be reported 12. Details of image quality (and missing data) should be reported 13. Details of global condition of the hands (e.g. flexion contractures) should be reported 14. Details on image reading (e.g. blind reading) should be reported (if part of a research study) 15. Report the overall pattern (i.e. normal: stereotype normal and non-specific abnormalities vs abnormal: scleroderma patterns)[9] 16. Report the validated scleroderma patterns (i.e. early, active, late or scleroderma-like)[12]	3	7.4±2.8	81.8	H
How to interpret results Based on the abnormalities, results are reported in three main categories: **1. Normal capillaroscopy.** When all five groups of findings are negative except for some degree of tortuosity, the term of "normal capillaroscopic findings" is applied. Tortuosity is relatively frequent in healthy subjects following microtrauma to the nailfold. **2. Nonspecific morphological abnormalities:** The presence of one abnormal finding, except severe capillary density loss. **3. Scleroderma pattern** The existence of more than one abnormal finding in NFC is named "scleroderma pattern" or "SSD."	2	7.8±2.3	81.8	H

Table 3. Continued

Statement	Level of evidence	Mean±SD	Percent of agreement	Level of agreement
Microvascular alterations detected by NFC in patients with SSc were reclassified into three different subgroups:				
Early:				
1. Very mild architectural derangement				
2. No changes in capillary density				
3. Slightly enlarged loops and giant capillaries				
4. Rare occurrence of microhemorrhage				
5. Angiogenesis				
Active:				
1. Mild architectural derangement				
2. Moderate changes in capillary density				
3. Moderately enlarged loops and giant capillaries				
4. Moderate to severe microhemorrhages				
5. Moderate angiogenesis				
Late:				
1. Severe architectural derangement				
2. Severe changes in capillary density				
3. Enlarged loops or giant capillaries				
4. Microhemorrhage				
5. Angiogenesis				
Recommendations/suggestions and images	3			

NFC: Nailfold capillaroscopy; RP: Raynaud's phenomenon; SSc: Systemic sclerosis; PAH: Pulmonary artery hypertension; SSD: Scleroderma spectrum disorder; ILD: Interstitial lung disease; PC: Personal computer.

signs of NFC, there were a few more comments, excluding minor editing suggestions. Following the second round, two sentences in the indication section and one sentence in the how-to-read NFC section were slightly amended.

DISCUSSION

Nailfold capillaroscopies safety, simplicity, and noninvasiveness are essential in recognizing the possibility of whether Raynaud's phenomenon patients are developing or having an underlying connective tissue disease. Microvascular changes manifested as gradual functional and structural microvessel damage are crucial in the pathophysiology of connective tissue diseases, particularly systemic sclerosis.[15] However, the standardization of NFC remains an issue. This was the motivating factor behind this study, which aimed to establish a consensus on capillaroscopic image capture and analysis standardization.

In contrast with the guideline recommendations of the Brazilian Society of Rheumatology for the indication, interpretation, and performance of NFC, which was based on a position article,[16] this was an evidence-based consensus on the clinical applications and interpretations of the NFC standards in clinical practice. While the results of this work are in agreement with the standards of NFC for the assessment of patients with Raynaud's phenomenon and systemic sclerosis published by the EULAR study group[7] and the recommendations included in the Brazilian Society of Rheumatology, this work added further details on reporting and how to interpret results. The guidelines proposed a simple definition for the parameters evaluated in the NFC and ways of scoring. The Egyptian Society of Microcirculation was developed to build a national network of centers and set a framework and guidelines for the NFC and launch teamwork facilitating future research both nationally and internationally.

This work highlights the importance of NFC not only for early diagnosis of systemic sclerosis but also for the detection of severe microangiopathy and prognostic evaluation in systemic sclerosis, monitoring treatment and disease activity in dermatomyositis, evaluating cases of idiopathic pulmonary fibrosis for possible underlying connective tissue diseases, and monitoring the transition from primary to secondary Raynaud's phenomenon. To distinguish primary from secondary Raynaud's phenomenon, correlations between morphological analysis of microcirculation employing NFC and functional analysis of microcirculation have been implemented. NFC has an advantage over other methods, such as thermography and laser Doppler imaging, for assessing cutaneous blood artery function (i.e., the flow of blood) as it can measure capillary morphology. However, in comparison to NFC, the signal collected by these two technologies assesses blood flow from more than simply the capillary bed. The superficial capillary blood flow is measured by laser Doppler, as are the arterial and venous vessels of the superficial and mid-dermis.[16] In concordance, thermography reflects skin temperature, which represents the underlying blood flow, with both skin and muscle perfusion contributing to the signal.[3]

A consensus is usually reached in the Delphi methodology when ≥75% of respondents strongly agree or agree on the clinical standards.[12,17,18] When the experts were asked about image acquisition and analysis, different capillaroscopic procedures, normal and abnormal capillaroscopic characteristics and their meaning, scoring systems, image acquisition, and interpretation dependability, there was a wide consensus. There were 16 recommendations in total, and the proportion of agreement ranged from 81.8 to 90.9%, demonstrating a significant trend among healthcare experts. The section on reporting attracted several comments. Although there was 81.8% consensus on the NFC assessment, results of this study highlight the need for further work to identify core domains for NFC reporting. A study carried out by Ingegnoli et al.[19] reported that the description of NFC methods was highly heterogeneous and differed markedly on several items. A reporting checklist of 33 items was developed based on practical suggestions. However, the study concluded that there was insufficient evidence to make definitive recommendations on reporting items for capillaroscopy in clinical research and stated that a further step toward standardization of NFC reporting is required.

There are some limitations to this guideline. Although the guideline represents the greatest data available at the time the report was written, one of its flaws is the lack of comparative evidence for acquiring the best data. Another limitation is that we only looked at the English literature. The findings should be treated with caution, and future research may necessitate adjustments to the report's conclusions or recommendations. The major strength of this work is the diversity of the expert panel that is shared in this work, which adds robustness to the work and its outcomes.

In conclusion, NFC is an important, reliable, and useful tool in rheumatology, and it is increasingly being used in standard clinical practice; however, care is required in interpretation and terminology. This work highlighted the main NFC indications, the technical equipment that should be used, how to carry out the procedure, standardization of terminology of the parameters, and the interpretation of NFC findings and yielded an evidence-based consensus that took into account the expert panel's advice and expertise. As a result of the standardized indications and definitions, both rheumatologists and clinicians are expected to improve the quality and reliability of NFC.

Ethics Committee Approval: The study protocol was approved by the Tanta University Ethics Committee (date: 16.08.2021, no: 34842/8/21). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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