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Editorial

Is there a role for nailfold videocapillaroscopy in interstitial lung disease?

Interstitial lung diseases (ILDs) are heterogeneous disorders with a variety of causes, clinical manifestations and treatment options. Idiopathic pulmonary fibrosis (IPF) is the most common fibrotic ILD and is characterized by a radiological and/or histological pattern of usual interstitial pneumonia (UIP) and progressive fibrosis [1]. ILDs may also be associated with autoimmune and CTDs, sarcoidosis, and chronic hypersensitivity pneumonitis (CHP) or have clinical features that suggest an underlying autoimmune process but do not meet the established criteria for a CTD [interstitial pneumonia with autoimmune features (IPAF)] [1, 2]. In their manuscript, Umashankar *et al.* [3] correctly point out that, first, the appropriate classification of ILD is paramount, because the therapeutic strategy can differ based on disease aetiology; second, that classifying ILD may be complicated, with the need of multidisciplinary assessment, stipulating a role for the rheumatologist; third, that the utility of nailfold videocapillaroscopy (NVC), a tool frequently used by rheumatologists, is unclear in IPF, CTD-ILD and IPAF.

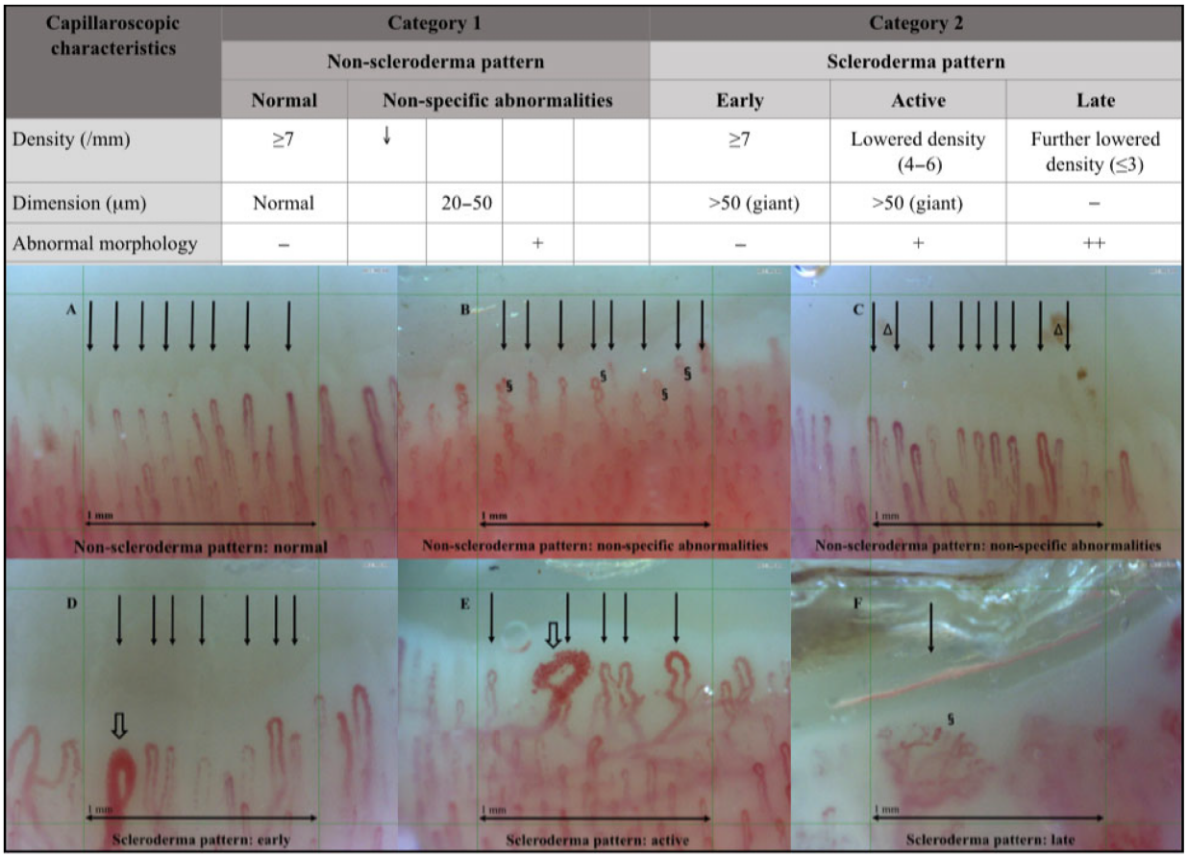
Subsequently, to evaluate the diagnostic utility of NVC, Umashankar *et al.* executed a systematic review and meta-analysis (with an exhaustive assessment of quality of evidence using personalized risk-of-bias tools and a tailored GRADE assessment tool) and described capillaroscopic characteristics (named nailfold videocapillaroscopic 'abnormalities') based upon the EULAR Study group on microcirculation in Rheumatic Diseases definitions (combining non-specific abnormalities and scleroderma patterns, see below and Fig. 1). A prevalence ratio of nailfold videocapillaroscopic 'abnormalities' of 13.8% in IPF, of 80.4% in CTD-ILD and of 27.4% in IPAF were distilled from 21 manuscripts retained in the systematic review. Umashankar *et al.* conclude first, that NVC can increase the diagnostic accuracy of ILD when used in a multidisciplinary setting, and appears to have greatest utility in CTD-ILD, followed by IPAF and IPF; also, that further evidence from larger studies using the EULAR capillaroscopic definitions is needed to support the diagnostic utility of NVC in CTD-ILD and IPAF in routine clinical practice.

Second, they found that the presence of SSc-ILD is associated with a high (almost universal) frequency of late and active (scleroderma) patterns; that consequently SSc patients with those active and late patterns in particular should be screened for the development of ILD to allow for the early diagnosis of SSc-ILD; and that this practice could be extended to any of the CTDs or myositis spectrum disorders to improve the likelihood of early diagnosis of CTD-ILD.

We laud the authors for having used the internationally standardized capillaroscopic definitions to describe capillaroscopic characteristics at the nailfold [4, 5]. As the authors clearly described in their methodology, the EULAR Study Group on Microcirculation in Rheumatic Diseases first published, jointly with the Scleroderma Clinical Trials Consortium, a multi-country, multi-expert consensus on how to standardly describe capillaroscopic characteristics (density, dimension, abnormal shapes and haemorrhages) in evaluation of the nailfold and grouping them into two categories (see Fig. 1). The first category, defined as 'non-scleroderma pattern', can be subgrouped into 'normal' and 'non-specific abnormalities' (the latter occurring in 34% of healthy controls but also occurring in CTDs such as, non-exhaustively, SS or SLE [6–8]). The second category, defined as 'scleroderma pattern', can be subgrouped into early, active and late scleroderma patterns (occurring in SSc and diseases of the scleroderma spectrum such as inflammatory myopathy and mixed CTDs). Of note, through the recently published fast-track algorithm, a capillaroscopic picture can be readily and reliably classified as having a scleroderma pattern or not by capillaroscopists of any level of experience [5].

Before the EULAR/Scleroderma Clinical Trials Consortium study group consensus, a plethora of definitions for describing capillaroscopic characteristics had made comparability between studies cumbersome. In addition to that, the attributed role of capillaroscopy in various rheumatologic conditions also depends on how the capillaroscopic characteristics are categorized in the analyses of the studies. Two recent examples of evaluating the role of capillaroscopy in assessing RP elucidates this. In one study (Koenig *et al.*), 'scleroderma pattern' was used as a covariable; in another (Bellando-Randone *et al.*), non-specific abnormalities in addition to the SSc-specific abnormalities were used to define the category 'abnormal capillaroscopy' as a covariable. Koenig *et al.* (who notably were the first to attest that in a RP population without any sign of CTD at baseline, 12.6% develop SSc and 1% other CTDs over the long term) attested a major role for capillaroscopy in evaluating patients with RP in terms of prediction of future SSc [9]. In this way, the combination of a scleroderma pattern and SSc-specific antibodies was attested to have a positive predictive value of 79%, and a negative predictive value of 93%, for discerning those patients who will

FIG. 1 EULAR Study Group on Microcirculation in Rheumatic Diseases classification of scleroderma patterns *vs* non-scleroderma patterns



Based on capillaroscopic characteristics (density, dimension, abnormal morphology and haemorrhages), capillaroscopic images can be categorized as 'non-scleroderma patterns' (A–C) or 'scleroderma patterns' (D–F). (A) An example of a normal stereotype. Density: eight capillaries per linear mm (line arrows). Dimension: no giants. Morphology: no abnormal shapes. Haemorrhages: absent. Interpretation: non-scleroderma pattern. (B) An example of non-specific abnormalities. Density: eight capillaries per linear mm (line arrows). Dimension: no giants. Morphology: presence of abnormal shapes (section symbol/double-s). Haemorrhages: absent. Interpretation: non-scleroderma pattern. (C) An example of non-specific abnormalities. Density: nine capillaries per linear mm (line arrows). Dimension: no giants. Morphology: no abnormal shapes. Haemorrhages: present (delta symbol). Interpretation: non-scleroderma pattern. (D) An example of an early scleroderma pattern. Density: seven capillaries per linear mm (line arrows). Dimension: presence of a giant (arrow shape). Morphology: no abnormal shapes. Haemorrhages: absent. Interpretation: an early scleroderma pattern. (E) An example of an active scleroderma pattern. Density: five capillaries per linear mm (line arrows). Dimension: presence of a giant (arrow shape). Morphology: no abnormal shapes. Haemorrhages: absent. Interpretation: an active scleroderma pattern. (F) An example of a late scleroderma pattern. Density: one capillary per linear mm (line arrow). Dimension: no giants. Morphology: abnormal shape (section symbol/double-s). Haemorrhages: absent. Interpretation: a late scleroderma pattern. Adapted from Ref. [5].

or will not develop SSc. Conversely, the study of Bellando-Randone *et al.* described a much more minor role for capillaroscopy: specifically, a relative risk ratio of 1.70. The reason for the discrepancy regarding the role of capillaroscopy in these two studies is likely that in the latter study non-specific abnormalities were also taken into account.

In parallel to what has been described in healthy controls and rheumatological conditions, as mentioned above, it is unsurprising that Umashankar *et al.* have found a higher proportion of nailfold videocapillaroscopic 'abnormalities' (non-specific and scleroderma patterns) in CTDs than in IPF. We're also in agreement with the authors that, as previous literature has described, within a SSc population there is an association between more severe organ involvement and more severe scleroderma patterns, i.e. active and late scleroderma pattern [10, 11]. However, to rely on

capillaroscopy before screening for ILD, as suggested by the authors, might be a brook that is too wide for leaping. Until large prospective studies are at hand, screening for ILD should be done at baseline in all SSc patients, and by the gold standard, which is high-resolution CT [12]. Discussion on a classification of ILD should be held within a multidisciplinary team including a rheumatologist, whose knowledge of capillaroscopy is valuable. An example from daily practice can elucidate this: a rheumatologist may for example hint in the multidisciplinary team at an underlying inflammatory myopathy in an ANA-negative ILD patient with subtle heliotrope rash and a scleroderma pattern on capillaroscopy. The patient might otherwise be misclassified as having IPAF or no CTD at all. However, there are no statistics within the meta-analysis of Umashankar *et al.* (i.e. no display of receiver operator curve, nor of positive or negative predictive values) supporting higher diagnostic accuracy from using capillaroscopy to classify ILD patients. Hence, we cannot conclude from the data of Umashankar *et al.* that classifying ILD patients based on capillaroscopy has higher diagnostic accuracy. On the other hand, we do believe that there may be a role for capillaroscopy in monitoring patients with ILD. To this end, indeed, as the authors suggest, large standardized prospective cohorts are needed in whom evaluation of capillaroscopy is undertaken using consensus definitions, i.e. the EULAR/Scleroderma Clinical Trials Consortium definitions). In this way, for example, capillaroscopy of untreated ILD patients may be distinguishable from that of those treated with a therapeutic agent. Capillaroscopy may also turn out to play a role in predictive algorithms for complications in rheumatic diseases for which currently we have models with high negative predictive values but low positive predictive values, such as pulmonary arterial hypertension in SSc [13]. In this way, it is to be investigated whether capillaroscopy may enhance the positive predictive value of existing models.

In conclusion, efforts towards evaluation of the role of capillaroscopy in ILD are worthwhile, and further studies, such as the one elegantly performed by Umashankar *et al.* [3], are needed. While high-resolution CT is the gold standard for the diagnosis of SSc-ILD and other CTD-ILDs, it may be of interest to evaluate whether capillaroscopy may play a role in monitoring ILD patients.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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