Nailfold Videocapillaroscopy in Systemic Sclerosis–related Pulmonary Arterial Hypertension: A Systematic Literature Review

Vanessa Smith, Amber Vanhaecke, Els Vandecasteele, Miguel Guerra, Sabrina Paolino, Karin Melsens, and Maurizio Cutolo

ABSTRACT. ***Objective.*** Pulmonary arterial hypertension (PAH) is one of the leading causes of death in systemic sclerosis (SSc). Current screening algorithms are hampered by low positive predictive values. Outcome measures that could add to performance characteristics would be welcome. We aim to evaluate the role of nailfold videocapillaroscopy (NVC) using standardized definitions, in SSc-related PAH (SSc-PAH).

Methods. A systematic review to identify original research papers documenting an association between NVC and right heart catheterization-defined SSc-PAH was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Subsequently, NVC characteristics were subdivided into quantitative (capillary density, dimension, morphology, and hemorrhages), semiquantitative, and qualitative assessment (NVC pattern), according to the definitions of the European League Against Rheumatism Study Group on Microcirculation in Rheumatic Diseases.

Results. The systematic search identified 316 unique search results, of which 5 were included in the final qualitative analysis. The occurrence of incident SSc-PAH unequivocally associated in 2 longitudinal studies with progressive capillary loss ($p = 0.04$ and $p = 0.033$) and the progression to a severe (active/late) NVC pattern ($p = 0.05/0.01$ and HR = 5.12, 95% CI 1.23–21.27). In 3 cross-sectional studies, SSc-PAH was found to be unequivocally inversely associated with capillary density ($p = 0.001$ and $p < 0.05$) and associated with the presence of a severe NVC pattern ($p = 0.03$ and $p < 0.05$).

Conclusion. This is the first systematic literature review investigating the role of NVC in SSc-PAH using standardized description, to our knowledge. Unequivocal associations were found between (incident) SSc-PAH and capillary density and NVC pattern. Integration of NVC into current screening algorithms to boost their performance may be a future step. (J Rheumatol First Release March 15 2020; doi:10.3899/jrheum.190296)

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Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by microvasculopathy and fibrosis of skin and visceral organs. Vascular changes are ubiquitous in the small and medium-sized vessels (capillaries and arterioles) of patients with SSc. The lesions are marked by loss of endothelial cells, intimal and periadventitial fibrosis, medial hypertrophy/hyperplasia, and perivascular mononuclear cell infiltration. In SSc, these structural changes might

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be seen in both the peripheral vessels and the pulmonary arteries[1]. Pulmonary arterial hypertension (PAH) is a leading cause of death in SSc[2,3]. Even though no cure is available, timely detection of pulmonary involvement and subsequent initiation of appropriate therapies might slow down the progression of SSc-related PAH (SSc-PAH)[4,5,6].

Current screening algorithms have a high negative predictive value but unfortunately a low positive predictive value (PPV), in both unselected patients with SSc and high-risk patients: 6% for the DETECT algorithm and 11% for the 2015 European Society of Cardiology (ESC)/European Respiration Society (ERS) guidelines in unselected patients with SSc, and 47% and 40%, respectively, in high-risk patients[7,8,9]. Outcome measures that would add to the performance characteristics of the screening algorithms would be welcome[10]. Nailfold videocapillaroscopy (NVC), a noninvasive tool that allows reliable morphological evaluation of the peripheral microcirculation, may be such an outcome measure[11,12,13,14]. In past decades, it has played a clear role in Raynaud phenomenon (RP)[15,16,17]. It is the tool with the highest performance characteristics to discern a primary from a secondary RP and it has also been incorporated into the 2013 American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria for SSc[18,19].

Against this background, the EULAR Study Group on Microcirculation in Rheumatic Diseases (EULAR SG MC/RD) considered it timely to investigate whether capillaroscopy has been associated with SSc-PAH. If it has, then it might be a candidate covariable in future studies trying to improve the performance characteristics of existing algorithms. Hence, the study described herein is a systematic literature review to assess what is known about NVC and SSc-PAH diagnosed with right heart catheterization (RHC) and to stipulate whether the retained literature met the available guidelines on pulmonary hypertension[9,20,21,22]. Moreover, the NVC results will be described, for reasons of international standardization and comparability of study results, through the EULAR SG MC/RD–consented simple standardized capillaroscopic definitions to describe and report NVC characteristics[23,24,25,26].

MATERIALS AND METHODS

Data source and search strategy. The systematic literature review was designed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines to identify all full-text manuscripts that document an association between NVC and SSc-PAH diagnosed with RHC[9,20,21,22,27]. The search of PubMed, EMBASE, and Web of Science was conducted based on a combination of the following keywords: nailfold videocapillaroscopy, systemic sclerosis, and pulmonary arterial hypertension. The search was performed without limitation of date of publication, up to July 4, 2018. The systematic search was last updated on January 15, 2019. For the 3 searches, keywords referred to keywords present in the title/abstract. Details on the complete search strategy are shown in Supplementary File 1, available with the online version of this article.

Screening process and selection criteria. First, after deleting duplicates, 2 investigators (AV, MG) independently screened the records identified by database search on title, abstract, and full-text level regarding inclusion and exclusion criteria. Second, both reviewers manually searched the reference lists of the retained full texts for supplementary records and applied the same screening process. During the title and abstract screening process, records were considered eligible when both investigators included them for the next step. When the 2 investigators disagreed about whether to include a record for the qualitative analysis, consensus was reached by discussing those disagreements with an expert (VS).

Records were selected if they were original prospective longitudinal or cross-sectional studies documenting the use of NVC in SSc-PAH diagnosed with RHC, with a minimum sample of 5 patients with SSc. Reviews, letters, editorials, abstracts of scientific congresses, case studies ($n < 5$), and retrospective studies were noted but not included. Articles in languages other than English, Dutch, and French were excluded. Studies that were not available in full-text version format were also excluded. Subsequent to the screening process, relevant data were extracted and analyzed by the same 2 investigators and discussed with the academic cardiologist (EV) and the first author (VS). The following data were extracted using a standardized electronic spreadsheet designed for this systematic review: author, year, country of origin, objective, study design, classification criteria, study population size (no. patients and controls, mean age), disease subset, NVC technique, assessment and evaluation, RHC characteristics, statistical analysis, and results.

Quality appraisal. All selected original studies underwent methodological quality assessment by the same 2 investigators, using the US National Institutes of Health (NIH) tool for observational cohort and cross-sectional studies (Supplementary File 2, available with the online version of this article)[28]. Consensus on the scores was reached and discrepancies were resolved through discussion.

Evaluation of NVC assessment. NVC assessment was described according to the consensus of the EULAR SG MC/RD[23,24,25,26]. Quantitative assessment was evaluated as follows: number of capillaries per linear millimeter (i.e., capillary density), number of giant capillaries (dilation > 50 μm) per linear millimeter (i.e., capillary dimension), presence of capillary bleeding (i.e., hemorrhages), and number of abnormally shaped (not hairpin-shaped, not tortuous, > 2 crossings, no convex head) capillaries per linear millimeter (i.e., abnormal capillary morphology)[23,24,25,26].

Semiquantitative assessment was described as defined per study. Qualitative assessment was evaluated as defined by Cutolo, *et al*, classifying images as having a "normal," "non-specific," "early," "active," or "late" NVC SSc pattern[25,29].

RESULTS

Systematic search and screening process. The systematic search identified 44 records in MEDLINE (PubMed), 208 in EMBASE, and 64 in Web of Science. Primary electronic database searching identified 234 records after the removal of duplicates and an additional 3 records were retrieved after reference list searching. Full-text review was performed on 28 records, to finally retain 5 original studies eligible for qualitative analysis (Figure 1). Two of the included articles were longitudinal studies and the others were cross-sectional studies. Table 1 contains the most important demographic characteristics of the 5 included studies, altogether comprising 281 patients with SSc (64 SSc-PAH and 217 SSc-noPAH) from 3 different European countries.

Quality appraisal. The methodological quality ratings according to the NIH are presented in Supplementary File 2 (available with the online version of this article). Of the 5

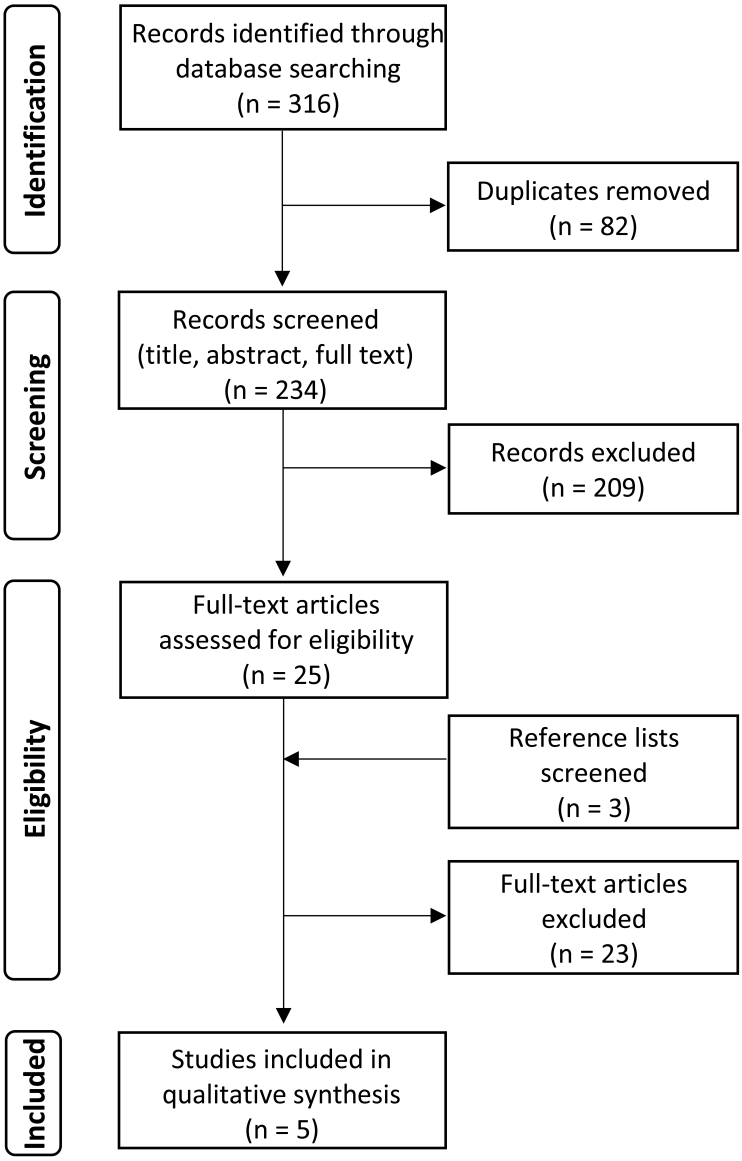

Figure 1. Flowchart systematic review according to PRISMA 2009 guidelines. Data are given as no. selected articles categorized according to 4 different parts of the search process: identification, screening, eligibility, and inclusion. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

selected articles, 2 were rated as having good quality and 3 as having fair quality. Of note, aiming to descriptively present the existing literature concerning NVC and SSc-PAH, no articles were excluded solely based on their quality.

Longitudinal studies. Two longitudinal studies, investigating the prognostic value of NVC alterations as a primary outcome in patients with SSc, were included in this systematic literature review (Table 2)[30,31]. Each described a RHC definition of SSc-PAH, and Avouac, *et al* stated the 2009 ESC/ERS guidelines had been followed to screen for PAH[21,30,31]. Both articles were judged to have good quality (Supplementary File 2, available with the online version of this article)[28]. NVC examination and assessment were similarly performed in both studies at baseline and during followup, using a videocapillaroscope with a 200× magnification contact lens connected to image analysis software[30,31]. Subsequently, NVC images were assessed both quantitatively and qualitatively[30,31].

Sulli, *et al* undertook a longitudinal medium-term study with a median followup of 84 months in 38 SSc patients with an early NVC pattern at baseline, to investigate the timing of transition through different NVC patterns[30]. At the end of

Table 1. Demographic characteristics of records included in the systematic review.

Study	Study Design	SSc Criteria	Sample Size, n = SSc/IPAH/HC	SSc-PAH/ SSc-noPAH	Right Heart Catheterization Diagnosis of SSc-PAH (mPAP, PCWP, PVR) and Guidelines Followed by the Authors	NVC Assessment
Sulli, 2012, Italy[30]	Longitudinal	(29a)	38/0/0	4*/34	mPAP > 25 mmHg. Other guidelines not stated	Videocapillaroscopy, 200× magnification
Avouac, 2017, France[31]	Longitudinal	(18)	140/0/0	8*/132	mPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, 2009 ESC/ERS guidelines[21]	Videocapillaroscopy, 200× magnification
Hofstee, 2009, Netherlands[32]	Cross-sectional	(29a)	40/20/21	21/19	mPAP > 25 mmHg, 2004 ESC guidelines[20]	Computer-based panorama mosaic videocapillaroscopy
Riccieri, 2013, Italy[33]	Cross-sectional	(29a)	24/0/0	12/12	mPAP > 25 mmHg, 2009 ACCF/AHA guidelines[22]	Videocapillaroscopy, 200× magnification
Corrado, 2017, Italy[34]	Cross-sectional	(18)	39/21/25	19/20	mPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, PVR > 3 WU, 2015 ESC/ERS guidelines[9]	Videocapillaroscopy, 200× magnification

* Occurrence of incident SSc-PAH during followup period. ACCF: American College of Cardiology Foundation; AHA: American Heart Association; ERS: European Respiratory Society; ESC: European Society of Cardiology; HC: healthy controls; IPAH: idiopathic pulmonary arterial hypertension; mPAP: mean pulmonary arterial pressure; NVC: nailfold videocapillaroscopy; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; SSc: systemic sclerosis; SSc-noPAH: systemic sclerosis without PAH; SSc-PAH: systemic sclerosis–related PAH; WU: Wood units.

Table 2. SSc-PAH diagnosed according to right heart catheterization criteria – longitudinal studies.

Capillaroscopic Characteristics		Significant Association	Non-significant Association	Conclusion
Quantitative				
Density	Capillary loss at inclusion	N/A	SSc-PAH (HR 3.92, 95% CI 0.88–17.36, p = 0.074)[31]	Progressive capillary loss was unequivocally associated with incident SSc-PAH in 2 longitudinal studies
	Progressive capillary loss	SSc-PAH (p = 0.04; HR 18.53, 95% CI 1.28–78.33, p = 0.033)[30,31]	N/A	
Dimension	Presence of giant capillaries at inclusion	N/A	SSc-PAH (HR 0.68, 95% CI 0.28–2.09, p = 0.638)[31]	No association
	Progression of giant capillaries	N/A	SSc-PAH (HR 0.31, 95% CI 0.15–1.07, p = 0.062)[31]	
Morphology	Abnormal morphology at inclusion	SSc-PAH (HR 11.12, 95% CI 1.19–103.79, p = 0.036)[31]	N/A	Abnormal morphology at inclusion was more commonly associated with incident SSc-PAH in 1 longitudinal study
	Progression of abnormal morphology	SSc-PAH, p = 0.04[30]	SSc-PAH (HR 1.14, 95% CI 0.22–5.86, p = 0.872)[31]	
Hemorrhages	Presence of hemorrhages at inclusion	N/A	SSc-PAH (HR 0.98, 95% CI 0.42–2.30, p = 0.969)[31]	No association
	Progression of hemorrhages	N/A	SSc-PAH (HR 0.44, 95% CI 0.05–3.55, p = 0.443)[31]	
Semiquantitative				
NVC score		N/A	N/A	Not investigated
Avascular area grade		N/A	N/A	Not investigated
Qualitative				
Progression to a severe NVC pattern (active/late vs normal/early)		SSc-PAH (p = 0.05/p = 0.01; HR 5.12, 95% CI 1.23–21.27)[30,31]	N/A	Progression to a severe NVC pattern (active/late) was unequivocally associated with incident SSc-PAH in 2 longitudinal studies

SSc-PAH: systemic sclerosis–related pulmonary arterial hypertension; NVC: nailfold videocapillaroscopy; N/A: not applicable.

followup, 4 patients (2 with active and 2 with late NVC pattern) presented SSc-PAH confirmed by RHC [mean pulmonary arterial pressure (mPAP) > 25 mmHg][21,30]. Concerning the progression of quantitative NVC findings during followup, SSc-PAH significantly correlated with loss of capillaries ($p = 0.04$) and abnormal capillary morphology ($p = 0.04$). No statistically significant correlation has been reported between SSc-PAH and capillary dimension or presence of hemorrhages[30]. Concerning qualitative NVC assessment, the occurrence of SSc-PAH was found more frequently in those patients who progressed from an early to either an active or a late NVC pattern at the end of followup ($p = 0.05$ and $p = 0.01$, respectively)[30].

In the second longitudinal study, an unselected cohort of 140 consecutive patients with SSc was prospectively followed up during 3 years by Avouac, *et al*, to determine the association of NVC alterations with organ progression in SSc, including SSc-PAH[31]. During the 3-year followup period, SSc-PAH as confirmed by RHC [mPAP ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg] was observed in 8 patients[21,31]. Concerning the quantitative NVC assessment at inclusion, solely neoangiogenesis (abnormal capillary morphology) reached statistical significance in univariate Cox analysis (HR 7.38, 95% CI 1.44–37.73, $p = 0.017$) and could be confirmed by multivariate analysis with additional stratification on disease duration as an independent risk factor for the occurrence of SSc-PAH (HR 11.12, 95% CI 1.19–103.79, $p = 0.036$[31]. In the univariate Cox analysis, neither capillary loss (capillary density) nor presence of giants (capillary dimension) or presence of hemorrhages were found to be predictive for the occurrence of SSc-PAH ($p = 0.074$; $p = 0.638$; $p = 0.969$; respectively)[31]. Concerning the progression of quantitative NVC findings during the 3-year followup, only progressive loss of capillaries reached statistical significance in both univariate (HR 4.85, 95% CI 1.17–20.20, $p = 0.031$) and multivariate analysis (HR 18.53, 95% CI 1.28–78.33, $p = 0.033$), meaning that progressive loss of capillaries was identified to be strongly predictive for the occurrence of SSc-PAH[31]. Neither the progression of the number of giant capillaries (capillary dimension), nor progression of neoangiogenesis (abnormal capillary morphology), nor progression of presence of hemorrhages could reach statistical significance in the univariate Cox analysis ($p = 0.062$; $p = 0.872$; $p = 0.443$, respectively). Hence, these progressive quantitative NVC characteristics were not identified as predictive markers for the occurrence of SSc-PAH[31].

Of note, considering the qualitative NVC assessment, worsening from a normal, early, or active to a late NVC pattern was associated with the occurrence of SSc-PAH (HR 5.12, 95% CI 1.23–21.27)[31].

Cross-sectional studies. Associations between NVC alterations as a primary outcome in SSc patients with SSc-PAH as determined by RHC were examined in 3 cross-sectional studies (Table 3)[32,33,34]. All described an RHC definition of SSc-PAH according to the then-available guidelines on pulmonary hypertension. The quality of the cross-sectional studies was considered fair, according to the NIH qualitative assessment tool for observational cohort and cross-sectional studies (Supplementary File 2, available with the online version of this article)[28].

Hofstee, *et al* studied between September 2006 and July 2007 capillary density and dimensions and their association with pulmonary hemodynamic characteristics in 21 healthy controls (HC), 20 patients with idiopathic PAH (IPAH), and 40 patients with SSc, of whom 21 had SSc-PAH as determined by RHC (mPAP > 25 mmHg)[20,32]. Unlike the other cross-sectional studies, a computer-based panorama mosaic video-capillaroscope was used for NVC examination and assessment[32,35]. The authors reported a significantly lower capillary density in patients with SSc-PAH, compared to those with SSc-noPAH ($p = 0.001$)[32]. No statistical significance was reached concerning capillary dimensions ($p = 1.000$)[32].

A few years later, Riccieri, *et al* evaluated NVC alterations in 12 consecutive patients with SSc-PAH, as confirmed by RHC (mPAP > 25 mmHg) as well as 12 age- and sex-matched SSc-noPAH patients[33]. NVC examination was performed using a videocapillaroscope with a 200× magnification contact lens connected to image analysis software[33]. The images were semiquantitatively assessed as follows: (1) NVC score, combining a semiquantitative score for density, dimension, presence of hemorrhage and morphology (score ranging from 0 = no changes to 3 = ≥ 6 alterations/mm), and (2) avascular area grading (score ranging from 0 = no obvious avascular areas to 3 = severe, the presence of large, confluent avascular areas)[29,33,36]. Additionally, qualitative assessment was performed, according to Cutolo, *et al*, classifying patients into normal/early/active or late NVC pattern[29,33]. Significant correlations were found between the presence of SSc-PAH and more severe semiquantitative assessments: NVC score ($p = 0.03$) and avascular area grading ($p = 0.003$)[33]. Additionally, patients with SSc-PAH showed significantly more often a severe (active/late) NVC pattern than those with SSc-noPAH (92% vs 42%, $p = 0.03$)[33].

More recently, Corrado, *et al* evaluated both quantitative and qualitative NVC alterations using a videocapillaroscope with 200× magnification, in 25 HC, 21 patients with IPAH, and 39 consecutive patients with SSc, of whom 19 had SSc-PAH determined by RHC (mPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, pulmonary vascular resistance > 3 Wood units)[9,34]. Concerning the quantitative NVC assessment in patients with SSc, SSc-PAH significantly inversely correlated with capillary density ($p < 0.05$), correlated with both capillary dimension and giants ($p < 0.05$), and correlated with abnormal capillary morphology ($p < 0.01$)[34]. Hemorrhages were equally present in SSc patients with and without SSc-PAH[34]. Similar to the cross-sectional study of Riccieri, *et al*[33], a severe (active/late) NVC pattern was presented more

Table 3. SSc-PAH diagnosed according to right heart catheterization criteria — cross-sectional studies.

Capillaroscopic Characteristics		Significant Association	Non-significant Association	Conclusion
Quantitative				
Density	Mean density	SSc-PAH ($p = 0.001$)[32], ($p < 0.05$)[34]	N/A	Density unequivocally inversely associated with SSc-PAH in 2 cross-sectional studies
	Capillary loss	N/A	N/A	
Dimension	Width	SSc-PAH ($p < 0.05$)[34]	SSc-PAH ($p = 1.000$)[32]	No unequivocal results
	Giant	SSc-PAH ($p < 0.05$)[34]	N/A	
Morphology	Normal	N/A	N/A	Abnormal morphology was more commonly present in SSc-PAH in 1 cross-sectional study
	Abnormal	SSc-PAH ($p < 0.01$)[34]	N/A	
Hemorrhages		N/A	SSc-PAH (NR)[34]	No association
Semiquantitative				
NVC score		SSc-PAH ($p = 0.03$)[33]	N/A	NVC score was more commonly associated with SSc-PAH in 1 cross-sectional study
Avascular area grade		SSc-PAH ($p = 0.003$)[33]	N/A	Avascular area grade was more commonly associated with SSc-PAH in 1 cross-sectional study
Qualitative				
Scleroderma pattern vs non-scleroderma pattern		N/A	N/A	
Severe NVC patterns (active/late vs normal/early)		SSc-PAH ($p = 0.03$)[33], ($p < 0.05$)[34]	N/A	Severe NVC patterns (active/late) are unequivocally associated with SSc-PAH in 2 cross-sectional studies

SSc-PAH: systemic sclerosis–related pulmonary arterial hypertension; N/A: not applicable; NR: not recorded; NVC: nailfold videocapillaroscopy.

often in SSc-PAH patients than in those with SSc-noPAH (73% vs 50%, $p < 0.05$)[34].

DISCUSSION

This is the first systematic review, to our knowledge, assessing an association between standardly described NVC and SSc-related PAH, defined by RHC. Even though the literature is not abundant (only 2 longitudinal and 3 cross-sectional studies had been retained), it suggests that number of capillaries both in cross-sectional as well as in longitudinal studies may be a common denominator[30,31,32,33,34]. This is useful, because number of capillaries is the most reliable of all assessable capillaroscopic characteristics[11]. Systemic microvascular changes, marked by loss of endothelial cells, intimal and periadventitial fibrosis, medial hypertrophy/hyperplasia, and perivascular mononuclear cell infiltration are hallmark features of SSc, and are detectable with NVC. By comparing capillaroscopic examinations of SSc-PAH and SSc-noPAH patients, both Hofstee, *et al* and Riccieri, *et al* suggested that structural microvascular abnormalities in the peripheral microcirculation in patients with SSc as detected by NVC, more specifically concerning capillary density, may be related to the vascular abnormalities in the pulmonary circulation in SSc-PAH[32,33]. Longitudinal studies by both Sulli, *et al* and Avouac, *et al* confirmed that progressive loss of capillaries over time correlates with incident SSc-PAH[30,31]. Whether the same is true for IPAH, a disease lacking evidence for characteristic scleroderma pattern at the nailfolds, remains debatable because both Hofstee, *et al* and Corrado, *et al* found a lower capillary density in small groups of patients with IPAH compared to HC[32,34]. Indeed, IPAH and SSc-PAH are similar diseases with indistinguishable pulmonary vessel abnormalities, but they present clinically differently (i.e., patients with SSc-PAH demonstrate a poorer response to therapy and have a worse longterm survival)[37].

Hence, we consider number of capillaries the new covariable to assess the option of boosting the PPV of existing algorithms, i.e., the DETECT algorithm[7,8]. Also, more severe SSc patterns, such as active and late SSc pattern, or a conversion over time to worse patterns, are associated with (incident) RHC-defined SSc-PAH. Of note, after the completion of this systematic review, a cross-sectional study by Guillén-Del-Castillo, *et al* was published, reporting a negative correlation of higher capillary density and a positive correlation of number of abnormal shapes (neoangiogenesis) with right ventricular systolic pressure in patients with SSc-PAH compared to SSc-noPAH patients[38].

The low number of retained manuscripts might seem a limitation of this systematic review. The reason for this was our requirement that SSc-PAH be RHC-defined according to the available guidelines on pulmonary hypertension for reasons of interpretability in between studies[9,20,21,22]. Interpretability and comparability of the results in all the retained manuscripts were also our motivations for describing all NVC studies with the EULAR SG MC/RD format.

Of note, 5 manuscripts documenting the use of NVC in

SSc-PAH diagnosed with RHC were withheld in this systematic literature review, of which one followed the 2003 ESC guidelines, one followed the 2009 ESC/ERS guidelines, one followed the 2009 American College of Cardiology Foundation/American Heart Association guidelines, and one strictly followed the 2015 ESC/ERS guidelines. Although the remaining article, by Sulli, *et al*, did not clearly state the guidelines followed[30], we can assume, according to the author definitions, that SSc-PAH was diagnosed by following the 2009 ESC/ERS guidelines[21]. Ideally, future studies would rigorously follow SSc-PAH screening guidelines to avoid underdiagnosis of SSc-PAH.

The future research agenda of the SSc community should involve, next to standard adherence to existing guidelines for screening for PAH in SSc populations (non) at risk, also standard evaluation by NVC[26]. Only in this way will there be enough power to truly evaluate whether NVC, and more specifically capillary density, is the new development to boost the performance characteristics (more specifically, to boost the PPV) of existing algorithms.

Nailfold capillaroscopy may be new and number of capillaries may be the chosen covariable in future trials assessing how to boost the PPV of existing algorithms to predict SSc-PAH in patients with SSc.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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