NEW KIDS ON THE BLOCK IN SSC-PAH: MAY WE FUTURELY NAIL IT ADDITIONALLY DOWN TO CAPILLAROSCOPY? A SYSTEMATIC LITERATURE REVIEW

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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 futurely add to performance characteristics would be very welcome. Against this background, 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 catheterisation defined SSc-PAH was performed according to the PRISMA guidelines. Subsequently, NVC parameters were subdivided into quantitative (capillary density, dimension, morphology, and haemorrhages), semi-quantitative and qualitative assessment (NVC pattern), according to the definitions of the EULAR 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. 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.

KEY WORDS

Systemic sclerosis, nailfold videocapillaroscopy, microcirculation, systematic literature review,

EULAR Study Group on Microcirculation in Rheumatic Diseases

ABBREVIATIONS

ACCF: American College of Cardiology Foundation

ACR: American College of Rheumatology

AHA: American Heart Association

CI: Confidence Interval

ERS: European Respiratory Society

ESC: European Society of Cardiology

EULAR: European League against Rheumatism

EULAR SG MC/RD: EULAR Study Group on Microcirculation in Rheumatic Diseases

HR: Hazards Ratio

IPAH: Idiopathic Pulmonary Arterial Hypertension

mPAP: mean Pulmonary Arterial Pressure

NIH: National Institute of Health

NVC: Nailfold Videocapillaroscopy

SSc-noPAH: Systemic Sclerosis without Pulmonary Arterial Hypertension

SSc-PAH: Systemic Sclerosis related Pulmonary Arterial Hypertension

PAH: Pulmonary Arterial Hypertension

PCWP: Pulmonary Capillary Wedge Pressure

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PVR: Pulmonary Vascular Resistance

RP: Raynaud's Phenomenon

SSc: Systemic Sclerosis

WU: Wood Units

1. INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by micro-vasculopathy 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 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, yet timely detection of pulmonary involvement and subsequent initiation of appropriate therapies might slow down its progression. Hence, early detection may be convenient (4-6). Current screening algorithms have a high negative predictive value but unfortunately a low positive predictive value, both in unselected SSc patients as well as high risk SSc patients, more specifically: 6% for the DETECT algorithm and 11% for the 2015 European Society of Cardiology (ESC)/ European Respiration Society (ERS) guidelines in unselected SSc patients and 47% and 40% respectively in high risk SSc patients (7-9). Outcome measures that would futurely add to their performance characteristics may be very welcome (10). Conceivably nailfold videocapillaroscopy (NVC), a non-invasive tool that allows reliable morphological evaluation of the peripheral microcirculation, may be such an outcome measure (11-14). Past decades it has taken up a clear role in Raynaud's Phenomenon (RP) (15-17). In this way it is the tool with the highest performance characteristics to discern a primary from a secondary RP and in between others it has also been incorporated in the 2013 American College of Rheumatology (ACR)/ 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) felt it timely to investigate whether capillaroscopy has been associated with SSc related PAH (SSc-PAH). If such would be the

case, then it might be a candidate covariable in future studies trying to ameliorate 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 and stipulating whether the retained literature met the at that moment available guidelines on pulmonary hypertension (9, 20-22). 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 (23-26).

2. MATERIAL AND METHODS

2.1. 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 in order to identify all full-text manuscripts that document an association between NVC and SSc-PAH diagnosed with right heart catheterization (9, 20-22, 27). The search of Pubmed, EMBASE and Web of Science was conducted based on a combination of following keywords: 'nailfold videocapillaroscopy', 'systemic sclerosis' and 'pulmonary arterial hypertension'. The search was performed without limitation of date of publication, up to the 4th of July 2018. The systematic search was last updated on the 15th of January 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.

2.2. 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, with regard to 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 different opinions existed among the 2 investigators 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 right heart catheterization, with a minimum sample of 5 SSc patients. Reviews, letters, editorials, abstracts of scientific congresses, case studies (n < 5) and retrospective studies were noted but not included.

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 analysed by the same 2 investigators and discussed both 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 (number of patients and controls, mean age), disease subset, NVC technique, assessment and evaluation, right heart catheterization parameters, statistical analysis and results.

2.3. Quality appraisal

All selected original studies underwent methodological quality assessment by the same 2 investigators, using the National Institute of Health (NIH) tool for observational cohort and cross-sectional studies (see supplementary file 2) (28). Consensus on the scores was reached and discrepancies were resolved through discussion.

2.4. Evaluation of nailfold videocapillaroscopic assessment

NVC assessment was described, as per consensus of the EULAR SG MC/RD (23-26).

Quantitative assessment was evaluated as follows: number of capillaries per linear millimetre (i.e. capillary density), number of giant capillaries (dilation $> 50\mu m$) per linear millimetre (i.e. capillary dimension), presence of capillary bleeding (i.e. haemorrhages) and number of abnormally shaped (not hairpin-shaped, not tortuous, > 2 crossings, no convex head) capillaries per linear millimetre (i.e. abnormal capillary morphology) (23-26).

Semi-quantitative 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 scleroderma pattern (25, 29).

3. RESULTS

3.1. 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 (see figure 1 for the flowchart). Two of the included articles were longitudinal studies, the others were cross-sectional studies. Table 1 contains the most important demographic characteristics of the 5 included studies, altogether comprising 281 SSc patients (64 SSc-PAH and 217 SSc-noPAH) from 3 different European countries.

3.2. Quality appraisal

The methodological quality ratings according to the NIH are presented in supplementary file 2. Of the 5 selected articles, 2 articles were rated to have good quality and 3 to have a 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.

3.3. Longitudinal studies

Two longitudinal studies, investigating the prognostic value of NVC alterations as a primary outcome in SSc patients, were included in this systematic literature review (30, 31). Both of them described a right heart catheterization definition of SSc-PAH and Avouac stated the 2009 ESC/ESR guidelines had been followed to screen for PAH (21, 30, 31). Both articles were judged to have a good quality (see Supplementary File 2) (28). NVC examination and

assessment were similarly performed in both studies at baseline and during follow-up, using a videocapillaroscope with a 200x 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 medium follow-up 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 follow-up, 4 patients (2 with active and 2 with late NVC pattern) presented SSc-PAH confirmed by right heart catheterization ("mPAP > 25 mmHg") (21, 30). Concerning the progression of quantitative NVC findings during follow-up, SSc-PAH significantly correlated with loss of capillaries (p = 0.04) and abnormal capillary morphology (p = 0.04). No statistical significant correlation has been reported between SSc-PAH and capillary dimension or presence of haemorrhages (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 follow-up (p = 0.05 and p = 0.01, respectively) (30).

In the second longitudinal study, an unselected cohort of 140 consecutive SSc patients 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 follow-up period, SSc-PAH as confirmed by right heart catheterization (mPAP $\geq$ 25 mmHg and PCWP $\leq$ 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 PAH (HR = 11.12, 95% CI: 1.19-103.79, p = 0.036) (31). In the univariate Cox analysis, capillary loss (capillary density) nor presence of

giants (capillary dimension) or presence of haemorrhages were found to be predictive for the occurrence of PAH (p = 0.074; p = 0.638; p = 0.969; respectively) (31). Concerning the progression of quantitative NVC findings during the 3 year follow-up, 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). Progression of the number of giant capillaries (capillary dimension), nor progression of neoangiogenesis (abnormal capillary morphology) or progression of presence of haemorrhages could reach statistical significance in the univariate Cox analysis (p = 0.062; p = 0.872; p = 0.443. Hence, these progressive quantitative NVC parameters 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).

3.4. Cross-sectional studies

Associations between NVC alterations as a primary outcome in SSc patients with SSc-PAH as determined by right heart catheterization was studied in 3 cross-sectional studies (32-34). All three described a right heart catheterization definition of SSc-PAH according the at that moment 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 (see Supplementary File 2) (28).

Hofstee et al. studied between September 2006 and July 2007 capillary density and dimensions and their association with pulmonary hemodynamic parameters in 21 healthy controls (HCs),

20 patients with idiopathic PAH (IPAH) and 40 SSc patients, of which 21 had SSc-PAH as determined by right heart catheterization ("mPAP > 25 mmHg") (20, 32). Unlike the other cross-sectional studies, a computer-based panorama mosaic videocapillaroscope 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 in 2013, Riccieri et al. evaluated NVC alterations in 12 consecutive SSc-PAH patients, as confirmed by right heart catheterization ("mPAP > 25 mmHg") as well as 12 age- and gender matched SSc-noPAH patients (22, 33). NVC examination was performed using a videocapillaroscope with a 200x magnification contact lens connected to image analysis software (33). The images were semi-quantitatively assessed as follows: a) NVC score, combining a semi-quantitative score for density, dimension, presence of haemorrhages and morphology (score ranging from 0 = no changes; to 3 = ≥6 alterations per linear millimetre) and b) 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 semi-quantitative 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).

Recently in 2017, Corrado et al. evaluated both quantitative and qualitative NVC alterations using a videocapillaroscope with 200x magnification, in 25 HCs, 21 patients with IPAH and 39 consecutive SSc patients, of which 19 had SSc-PAH determined by right heart catheterization (mPAP ≥ 25 mmHg, PCWP ≤ 15 mmHg, PVR > 3 WU) (9, 34). Concerning the quantitative

NVC assessment in SSc patients, 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). Haemorrhages were equally present in SSc patients with and without SSc-PAH (34). Similar to the cross-sectional study of Riccieri et al., a severe (active/late) NVC pattern was presented more often in SSc-PAH patients than in those with SSc-noPAH (73% vs. 50%, $p < 0.05$) (34).

4. DISCUSSION

This is the first systematic review assessing an association between standardly described nailfold videocapillaroscopy and systemic sclerosis related pulmonary arterial hypertension, defined by right heart catheterization. Even though the literature is not abundant, as 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 (30-34). This is useful, given the fact that number of capillaries is the most reliable parameter of all assessable capillaroscopic parameters (11). As mentioned before, 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 which are detectable with NVC. By comparing capillaroscopic examinations of SSc-PAH and SSc-noPAH patients, both Hofstee et al. and Riccieri et al. suggested the hypothesis that structural microvascular abnormalities in the peripheral microcirculation in SSc patients 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). Both longitudinal studies, by 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 since both Corrado et al. and Hofstee et al. found a lower capillary density in small groups of IPAH patients compared to healthy controls (32, 34). Indeed, IPAH and SSc-PAH are similar diseases with indistinguishable pulmonary vessel abnormalities, but they present clinically different (i.e. SSc-PAH patients demonstrate a poorer response to therapy and have a worse long-term survival) (37).

Hence, we would go for number of capillaries as the new kid on the block covariable to assess the option of boosting its positive predictive value of existing algorithms, i.e. the DETECT

algorithm (7, 8). Also more severe scleroderma patterns, i.e. active and late scleroderma pattern, or a conversion over time to worse scleroderma patterns, are associated with (incident) right heart catheterization defined SSc-PAH. Of note, post hoc, 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 SSc-PAH patients compared to SSc-noPAH patients (38).

The low number of retained manuscripts might seem a limitation of this systematic review until one realises that the reason for this was our definition that SSc-PAH should have been right heart catheterization defined according to the at that moment available guidelines on pulmonary hypertension for reasons of interpretability in between studies (9, 20-22). Interpretability of results was also our motivation why we have described all NVC studies with the EULAR Study Group on Microcirculation in Rheumatic Diseases format facilitating comparability of the results throughout the retained manuscripts.

Of note, 5 manuscripts documenting the use of NVC in SSc-PAH diagnosed with right heart catheterization 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 (ACCF)/ American Heart Association (AHA) guidelines and one strictly followed the 2015 ESC/ERS guidelines. Although the remaining article which was written by Sulli et al. did not clearly state the followed guidelines, 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 PAH screening guidelines to avoid underdiagnosis of PAH.

Ideally, the future research agenda of the SSc community might involve, next to standard adherence to existing guidelines for screening for PAH in SSc populations (non) "at risk", also

standard evaluation of NVC (26). Only this way, there will be enough power to truly evaluate if NVC, and more specifically "capillary density", is the "new kid on the block" to boost the performance characteristics (more specifically to boost the positive predictive value) of existing algorithms.

5. CONCLUSION

Nailfold capillaroscopy may be a new kid on the block and number of capillaries may be "the chosen" covariable in future trials assessing how to boost the positive predictive value of existing algorithms to predict pulmonary arterial hypertension in SSc patients.

HIGHLIGHTS

- This is the first systematic literature review investigating the role of NVC in SSc-PAH, using standardized definitions consented by the EULAR SG MC/RD.

- Capillary density and (worsening to) a severe NVC pattern are the only NVC characteristics associated with the presence or occurrence of incident SSc-PAH.

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APPENDICES

Figure 1: Flowchart systematic review according to PRISMA 2009 guidelines

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

Table 2: SSc-PAH diagnosed according to right heart catheterization criteria – LONGITUDINAL studies

Table 3: SSc-PAH diagnosed according to right heart catheterization criteria – CROSS-SECTIONAL studies

Supplementary file 1: Details on search strategy

Supplementary file 2: Quality assessment of the selected article**s**

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FIGURES

Figure 1: Flowchart systematic review according to PRISMA 2009 guidelines

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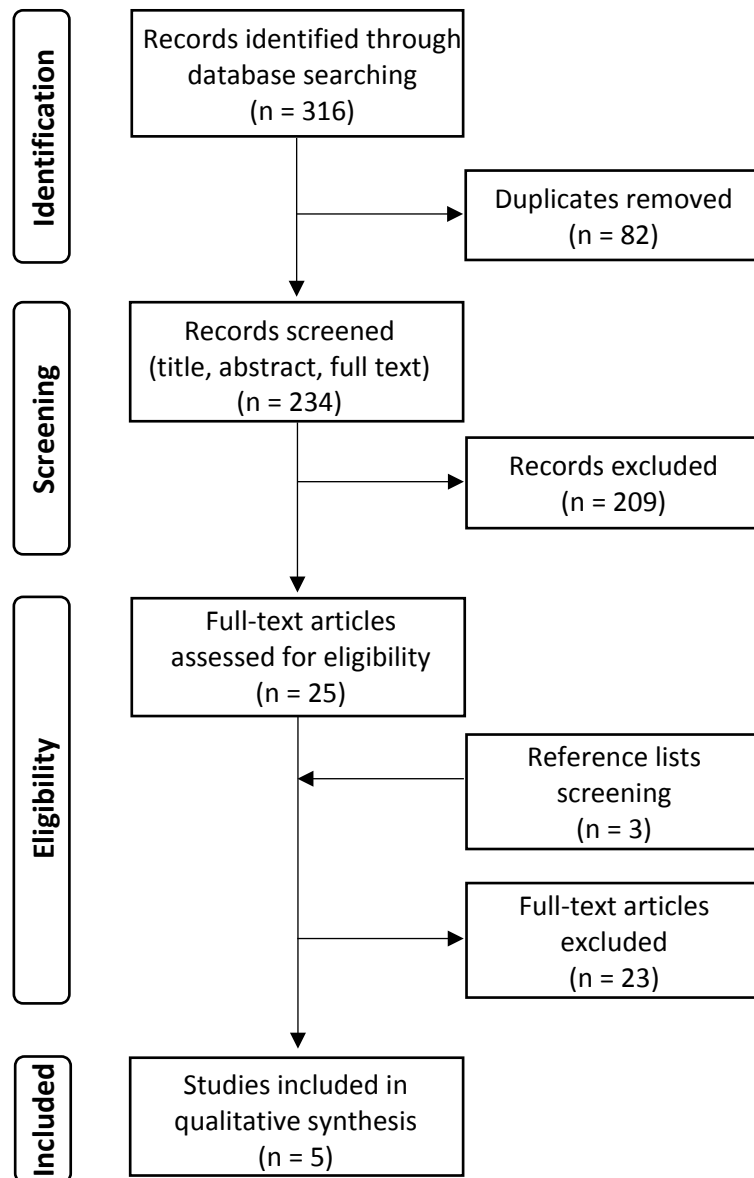
Data are given as number of selected articles categorized according to 4 different parts of the search process: identification, screening, eligibility and inclusion. The format of this figure is based on PRISMA 2009 guidelines (25).

Table 1: Demographical 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 (IT) (28)	Longitudinal	(29)	38/0/0	4*/34	*("mPAP > 25mmHg")* **Followed guidelines not stated**	Videocapillaroscopy, 200x magnification
Avouac, 2017 (FR) (30)	Longitudinal	(17)	140/0/0	8*/132	*(mPAP ≥ 25mmHg & PCWP ≤ 15mmHg)* **2009 ESC/ERS guidelines** (20)	Videocapillaroscopy, 200x magnification
Hofstee, 2009 (NL) (31)	Cross-sectional	(29)	40/20/21	21/19	*("mPAP > 25mmHg")* **2004 ESC guidelines** (19)	Computer-based panorama mosaic videocapillaroscopy
Riccieri, 2013 (IT) (32)	Cross-sectional	(29)	24/0/0	12/12	*("mPAP > 25mmHg")* **2009 ACCF/AHA guidelines** (21)	Videocapillaroscopy, 200x magnification
Corrado, 2017 (IT) (33)	Cross-sectional	(17)	39/21/25	19/20	*(mPAP ≥ 25mmHg & PCWP ≤ 15mmHg & PVR > 3 WU)* **2015 ESC/ERS guidelines** (8)	Videocapillaroscopy, 200x magnification

*Occurrence of incident SSc-PAH during follow-up period

ACCF = American College Cardiology Foundation; AHA = American Heart Association; ERS = European Respiratory Society; ESC = European Society of Cardiology; HC = healthy control; 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 pulmonary arterial hypertension; SSc-PAH = systemic sclerosis related pulmonary arterial hypertension.

Table 2: SSc-PAH diagnosed according to right heart catheterization criteria – LONGITUDINAL studies

CAPILLAROSCOPIC PARAMETER			SIGNIFICANT ASSOCIATION	NON-SIGNIFICANT ASSOCIATION	CONCLUSION
QUANTITATIVE	Density	Capillary loss at inclusion	NA	SSc-PAH (HR=3.92, 95% CI: 0.88-17.36, p=0.074) (30)	**Progressive capillary loss was <u>unequivocally</u> 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) (28, 30)	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) (30)	No association
		Progression of giant capillaries	N/A	SSc-PAH (HR=0.31, 95% CI: 0.15-1.07, p=0.062) (30)	
	Morphology	Abnormal morphology at inclusion	SSc-PAH (HR=11.12, 95% CI: 1.19-103.79, p=0.036) (30)	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) (28)	SSc-PAH (HR=1.14, 95% CI: 0.22-5.86, p=0.872) (30)	
	Hemorrhages	Presence of hemorrhages at inclusion	N/A	SSc-PAH (HR=0.98 95% CI: 0.42-2.30, p=0.969) (30)	No association
		Progression of hemorrhages	N/A	SSc-PAH (HR=0.44 95% CI: 0.05-3.55, p=0.443) (30)	
SEMI-QUANTITATIVE	NVC score		N/A	N/A	
	Avascular area grade		N/A	N/A	
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) (28, 30)	N/A	**Progression to a severe NVC pattern (active/late) was <u>unequivocally</u> associated with incident SSc-PAH in 2 longitudinal studies**

Table 3: SSc-PAH diagnosed according to right heart catheterization criteria – CROSS-

SECTIONAL studies

CAPILLAROSCOPIC PARAMETER			SIGNIFICANT ASSOCIATION	NON-SIGNIFICANT ASSOCIATION	CONCLUSION
QUANTITATIVE	Density	Mean density	SSc-PAH (p=0.001) (31) (p<0.05) (33)	N/A	**Density <u>unequivocally</u> inversely associated with SSc-PAH in 2 cross-sectional studies**
		Capillary loss	N/A	N/A	
	Dimension	Width	SSc-PAH (p<0.05) (33)	SSc-PAH (p=1.000) (31)	No unequivocal results
		Giant	SSc-PAH (p<0.05) (33)	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) (33)	N/A	
	Hemorrhages		N/A	SSc-PAH (NR) (33)	No association
SEMI-QUANTITATIVE	NVC score		SSc-PAH (p=0.03) (32)	N/A	**NVC score was more commonly associated with SSc-PAH in 1 cross-sectional study**
	Avascular area grade		SSc-PAH (p=0.003) (32)	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) (32) (p<0.05) (33)	N/A	**Severe NVC patterns (active/late) are <u>unequivocally</u> associated with SSc-PAH in 2 cross-sectional studies**

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