Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Review Article – Meta-analysis

Prognostic value of capillaroscopy in organ involvement and identification of subtypes in systemic sclerosis (SS): A systematic literature review

Jenny Leandra Londoño-Mora[a,b], *Drixie Dalyla Leal-Vargas*[a,b,c], *Gerardo Quintana-Lopez*[c,d,e,*]

[a] *Fundación Santa Fe de Bogotá, Hospital, Bogotá, DC, Colombia*
[b] *School of Medicine, Universidad El Bosque, Bogotá, DC, Colombia*
[c] *School of Medicine, Universidad de los Andes, Bogotá, DC, Colombia*
[d] *School of Medicine, Universidad Nacional de Colombia, Bogotá, DC, Colombia*
[e] *REUMAVANCE Group, Section of Rheumatology, Department of Internal Medicine, Fundación Santa Fe de Bogotá, University Hospital, Bogotá, DC, Colombia*

ARTICLE INFO

Article history:
Received 16 November 2019
Accepted 2 June 2020

Keywords:
Systemic sclerosis
Capillaroscopy
Predictive value
Prognosis
Organ involvement
Clinical phenotypes

ABSTRACT

Background: Capillaroscopy is an essential tool for the diagnosis of systemic sclerosis. Using this exam as a prognostic factor will allow earlier intervention and probably, delay on disease progression. We aimed to evaluate the prognostic value of capillaroscopy for the prediction of systemic compromise and subtype differentiation in systemic sclerosis.

Methods: A systematic literature search was applied in the following electronic databases: Medline, PubMed, Embase, Cochrane, and Lilacs. The research question was designed based on the PICOT model, and the search strategy was built using the MeSH terms "Microscopic Angioscopy," "Scleroderma systemic," "Scleroderma diffuse," Scleroderma Limited," "Early Diagnosis" and Boolean operators. The language was restricted to papers published in Spanish or English, from 1990 to 2019. The search terms were explored for each database, and new terms were added, as appropriate. The searches were made again before the final analyses and further studies were retrieved for inclusion at that time. Reference lists of included studies and recent aligned systematic reviews were also screened. Gray literature was not considered in this review.

Results: A total of 183 articles were found in the selected databases: Medline (*n*: 115), Embase (*n*: 66), Cochrane (*n*: 2), Lilacs (*n*: 0). After excluding articles due to duplication, a total of 66 studies were selected. Within these articles, a screening process was applied based on the title and abstract, taking into account the eligibility criteria, finally obtaining 21 references. Two researchers assessed the selected articles, and all disagreements were solved by consensus. Finally, a total of 14 articles were included.

* *Corresponding autor at*: Department of Internal Medicine, School of Medicine, Universidad Nacional de Colombia, Carrera 30 No. 45-03, Postal Code 111321, Bogotá, DC, Colombia.
E-mail address: gquintanal@unal.edu.co (G. Quintana-Lopez).

Conclusions: The different abnormalities found in capillaroscopy, especially loss of capillaries, have been consistently associated not only with organ involvement but also with severity of the disease, especially with vascular manifestations (digital ulcers and pulmonary hypertension).
The importance of capillaroscopy is not only its diagnostic value but also its predictive value with its consequent implications in the follow-up and management of systemic sclerosis.

Valor pronóstico de la capilaroscopia en el compromiso de organos e identificación de subtipos en esclerosis sistémica: una revisión sistemática de la literatura

Palabras clave:
Esclerosis sistémica
capilaroscopia
valor predictivo
pronóstico
compromiso de órganos
fenotipos clínicos

RESUMEN

La capilaroscopia es una herramienta esencial para el diagnóstico de la esclerosis sistémica. Usar este examen como factor pronóstico permitirá realizar una intervención temprana y probablemente retardará la progresión de la enfermedad. Se realizó una revisión de la literatura evaluando el valor pronóstico de la capilaroscopia para predecir el compromiso sistémico de la esclerosis sistémica y su diferenciación por subtipos.
Métodos: Se realizo una revisión sistemática de la literatura en las siguientes bases de datos: Medline, PubMed, Embase, Cochrane y Lilacs. La búsqueda se hizo basada en el modelo PICOT y la estrategia de búsqueda fue construida mediante los términos MeSH "Microscopic Angioscopy," "Scleroderma systemic," "Scleroderma diffuse," Scleroderma Limited," "Early Diagnosis" y Boolean operators. El lenguaje fue restringido a artículos publicados en español e ingles desde 1990 hasta 2019. Se realizó la búsqueda en cada base de datos y se adicionaron nuevos términos según fuera apropiado. La búsqueda se realizó de nuevo al final del análisis y se incluyeron los estudios más recientes. La lista de referencias de los estudios incluidos y las revisiones sistemáticas recientemente adicionadas también fueron registradas. No se consideró literatura gris en esta revisión.
Resultados: Un total de 183 artículos fueron encontrados en las siguientes bases de datos: Medline (n: 115), Embase (n: 66), Cochrane (n: 2), Lilacs (n: 0). Después de excluir los que estaban duplicados, un total de 66 estudios fueron seleccionados. Dentro de estos artículos, se realizó un proceso de selección basado en titulo y resumen tomando en cuenta los criterios de elegibilidad, obteniendo finalmente 21 referencias. Dos investigadores revisaron los artículos seleccionados y todas las discrepancias fueron resueltas en consenso. Finalmente. Un total de 14 artículos fueron incluidos.
Conclusiones: La diferentes anormalidades encontradas en la capilaroscopia, especialmente la pérdida de capilares, han sido constantemente asociadas no solo a compromiso de órganos sino también a la severidad de la enfermedad, especialmente con manifestaciones vasculares (úlceras digitales e hipertensión pulmonar).
La importancia de la capilaroscopia no solo es por su valor diagnóstico sino también por su valor predictivo en relación al seguimiento y manejo de la esclerosis sistémica.

Introduction

Capillaroscopy is a simple, non-invasive microscopy method that allows a morphological evaluation of the vascular bed in a qualitative and semi-quantitative manner in different areas of the body in order to detect abnormal patterns. This method facilitates the diagnosis of some autoimmune diseases. In some cases, it offers information about the degree of activity and severity of the disorder.[1,2]

There are three types of systemic scleroderma, defined by the tissues affected in the disease. First, there is the limited cutaneous systemic scleroderma, which has a skin involvement limited to the hands, face, feet and forearms. It has a nailfold capillary pattern typical of scleroderma predominantly with nailfold capillary loops and capillary dropout. The common features of the condition are: calcinosis, Raynaud's phenomenon, esophageal motility dysfunction, sclerodactyly, and telangiectasia. Renal disease rarely occurs and the blood

tests show a high incidence of anticentromere antibodies (ACA) in 50–60%.

Second, diffuse cutaneous scleroderma is a subtype characterized by truncal and acral skin involvement with tendon friction rubs. The nailfold capillary pattern typical of scleroderma has dilatation (early), dilatation and dropout (active), and tortuosity with dropout (late). The disease usually manifests itself in people between 40 and 50 years of age. Pulmonary fibrosis is frequently seen (60% of cases) and pulmonary hypertension may also occur in 10–15% of cases. Significant incidence of renal, interstitial lung, diffuse gastrointestinal, and myocardial disease occurs earlier than in other types of the condition and blood tests show Anti-Scl-70 in 30–40% of cases and anti-RNA polymerase I, II, or III antibodies in 12–15%. In the third type of systemic scleroderma, called systemic sclerosis sine scleroderma there is not skin involvement. Fibrosis affects one or more internal organs and antinuclear antibodies (anti-Scl-70, ACA, or anti-RNA polymerase I, II, or III) may be present in the laboratory tests.

In the case of Systemic Sclerosis (SS), it has been concluded that 90–95% of patients develop peripheral microangiopathy that is followed by a typical scleroderma pattern, which can be characterized as early, active and late. In the early pattern, the presence of isolated mega-capillaries is observed, with relative preservation of the distribution of the capillaries in the nail bed and scarce microhemorrhages without evidence of capillary loss.[3] The active pattern highlights the presence of mega-capillaries, microhemorrhages, moderate loss of capillaries, and slight disorganization of the capillary structure with the presence of edema without branched capillaries or neoangiogenesis. Finally, the late pattern is characterized by irregular thickening of capillaries, irregular capillary dilatation, avascular areas, disorganization of the capillary structure, and aberrant neoangiogenesis of ramified or bushy capillaries with few or no mega-capillaries.[4]

It is believed that the progression from early to active stage and from early to late stage is 28±20 months and 36±29 months, respectively. It is currently clear that these patterns are useful in the diagnosis and monitoring of systemic sclerosis.[21] Therefore, capillaroscopy has been included within the diagnostic criteria of 2013, by the American College of Rheumatology.[5]

Capillaroscopy has also been used as a predictor of organ involvement in SS, including the development of skin ulcers. The Risk Index of Ulceration in Systemic Sclerosis (CSURI) assesses the risk of developing a digital ulcer in the next 3 months when the score obtained is higher than 2.96, with an area under the curve of 0.884 (95% CI: 0.835–0.922), a specificity of 81.4% and a sensitivity of 92.9%.[6,7]

Likewise, it has been found that capillaroscopy allows the detection of patients that will present organ involvement, with the development of pulmonary hypertension, interstitial lung disease, digital ulcers or esophageal, heart, and kidney involvement.[8]

Methods

This review was developed according to the Cochrane Handbook for Systematic Reviews of Interventions. Eligible studies were those that reported the relationship between the findings of capillaroscopy and the development of organ involvement in SS and the relation with different subtypes. Based on the PICOT strategy, eligibility criteria were defined by formulating inclusion and exclusion criteria within the literature.

Inclusion criteria

- **Population:** All studies conducted on patients over 18 years of age diagnosed with SS were considered eligible.
- **Intervention:** Studies that reported the usefulness of capillaroscopy in the prediction of organ involvement in patients diagnosed with SS.
- **Comparison:** It was not made.
- **Study designs:** Descriptive studies.
- **Time:** Publication dates limited between 2000 and 2019.

Information sources and search criteria

A systematic and exhaustive literature search was conducted in the following electronic databases: Medline Pubmed, Embase, Cochrane, and Lilacs. The research question was structured under the PICOT model, and a generic search strategy was designed based on the key terms “Microscopic Angioscopy,” “Scleroderma systemic,” “Scleroderma diffuse,” Scleroderma Limited,” “Early Diagnosis”. The search strategy used MeSH terms with Boolean operators and was restricted to Spanish and English languages, with publication dates between 2000 and 2019.

Studies selection

The references were assessed by two independent reviewers (DL AND JL) based on titles and abstracts, applying the eligibility criteria. The articles that met those criteria were selected. In case there were disagreements between the peer reviewers, a discussion and verification of the information was carried out with the full texts of the articles in which there was assurance about compliance with the inclusion criteria, resolving the discrepancies by consensus. Finally, the results were summarized using the PRISMA flow chart.

Data selection and summary of selected studies

The data selection was carried out independently by two reviewers (DL and JL), based on what was reported in the original publications, the characteristics of each study and its results. The information was organized in a standard Microsoft Excel 2011 format. The data extracted included

Table 1

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Scussel-Lonzetti et al.	2002	Canada	309 patients	Prospective cohort	N/A	Classification Criteria for SS of 1980 from the American College of Rheumatology and clinical diagnosis given by Barnett et al, Giordano et al, and Ferri et al. and based on the compromise of skin disease.	Maricq	Semi-quantitative	Univariate Cox regression analysis followed by a multivariable analysis.	The frequency of moderate or extensive capillary loss (grade C or D) at diagnosis was 24.5% in the normal skin group, 63% in the limited group, and 79% in the other subsets ($p < 0.0001$).	Capillary loss and capillary dilatations at baseline assessment are not independent risk factors for mortality. These data suggested that the rate of onset of severe nailfold capillary abnormalities might vary according to the systemic sclerosis subsets.
Alivernini et al.	2009	Italy	130 patients	Prospective cohort	N/A	Classification Criteria for SS of 1980 from the American College of Rheumatology.	Cutolo	Qualitative	Mann–Whitney *U* test to compare the average between groups. Standard deviation for the categorical and quantitative variables. Fisher test or chi square to analyze categorical variables.	From the total of patients 26.2% (n: 34) had digital ulcer at the beginning and 26.9% (n: 35) diffuse involvement in skin. The follow-up for 20 months was carried out in 30 of the 34 patients, with initial digital ulcer, 11 healed and 19 did not heal presenting 8 of them additional digital ulcer. The patients whose digital ulcer healed had a high capillary density (4.9±2.3) compared to those who persisted with digital ulcer (3.3± 1.3, $p = 0.05$).	The healing process of digital ulcer is related to the presence of infection and avascular areas. The most common comorbidity in a patient with digital ulcer is pulmonary involvement (alveolitis: 89.5%). Diffuse systemic sclerosis with avascular areas in capillaroscopy, thrombophilia and high levels of plasma IL-6 is the phenotype with the highest risk of developing digital ulcer.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Hissaria, P., et al.	2011	Australia	786 patients (331 died)	Retrospective cohort	N/A	Modified Classification criteria for SS of 1980 from the American College of Rheumatology	Cutolo	Quantitative	Long-Rank test to assess the variables associated with survival. COX proportional hazards regression to assess the relationship between capillaroscopy findings and mortality.	Patients with the capillary drop-out pattern were significantly associated with the diffuse scleroderma variant ($p < 0.001$, Capillary drop-out was most apparent in diffuse scleroderma and capillary dilatation in limited scleroderma.	Systemic sclerosis reduces life time. Survival is affected by factors such as: male gender, age of onset, skin involvement and vice, cancer development and vascular damage, along with the association between Systemic sclerosis and the presence of positive antibodies Scl-70 and RNP. There is a high relationship between renal crisis and high mortality.
Smith V., et al.	2012	Belgium	66 patients	Prospective cohort	8 patients were excluded because the follow-up phase was not achieved.	LeRoy and Medsger criteria.	Cutolo.	Semi-quantitative	Logistic Regression Analysis between the capillaroscopy pattern and organ involvement. P values of likelihood ratio were used considering small samples.	The odds for the development of peripheral vascular disease were 2.49/2.52 for early versus normal pattern, 6.18/6.37 for active form versus normal pattern and 15.35/16.07 for late versus normal pattern in regression analysis and to develop lung disease was 2.54/2.33 for early vs. normal pattern, 6.43/5.44 for active vs. normal pattern and 16.30/12.68 and for late vs. normal pattern. The scleroderma pattern had OR: 16.07 for future vascular compromise and 12.68 for pulmonary compromise.	The study showed that there is an association between baseline capillaroscopy patterns and the future presentation of severe peripheral pulmonary and vascular involvement.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Smith V., et al.	2013	Italy – Belgium	148 patients	Prospective cohort, multicentric	Patients were excluded due to limitations for follow-up.	Clinical diagnosis of SS.	Cutolo	Qualitative	Simple and multiple logistic regression analysis.	The OR for future severe peripheral disease was 2.49/2.52 for early, 6.18/6.37 for active and 15.35/16.07 for late capillaroscopy scleroderma patterns versus the normal pattern. The OR for future severe lung involvement based was 2.54/2.33 for early, 6.43/5.44 for active and 16.30/12.68 for late patterns.	Capillaroscopy could be a good predictive method to detect patients with systemic sclerosis at risk of organ involvement.
Voilliot D., et al.	2015	Belgium	65 patients	Prospective cohort	15 patients were excluded from the total population due to non-quantifiable systolic pulmonary pressure, 1 patient for moderate MI and 2 for coronary heart disease.	Without description	Cutolo	Qualitative	The comparison of data was performed using Student unpaired and paired t test, test2 test or Fischer exact test. The relationship between BNP levels and other continuous variables was evaluated with simple linear regressions. Independent predictors of cardiovascular events were obtained with the use of multiple logistic regression analysis.	During follow-up (27±18 months), 13 patients developed pulmonary hypertension and 9 presented cardiovascular complications. Cardiovascular disease predominantly in the elderly patient (63±14 vs. 52±13 years; $p = 0.03$), most frequent pattern of capillaroscopy grade >2 (89 vs. 43%; $p = 0.009$). Despite the age, increase in values of exercise-induced pulmonary hypertension, BNP and capillaroscopy grade >2 was predictive of cardiovascular events ($p < 0.001$).	Predicting cardiovascular disease in patients with systemic sclerosis may be possible with the association with capillaroscopy >grade 2, high BNP values, and pulmonary hypertension. When presented in a patient, the risk of cardiovascular disease is very high (63% vs. 9%, $p = 0.002$).

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Silva I., et al.	2015	Portugal	77 patients	Prospective cohort	Patients with risk factors that could potentially interfere with flow-mediated dilation, smokers, diabetics, hyperlipidemia, history of myocardial infarction, treatment with Bosentan. Late patterns of capillaroscopy. (Absence of mega-capillaries)	Classification Criteria for systemic sclerosis from the American College of Rheumatology 2013 Capillaroscopy classification criteria	Cutolo	Qualitative	Unpaired two-sided Student's t test or analysis of variance (ANOVA).	40 of the 77 patients with systemic sclerosis (51.9%) developed at least one ischemic lesion in the fingertip. 30 of these patients – 75% belong to the subgroup with active digital ulcer at the start of the study. Late pattern capillaroscopy is a predictive factor for the first digital ulcer event (HR 12.66, 95% CI; 2.06–77.89) and for recurrence (HR 2.29, 95% CI: 0.97–5.38)	Late scleroderma pattern is the strongest independent predictive risk factor for the occurrence of digital ulcer in patients with scleroderma.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Cutolo et al.	2016	Italy	623 patients	Prospective cohort, multicentric	Patients with systemic sclerosis without scleroderma were excluded; they present no risk of developing DU in an observation period of 6 months. Patients with bone marrow transplantation, and who participated in a clinical trial in the 3 months before admission to the study.	Classification Criteria for SS from the American College of Rheumatology and Criteria of LeRoy and Medsger	Cutolo	Qualitative and Quantitative	Chi-square or Fisher's Test to associate the individual categorical covariates and the development of new digital ulcer. Logistic regression model to examine the association and discriminate the risk factors for the development of new digital ulcer.	Group with digital ulcer ($n = 468$), 79.5% women, mean age 54.0±13.7 years, 59.8% limited sclerosis, and 22% developed digital ulcer in the follow-up. The predominant risk factors for digital ulcer include: average number of capillaries/mm, in the middle finger of the dominant hand, number of digital ulcers (0, 1, 2, ≥3), and the presence of digital ischemia.	Among the strong risk factors for the development of new digital ulcers at 6 months are the number of previous digital ulcers, the number of capillaries per mm displayed on the third dominant finger and the presence of critical digital ischemia.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
L.C. Teixeira	2016	Portugal	197 patients	Retrospective cohort	It is not described	Capillaroscopy classification criteria according to Cutolo 2005	Cutolo	Qualitative	It is not described	Total of capillaroscopies performed: 221 138 patients (62.4%) without definitive diagnosis 53 (24% diagnosis of systemic sclerosis), 7 (3.2%) mixed connective tissue disease, 3 (1.4%) dermatomyositis, polymyositis. Early pattern 15%, late pattern 13% In 10 patients (7.2%) the diagnosis was established: VEDOSS very early diagnosis of systemic sclerosis.	Most frequent capillaroscopy findings in patients with positive Raynaud phenomenon and Antinuclear antibodies ANA. Patients with isolated Raynaud's phenomenon have fewer pathological findings than patients with positive ANA.
L.C. Teixeira	2016	Portugal	103 patients	Retrospective cohort	It is not described	It is not described	Cutolo	Qualitative	Non-parametric tests used to determine the association between findings of capil-laroscopy and presence of digital ulcers, gastrointesti-nal involvement, pulmonary hypertension and interstitial lung disease.	Digital ulcers associated with avascular areas ($p = 0.02$) Interstitial lung disease association with avascular areas ($p = 0.056$) There was no relationship with intestinal involvement.	The presence of avascular areas and high angiogenesis association with digital ulcers. And the relation with the presence of interstitial lung disease.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Voilliot D, et al,	2016	Belgium	40 patients	Prospective cohort	Inability to sign informed consent, coronary ischemic disease, or valvular disease, inability to perform stress test, resting pulmonary hypertension, and non-quantifiable pulmonary artery systolic pressure.	In 4 different stages, depending on the presence and importance of giant capillaries, microhemorrhages, and loss of capillaries, from normal to late grade in capillaroscopy (Smith et al.)	N/A	Qualitative	Data comparison was performed according to the presence or absence of arterial hypertension in the follow-up, using Student's unpaired and paired t tests, the 2 test or Fisher's exact test.	Pulmonary hypertension at rest during follow-up was more frequent in capillaroscopy grade >2 (90% vs. 35%; $p = 0.0009$).	Capillaroscopy grade >2 is a strong predictor to follow-up pulmonary hypertension occurrence in patients with systemic sclerosis; and pulmonary systolic blood pressure at rest and in exercise can predict the evolution. The data propose that evaluation with exercise echocardiography and capillaroscopy could alert patients with systemic sclerosis at risk of developing pulmonary hypertension.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
Avouac J., et al.	2017	France-Paris	120 patients	Prospective cohort	Patients with a single capillaroscopy performed.	Classification according to Cutolo in normal, early, active, and late pattern.	Cutolo	Qualitative and Quantitative	All statistical calculations were performed with MedCalc v16.4.3.	Patients with an increased number of giant capillaries were at a lower risk of developing digital ulcer (HR: 0.53, 95% confidence interval, CI: 0.07–0.93). Loss of capillaries over time was confirmed as a strong independent marker of organ involvement and progression. The reduction in the number of capillaries was associated with disease progression. (HR: 4.35, 95% CI: 1.87–10.12), occurrence of new digital ulcer (HR: 5.33, 95% CI: 1.69–16.71), Pulmonary vascular progression (HR: 18.53, 95% CI: 1.28–78.33), Fibrosis progression in skin (HR: 4.22, 95% CI: 1.24–14.36) and worsening of the Medsger severity score (HR: 5.26, 95% CI: 1.78–15.52).	Significant changes in capillaroscopy were observed in almost half of the patients with systemic sclerosis during a 3-year follow-up period. The sequential evaluation with capillaroscopy is useful in the monitoring of the disease; likewise, the progressive loss of capillaries over time is a potential surrogate for the progression of the disease.

– Table 1 (*Continued*)

Author	Date	Country	Study population	Study design	Exclusion criteria	Classification criteria for systemic sclerosis	Pattern	Capillaroscopy analysis	Statistical analysis	Results	Conclusions
A.C. Duarte	2018	Portugal	146 patients	Prospective cohort, multicentric	It is not described	Classification Criteria for SS ACR/EULAR 2013	Cutolo	Qualitative	Descriptive analysis of the SS cohort. Logistic regression model to identify independent ILD variables	Of the total patients 88.4% women 42 patients 28.8% had interstitial lung disease of whom 83.2% were women 45.2% systemic sclerosis diffuse 42.9%, limited sclerosis antiScl 70 (OR 3.7, 95% CI: 1.3 –10.5) Anti-estrogen protective effect antibodies (OR 0.3, 95% CI: 0.1–0.8)	Clinical variables are related to the development of pulmonary complications.
A.C. Duarte	2018	Portugal	117 patients	Retrospective cohort	Patients who had no capillaroscopy in the last 6 years	Classification Criteria for SS ACR/EULAR 2013	Cutolo	Qualitative	Non-parametric tests comparing patients with and without pattern for SS	70 patients with capillaroscopy who presented a systemic sclerosis pattern were analyzed. Two-time analysis: Initial assessment: 46 patients (39.4%) scleroderma pattern, 12 (10.3%) nonspecific abnormalities in capillaroscopy, and 12 normal capillaroscopy 6 years of follow-up: 49 (70%) scleroderma pattern. Early pattern 13 patients (26.5%), active pattern in 21 (42.9%), active/late in 3 (6.1%) late pattern in 12 (24.5%).	A pattern of scleroderma in capillaroscopy is related to higher number of digital ulcers and esophageal complications.

author, year, location, sample size, study design, exclusion criteria, classification criteria used in SS, results, population percentages for the limited, diffuse and Very Early Diagnosis of Systemic Sclerosis (VEDOSS) samples, and conclusions. With the extracted information, a summary table of evidence was constructed. (Table 1)

Risk of bias assessment

It was performed independently by the two authors (DL and JL) using the Cochrane QUIPS tool to assess the risk of bias of the clinical trials. All the articles were evaluated by the two researchers, and by common agreement, the risks of bias were established (Table 2).

Results

The search was carried out independently by each of the researchers. The databases used by each researcher were randomly assigned. A total of 138 articles were found in the selected databases: Medline (*n*: 115), Embase (*n*: 66), Cochrane (*n*: 2), Lilacs (*n*: 0). After carrying out the removal of articles by title and abstract, a total of 66 items were obtained. For these articles, a screening process was carried out based on the title and the abstract, taking into account the eligibility criteria, obtaining 21 references. Both researchers assessed the selected articles (full text), and all disagreements were solved by a consensus decision. Finally, a total of 14 articles were included. The majority of studies (11/14, 78%) reported associations between baseline capillaroscopic features (using qualitative, semi-quantitative and quantitative endpoints) and organ involvement including digital ulcers occurrence, progression of skin lesions, pulmonary arterial hypertension, interstitial lung disease, esophageal complications and analysis of cardiovascular risk. Among them (2/14, 14.2%) found a progressive loss of capillaries as a potential surrogate for the progression of the disease; and (2/14, 14.2%) considered a relationship with mortality (Fig. 1).

Studies description

Most of the studies were conducted in Italy (*n*: 6), Portugal (*n*: 5) and Belgium (*n*: 4), one of them being the product of a collaboration between two of these countries: Belgium and Italy. Regarding the research group, Sebastiani et al., Smith V., et al. and L.C. Teixeira and collaborators, conducted the majority of these studies. The other publications were made by researchers in Spain, Australia, France, Brazil and Canada. Regarding the publication year, the articles were published between 2002 and 2018. The included references were primary studies with diagnostic validity in men and women in adulthood, and no studies conducted in Colombia were identified. The study sample sizes varied between 40 and 786 patients.

The majority of the studies were prospective cohorts and the criteria used for the classification of SS were those of the American College of Rheumatology of 1980, Criteria of Le Roy and Medsger, Criteria of Classification for ES ACR/EULAR 2013 and Cutolo's criteria.

In several articles, scleroderma patterns were associated with multisystemic involvement, including the kidneys, scleroderma "renal crisis"; heart, cardiomyopathy, symptomatic pericarditis, or arrhythmia; lungs, pulmonary fibrosis; GI tract, malabsorption, skin, digital ulcers, and vascular complications and their respective clinical manifestations, as in the case of pulmonary hypertension which is one of the most common complications in patients with SS. Voilliot et al.[9] found that capillaroscopy grade >2 according to the LeRoy and Medsger criteria (semi-quantitative method on the report of Cutolo's criteria) is a strong predictor of the development of pulmonary hypertension in patients with SS; pulmonary systolic blood pressure at rest and during exercise could be helpful measures to predict its evolution. The data show that evaluation with exercise echocardiography and capillaroscopy could alert patients with SS who are at risk of developing pulmonary hypertension.

In 2012, Smith et al.[10] conducted a prospective cohort study in Belgium, in which they found an association between baseline capillaroscopy patterns and the future development of pulmonary (*p*: 0.003) and severe peripheral vascular (*p*: 0.001) involvement. An initial patient evaluation was made and images described as normal, early, active and late pattern were obtained. Subsequently, a second measurement was made in a period between 18 and 24 months, in which they found a relationship between the progression of severity at the pulmonary level and the presence of digital ulcers, although it was not predictive. In this study, the baseline clinical data were not described. Therefore, it was not possible to confirm if a variation of clinical characteristics occurs during the period between measurements.

Silva and Collaborators[11] found that among scleroderma patterns, the late pattern was the strongest independent predictive risk factor for the occurrence of digital ulcers for the first event and subsequent events in patients with SS (HR: 12.66, 95% CI: 2.06–77.89 and HR: 2.29, 95% CI: 0.97–5.38). In this study, smokers, diabetic patients with hyperlipidemia, history of myocardial infarction and patients on Bosentan treatment, who might have risk factors that could potentially interfere with flow-mediated dilation or could skew the findings of capillaroscopy, were excluded from the study. The most important limitation was not having the number of fingers that were evaluated and the description of the images obtained.

Cutolo and colleagues[12] described other findings related to the development of new digital ulcers at 6 months. Among these are the number of previous digital ulcers, the number of capillaries per millimeter displayed on the 3rd finger of the dominant hand, and the presence of critical digital ischemia, which were considered strong risk factors for recurrence.

Furthermore, Avouac et al.[13] found in a 3-year prospective cohort study, that progressive loss of capillaries over time is a finding related to disease progression (HR: 4.35, 95% CI: 1.87–10.12), organ involvement, occurrence of new digital ulcers (HR: 5.33, 95% CI: 1.69–16.71), pulmonary vascular progression (HR: 18.53, 95% CI: 1.28–78.33) and progression of skin fibrosis (HR: 4.22, 95% CI: 1.24–14.36) so the capillaroscopy, would be considered a useful method for monitoring it.

Regarding the healing of digital ulcers, Alivermini[14] found a relationship between the presence of greater avascular areas and a longer duration of lesions, apparently related to the

Table 2

	Articles	Year	Selection bias	Desertion bias	Measurement bias	Assessment bias	Confounding factors	Bias in relation to analysis and statistical reports
1	Scussel-Lonzetti et al.	2002	High	Low	Low	Unclear	Low	No
2	Alivernini et al.	2009	Low	Low	High	Moderate	Low	High
3	Hissaria P., et al.	2011	Low	Low	Low	Low	High	Moderate
4	Smith V., et al.	2012	Low	Low	Low	Low	High	Moderate
5	Smith V., et al.	2013	Moderate	Moderate	Low	Low	Low	Moderate
6	Voilliot D., et al.	2015	Moderate	Low	Moderate	Low	High	Moderate
7	Silva I., et al.	2015	Low	Low	Moderate	Low	Moderate	Low
8	Cutolo et al.	2016	Moderate	Low	Low	Moderate	Low	Low
9	L.C. Teixeira	2016	Moderate	Moderate	Moderate	Moderate	Moderate	High
10	L.C. Teixeira	2016	Moderate	Moderate	Moderate	Moderate	Moderate	High
11	Voilliot D., et al.	2016	Moderate	Moderate	Moderate	Low	High	Moderate
12	Avouac J., et al.	2017	Low	Low	Low	Low	Low	Low
13	A.C. Duarte	2018	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
14	A.C. Duarte	2018	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

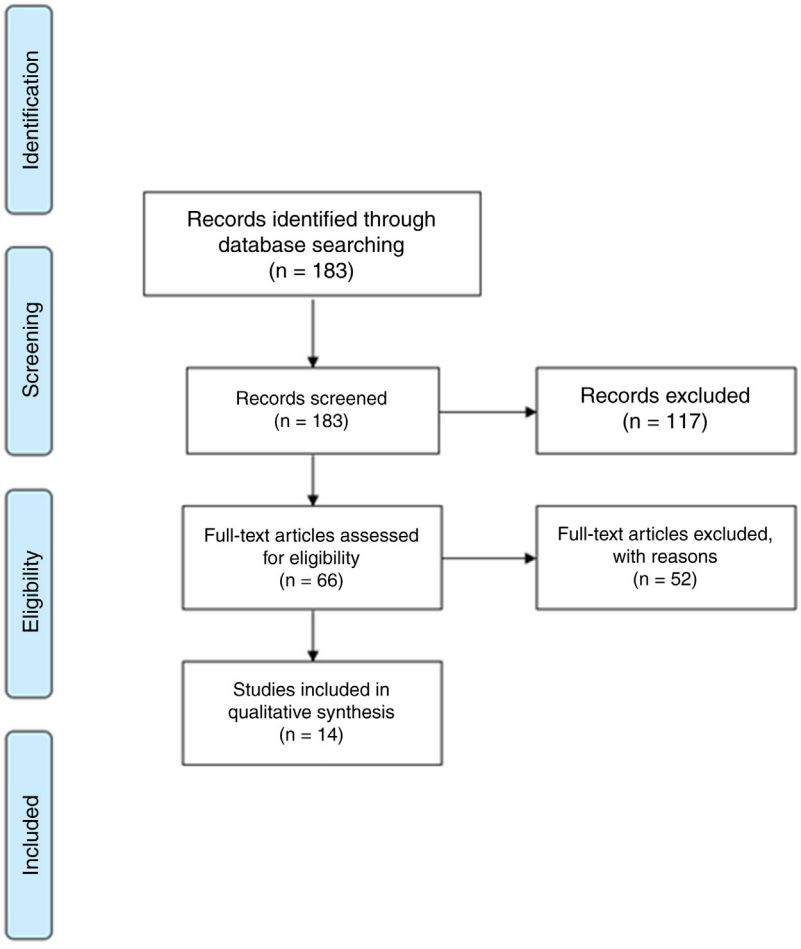

Fig. 1 – Flow chart of the studies included in the review.

microangiopathic damage caused by the disease. Additionally, he reported as direct risk factors for the development of digital ulcers: the simultaneous presence of diffuse sclerosis, avascular areas, thrombophilia and high levels of IL-6. The most common comorbidity found in this study was pulmonary alveolitis in 89.5% of the patients.

Hissaria[15] in 2011, conducted a retrospective study for 14 years with 786 patients and described the relationship between various subtypes of scleroderma compromise and systemic complications. The most common were scleroderma renal crisis, pulmonary arterial hypertension and pulmonary fibrosis with a high impact on survival rates. A relationship between capillaroscopy patterns and mortality was also

reported (95% CI: 1.06–2.42); however, it was not clear whether the analysis was adjusted for the presence of diffuse scleroderma, interstitial lung disease or the presence of anti-Scl-70 autoantibodies, as each of them has been independently related to mortality in other studies.

Reported prognostic associations of NVC in subtypes identification

Findings regarding systemic complications and classification by subtype have been described. In 2002, Scoussel-Lonzetti[8] in a prospective study with 309 patients being studied for 15 years, described the correlation between different rates of capillary loss and the subtype found. Thus, after 2.5 years of initial symptoms of SS, 75% of patients presenting with diffuse pattern had already presented severe capillary loss, in contrast with 40% and 15% in the intermediate and limited subtypes, respectively.

Smith et al.,[16] established the association between findings in capillaroscopy and different findings in systemic sclerosis, (early, active and late), with organ involvement in 2 independent cohorts. As for the Belgian cohort, 25/55 patients (45%) had severe involvement of any of the organs of the nine systems. This study showed a statistically significant association between the NVC pattern and the involvement of some of the organs. The estimated OR after the simple and multiple logistic regression analysis, showed that organ involvement was stronger in those patients in whom the NVC patterns were more severe. These findings were similar to those found in the Italian cohort, in which 31/79 patients (39%) had any of the nine organs affected.

L.C. Teixeira, in two different studies[17,18] revealed the association between stages and organ involvement. The first study was conducted from January 2013 to December 2015. Capillaroscopy was considered abnormal in 79.4% of patients with positive Raynaud's phenomenon and ANA, and 41.2% had specific findings of rheumatic disease, suggesting that this combination is associated with a higher disease incidence. Patients with isolated rheumatoid factor had less pathologic capillaroscopy findings than those with isolated ANA positivity. Similarly, in patients with SS, the late and early patterns were the most frequent in capillaroscopy.

The other study showed that the presence of avascular areas and neo-angiogenesis in capillaroscopy was significantly associated with the existence of digital ulcers. Also, interstitial lung disease and higher values of NT-proBNP were more common in patients who presented avascular areas. These results suggest that abnormalities detected in the capillaroscopy might help predict organ involvement.

Duarte,[19] in Portugal, analyzed 146 patients of which 42 developed interstitial disease, identifying results of capillaroscopic findings in 23 of them; 21 presented a pattern for SS at different stages (5 early, 6 active and 10 late). In addition, in a multivariate analysis, the presence of anti-Scl70 (OR: 3.7, 95% CI: 1.3–10.5) and digital ulcers (OR: 2.2, 95% CI: 1.9–5.3) was associated with the development of pulmonary interstitial disease. Otherwise the presence of anti-centromere antibodies behaves as a protective factor (OR: 0.3, 95% CI: 0.1–0.8).

In a second retrospective cohort study, Duarte[20] found that the scleroderma pattern was significantly associated with a higher number of digital ulcers and these patients had a higher prevalence of esophageal involvement. Scleroderma pattern was associated with the presence of digital ulcers (OR 1.49, 95% CI: 1.17–1.92).

This study demonstrates that nailfold capillaroscopy is useful for monitoring endothelial injury and potential vascular and systemic damage.

Discussion

This review identified an essential relationship between the evolution of capillary abnormalities and the progression of the disease in systemic sclerosis. The increase in capillary loss predicts more significant vascular and organic complications.

Once more, capillaroscopy seems to play a crucial role in early identification and as a follow-up tool in patients with systemic sclerosis. It is also useful as a method for predicting secondary complications, as it was observed with the development of digital ulcers, pulmonary hypertension, and other vascular complications.

The results from the studies included were similar over time without finding significant differences between the data obtained in each of them.

These results support why this diagnostic method has been included within the diagnostic criteria of the American College of Rheumatology of 2013 and reflect its importance as an economical, reproducible and non-invasive technique reinforcing the need for its incorporation as a prognostic factor for disease progression.

Capillaroscopy follow-up directions

1. In patients with autoimmune disease (mainly systemic sclerosis) and Raynaud's phenomenon that remains active, it is important to perform video-capillaroscopic monitoring every 3–6 months to verify the evolution and changes derived from treatment, and which in turn determines the need for optimize vasodilator and/or immunomodulator treatment.
2. In patients with autoimmune disease and Raynaud's phenomenon who have had adequate control in the frequency and intensity of attacks, annual video-capillaroscopic control is indicated.

Study limitations

There are several limitations in the present study:

1. The wide heterogeneity of the primary studies (which in turn prevents the meta-analysis of the studies), about the follow-up time after the symptoms appear (mainly the Raynaud's phenomenon), the temporality of the studies (retrospective, mostly cross-sectional and small prospective), and the lack of unification of the evaluation criteria for the findings of abnormality in the capillaries.

2. Lack of standardization in the procedure (not explained) and the process of concordance between the observers to verify the confirmation of the results.
3. Being a predominantly semi-quantitative method, it lends itself to classification biases and diagnostic error.
4. The overlapping of the findings in various autoimmune conditions, including in some healthy patients (moderate performance of the technique).

In daily clinical practice, capillaroscopy is useful not only for confirming the diagnosis of systemic sclerosis but also for monitoring endothelial injury, potential macrovascular systemic damage, and cardiovascular risk. However, more studies are required to determine its real predictive value.

Declaration of Competing Interest

There are no conflicts of interests.

REFERENCES

1. Cutolo M, Pizzorni C, Secchi ME, Sulli A. Capillaroscopy. Best Pract Res Clin Rheumatol [Internet]. 2008;22:1093–108.
2. Avouac J, Fransen J, Walker U, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis [Internet]. 2011;70:476–81.
3. Lambova SN, Müller-Ladner U. The role of capillaroscopy in differentiation of primary and secondary Raynaud's phenomenon in rheumatic diseases: a review of the literature and two case reports. Rheumatol Int. 2009;29:1263–71.
4. Lambova SN, Müller-Ladner U. Capillaroscopic pattern in systemic sclerosis — an association with dynamics of processes of angio- and vasculogenesis. Microvasc Res [Internet]. 2010;80:534–9.
5. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi consensus study from EULAR scleroderma trials and research group. Ann Rheum Dis. 2011;70:476–81.
6. Rossi D, Russo A, Manna E, Binello G, Baldovino S, Sciascia S, et al. The role of nail-videocapillaroscopy in early diagnosis of scleroderma. Autoimmun Rev [Internet]. 2013;12:821–5.
7. Sebastiani M, Manfredi A, Colaci M, Damico R, Malagoli V, Giuggioli D, et al. Capillaroscopic skin ulcer risk index: a new prognostic tool for digital skin ulcer development in systemic sclerosis patients. Arthritis Care Res. 2009;61:688–94.
8. Éricr I, Jeanig O, Yvesr A, Jeanucs E, Scussel-Lonzetti L, Joyal F, et al. Predicting mortality in systemic sclerosis: analysis of a cohort of 309 French Canadian patients with emphasis on features at diagnosis as predictive factors for survival. Medicine (Baltimore) [Internet]. 2002;81:154–67.
9. Voilliot D, Magne J, Dulgheru R, Kou S, Henri C, Caballero L, et al. Prediction of new onset of resting pulmonary arterial hypertension in systemic sclerosis. Arch Cardiovasc Dis [Internet]. 2016;109:268–77.
10. Smith V, Decuman S, Sulli A, Bonroy C, Piettte Y, Deschepper E, et al. Do worsening scleroderma capillaroscopic patterns, predict future severe organ involvement? A pilot study. Ann Rheum Dis. 2012;71:1636–9.
11. Silva I, Teixeira A, Oliveira J, Almeida I, Almeida R, Águas A, et al. Endothelial dysfunction and nailfold videocapillaroscopy pattern as predictors of digital ulcers in systemic sclerosis: a cohort study and review of the literature. Clin Rev Allergy Immunol. 2015;49:240–52.
12. Cutolo M, Herrick AL, Distler O, Becker MO, Beltran E, Carpentier P, et al. Nailfold videocapillaroscopic features and other clinical risk factors for digital ulcers in systemic sclerosis: a multicenter, prospective cohort study. Arthritis Rheumatol [Internet]. 2016;68:2527–39.
13. Avouac J, Lepri G, Smith V, Toniolo E, Hurabielle C, Vallet A, et al. Sequential nailfold videocapillaroscopy examinations have responsiveness to detect organ progression in systemic sclerosis. Semin Arthritis Rheum [Internet]. 2017;47:86–94.
14. Alivernini S, De Santis M, Tolusso B, Mannocci A, Bosello SL, Peluso G, et al. Skin ulcers in systemic sclerosis: determinants of presence and predictive factors of healing. J Am Acad Dermatol [Internet]. 2009;60:426–35.
15. Hissaria P, Lester S, Hakendorf P, Woodman R, Patterson K, Hill C, et al. Survival in scleroderma: results from the population-based South Australian Register. Intern Med J. 2011;41:381–90.
16. Smith V, Riccieri V, Pizzorni C, Decuman S, Deschepper E, Bonroy C, et al. Nailfold capillaroscopy for prediction of novel future severe organ involvement in systemic sclerosis. J Rheumatol. 2013;40:2023–8.
17. Teixeira LC, Cordeiro I, Canas da Silva J, Santos MJ, Cordeiro A. OP0129 nailfold capillaroscopy in rheumatology practice – a single center experience. Ann Rheum Dis [Internet]. 2016;75 Suppl. 2, 104.3–105.
18. Teixeira LC, Cordeiro I, Sousa S, Duarte AC, Canas da Silva J, Cordeiro A, et al. SAT0237 nailfold capillaroscopy findings in scleroderma patients - prognostic implications. Ann Rheum Dis [Internet]. 2016;75 Suppl. 2, 754.2–754.
19. Duarte AC, Cordeiro A, Santos MJ, Canas da Silva J. AB0727 antibody profile and systemic sclerosis clinical features – myth or reality?; 2019, 1502.2–1503.
20. Duarte AC, Cordeiro A, Santiago T, Salvador MJ, Santos MJ. AB0726 interstitial lung disease in scleroderma patients – a Portuguese portrait; 2019, 1502.1–1502.
21. Sulli A, Pizzorni C, Smith V, Zampogna G, Ravera F, Cutolo M. Timing of transition between capillaroscopic patterns in systemic sclerosis. Arthritis Rheum. 2012;64:821–5, http://dx.doi.org/10.1002/art.33463.