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Capillary density: An important parameter in nailfold capillaroscopy

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ABSTRACT

Nailfold capillaroscopy is one of the various noninvasive bioengineering methods used to investigate skin microcirculation. It is an effective examination for assessing microvascular changes in the peripheral circulation; hence it has a significant role for the diagnosis of Systemic sclerosis with the classic changes of giant capillaries as well as the decline in capillary density with capillary dropout. The decline in capillary density is one of microangiopathic features existing in connective tissue disease. It is detectable with nailfold capillaroscopy. This parameter is assessed by applying quantitative measurement. In this article, we reviewed a common method for calculating the capillary density and the relation between the number of capillaries as well as the existence of digital ulcers, pulmonary arterial hypertension, autoantibodies, scleroderma patterns and different scoring system.

Contents

Abbreviations: RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; RP, Raynaud phenomenon; SSc, systemic sclerosis; CTD, connective tissue diseases; CSURI, capillaroscopic skin ulcer risk index; DU, digital ulcer; PRINCESS, Prognostic Rule-based Instructions using Nailfold Capillaroscopy Examination and Scleroderma-related Serology; NFC, nailfold capillaroscopy; NVC, nailfold videocapillaroscopy; ERS, erythrocyte sedimentation; ANA, Antinuclear antibodies; ACA, Anticentromere antibodies; AECA, Anti-endothelial cell antibodies; DTD, digital trophic lesions; MES, microangiopathy evolution score; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; VEGF, vascular endothelial growth factor.

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1. Introduction

For studying skin microcirculation, several techniques are presently available, which are applicable to cosmetology and pathology. Microcirculation is defined as the circulation of blood in arterioles (<300 μm), capillaries, and venules (Koscielny et al., 1998). Although it is difficult to analyze capillary function in humans due to the limited access to the vascular bed. Nowadays, the development of medical devices and equipment has allowed to studying skin capillaries by using capillaroscopy. Capillaroscopy offers the most practical technique for instantly visualizing skin capillary circulation and for assessing capillary density and blood flow velocity (Hosking et al., 2013). Microvessels in the papillary dermis range from 10 to 35 μm routinely discovered by capillaroscopy, considering those in the mid to deep dermis vary in size from 40 to 50 μm with an occasional arteriole as large as 100 μm being discovered (Braverman, 1997).

Capillary pathologies may occur in conjunction with endocrinologic, neurologic, cardiovascular, and especially with rheumatic diseases, including the antiphospholipid syndrome (Vayssairat et al., 1997; Vaz et al., 2004), Systemic lupus erythematosus (SLE) (Bergman et al., 2003; Bongard et al., 1995; Cutolo et al., 2006; Furtado et al., 2002), systemic sclerosis (SSc) (Ingegnoli et al., 2013; Kayser et al., 2013), dermatomyositis (Bergman et al., 2003; Selva-O'Callaghan et al., 2010) Sjögren's syndrome, (Selva-O'Callaghan et al., 2010; Tektonidou et al., 1999) and psoriatic arthritis (Grassi et al., 1992; Hoerth et al., 2012). The vascular abnormalities predominantly affecting the small blood vessels not only appear in the fingers (Houtman et al., 1985) but also in the internal organs such as lungs, kidneys, and heart; this has been actually demonstrated in the functional and histological scleroderma studies (Campbell and LeRoy, 1975; Follansbee et al., 1984). In the early stages of connective tissue diseases (CTD), capillary abnormalities in the nailfold can be visualized clearly by capillaroscopy (Maricq, 1981). By applying this technique, nailfold capillary density and morphological changes such as capillary loops enlargement can be surely ascertained (Houtman et al., 1985).

Different qualitative, semi-quantitative and quantitative methods are employed in capillaroscopic studies. The architecture of the nailfold microvascular bed, shape and distribution homogeneity of capillaries and the morphological characteristics of single loops are evaluated by the qualitative/descriptive approach (Etehad Tavakol et al., 2015; Murray et al., 2011). The main capillary abnormalities (giant, ramified, tortuous, and irregularly-enlarged capillary loops) are studied by the semi-quantitative technique. However, capillary density, width and length, arterial and venous limb diameter, apex width and loop length, arterial and venous limb diameter, apex width and loop diameter are determined via quantitative evaluation (Grassi and De Angelis, 2007). In the most nailfold capillaroscopy (NFC) studies, capillary density is considered as a common parameter among the quantitative parameters. The aim of this paper is to discover the relationship between capillary density and parameters such as: autoantibodies, digital ulcers (DU), pulmonary arterial hypertension (PAH), as well as classification of capillaroscopic patterns in the SSc patients, effective capillary density in different scoring system like Skin Ulcer Risk Index (CSURI) and microangiopathy evolution score (MES) (Fig. 1).

2. Search strategy

By employing a systematic literature search, published studies from 1972 up to 2016 in "PubMed" and "Embase" databases have been collected. In addition, the bibliographies of these articles and the previously published ones have been manually searched to improve the process. A total of 468 citations are provided in our search which 315 are discarded after reviewing the title and abstract for not meeting the proposed criteria. Also the repeated references have been excluded. Finally, a total of 122 papers are identified for the review.

Included studies in many papers were associated with small sample sets, non-randomized controlled trials, retrospective or prospective cohort studies, cross-sectional and post-hoc analysis of registries due to rarity of disease. In addition, clinical cases were excluded.

3. Materials and methods

3.1. Capillary shape

The orientation of capillary loops may vary depending on the examined skin area and its microvascular anatomy. Videocapillaroscopy can display the normal architectural patterns of capillary loops, including their two main patterns (parallel or perpendicular with respect to the skin surface). There are some irregularities in the development of capillary loops. For example, in the forearm skin, the dermal papillae are not completely developed; so the arterioles connect to the capillaries that run into the dermal epidermal interface before joining a post-capillary venule of the subpapillary plexus (Shore, 2000).

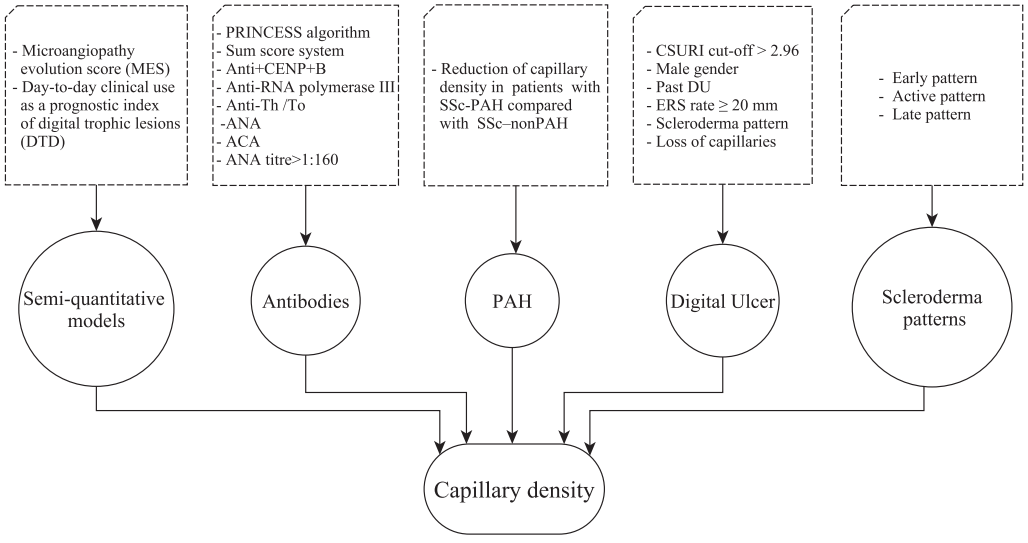

Fig. 1. Brief description of the relationship between capillary density and different parameters. CSURI: Capillaroscopic Skin Ulcer Risk Index; PHD: pulmonary arterial hypertension; PRINCESS: Prognostic Rule-based Instructions Examination and Scleroderma-related Serology; SSc: Systemic sclerosis; ERS: erythrocyte sedimentation; ACA: Anticentromere antibodies; AECA: Anti-endothelial cell antibodies; ANA: Antinuclear antibodies;

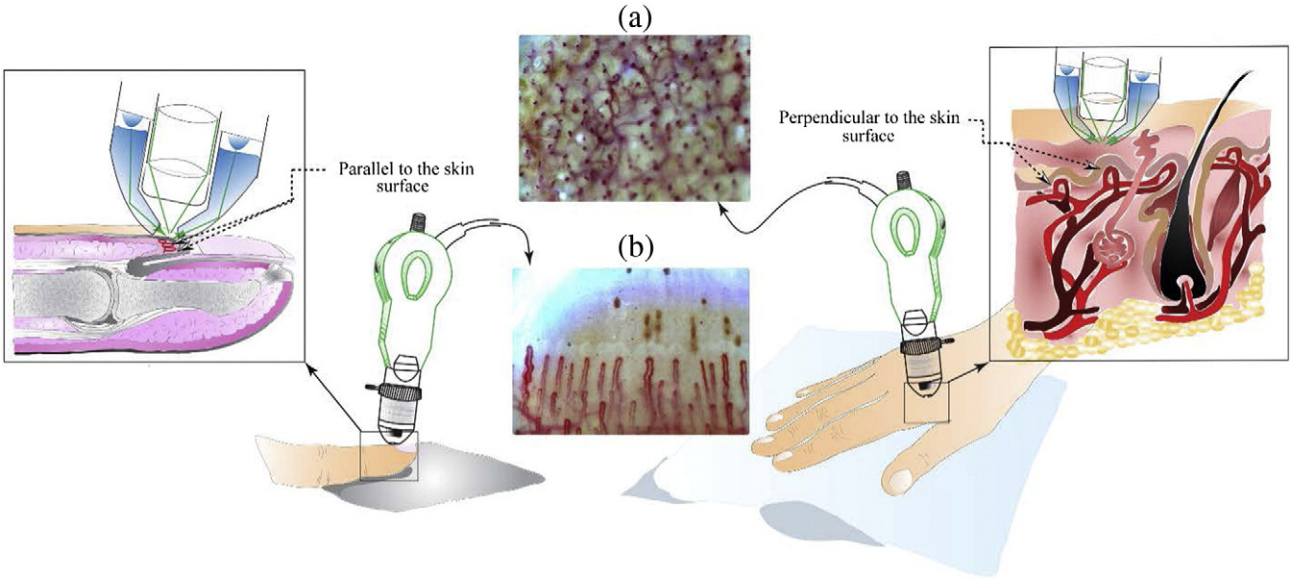

Fig. 2. A capillaroscope used on a nailfold (b) and on a portion of hand skin (a); Skin areas with black and red dots indicating the papillary loops, Out-of-focus superficial part of the subepidermal vascular plexus.

Capillaries are perpendicular to the skin surface in most areas hence, only their summits can be observed (Fig. 2b); which appear as dots or commas (Humbert et al., 2005). Depending on the examined skin area, some reports show capillary density differences over small areas such as the dorsum of the foot (Lamah et al., 1996; Shore, 2000). Capillary densities of four anatomical sites were compared. It has been shown that the hand area has the highest capillary density, followed by the forearm, forehead and the crow's feet regions (Li et al., 2005). The capillary density in the hand is about 4 times greater than that in the crow's feet area. In the skin regions where capillary loops are arranged perpendicularly to the skin surface, the capillary density ranges from 14 to 30 capillary loops per mm^2 of skin (Cutolo et al., 2007; Hosking et al., 2013).

The terminal row of dermal capillary loop lies parallel to the surface of the skin in the toe and finger nailfolds. This allows the visualization of the full length of capillaries at the distal row. The classical physiological pattern of a nailfold capillary loop ordinarily looks like a hairpin or an elongated letter "U" upside-down (Fig. 2a). All the capillary loops of this type, whose limbs are not markedly undulated, as well as those whose afferent and efferent limbs cross each other at just a single point, are considered as normal loops. Such single crossovers usually depend on the orientation angle of the capillary relative to the plane in which it approaches the skin surface (Rouen et al., 1972).

The hairpin shape is noticeable in the nailfold areas as well as in other tissues where the outer layers of epithelium are thicker and the microvasculature has hairpin-shaped capillary loop patterns (e.g., lip mucosa and buccal mucosa) (Hofstee et al., 2013; Scardina et al., 2009). Every capillary loop in each dermal papilla has a regular structure. A thinner arterial limb, a wider venous limb, a connecting part between the limbs, and an apical loop are present in every single capillary loop (Lambova et al., 2011). In general the normal pattern of capillary under physiological conditions is characterized by: i) density of 9–13/mm; ii) the orderly arrangement of the capillaries to comb; iii) afferent branch with 6–9 μm, efferent branch with 8–21 μm; iv) capillary length 200–500 μm (Faggioli et al., 2015).

In healthy individuals, usually the capillaries have homogeneous shapes and normal dimensions described above. The capillary loops may present discreet morphological variations, such as Tortuous capillary (afferent and efferent limb are curled but do not alterations cross, also called "torsion"), Crossed capillaries (afferent and efferent limb cross at least 2 points) (Andrade et al., 1990; Cutolo and Smith, 2015), Cuticulitis capillary (the limbs are not visible; only tiny red dots in high density are apparent) (Cutolo and Smith, 2015; Jones et al., 2001), Dilated capillary (A capillary whose venous limb diameter > 20 μm or whose arterial limb >15 μm), Giant capillary (A capillary with arterial or venous limb diameter > 50 μm, also known as a "megacapillary"), Elongated capillary (Capillary loops longer than 300 μm (0.300 mm), also known as a "elongation"), Ramified capillaries (abnormal connections between arterial and venous limb, different capillaries or vascular neoplasms, also known as a "ramification"), bushy capillaries (multiple branching of a capillary) (Sander et al., 2010), meandering capillaries (presence of more than one capillary loop in a single dermal papilla) (Lambova and Müller-Ladner, 2012), Some of these capillary deformations such as small number of capillary dilations and small areas of micro-bleeding with focal distribution may be observed in healthy individuals. However, in patients suffering from secondary Raynaud's Phenomenon (RP), one or more of the following deformation capillary findings can alert physicians for the possibility of a connective autoimmune disease not yet detected (Cutolo et al., 2007).

3.2. Capillary density

The number of capillaries per unit area of skin is called capillary density. Basically, it is obtained by acquiring the images of capillaries from a specific skin area by means of a capillary microscope and then counting the observed capillaries. Nevertheless, some authors consider the capillary density as the detectable capillaries in the entire distal front line, including capillaries placed at different levels (Alivernini et al., 2009). The exact procedure will depend on the method used for counting the capillaries. For example, four color photographs could be taken around a central point tattooed on the skin. Then, the number of capillaries could be counted by using these photographs. In another method, by systematically focusing the microscope, six consecutive skin fields could be recorded for 2 min each and the capillaries could be counted during the video playback. Ideally, capillaries should be counted during the movement of red blood cells and plasma through them, as observed in the video replay. We can also combine the two methods by counting the capillaries from video prints as well as still photos (Shore, 2000). Two definitions for capillary density in a nailfold are as follows:

Definition 1. Capillary density is described by the number of erythrocyte-perfused capillaries per square millimeter which are displayed at least as two visible limbs on nailfold skin.

The above definition is used in some of nailfold capillaroscopy studies (Paparde et al., 2014; Serné et al., 2001). Which is used to count the number of capillary in the labial oral mucosa (Scardina et al., 2014) and the skin (Gronenschild et al., 2013) on the dorsum of the middle phalanx of the third finger, or fourth finger if rings were not removed from both hands (Govoni et al., 2016). Although, an automated counting algorithm was proposed by image processing techniques to standardize capillary counting in NFC image (Cheng et al., 2015). In this algorithm, authors standardize the cropped segment of the image to count capillaries. The suitable segment should show the first row of capillaries at the very top of the image without any blank spaces above the segment. Fig. (3a, b) illustrates this method properly,

Definition 2. Capillary density is defined as the number of capillaries in a one millimeter span of the distal row in each finger or toe.

In many studies this definition is used to measure capillary density parameter (Etehad Tavakol et al., 2015). It is also known as the "number of capillaries" or "capillaries number".

There are different modalities that can be employed to obtain the number of capillaries and ramifications. Some researchers obtain capillary density by counting the number of clearly visible end row capillaries that depends on the sharpness of images. Then the end row capillary number is divided by the end row length, and expresses as capillaries/mm (Dolezalova et al., 2003) (Fig. 3d). However, generally two methods are proposed for estimating the capillary density. The first one is the direct observation method that the capillary loops are observed directly, and then considered distal loops are marked (Le and Im Cho, 2014) (Fig. 3e). Under the second method or the 90° method, a capillary loop will be considered as a distal loop if the angle between the apex of that capillary and the apex of its two adjacent capillaries is >90° (Hofstee et al., 2011; Wildt et al., 2012) (Fig. 3c). In international multicenter study on the reliability of nailfold assessment, measuring capillary density with the 90° method was investigated that was superior to the direct observation method (Hofstee et al., 2011). It showed almost-perfect inter observer agreement and intra-observer agreement on capillary density which were not different in the 90° method and the direct observation method. Since there is no standardized approach for measuring the capillary density, most researchers employ the direct observation or the 90° method to measure the number of capillaries.

The normal range of finger capillary density and the morphological variations of capillaries in healthy individuals depend on their age, sex and ethnicity (as shown in Table 1). Capillary density changes with age, as part of the maturation process. This trend is less obvious in older children and adolescents. In fact, the number of capillaries (capillary density) is the same in adults and in children older than 10 years (Ingegnoli and Herrick, 2013). In a study, the average capillary density

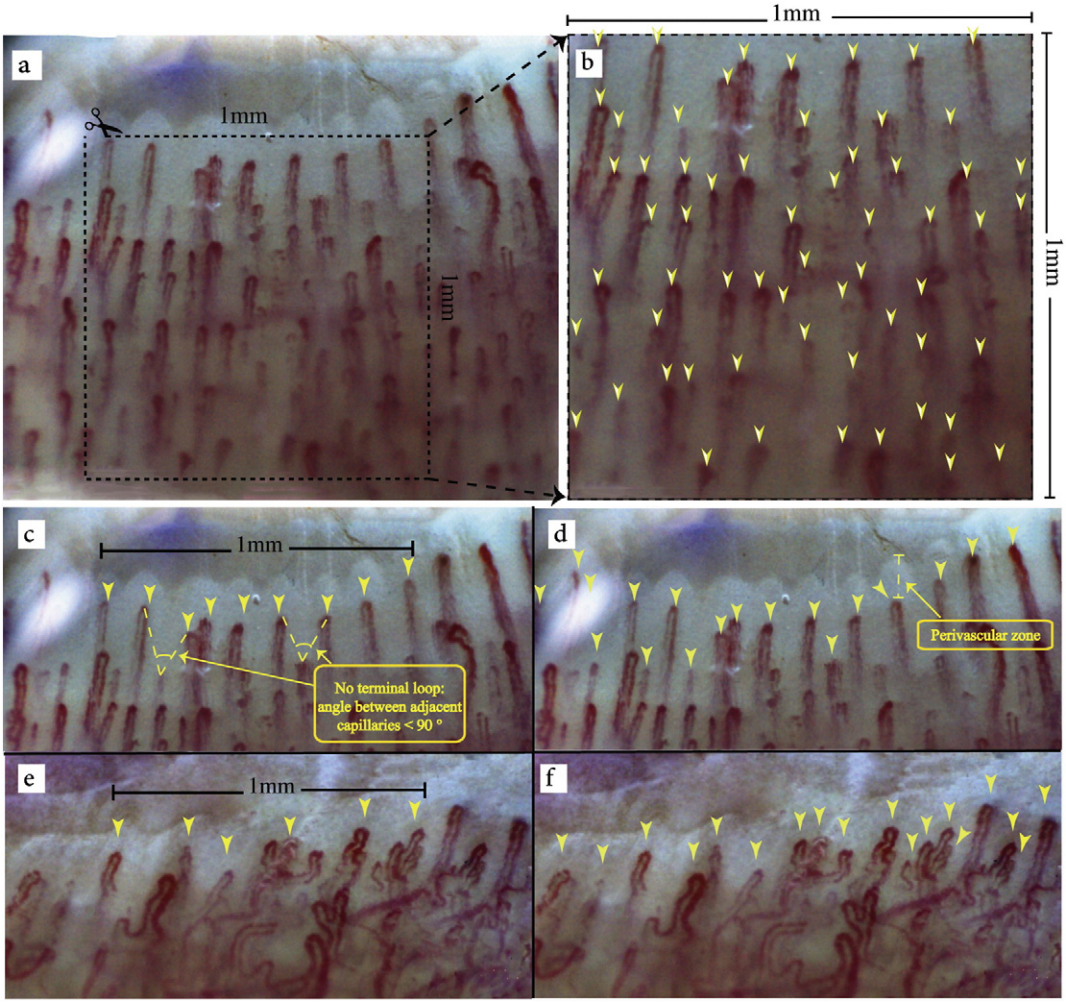

Fig. 3. Different methods for calculating number of capillaries and ramifications; (a): Initial image taken from the subject's nailbed with a nailfold capillaroscopy with the black box showing a 1 × 1 mm box for the camera; (b): 1 mm box cropped from image (a); (c):) all capillaries placed in one millimeter; (d): all detectable capillaries in the entire distal front line, including capillaries in different positions; (e) ramified capillaries counted as the single capillaries in one millimeter; (f) and ramified capillaries according to the number of the apical loops.

Table 1
Densities of finger capillaries in healthy control subjects.

(Researcher, study year)(country)	No. of patients	Gender	Capillary density (median ± SD)
(Andrade et al., 1990)(Brazil)	668		9.11
(Grassi et al., 1992)(Italy)	25		8.8 ± 1.6
(Gasser and Bühler, 1992)(Switzerland)	18	Male (11) Female (9)	7.2 ± 1.5
(Terreri et al., 1999)(Brazil)	329 Children	White Male Non-white Male White Female Non-white Female	7.3 ± 0.75 6.9 ± 0,74 7.3 ± 0.73 6.8 ± 0.82
(Schiavon et al., 1999)(Italy)	26		10.3 ± 1.2
(Dolezalova et al., 2003)(Czech Republic)	17 Children 20 Adults		6.9 ± 0.9 8.6 ± 1.6
(Ingegnoli et al., 2005)(Italy)	50 Children	Male (25) Female (25)	6.1
	20 Adult	Male (7) Female (13)	7.3
(da Silva Facina et al., 2006)(Brazil)	32	Male (10) Female (22)	9.53 ± 0.11
(Hofstee et al., 2009)(the Netherlands)	21		9.87 ± 1.38
(Correa et al., 2010)(Brazil)	40	Male (3) Female (37)	10.1 ± 0.6
(Bhakuni et al., 2012)(India)	42	Male (21) Female (21)	8.7 ± 1.2
(Hoerth et al., 2012)(Austria)	100	Male (63) Female (57) Age < 40 = 75 Age > 40 = 45	8.60 ± 1.26 8.83 ± 1.52 8.45 ± 1.32 9.15 ± 1.42
(Lambova and Müller-Ladner, 2013)(Bulgaria)	34	Male (17) Female (17)	10 ± .59
(Jung and Trautinger, 2013)(Germany)	50		8,73 ± 1,05
(Sekiyama et al., 2013)(Brazil)	53	Male (9) Female (44)	10.10 ± 0.56
(Le and Im Cho, 2014)(Korea)	25		10.2 ± 6.1
(Erol et al., 2016)(Turkey)	82	Male (65) Female (17)	11

was 8.45 ± 1.32/mm for individuals aged 40 or less and 8.71 ± 1.40 for individuals older than 40 years of age in healthy subjects. Moreover, the impact of gender on capillary density is insignificant, and the morphological variations of finger capillaries are more extensive in men than in women. Also in this study the average capillary densities in healthy males and females were found to be 8.83 ± 1.50 and 8.60 ± 1.26/mm, respectively (Hoerth et al., 2012). A conducted study showed that there is a statistically significant differences between the capillary densities in healthy white and healthy nonwhite children (Terreri et al., 1999). This research was shown the average capillary densities of 7.3 ± 0.74 and 6.85 ± 0.77/mm for healthy white and nonwhite children, respectively.

Although the microscopic examination of finger nailfolds is widely practiced nowadays, this technique is not common for toe nailfolds in clinical rheumatologic examinations. In a study on 84 healthy subjects was found that, capillary loops in feet are shorter than in hands (Noy-Delcourt and Thébaut, 1985). Toes of healthy subjects have significantly lower capillary densities (6.6 ± 0.97/mm) than their fingers (8.73 ± 1.05/mm) (Jung and Trautinger, 2013). Toe capillary density appears to vary in healthy adults across Europe (see Table 2). For example, a mean capillary density of 6.6 ± 0.97 (mean ± standard deviation) per millimeter, with a range of 5–9/mm, has been reported by German authors. However, a Bulgarian group has observed slightly higher capillary values than those found by German researchers. They have obtained an average value of 10 ± 59 for the capillary density of toes (Lambova et al., 2011).

3.3. How we perform capillaroscopy?

Various optical devices can be used to perform capillaroscopic examinations: the ophthalmoscope, the dermatoscope (which have 10–20 times magnification), the stereo-zoom microscope (with 20–50 times magnification) and the videocapillaroscope. It is best to perform the examination with digital videocapillaroscope which includes a digital video camera and a microscope. In addition, it can be used as a handheld probe in any situations. This feature enables physicians to examine patients with severe finger flexion contractures (Martinis and Ginaldi, 2014).

Magnifying power of optical probes can range from 50× to 1000×. In order to enhance skin transparency, a drop of vegetable oil (neutral oils) can be applied to the nailfold of each finger or toe for better observation before capillaroscopy (Humbert et al., 2005). Since there are no limitations on the number of fingers to be chosen for examination, some authors have chosen all the fingers of both hands except the thumbs, others chosen the fourth and fifth fingers of both hands due to the greater transparency (Etehad Tavakol et al., 2015). It is better to

Table 2
Densities of toe capillaries in healthy control subjects.

Researcher (study year - country)	No. of patients	Gender	Capillary density (median ± SD)
S. Lambova et al. (2011 - Bulgaria)	22	Male (3) Female (19)	10 ± 1.13
Jung and Trautinger (2013) - Germany)	50		6.6 ± 0.97

examine each finger in two magnifications 50× and 200×, lower magnifications for showing the general architecture and higher magnifications for assessing morphological details of a single capillary (Chojnowski et al., 2016). By increasing magnification, the blood cells inside the capillaries can be better visualized. For more information, the reader can refer to the following article (Etehad Tavakol et al., 2015).

Before starting to measure capillary density, some requirements must be considered. The following are a few points to count the number of capillaries. The capillaries points should be upward when the observer want to count the number of capillaries. If captured image is not in the desired state, rotation is needed to satisfy the requirements. This parameter is computed as the mean value of four measurements obtained from the four most clearly focused images (Cheng et al., 2013). Starting calculation in both methods by considering moving a one-millimeter ruler in the center of image so that includes more visible capillaries. Then each capillary on the top should be counted. If there is any doubt in counting a capillary, we can solve this problem by using 90° method that was explained it before.

4. Relationship between capillary density and clinical findings

4.1. Digital ulcer and capillaroscopic skin ulcer risk index

Patients with SSc develop digital ulcers (DUs) which are common vascular complications. DUs have been associated with significantly reduced blood flow to the fingertips; Besides, SSc patients with the scleroderma "active" and "late" NVC patterns experiencing reduced blood flow velocity, and exclusively the reduced blood flow velocity was greatly associated with capillary ramification and capillary loss (Cutolo et al., 2010). Different studies have shown that there is an association between number of missing capillaries or severe changes in the NFC and the increased risk of developing DU (Sebastiani et al., 2009; Smith et al., 2010; Souza and Kayser, 2014). In a multicenter study at the Italian Rheumatology Center, 229 SSc patients were enrolled and followed for 3 months. All the patients with 12 or more capillaries in the distal row had no DU, while those with 4 or less capillaries developed DU, except two cases.

In a quantitative analysis of NFC including 6 fingers examining the number of capillaries, number of missing capillaries (deletions in a 3 mm span in the central part of digits), apical limb width, capillary width and the Endothelin-1 (ET-1) showed that the parameters of capillary dimension and capillary loss strongly correlate with the development of DU in the examined patients (Kim et al., 2010). The major obstacle in this investigation was that the capillaries had to be dilated.

In addition, there were other significant parameters such as the apical limb width, capillary width, capillary hemorrhage and the capillary loop dimension. The capillary dimension parameter was observed to have a negative correlation with the number of capillaries and a positive correlation with the apical and capillary widths, especially in patients with DU. Patients with active ulcers have a greater intercapillary distance and a slightly lower capillary density (Ennis et al., 2014). Moreover, no differences in terms of capillary width, tortuosity or derangement were found between patients with and without DU (Silva et al., 2015a). Patients with active skin ulcers have more avascular areas with a lower capillary density (Alivernini et al., 2009). The association between ischemic lesions and the capillary density (N), the maximum diameter of the largest giant loop (D) and M/N ratio (where M is the number of giant capillaries) was observed (Sebastiani et al., 2009). Given their observation, a quantitative scoring method named capillaroscopic skin ulcer risk index (CSURI) introduced for predicting the emergence of new ulcers in SSc patients. It is described by the formula "$D \times M/N^2$ and detailed calculation of CSURI index were explained (Manfredi et al., 2015; Sebastiani et al., 2009, 2012; Silva et al., 2015a; Souza and Kayser, 2014).

In addition, it is important to remember that counting the capillaries to obtain the CSURI is quite different from the traditional way of counting which is usually used in routine capillaroscopic evaluations (Cutolo et al., 2004; Grassi and Del Medico, 2004; Ingegnoli et al., 2008). Hence the nailfold videocapillaroscopy (NVC) operators should be appropriately trained for this task (Sebastiani et al., 2012). In this proposed method for counting number of capillaries, all the capillaries in the distal row are considered for counting, even those that are not at the same level. If a ramified capillary occupies more than one dermal papilla, the number of papillae or the number of apical loops will also be counted. Based on the number of occupied papillae, in this method, a ramified giant capillary counts as 1 in the megacapillary count system and as 2 or higher (≥2) in the total capillary count system (Manfredi et al., 2015) (Fig. 3d, f).

The relationship between DU and capillaroscopy findings include quantitative and semi-quantitative parameters (capillary density, capillary dimension, avascular areas, giant capillary, hemorrhages, past DU, gender, CSURI cut-off >2.96) and qualitative parameter (scleroderma patterns include "early", "active" and "late" pattern) are demonstrated in Table 3.

4.2. Semi-quantitative evaluation models and scleroderma pattern

A semi-quantitative microangiopathy evolution score (MES) was proposed in 2008 (Sulli et al., 2008). In this study 90 patients with SSc were followed for an average 72 months, and capillaroscopy findings were scored by three parameters: loss of capillaries, disorganization of the microvascular array and the scored capillary ramifications. Capillary abnormalities were scored by a semiquantitative scale with 0 = no changes, 1 = <33% of capillary alterations/reduction, 2 = 33%–66% of capillary alterations/reduction, and 3 = >66% of capillary alterations/reduction, per linear millimeter. The mean score value for each capillaroscopic parameter was calculated by analyzing 4 consecutive regions (1 linear millimeter for each one) in the middle of the nailfold of the 2nd, 3rd, 4th, and 5th finger of both hands; the average score values of the 8 fingers were added together, and then divided by 8 to obtain the final value. The resulted value represents the score of each analyzed capillaroscopic parameter. The scores of these parameters were also added together to globally assess changes of the SSc microangiopathy during the time ("microangiopathy evolution score": score, 0–9). The SSc microangiopathy score increases as the score increases through disease evolution. However, giant capillaries and microhemorrhages were not contributed for computing the score as the disease progresses they are reduced in number.

A simple semi-quantitative NVC evaluation was introduced for day-to-day clinical use as a prognostic index of digital trophic lesions (DTD index) (Smith et al., 2010). They studied seventy-one subjects and classified based on the mean score of capillary loss over eight fingers (one field per finger). With a cut-off value of the mean score of capillary loss of 1.67 (based on the ROC analysis) this score had a specificity of 69.77% and sensitivity of 70.00% to predict the development of digital trophic lesions within 6 or 12 months after the first capillaroscopic visit. By this method they were able to compare serious digital pitting scars, digital tip ulcerations and gangrene. However, they could not differentiate the presentations and outcomes. It is considered as the limitation of this study. This study was further investigated and validated through a study of 18–24 month follow-up of 148 SSc patients in 2 Italian–Belgian Centers. Besides it was validated by a large pan-European multi-center study (CAP study) (Cutolo et al., 2013a). The CAP multicenter observational, longitudinal prospective study was conducted in SSc patients with or without history of DU. The findings showed a reduced mean number of capillaries in the middle finger of the dominant hand in SSc patients with a past history of DUs. Although with the same limitation of the previous study, higher prevalence's of novel future severe peripheral vascular involvement occurred according to more severe NVC patterns (Smith et al., 2013).

Capillary density plays a significant role in the classification of capillaroscopic patterns. The SSc patients have a particular

Table 3
Qualitative, semi-quantitative and quantitative capillaroscopic parameters associated with digital ulcers.

Researcher (study year)	Links to capillaroscopy parameters	
	Quantitative and semi-quantitative parameter	Qualitative
Caramaschi et al. (2007)		Late pattern
Alivernini et al. (2009)	Presented avascular areas Lower capillary density	
Sebastiani et al. (2009)	CSURI cut-off > 2.94	
Caramaschi et al. (2009)		Late pattern
Kim et al. (2010)	Loss of capillaries Capillary dimension	
Sulli et al. (2009)		Active and late patterns
Smith et al. (2010)	Mean score of capillary loss of 1.67 in eight fingers	
Lambova and Mueller-Ladner (2011)	Avascular areas Giant capillaries Hemorrhages	Active pattern
Sebastiani et al. (2012)	CSURI cut-off > 2.96	
Ennis et al. (2014)	Capillary density was lower in patients with active ulcers.	
Cutolo et al. (2013a)	Reduced mean number of capillaries in the middle finger	
Ghizzoni et al. (2015)		Scleroderma pattern
Silva et al. (2015b)		Late patterns
Manfredi et al. (2015)	CSURI cut-off > 2.96 Male gender Past DU ERS rate ≥ 20 mm	

CSURI: Capillaroscopic Skin Ulcer Risk Index; DU: digital ulcers. ERS: erythrocyte sedimentation.

capillaroscopic pattern, which could be classified by using the following parameters: capillary shape (tortuous, branched, bushy, dilated, and giant capillaries), hemorrhaging capillaries, elongated capillaries, capillary density as well as the arrangement of capillaries. This type of capillaroscopic pattern was described and called "scleroderma" for the first time (Maricq et al., 1980). In another study in 1983, described two types of capillary abnormalities with "active" and "slow" patterns were introduced (Maricq et al., 1982); which are distinguishable in the prognosis of SSc (Grassi et al., 2001; Lambova and Mueller-Ladner, 2011) (see Table 4). In order to improve the diagnostic and prognostic capabilities of capillaroscopic analysis, a new classification method was proposed based on some selected characteristics of disease progression (Cutolo et al., 2000, 2008). In patients with SSc, the microvascular lesions detected by NVC have been reclassified into three different patterns: early, active, and late. Moreover, another pattern was designed which is based on the qualitative and quantitative parameters listed in Table 4 (Ingegnoli et al., 2005). They classified the overall capillaroscopic patterns as normal, those with minor and major abnormalities, and the scleroderma pattern. A pilot computer-based system by analyzing nailfold capillary microscopy images was developed for early diagnosis of SLE and SSc (Wen et al., 2009). This system based on the number of abnormal capillaries to characterize the patient with scleroderma pattern (Fig. 4). Although Wen et al. reported that correct diagnoses of the disease progression as early, active, or late pattern were 91.6, 73.3, and 66.6%, respectively but this algorithm was not approved through published documents.

4.2.1. Capillaroscopy and monitoring the drug effects on microvascular structure

Capillaroscopy has potential to be useful to monitor non-invasively remodeling of microcirculation in various therapies and thus to assess their effectiveness. Some data on the effect of neoangiogenic therapies with prostanoids like iloprost indicate the mainstay of treatment of severe SSc-related digital ischemia and healing of DU currently. The trend toward increasing capillary density was observed immediately following iloprost administration, although it was not being sustained after 12 or 36 months of therapy. However, an improvement of peripheral vascularization, with an increase of capillary numbers after three months was observed in a iloprost group (Faggioli et al., 2006).

Bosentan might alter the microvasculature in SSc-PAH patients with new capillary formation and microhemorrhages (Guiducci et al., 2012). In addition, It has been shown that haemopoietic stem cell transplantation (HSCT) has remodeling effects on microvessels in patients with SSc and MCTD. Various changes from a severely pathologic scleroderma pattern to a normal figure have been reported after HSCT (Aschwanden et al., 2008). However, the results might be biased, because of small sample size and short-term follow-up to observe changes in microvasculature. Moreover, an improvement of microcirculatory parameters was observed with combination of some therapies and long term treatment. An increased capillary number and ramifications was reported after one year treatment with Iloprost and Cyclosporin (Faggioli et al., 2006). In particular, NVC revealed the treatment with the combination of Bosentan with Iloprost the de-remodeling process of the capillary microcirculation and increased capillary number in the SSc patient after 3 years of treatment (Cutolo et al., 2013b). In addition, after 6 months therapy with Aminaftone, an improvement in the organization and morphology of capillary bed was shown (Faggioli et al., 2014, 2015).

4.3. Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is the principal pro-angiogenic factor and it plays as a key mediator in endothelial dysfunction and modulator of neovascularization. The serum concentrations of VEGF in patients with SSc increased in scleroderma patterns compared with those in healthy controls. Moreover, there is no significant differences of VEGF levels between the three capillaroscopy patterns and single capillaroscopy findings such as presence or absence of giant capillaries, microhemorrhages, avascular areas and pericapillary edema (Distler et al., 2002). In addition, there is an inverse relationship between VEGF levels and capillary density in patients with SSc (Ferri et al., 2007; Koch and Distler, 2007).Two independent research groups reported higher VEGF levels observed in the late pattern as compared with the early and active patterns (Avouac et al., 2013; Distler et al., 2002). In contrast to the previous findings, three year follow up studies of 77 patients with SSc have been shown that VEGF in SSc patients with late patterns lower than in those with early/active patterns (Silva et al., 2015b). However, a more recent study with 44 SSc patients was reported that serum VEGF-A levels did not have any association with NVC alterations (Santis et al., 2016). To explore this point, a large study enrolling early SSc is necessary, especially when aiming at defining biomarkers for early diagnosis and treatment patients with SSc (Bournia et al., 2009).

Table 4
Nailfold capillaroscopic patterns.

Researcher	Patterns	Description
Maricq et al. [96]	Slow	Minimal loss of capillaries with extremely dilated nail fold capillary (no obvious avascular areas)
	Active	Extensive loos of capillaries with a general disorganisation of the capillary bed and/or enlarged and distorted capillary loop
Pavlov-Dolijanovic et al. [101]	Normal	Typical hair pin structure or minor capillary morphological changes in distribution or size of loops
	Nonspecific	Meandering and crossed capillaries, capillary thinning, linear elongation of the loop, focal distribution of capillary hemorrhages, prominent subpapillary plexus, capillary spasm, nonhomogeneous distribution or size of loops, widening of the afferent, and apical and efferent part of loop
	Scleroderma[98, 99]	**Early:** no evident loss of capillaries, few enlarged/giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution. **Active:** moderate loss of capillaries, frequent giant capillaries, frequent capillary hemorrhages, mild disorganisation of the capillary architecture and absent or mild ramified capillaries. **Late:** severe loss of capillaries with extensive avascular areas, irregular enlargement of the capillaries, few or absent giant capillaries and hemorrhages, disorganization of the normal capillary array and ramified/bushy capillaries
	Normal	6–8 capillaries/mm, capillaries length between 200 and 500 μ, hairpin-shaped, loops arranged in parallel rows, absence of hemorrhages.
	Minor abnormalities	6–8 capillaries/mm, <10% of the total loops can be longer than normal, <50% can be tortuous loops, arranged in parallel rows, with the absence of hemorrhages.
Ingegnoli et al. [51]	Major abnormalities	≤6–8 capillaries/mm, >10% of the total loops can be longer than normal, >50% can be tortuous, enlarged, meandering, branched loops, disarranged, with the presence hemorrhages.
	Scleroderma pattern	<6 capillaries/mm, >10% of the total loops can be longer than normal, tortuous, branched, bushy, enlarged, giant, disarranged, presence of hemorrhages.

Serum concentrations of VEGF in patients with SLE are significantly higher than in healthy control groups. Serum levels of VEGF in patients with SLE associated with changes in microcirculation visualized by NVC. A study has been shown that showed increased serum VEGF levels associated with microvascular abnormalities such as loops irregularity and presence of hemorrhages as an expression of pathological angiogenesis (Ciołkiewicz et al., 2010). Higher levels of VEGF have been observed in lupus patients with severe/moderate capillaroscopy abnormalities than in compared mild changes (Kuryliszyn-Moskal et al., 2009). An association between VEGF and capillaroscopic abnormalities in SLE has been observed recently. This might be due to the endothelial damage, inflammation and increased of angiogenic stimulators. (Bărbulescu et al., 2015).

4.4. Autoantibodies

Another example of applying capillary density parameter is in the Prognostic Rule-based Instructions Examination and Scleroderma-related Serology (PRINCESS) algorithm. By applying a weighted combination of different capillaroscopy parameters, this algorithm allows physicians to classify RP patients easily by using a relatively simple prognosis diagram. Different parameters are involved to construct the PRINCESS algorithm such as: the Antinuclear antibodies (ANA), capillary density and the number of giant capillaries (Ingegnoli et al., 2010; Ingegnoli and Gualtierotti, 2013) (Fig. 5). Another algorithm is helpful in predicting the development of digital trophic lesions within a period of 6 or 12 months which relies on the mean score of capillaries loss over eight fingers (Smith et al., 2010). In a prospective study have shown that SSc-specific autoantibodies, such as anticentromere (Anti-CENP-B), anti-topoisomerase I (anti-topo I), anti-RNA polymerase I/III (anti-RNAP III) and anti-Th/To are responsible for further increases the risk of developing SSc-hazard ratio (HR) between 2.44 and 3.8 (Koenig et al., 2008). They are associated with the disease course and also the type of capillary abnormalities such as capillary loss. Recently, an association between abnormal nailfold capillaries and ANA to mortality in patients with RP was found (Mueller et al., 2016).

In a clinical study of 2971 patients with incipient RP without any knowledge about their CTD in advance, certain capillary abnormalities were detected by NC that closely related to the presence of elevated ANA (Schlager et al., 2014). Moreover, a sum score formula was developed that involves the following parameters: respective giant capillaries, reduced capillary density, avascular fields, ramifications, oedema, female sex, and age parameter selected by forward model selection based on the Akaike information criterion (AIC). In this formula female and male sex are indicated by 1 and 0 [yes/no] as well as the

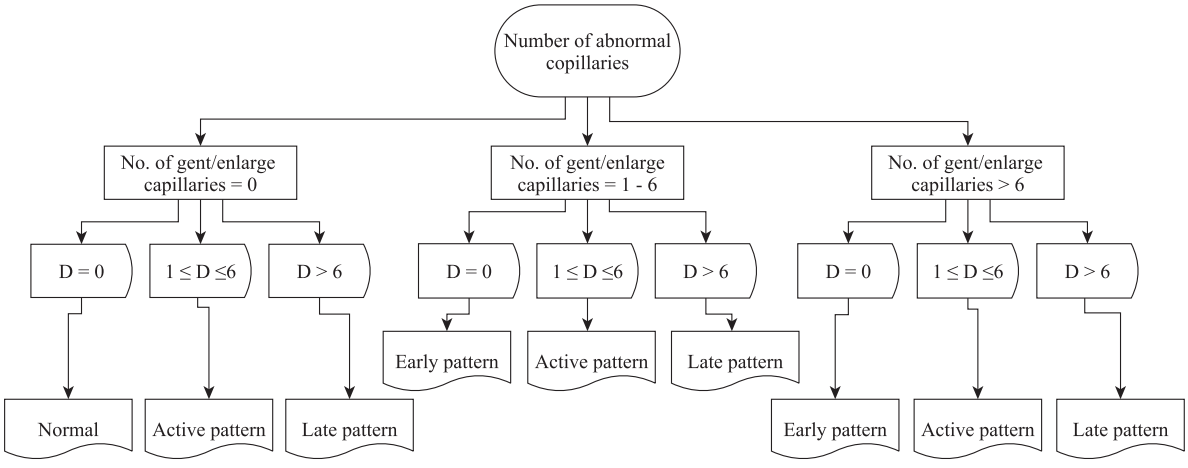

Fig. 4. Decision tree for determining disease progression by using number of gent/enlarge capillaries and number of disorganized capillaries (Wen et al., 2009). D: number of disorganized capillaries.

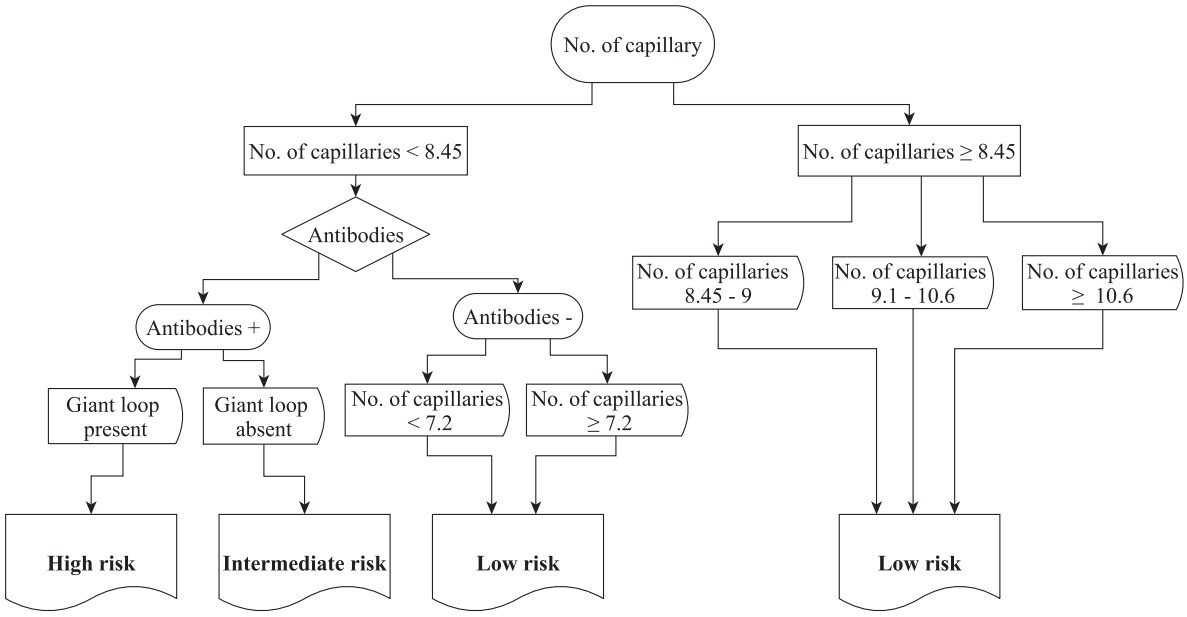

Fig. 5. Regression tree to build prognostic classification (Ingegnoli et al., 2010).

presence of respective capillary abnormalities is indicated by yes/no. The formula is described by Eq. (1)

$$\begin{aligned}\text{Sum score} = {} & \text{age (years)} \times 0.02 + \text{female [y/n]} \times 0.8 \\ & + \text{giant capillaries [y/n]} \times 0.9 \\ & + \text{reduced capillary density [y/n]} \times 0.7 \\ & + \text{avascular fields [y/n]} \times 1.3 + \text{ramifications [y/n]} \\ & \times 0.3 + \text{oedema [y/n]} \times 0.5 \end{aligned} \quad (1)$$

Consequently, the probability of the presence of ANA can be calculated as Eq. (1):

$$p = \frac{1}{[1 + e^{-(\text{Sum score} - 2.915)}]} \quad (2)$$

where 2.915 refers to the negative of the intercept estimate in the multiple logistic regression model. This score allows estimating each patient's individual probability of the presence of an ANA titre ≥1:160. The sum score formula can be used to calculate the individual probability of an immunological process associated with RP. Although a sum score can represent the patient's probability of elevated ANA titres, but NC cannot be substituted for immunological tests in patients with incipient RP. It is generally accepted that when autoantibodies and capillaroscopic findings are used together in a complementary way, they are powerful predictive tools (Table 5).

4.5. Patients with pulmonary arterial hypertension

Common loss of capillaries at nailfold and pulmonary bed may be in a similar way, although the greater loss of capillaries may be due to PAH itself, a condition which amplifies the reduction of vascularity. Thus NVC findings demonstrate what happens in the pulmonary circulation of SSc patients, whereas a reduced number of capillaries may represent a marker of disease severity (Herrick et al., 2010). Capillary rarefaction can be described as the reduction in the number of capillaries per visual field. It is the most typical sign in patients with hypertension (Chen et al., 1981; Triantafyllou et al., 2015). In the past years, some researchers observed a relation between reduction of the capillary density and the severity of PAH (but not with the capillary loop dimension) in SSc patients, suggesting that either systemic microvascular changes play a part in development of PAH or PAH itself contributes to the systemic microvascular changes. A significant reduction of capillary density was observed in eight SSc patients with PAH compared to twelve SSc patients without PAH (Ong et al., 2011). For better understanding of the pathophysiology of SSc-associated PAH, in a project, the hypothesis was investigated and differences in capillary density between SSc-PAH patients and SSc–nonPAH patients were observed (Hofstee et al., 2009). Their findings showed that capillary density in healthy controls (9.87/mm) was significantly higher when compared with SSc–nonPAH (6.56/mm), SSc–PAH (4.33/mm) and with idiopathic pulmonary arterial hypertension (IPAH) (7.86/mm). Also No differences in capillary density between SSc–PAH at rest and SSc–PAH during exercise were detected. Besides, patients with IPAH had a higher capillary density

Table 5
Relation between different autoantibodies and capillaroscopic parameters.

Researcher (study year)	Autoantibodies	Links to capillaroscopy	
		Single parameter	Patterns
Cutolo et al. (2004)	Anti-topo I		More frequent in the active/late pattern
Koenig et al. (2008)	Anti + CENP + B	Capillary loss	
	Anti-RNA polymerase III Anti-Th/To	Capillary loss	
		Capillary loss	
Riccieri et al. (2008)	AECA reduced		Late pattern significantly more frequent
Ingegnoli et al. (2010)	ANA	Capillary number reduction	
Herrick et al. (2010)	ACA	Reduced capillary density	
Schlager et al. (2014)	ANA titre>1:160	Reduced capillary density	

ACA: Anticentromere antibodies; AECA: Anti-endothelial cell antibodies; ANA: Antinuclear antibodies.

comparing to the patients with SSc–PAH. The loss of capillaries strongly had connection with PAH (Kim et al., 2010). Recent evidence was reported indicating of an association between more severe scores of avascular areas (i.e., reduced capillary density) and PAH in SSc patients (Riccieri et al., 2013). More serious overall capillaroscopy scores and patterns (active or late) were also significantly associated with the presence of PAH in such patients, thus confirming previous reports (Riccieri et al., 2013). In a study of patients with IPAH as well as patients with primary PAH and SSc-PAH, no differences in capillary density and capillary patterns between healthy and patients with IPAH were reported. Also no differences in capillaroscopy patterns between SSc patients with PAH and those without PAH were found, although their capillary densities have not been reported yet (Greidinger et al., 2001).

5. Conclusions

Many studies approve that the capillaroscopy is one of the benchmark methods for non-invasive examination of the microcirculation and it plays an important role in the screening of Raynaud's phenomenon. The incorporation of capillaroscopic abnormalities in establishing the new classification criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) for SSc gives a new motivation to consider the usefulness of capillaroscopy (Hoogen et al., 2013; Souza and Kayser, 2014). There are some reasons that make NFC an important tool in clinical practice and research including: the well-established role of capillaroscopy for the early diagnosis of SSc, its inclusion in the classification criteria, its predictive value for clinical complications of the disease and its potential for monitoring disease progression and treatment response.

The following items can be expressed as the strengths of using nailfold capillary density as diagnostic parameter. Firstly; capillary density determination is possible even with low magnification instruments such as stereo-zoom microscope with 20–50 times magnification. This advantage can help physician for basic evaluation or discrimination between primary and secondary RP when the NVC is not available. Secondly; if all SSc-specific antibodies are available this parameter can allow physicians to classify RP patients easily by using PRINCESS algorithm. Thirdly; although this is a quantitative parameter, however, combining it with another capillaroscopy findings can play important role in the classification of capillaroscopic patterns. Fourthly; capillary density could be an indicator of capillary abnormalities such as avascularity, hemorrhages, tortuous, and irregularly-enlarged capillary loops (Cutolo and Smith, 2015). Some of limitations for using nailfold capillary density as diagnostic parameter are as follows: 1) the measurement has a degree of subjectivity since capillary density has high spatial variation and there is no standard to measure capillary with different shape; 2) it is necessary to have image with high contrast without any movement artifacts in order to get a valid reading; 3) in SSc patients with RP, due to a variety of capillaroscopic abnormalities, capillary density cannot be used alone.(Murray et al., 2012; Yvonne-Tee et al., 2006).

This paper has presented a summary of common methods to calculate the number of capillaries as well as explaining the effectiveness of this quantitative parameter on autoantibodies, VEGF, SSc-PAH patients and scleroderma patterns, also the effectiveness of capillary density in quantitative scoring system like CSURI as well as Semi-quantitative scoring system like MES and DTD index.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

Alivernini, S., De Santis, M., Tolusso, B., Mannocci, A., Bosello, S.L., Peluso, G., Pinnelli, M., D'Antona, G., LaTorre, G., Ferraccioli, G., 2009. Skin ulcers in systemic sclerosis: determinants of presence and predictive factors of healing. J. Am. Acad. Dermatol. 60, 426–435.

Andrade, L.E.C., Gabriel, A., Assad, R.L., Ferrari, A.J.L., Atra, E., 1990. Panoramic Nailfold Capillaroscopy: A New Reading Method and Normal Range. Seminars in Arthritis and Rheumatism vol. 20. Elsevier, pp. 21–31.

Aschwanden, M., Daikeler, T., Jaeger, K., Thalhammer, C., Gratwohl, A., Matucci-Cerinic, M., Tyndall, A., 2008. Rapid improvement of nailfold capillaroscopy after intense immunosuppression for systemic sclerosis and mixed connective tissue disease. Ann. Rheum. Dis. 67, 1057–1059.

Avouac, J., Vallucci, M., Smith, V., Senet, P., Ruiz, B., Sulli, A., Pizzorni, C., Frances, C., Chiocchia, G., Cutolo, M., 2013. Correlations between angiogenic factors and capillaroscopic patterns in systemic sclerosis. Arthritis Res. Ther. 15, 1.

Bărbulescu, A.-L., Vreju, A.-F., Bugă, A., Sandu, R.E., Criveanu, C., Tudorascu, D.-R., Gheonea, I.-A., Ciurea, P.-L., 2015. Vascular endothelial growth factor in systemic lupus erythematosus–correlations with disease activity and nailfold capillaroscopy changes. Romanian J. Morphol. Embryol. 56, 1011.

Bergman, R., Sharony, L., Schapira, D., Nahir, M.A., Balbir-Gurman, A., 2003. The handheld dermatoscope as a nail-fold capillaroscopic instrument. Arch. Dermatol. 139, 1027–1030.

Bhakuni, D.S., Vasdev, V., Garg, M., Narayanan, K., Jain, R., Mullick, G., 2012. Nailfold capillaroscopy by digital microscope in an Indian population with systemic sclerosis. Int. J. Rheum. Dis. 15, 95–101.

Bongard, O., Bounameaux, H., Miescher, P.-A., Moerloose, P.D., 1995. Association of anticardiolipin antibodies and abnormal nailfold capillaroscopy in patients with systemic lupus erythematosus. Lupus 4, 142–144.

Bournia, V.K.K., Vlachoyiannopoulos, P.G., Selmi, C., Moutsopoulos, H.M., Gershwin, M.E., 2009. Recent advances in the treatment of systemic sclerosis. Clin. Rev. Allergy Immunol. 36, 176–200.

Braverman, I.M., 1997. The cutaneous microcirculation: ultrastructure and microanatomical organization. Microcirculation 4, 329–340.

Campbell, P.M., LeRoy, E.C., 1975. Pathogenesis of systemic sclerosis: a vascular hypothesis. Semin. Arthritis Rheum. 4, 351–368.

Caramaschi, P., Canestrini, S., Martinelli, N., Volpe, A., Pieropan, S., Ferrari, M., Bambara, L., Carletto, A., Biasi, D., 2007. Scleroderma patients nailfold videocapillaroscopic patterns are associated with disease subset and disease severity. Rheumatology 46, 1566–1569.

Caramaschi, P., Martinelli, N., Volpe, A., Pieropan, S., Tinazzi, I., Patuzzo, G., Mahamid, H., Bambara, L.M., Biasi, D., 2009. A score of risk factors associated with ischemic digital ulcers in patients affected by systemic sclerosis treated with iloprost. Clinical rheumatology. 28, 807–813.

Chen, I., Prewitt, R., Dowell, R., 1981. Microvascular rarefaction in spontaneously hypertensive rat cremaster muscle. Am. J. Phys. Heart Circ. Phys. 241, H306–H310.

Cheng, C., Daskalakis, C., Falkner, B., 2013. Non-invasive assessment of microvascular and endothelial function. J. Vis. Exp., e50008

Cheng, C., Lee, C.W., Daskalakis, C., 2015. A reproducible computerized method for quantitation of capillary density using nailfold capillaroscopy. J. Vis. Exp., e53088

Chojnowski, M.M., Felis-Giemza, A., Olesińska, M., 2016. Capillaroscopy–a role in modern rheumatology. Reumatologia 54, 67–72.

Ciołkiewicz, M., Kuryliszyn-Moskal, A., Klimiuk, P.A., 2010. Analysis of correlations between selected endothelial cell activation markers, disease activity, and nailfold capillaroscopy microvascular changes in systemic lupus erythematosus patients. Clin. Rheumatol. 29, 175–180.

Correa, M., Andrade, L., Kayser, C., 2010. Comparison of laser Doppler imaging, fingertip lacticemy test, and nailfold capillaroscopy for assessment of digital microcirculation in systemic sclerosis. Arthritis Res. Ther. 12, R157.

Cutolo, M., Smith, V., 2015. Nailfold capillaroscopy. In: Wigley, M.F., Herrick, L.A., Flavahan, A.N. (Eds.), Raynaud's Phenomenon: A Guide to Pathogenesis and Treatment. Springer New York, New York, NY, pp. 187–197.

Cutolo, M., Sulli, A., Pizzorni, C., Accardo, S., 2000. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J. Rheumatol. 27, 155–160.

Cutolo, M., Pizzorni, C., Tuccio, M., Burroni, A., Craviotto, C., Basso, M., Seriolo, B., Sulli, A., 2004. Nailfold videocapillaroscopic patterns and serum autoantibodies in systemic sclerosis. Rheumatology 43, 719–726.

Cutolo, M., Sulli, A., Secchi, M., Pizzorni, C., 2006. Capillaroscopy and rheumatic diseases: state of the art. Z. Rheumatol. 65, 290–296.

Cutolo, M., Sulli, A., Secchi, M.E., Olivieri, M., Pizzorni, C., 2007. The contribution of capillaroscopy to the differential diagnosis of connective autoimmune diseases. Best Pract. Res. Clin. Rheumatol. 21, 1093–1108.

Cutolo, M., Pizzorni, C., Secchi, M.E., Sulli, A., 2008. Capillaroscopy. Best Pract. Res. Clin. Rheumatol. 22, 1093–1108.

Cutolo, M., Ferrone, C., Pizzorni, C., Soldano, S., Seriolo, B., Sulli, A., 2010. Peripheral blood perfusion correlates with microvascular abnormalities in systemic sclerosis: a laser-Doppler and nailfold videocapillaroscopy study. J. Rheumatol. 37, 1174–1180.

Cutolo, M., Herrick, A., Distler, O., Becker, M., Beltran, E., Carpentier, P., Ferri, C., Inanç, M., Vlachoyiannopoulos, P., Chadha-Boreham, H., 2013a. OP0275 nailfold videocapillaroscopy and other predictive factors associated with new digital ulcers in systemic sclerosis: Data from the cap study. Ann. Rheum. Dis. 72, A146–A147.

Cutolo, M., Zampogna, G., Vremis, L., Smith, V., Pizzorni, C., Sulli, A., 2013b. Longterm effects of endothelin receptor antagonism on microvascular damage evaluated by nailfold capillaroscopic analysis in systemic sclerosis. J. Rheumatol. 40, 40–45.

da Silva Facina, A., Pucinelli, M.L.C., Vasconcellos, M.R.A., Ferraz, L.B., de Almeida, F.A., 2006. Capillaroscopy findings in lupus erythematosus Achados capilaroscópicos no lúpus eritematoso. An. Bras. Dermatol. 81, 523–528.

Distler, O., del Rosso, A., Giacomelli, R., Cipriani, P., Conforti, M.L., Guiducci, S., Gay, R.E., Michel, B.A., Brühlmann, P., Müller-Ladner, U., 2002. Angiogenic and angiostatic factors in systemic sclerosis: increased levels of vascular endothelial growth factor are a feature of the earliest disease stages and are associated with the absence of fingertip ulcers. Arthritis Res. Ther. 4, 1.

Dolezalova, P., Young, S., Bacon, P., Southwood, T., 2003. Nailfold capillary microscopy in healthy children and in childhood rheumatic diseases: a prospective single blind observational study. Ann. Rheum. Dis. 62, 444–449.

Ennis, H., Moore, T., Murray, A., Vail, A., Herrick, A.L., 2014. Further confirmation that digital ulcers are associated with the severity of abnormality on nailfold capillaroscopy in patients with systemic sclerosis. Rheumatology 53, 376–377.

Etehad Tavakol, M., Fatemi, A., Karbalaie, A., Emrani, Z., Erlandsson, B.-E., 2015. Nailfold capillaroscopy in rheumatic diseases: Which parameters should be evaluated? Biomed. Res. Int. (2015).

Erol, M.K., Balkarli, A., Toslak, D., Dogan, B., Durmaz, D., Süren, E., Altun, S., Bulut, M., Cobankara, V., 2016. Evaluation of nailfold videocapillaroscopy in central serous chorioretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 1–8.

Faggioli, P., Giani, L., Mazzone, A., 2006. Possible role of iloprost (stable analog of PG12) in promoting neoangiogenesis in systemic sclerosis. Clin. Exp. Rheumatol. 24, 220–221.

Faggioli, P., Sciascera, A., Gilardi, A.G., Tamburello, A., Rondena, M., Mazzone, A., 2014. Aminaftone: a possible role in the management of Raynaud's phenomenon. In: Nardi, R. (Ed.), XIX Congresso Nazionale Della Società Scientifica FADOI. Italian Journal of Medicine, Bologna, Italy. vol. 8(Suppl 2), p. 42.

Faggioli, P., Tamburello, A., Sciascera, A., Gilardi, A.G., Mazzone, A., 2015. Nailfold videocapillaroscopy in internal medicine. Ital. J. Med. 9, 234–242.

Ferri, C., Giuggioli, D., Sebastiani, M., Colaci, M., 2007. Treatment of severe scleroderma skin ulcers with recombinant human erythropoietin. Clin. Exp. Dermatol. 32, 287–290.

Follansbee, W.P., Curtiss, E.I., Medsger Jr., T.A., Steen, V.D., Uretsky, B.F., Owens, G.R., Rodnan, G.P., 1984. Physiologic abnormalities of cardiac function in progressive systemic sclerosis with diffuse scleroderma. N. Engl. J. Med. 310, 142–148.

Furtado, R.N., Pucinelli, M.L., Cristo, V., Andrade, L.E., Sato, E., 2002. Scleroderma-like nailfold capillaroscopic abnormalities are associated with anti-U1-RNP antibodies and Raynaud's phenomenon in SLE patients. Lupus 11, 35–41.

Gasser, P., Bühler, F.R., 1992. Nailfold microcirculation in normotensive and essential hypertensive subjects, as assessed by video-microscopy. J. Hypertens. 10, 83–86.

Ghizzoni, C., Sebastiani, M., Manfredi, A., Campomori, F., Colaci, M., Giuggioli, D., Ferri, C., 2015. Prevalence and evolution of scleroderma pattern at nailfold videocapillaroscopy in systemic sclerosis patients: clinical and prognostic implications. Microvasc. Res. 99, 92–95.

Govoni, V., Sanders, T.A., Reidlinger, D.P., Darzi, J., Berry, S.E., Goff, L.M., Seed, P.T., Chowienczyk, P.J., Hall, W.L., 2016. Compliance with dietary guidelines affects capillary recruitment in healthy middle-aged men and women. Eur. J. Nutr. 1–8.

Grassi, W., De Angelis, R., 2007. Capillaroscopy: questions and answers. Clin. Rheumatol. 26, 2009–2016.

Grassi, W., Del Medico, M., 2004. Atlas of Capillaroscopy. EDRA.

Grassi, W., Core, P., Carlino, G., Cervini, C., 1992. NaitFold capillary permeability in psoriatic arthritis. Scand. J. Rheumatol. 21, 226–230.

Grassi, W., Del Medico, P., Izzo, F., Cervini, C., 2001. Microvascular involvement in systemic sclerosis: capillaroscopic findings. Semin. Arthritis Rheum. 30, 397–402.

Greidinger, E.L., Gaine, S.P., Wise, R.A., Boling, C., Housten-Harris, T., Wigley, F.M., 2001. Primary pulmonary hypertension is not associated with scleroderma-like changes in nailfold capillaries. CHEST J. 120, 796–800.

Gronenschild, E., Muris, D., Schram, M., Karaca, Ü., Stehouwer, C., Houben, A., 2013. Semi-automatic assessment of skin capillary density: proof of principle and validation. Microvasc. Res. 90, 192–198.

Guiducci, S., Randone, S.B., Bruni, C., Carnesecchi, G., Maresta, A., Iannone, F., Lapadula, G., Cerinic, M.M., 2012. Bosentan fosters microvascular de-remodelling in systemic sclerosis. Clin. Rheumatol. 31, 1723–1725.

Herrick, A.L., Moore, T.L., Murray, A.K., Whidby, N., Manning, J.B., Bhushan, M., Vail, A., 2010. Nail-fold capillary abnormalities are associated with anti-centromere antibody and severity of digital ischaemia. Rheumatology 49, 1776–1782.

Hoerth, C., Kundi, M., Katzenschlager, R., Hirschl, M., 2012. Qualitative and quantitative assessment of nailfold capillaries by capillaroscopy in healthy volunteers. Vasa 41, 19–26.

Hofstee, H., Noordegraaf, A.V., Voskuyl, A., Dijkmans, B., Postmus, P., Smulders, Y., Serné, E., 2009. Nailfold capillary density is associated with the presence and severity of pulmonary arterial hypertension in systemic sclerosis. Ann. Rheum. Dis. 68, 191–195.

Hofstee, H.M., Serné, E.H., Roberts, C., Hesselstrand, R., Scheja, A., Moore, T.L., Wildt, M., Manning, J.B., Noordegraaf, A.V., Voskuyl, A.E., 2011. A multicentre study on the reliability of qualitative and quantitative nail-fold videocapillaroscopy assessment. Rheumatology 51, 749–755.

Hofstee, H., de Waal, T., Zweegman, S., Voskuyl, A., Smulders, Y., Schoordijk, M., Janssen, J., Serné, E., 2013. Nailfold capillary abnormalities in sclerodermatous chronic GVHD. Bone Marrow Transplant. 48, 1574–1577.

Hoogen, F., Khanna, D., Fransen, J., Johnson, S.R., Baron, M., Tyndall, A., Matucci-Cerinic, M., Naden, R.P., Medsger, T.A., Carreira, P.E., 2013. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum. 65, 2737–2747.

Hosking, S.P., Bhatia, R., Crock, P.A., Wright, I., Squance, M.L., Reeves, G., 2013. Non-invasive detection of microvascular changes in a paediatric and adolescent population with type 1 diabetes: a pilot cross-sectional study. BMC Endocr. Disord. 13, 41.

Houtman, P., Kallenberg, C., Wouda, A., 1985. Decreased nailfold capillary density in Raynaud's phenomenon: A reflection of immunologically mediated local and systemic vascular disease? Ann. Rheum. Dis. 44, 603–609.

Humbert, P., Sainthillier, J.M., Mac-Mary, S., Petitjean, A., Creidi, P., Aubin, F., 2005. Capillaroscopy and videocapillaroscopy assessment of skin microcirculation: dermatologic and cosmetic approaches. J. Cosmet. Dermatol. 4, 153–162.

Ingegnoli, F., Gualtierotti, R., 2013. A systematic overview on the use and relevance of capillaroscopy in systemic sclerosis. Expert. Rev. Clin. Immunol. 9, 1091–1097.

Ingegnoli, F., Herrick, A.L., 2013. Nailfold capillaroscopy in pediatrics. Arthritis Care Res. 65, 1393–1400.

Ingegnoli, F., Zeni, S., Gerloni, V., Fantini, F., 2005. Capillaroscopic observations in childhood rheumatic diseases and healthy controls. Clin. Exp. Rheumatol. 23, 905.

Ingegnoli, F., Boracchi, P., Gualtierotti, R., Lubatti, C., Meani, L., Zahalkova, L., Zeni, S., Fantini, F., 2008. Prognostic model based on nailfold capillaroscopy for identifying Raynaud's phenomenon patients at high risk for the development of a scleroderma spectrum disorder: PRINCE (prognostic index for nailfold capillaroscopic examination). Arthritis Rheum. 58, 2174–2182.

Ingegnoli, F., Boracchi, P., Gualtierotti, R., Biganzoli, E.M., Zeni, S., Lubatti, C., Fantini, F., 2010. Improving outcome prediction of systemic sclerosis from isolated Raynaud's phenomenon: role of autoantibodies and nail-fold capillaroscopy. Rheumatology 49, 797–805.

Ingegnoli, F., Ardoino, I., Boracchi, P., Cutolo, M., 2013. Nailfold capillaroscopy in systemic sclerosis: data from the EULAR scleroderma trials and research (EUSTAR) database. Microvasc. Res. 89, 122–128.

Jones, B.F., Oral, M., Morris, C., Ring, E., 2001. A proposed taxonomy for nailfold capillaries based on their morphology. IEEE Trans. Med. Imaging 20, 333–341.

Jung, P., Trautinger, F., 2013. Capillaroscopy of toes. J. Dtsch. Dermatol. Ges. 11, 855–866.

Kayser, C., Sekiyama, J.Y., Próspero, L.C., Camargo, C.Z., Andrade, L.E., 2013. Nailfold capillaroscopy abnormalities as predictors of mortality in patients with systemic sclerosis. Clin. Exp. Rheumatol. 31, S103–S108.

Kim, H.-S., Park, M.-K., Kim, H.-Y., Park, S.-H., 2010. Capillary dimension measured by computer-based digitalized image correlated with plasma endothelin-1 levels in patients with systemic sclerosis. Clin. Rheumatol. 29, 247–254.

Koch, A.E., Distler, O., 2007. Vasculopathy and disordered angiogenesis in selected rheumatic diseases: rheumatoid arthritis and systemic sclerosis. Arthritis Res. Ther. 9, S3.

Koenig, M., Joyal, F., Fritzler, M.J., Roussin, A., Abrahamowicz, M., Boire, G., Goulet, J.R., Rich, É., Grodzicky, T., Raymond, Y., 2008. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum. 58, 3902–3912.

Koscielny, J., Latza, R., Wolf, S., Kiesewetter, H., Jung, F., 1998. Early rheological and microcirculatory changes in children with type I diabetes mellitus. Clin. Hemorheol. Microcirc. 19, 139–150.

Kuryliszyn-Moskal, A., Ciolkiewicz, M., Klimiuk, P., Sierakowski, S., 2009. Clinical significance of nailfold capillaroscopy in systemic lupus erythematosus: correlation with endothelial cell activation markers and disease activity. Scand. J. Rheumatol. 38, 38–45.

Lamah, M., Mortimer, P., Dormandy, J., 1996. Heterogeneity of capillary density of skin over the dorsum of the foot and toes of healthy subjects. Int. J. Microcirc. 16, 271–276.

Lambova, S., Mueller-Ladner, U., 2011. Capillaroscopic findings in systemic sclerosis–are they associated with disease duration and presence of digital ulcers? Discov. Med. 12, 413–418.

Lambova, S.N., Müller-Ladner, U., 2012. Capillaroscopic pattern in inflammatory arthritis. Microvasc. Res. 83, 318–322.

Lambova, S., Hermann, W., Müller-Ladner, U., 2011. Capillaroscopic pattern at the toes of systemic sclerosis patients: does it “tell” more than those of fingers? J. Clin. Rheumatol. 17, 311–314.

Le, J.H., Im Cho, K., 2014. Association between endothelial function and microvascular changes in patients with secondary Raynaud's phenomenon. Clin. Rheumatol. 33, 1627–1633.

Li, L., Mac-Mary, S., Sainthillier, J.-M., Nouveau, S., Lacharriere, O.D., Humbert, P., 2005. Age-related changes of the cutaneous microcirculation in vivo. Gerontology 52, 142–153.

Manfredi, A., Sebastiani, M., Carraro, V., Iudici, M., Bocci, M., Vukatana, G., Gerli, R., Angelis, R.D., Del Medico, P., Praino, E., 2015. Prediction risk chart for scleroderma digital ulcers: a composite predictive model based on capillaroscopic, demographic and clinico-serological parameters. Clin. Hemorheol. Microcirc. 59, 133–143.

Maricq, H.R., 1981. Widefield capillary microscopy. Technique and rating scale for abnormalities seen in scleroderma and related disorders. Arthritis Rheum. 24, 1159–1165.

Maricq, H., LeRoy, E., D'angelo, W., Medsger, T., Rodnan, G., Sharp, G., Wolfe, J., 1980. Diagnostic potential of in vivo capillary microscopy in scleroderma and related disorders. Arthritis Rheum. 23, 183–189.

Maricq, H., Harper, F., Khan, M., Tan, E., LeRoy, E., 1982. Microvascular abnormalities as possible predictors of disease subsets in Raynaud phenomenon and early connective tissue disease. Clin. Exp. Rheumatol. 1, 195–205.

Martinis, D.M., Ginaldi, L., 2014. Capillaroscopy opens a window to look inside. Rheumatology 4, 4–6.

Mueller, M., Gschwandtner, M.E., Gamper, J., Giurgea, G.-A., Charwat-Resl, S., Kiener, H.P., Smolen, J.S., Perkmann, T., Koppensteiner, R., Schlager, O., 2016. Relation of nailfold

capillaries and autoantibodies to mortality in patients with Raynaud's phenomenon. Circulation.
Murray, A.K., Feng, K., Moore, T.L., Allen, P.D., Taylor, C.J., Herrick, A.L., 2011. Preliminary clinical evaluation of semi-automated nailfold capillaroscopy in the assessment of patients with Raynaud's phenomenon. Microcirculation 18, 440–447.
Murray, A.K., Vail, A., Moore, T.L., Manning, J.B., Taylor, C.J., Herrick, A.L., 2012. The influence of measurement location on reliability of quantitative nailfold videocapillaroscopy in patients with SSc. Rheumatology 51, 1323–1330.
Noy-Delcourt, D., Thébaut, P., 1985. Periungual capillaroscopy of the toes. Criteria for norms. J. Mal. Vasc. 11, 288–294.
Ong, Y.Y., Nikoloutsopoulos, T., Bond, C.P., Smith, M.D., Ahern, M.J., Roberts-Thomson, P.J., 2011. Decreased nailfold capillary density in limited scleroderma with pulmonary hypertension. Asian Pac. J. Allergy Immunol. 16, 81–86.
Paparde, A., Nēringa-Martinsone, K., Plakane, L., Aivars, J.I., 2014. Nail fold capillary diameter changes in acute systemic hypoxia. Microvasc. Res. 93, 30–33.
Riccieri, V., Germano, V., Alessandri, C., Vasile, M., Ceccarelli, F., Sciarra, I., Di Franco, M., Spadaro, A., Valesini, G., 2008. More severe nailfold capillaroscopy findings and anti-endothelial cell antibodies. Are they useful tools for prognostic use in systemic sclerosis? Clin. Exp. Rheumatol. 26, 992.
Riccieri, V., Vasile, M., Iannace, N., Stefanantoni, K., Sciarra, I., Vizza, C.D., Badagliacca, R., Poscia, R., Papa, S., Mezzapesa, M., 2013. Systemic sclerosis patients with and without pulmonary arterial hypertension: a nailfold capillaroscopy study. Rheumatology 52, 1525–1528.
Rouen, L.R., Terry, E.N., Doft, B.H., Clauss, R.H., Redisch, W., 1972. Classification and measurement of surface microvessels in man. Microvasc. Res. 4, 285–292.
Sander, O., Sunderkötter, C., Kötter, I., Wagner, I., Becker, M., Herrgott, I., Schwarting, A., Ostendorf, B., Iking-Konert, C., Genth, E., 2010. Capillaroscopy. Z. Rheumatol. 69, 253–262.
Santis, M.D., Ceribelli, A., Cavaciocchi, F., Crotti, C., Massarotti, M., Belloli, L., Marasini, B., Isailovic, N., Generali, E., Selmi, C., 2016. Nailfold videocapillaroscopy and serum VEGF levels in scleroderma are associated with internal organ involvement. Autoimmun. High. 7, 1–9.
Scardina, G.A., Ruggieri, A., Messina, P., 2009. Oral microcirculation observed in vivo by videocapillaroscopy: a review. J. Oral Sci. 51, 1–10.
Scardina, G.A., Cacioppo, A., Messina, P., 2014. Changes of oral microcirculation in chemotherapy patients: A possible correlation with mucositis? Clin. Anat. 27, 417–422.
Schiavon, F., Maffei, P., Martini, C., De Carlo, E., Fais, C., Todesco, S., Sicolo, N., 1999. Morphologic Study of Microcirculation in Acromegaly by Capillaroscopy 1. J. Clin. Endocrinol. Metab. 84, 3151–3155.
Schlager, O., Kiener, H., Stein, L., Hofkirchner, J., Zehetmayer, S., Ristl, R., Perkmann, T., Smolen, J., Koppensteiner, R., Gschwandtner, M., 2014. Associations of nailfold capillary abnormalities and immunological markers in early Raynaud's phenomenon. Scand. J. Rheumatol. 43, 226–233.
Sebastiani, M., Manfredi, A., Colaci, M., D'amico, R., Malagoli, V., Giuggioli, D., Ferri, C., 2009. Capillaroscopic skin ulcer risk index: a new prognostic tool for digital skin ulcer development in systemic sclerosis patients. Arthritis Care Res. 61, 688–694.
Sebastiani, M., Manfredi, A., Vukatana, G., Moscatelli, S., Riato, L., Bocci, M., Iudici, M., Principato, A., Mazzuca, S., Del Medico, P., 2012. Predictive role of capillaroscopic skin ulcer risk index in systemic sclerosis: a multicentre validation study. Ann. Rheum. Dis. 71, 67–70.
Sekiyama, J.Y., Camargo, C.Z., Andrade, L.E.C., Kayser, C., 2013. Reliability of Widefield Nailfold Capillaroscopy and Videocapillaroscopy in the Assessment of Patients With Raynaud's Phenomenon. Arthritis Care Res. 65, 1853–1861.
Selva-O'Callaghan, A., Fonollosa-Pla, V., Trallero-Araguás, E., Martínez-Gómez, X., Simeon-Aznar, C.P., Labrador-Horrillo, M., Vilardell-Tarrés, M., 2010. Nailfold capillary microscopy in adults with inflammatory myopathy. Semin. Arthritis Rheum. 39, 398–404.
Serné, E.H., Gans, R.O., ter Maaten, J.C., Tangelder, G.-J., Donker, A.J., Stehouwer, C.D., 2001. Impaired skin capillary recruitment in essential hypertension is caused by both functional and structural capillary rarefaction. Hypertension 38, 238–242.
Shore, A.C., 2000. Capillaroscopy and the measurement of capillary pressure. Br. J. Clin. Pharmacol. 50, 501–513.
Silva, I., Almeida, J., Vasconcelos, C., 2015a. A PRISMA-driven systematic review for predictive risk factors of digital ulcers in systemic sclerosis patients. Autoimmun. Rev. 14, 140–152.
Silva, I., Teixeira, A., Oliveira, J., Almeida, I., Almeida, R., Águas, A., Vasconcelos, C., 2015b. 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. 49, 240–252.
Smith, V., De Keyser, F., Pizzorni, C., Van Praet, J.T., Decuman, S., Sulli, A., Deschepper, E., Cutolo, M., 2010. Nailfold capillaroscopy for day-to-day clinical use: construction of a simple scoring modality as a clinical prognostic index for digital trophic lesions. Ann. Rheum. Dis. 70, 180–183.
Smith, V., Riccieri, V., Pizzorni, C., Decuman, S., Deschepper, E., Bonroy, C., Sulli, A., Piette, Y., De Keyser, F., Cutolo, M., 2013. Nailfold capillaroscopy for prediction of novel future severe organ involvement in systemic sclerosis. J. Rheumatol. 40, 2023–2028.
Souza, E.J.d.R.e., Kayser, C., 2014. Nailfold capillaroscopy: relevance to the practice of rheumatology. Rev. Bras. Reumatol. Eng. 55, 264–271.
Sulli, A., Secchi, M.E., Pizzorni, C., Cutolo, M., 2008. Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. Ann. Rheum. Dis. 67, 885–887.
Sulli, A., Soldano, S., Pizzorni, C., Montagna, P., Secchi, M.E., Villaggio, B., Seriolo, B., Brizzolara, R., Cutolo, M., 2009. Raynaud's phenomenon and plasma endothelin: correlations with capillaroscopic patterns in systemic sclerosis. J. Rheumatol. 36, 1235–1239.
Tektonidou, M., Kaskani, E., Skopouli, F., Moutsopoulos, H., 1999. Microvascular abnormalities in Sjögren's syndrome: nailfold capillaroscopy. Rheumatology 38, 826–830.
Terreri, M.T.R., Andrade, L.E.C., Puccinelli, M.L., Hilário, M.O.E., Goldenberg, J., 1999. Nail fold capillaroscopy: Normal findings in childrenand adolescents. Semin. Arthritis Rheum. 29, 36–42.
Triantafyllou, A., Anyfanti, P., Pyrpasopoulou, A., Triantafyllou, G., Aslanidis, S., Douma, S., 2015. Capillary rarefaction as an index for the microvascular assessment of hypertensive patients. Curr. Hypertens. Rep. 17, 1–8.
Vayssairat, M., Abuaf, N., Deschamps, A., Baudot, N., Gaitz, J.-P., Chakkour, K., Nussaume, O., 1997. Nailfold capillary microscopy in patients with anticardiolipin antibodies: a case–control study. Dermatology 194, 36–40.
Vaz, J., Dancour, M., Bottino, D., Bouskela, E., 2004. Nailfold videocapillaroscopy in primary antiphospholipid syndrome (PAPS). Rheumatology 43, 1025–1027.
Wen, C.-H., Liao, W.-D., Hsieh, T.-Y., Chen, D.-Y., Lan, J.-L., Li, K.-C., 2009. Computer-Aided Image Analysis Aids Early Diagnosis of Connective-Tissue Diseases. SPIE Newsroom, Biomedical Optics & Medical Imaging.
Wildt, M., Wuttge, D., Hesselstrand, R., Scheja, A., 2012. Assessment of capillary density in systemic sclerosis with three different capillaroscopic methods. Clin. Exp. Rheumatol. 30, S50–S54.
Yvonne-Tee, G.B., Rasool, A.H.G., Halim, A.S., Rahman, A.R.A., 2006. Noninvasive assessment of cutaneous vascular function in vivo using capillaroscopy, plethysmography and laser-Doppler instruments: its strengths and weaknesses. Clin. Hemorheol. Microcirc. 34, 457–473.