

Association of Capillaroscopic Findings with Autoantibodies in Systemic Sclerosis

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Abstract

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disease with multifaceted clinical manifestations, unclear etiology, and specific immunological phenomena that continue to be a challenge for modern science regarding their etiopathogenetic role in the onset and course of the disease. In SSc, different autoantibodies could be detected, and three are defined as diagnostic. They are considered potential biomarkers as they may eventually be used to distinguish distinct patient groups with specific clinical manifestations. Three specific autoantibodies and capillaroscopic abnormalities were included in the 2013 ACR/EULAR classification criteria for SSc. The autoantibodies defined as diagnostic in SSc are anti-centromere, anti-topoisomerase I, and anti-RNA polymerase III antibodies. Other SSc-associated antibodies are anti-Th/To, Ku, PDGFR, PM-Scl, etc. Growing evidence suggests an association between specific autoantibody

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profiles and distinct capillaroscopic patterns, indicating a link between immunological mechanisms and microvascular damage.

Keywords: systemic sclerosis, capillaroscopy, autoantibodies, immunological abnormalities

1. Introduction

Systemic sclerosis (SSc), often called scleroderma because of the high prevalence of skin thickening, is a rare systemic autoimmune rheumatic disease characterized by vasculopathy, immune dysregulation, and progressive fibrosis of the skin and internal organs. Despite the continuous improvement of diagnostic methods, the introduction of novel therapeutic strategies, and the pursuit of timely diagnosis, SSc remains a disease associated with significant morbidity, increased mortality, and impaired quality of life. Better knowledge of the disease and thorough analysis of its complications contribute to increased survival and better treatment outcomes [1].

The clinical manifestations of the disease are numerous and range from mild to life-threatening conditions. The earliest clinical presentation is typically Raynaud's phenomenon (RP), which can precede the development of definite SSc by several years [2]. RP is included in the 2013 ACR/EULAR classification criteria for SSc, and it is considered one of the major "red flags" warranting further evaluation. Thorough clinical evaluation should be performed in combination with nailfold capillaroscopy and antinuclear antibody (ANA) testing to differentiate primary from secondary forms of RP [2–4].

Previous studies have demonstrated that RP, together with the so-called "puffy fingers" or swollen fingers and the presence of scleroderma-associated antibodies, represents a major predictor of progression to definite SSc and forms the basis of the concept of very early diagnosis of SSc (VEDOSS) [5]. Timely diagnosis of patients at a stage when there is still no pronounced organ involvement may expand the therapeutic "window of opportunity" and improve long-term outcome [4,6].

Nailfold capillaroscopy is a non-invasive, reproducible imaging technique that enables direct visualization of microcirculation and plays a central role in the early diagnosis and classification of SSc and facilitating the differentiation between primary and secondary RP [7]. As a non-invasive and reproducible imaging technique, nailfold capillaroscopy allows both

early detection and monitoring of the microvascular damage throughout the disease course.

A characteristic capillaroscopic pattern, known as the “*scleroderma pattern*”, has been described in patients with SSc, characterized by the presence of giant capillaries, microhemorrhages, a reduction in capillary density, and ramified capillaries [8].

Screening for disease-specific antibodies is a mandatory step in the diagnostic work-up in patients with suspected SSc. Furthermore, these antibodies may facilitate the stratification of patients into clinically distinct subsets, as numerous studies have demonstrated associations between specific antibody profiles and particular clinical manifestations or organ involvement. Consequently, these antibodies may serve not only as diagnostic but also as valuable prognostic markers of disease progression and clinical outcomes [9].

This review aims to summarize the current literature regarding the association between systemic sclerosis–specific autoantibodies and nailfold capillaroscopic findings, with emphasis on their clinical and prognostic assessment.

To facilitate comparison of the major systemic sclerosis–specific autoantibodies and their associated clinical and capillaroscopic features, a summary is provided in Table 1.

Table 1. Major autoantibodies in systemic sclerosis and their associated clinical and capillaroscopic characteristics.

Autoantibody	Frequency in SSc	Main clinical associations	Capillaroscopic associations
Anti-topoisomerase I (anti-Scl-70)	20–40%	Diffuse cutaneous SSc, interstitial lung disease, digital ulcers, flexion contractures	More frequently associated with active and late scleroderma patterns, severe capillary loss, and progressive microangiopathy
Anti-centromere antibodies (ACA)	20–40%	Limited cutaneous SSc, pulmonary arterial hypertension, calcinosis, CREST phenotype	Associated with giant capillaries and capillary dilatation; slower progression of microvascular damage
Anti-RNA polymerase III (anti-RNAP III)	5–20%	Diffuse skin involvement, scleroderma renal crisis, rapidly progressive skin disease	Limited data; possible association with severe microvascular involvement

ANA	>90%	Early disease detection, risk stratification	ANA positivity associated with progression of capillaroscopic abnormalities
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Abbreviations: ACA, anti-centromere antibodies; ANA, antinuclear antibodies; CREST, calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia; RNAP III, RNA polymerase III; Scl-70, scleroderma-70; SSc, systemic sclerosis.

2. Materials and Methods

A literature search was performed in PubMed, Scopus, MEDLINE, and Web of Science databases from inception to March 2026. This search aimed to summarize the most recent available evidence regarding nailfold capillaroscopy in systemic sclerosis (SSc) and its association with immunological abnormalities and disease-specific autoantibodies.

The search strategy included combination of the following keywords and Medical Subject Headings (MeSH) terms: “systemic sclerosis”, “scleroderma”, “autoantibodies”, “Raynaud’s phenomenon”, “capillaroscopy”, “nailfold videocapillaroscopy”, “microangiopathy”, “overlap syndromes”, and “classification criteria.”

Eligible studies included original articles, observational studies, (prospective and retrospective), clinical trials, systematic reviews, and meta-analyses published in English. Studies with insufficient clinical data, duplicate publications, conference abstract without full-text availability, and reports not directly related to SSc or focusing on other autoimmune diseases with capillaroscopic abnormalities were excluded from the analysis. Two independent reviewers screened titles and abstracts for eligibility, followed by full-text evaluation of potentially relevant studies. Disagreements were resolved through consensus.

3. Overview

Nailfold capillaroscopy is one of the most valuable instrumental techniques in rheumatology. It is a simple, easy-to-perform, non-invasive, and reproducible method that enables the assessment of microvascular abnormalities in patients with SSc. It reflects early capillaroscopic diagnostic changes in the nailfold area in SSc patients and allows longitudinal follow-up of disease progression and evolution of microvascular abnormalities [10].

Maricq et colleagues made a significant contribution in the field of the use of capillaroscopy in SSc by introducing the concept of the term “scleroderma

pattern”, characterized by dilated and giant capillaries, microhemorrhages, capillary loss, and ramified capillaries [11]. Subsequently, Cutolo et al. proposed a widely accepted classification of capillaroscopic abnormalities in SSc, which defines three distinct patterns. The “early” pattern is characterized predominantly by the appearance of giant capillaries and microhemorrhages with relatively preserved capillary density. This stage evolves through “active” stages that demonstrate more frequent giant capillaries and progressive capillary loss. The “late” scleroderma pattern is characterized by advanced devascularization and the presence of ramified or bushy capillaries [8].

To facilitate a structured overview of these morphological changes, the main nailfold capillaroscopic patterns in systemic sclerosis according to Cutolo et al. are summarized in Table 2.

Table 2. Nailfold capillaroscopic patterns in systemic sclerosis according to Cutolo et al. [8].

Pattern	Main capillaroscopic features	Disease stage
Early	Few giant capillaries, few microhemorrhages, preserved capillary density	Early microvascular involvement
Active	Frequent giant capillaries, recurrent microhemorrhages, moderate capillary loss	Progressive disease
Late	Severe capillary loss, avascular areas, ramified/bushy capillaries, architectural disorganization	Advanced microvascular damage

The relationship between microangiopathy, circulating antibodies, and disease manifestations remains incompletely understood. Particular interest in rheumatology is the identification of early biomarkers capable of predicting progression and organ involvement in patients with even minor symptoms.

RP is one of the earliest and most common symptoms of SSc, affecting more than 95% of patients during the disease course. There are circulatory disturbances with varying severity at different stages of the disease. The coexistence of RP, capillaroscopic abnormalities, and disease – specific antibodies substantially increase the likelihood of progression to definite SSc and enhances the diagnostic and prognostic value of these findings.

The clinical significance of the observed capillaroscopic changes is reflected by their inclusion in the 2013 ACR/EULAR classification criteria for SSc [3]. The presence of a characteristic scleroderma pattern supports the diagnosis, whereas the absence of typical capillaroscopic abnormalities

considerably reduces the likelihood of SSc [12]. All patients presenting with RP should undergo a comprehensive evaluation, including capillaroscopic examination and serological testing to facilitate early diagnosis and risk stratification.

In SSc, the most common antibodies are those against nuclear antigens, with the most specific being anti-topoisomerase I (anti-Scl70), anti-centromere antibodies (ACA), and anti-RNA polymerase III antibodies (anti-RNA polymerase III, anti-RNAP3). Additional SSc-associated antibodies, such as anti-Th/To, anti-fibrillarin, anti-Ku, anti-PM-Scl, and anti-PDGFR antibodies, are detected significantly less frequently but may provide valuable diagnostic and prognostic information, particularly in atypical or diagnostically challenging cases [9,13].

Accumulating evidence suggests that specific autoantibody profiles are associated with distinct capillaroscopic patterns, microvascular progression, and specific organ involvement. However, the available data remains heterogeneous, and further studies are required to clarify the relationship between serological markers and microvascular damage in SSc.

4. Association of anti-topoisomerase I (anti-Scl-70), anti-centromere antibodies, anti-RNA polymerase III and total ANA screening test with capillaroscopic findings

Anti-topoisomerase I antibodies, also known as anti-Scl-70 antibodies, were first identified in 1979 and are the most specific serological markers for SSc [14]. These antibodies are found exclusively in SSc, whereas anti-topoisomerase II α antibodies may also be detected in other autoimmune diseases [14]. Anti-topoisomerase I antibodies (anti-Scl-70), together with anti-centromere antibodies, are highly specific for SSc and are considered important diagnostic and prognostic biomarkers. Anti-topoisomerase I positivity is predominantly associated with diffuse cutaneous systemic sclerosis (dcSSc), digital ulcers, flexion contractures, interstitial lung disease (ILD), and pulmonary arterial hypertension (PAH) secondary to pulmonary fibrosis [14,15]. Because ILD remains one of the leading causes of mortality in SSc, considerable attention has been directed toward identifying clinical and laboratory markers associated with disease progression.

Several studies have investigated the relationship between anti-Scl-70 antibodies and microvascular abnormalities assessed by nailfold

capillaroscopy. One of the first large studies addressing this issue was conducted by Cutolo et al., who evaluated 241 patients with SSc and Raynaud's phenomenon (RP) [16]. The authors demonstrated a significantly higher prevalence of anti-topoisomerase I (anti-Scl-70) antibody positivity among patients exhibiting active and late scleroderma patterns compared with those presenting with an early pattern. Furthermore, anti-Scl-70 positivity was associated with longer disease duration and more advanced microvascular damage.

These findings were subsequently supported by Sulli et al. in a prospective longitudinal study investigating the progression of microangiopathy in SSc [17]. Patients positive for anti-topoisomerase I (anti-Scl-70) antibodies were more likely to develop advanced capillaroscopic abnormalities during follow-up, whereas ANA-negative patients exhibited slower progression of microvascular damage. Interestingly, a substantial proportion of ANA-negative individuals demonstrated slower progression of capillaroscopic abnormalities during follow-up.

Additional evidence was provided by an analysis of the EUSTAR database, which included 2,754 patients with SSc, among whom capillaroscopic staging data were available for 1,870 individuals. In the EUSTAR cohort, late capillaroscopic pattern was associated with a more severe disease phenotype and was more frequently observed in anti-topoisomerase I (anti-Scl-70)-positive patients [18].

In very early systemic sclerosis, Valentini et al. demonstrated that the combined assessment of autoantibody profiles and videocapillaroscopic patterns allows the identification of distinct clinical subsets and significantly increases the likelihood of progression to definite disease [19].

Collectively, these findings highlight the complementary nature of serological and microvascular biomarkers and support their integrated use for early risk stratification and disease prediction in SSc.

Anti-centromere antibodies represent another highly specific serological marker for SSc and are detected predominantly in patients with limited cutaneous disease [20,21]. These antibodies are directed against centromere proteins, primarily CENP-A, CENP-B, and CENP-C, and are strongly associated with long-standing RP, limited skin involvement, calcinosis, telangiectasia, and PAH [22].

In contrast to anti-topoisomerase I (anti-Scl-70) antibodies, the relationship between anti-centromere antibody positivity and

capillaroscopic abnormalities remains less clearly defined. In the study by Cutolo et al., no statistically significant differences were observed between anti-centromere positivity and the three capillaroscopic stages [16].

Nevertheless, subsequent investigations have suggested that ACA-positive patients may exhibit characteristic capillary dilatation and giant capillaries, although the progression toward severe capillary loss appears less pronounced than in anti-topoisomerase I (anti-Scl-70)-positive patients [23]. These findings support the concept that distinct autoantibody profiles may be associated with different trajectories of microvascular damage.

The prognostic significance of anticentromere antibodies is particularly evident in relation to PAH. Unlike anti-topoisomerase I (anti-Scl-70) antibodies, anticentromere antibodies positivity has not been consistently associated with an increased risk of ILD but is considered a well-established marker of PAH development [14]. Consequently, anticentromere - positive patients represent a distinct clinical subset characterized by a relatively slower progression of skin and pulmonary fibrosis but an increased risk of vascular complications.

Anti-RNA polymerase III antibodies (anti-RNAP III) represent the third SSc-specific autoantibody subset among patients with SSc. They were first identified in 1993 in the serum of patients with SSc, and at that time their strong disease specificity was established, particularly in patients with diffuse cutaneous involvement. Studies show that they are most frequently detected after anti-topoisomerase I and anti-centromere antibodies, and they have high specificity for SSc [24]. Anti-RNAP III-positive patients typically experience rapid skin thickening during the early stages of the disease and are at increased risk of developing scleroderma renal crisis and malignant hypertension [25,26].

Compared with anti-topoisomerase I (anti-Scl-70) and anticentromere antibodies, data regarding the association between anti-RNAP III antibodies and capillaroscopic abnormalities remain limited. Available studies suggest that these patients frequently exhibit severe vascular involvement; however, no consistent capillaroscopic phenotype has yet been established. The relatively low prevalence of anti-RNAP III positivity in most cohorts and the limited number of dedicated capillaroscopic studies may partly explain the lack of definitive conclusions. Further prospective investigations are therefore required to clarify the relationship between anti-RNAP III antibodies and microvascular progression.

Although antinuclear antibodies (ANA) are not included in the current classification criteria for SSc, they remain an important screening tool in patients presenting with isolated RP [3,21]. However, they may be used as a screening tool for identifying patients with isolated RP who may subsequently develop a definite SSc diagnosis during their follow-up [27]. ANA positivity may precede the clinical onset of SSc and contribute to the identification of individuals at increased risk of disease development. Moreover, ANA positivity has been associated with progression of microangiopathy, whereas ANA-negative patients appear to exhibit slower capillaroscopic progression and a more favorable vascular course [17].

ANA positivity, as well as SSc-specific antibodies, may serve as biomarkers with predictive value for the progression of microangiopathy in patients with established disease [27]. However, a negative ANA result does not exclude the diagnosis of SSc [28].

Overall, the available evidence indicates that disease-specific autoantibodies and capillaroscopic abnormalities represent complementary biomarkers in systemic sclerosis. Among the currently recognized autoantibodies, anti-topoisomerase I (anti-Scl-70) demonstrates the strongest association with advanced microangiopathy and severe capillaroscopic abnormalities, whereas anticentromere antibodies is associated with a distinct vascular phenotype and anti-RNAP III remains insufficiently investigated. The integration of serological and capillaroscopic findings may improve patient stratification, facilitate risk assessment, and contribute to the early identification of patients at risk for severe organ involvement.

The principal studies investigating the association between SSc-specific autoantibodies and nailfold capillaroscopic abnormalities are summarized in Table 3.

Table 3. Major studies evaluating the association between systemic sclerosis-specific autoantibodies and nailfold capillaroscopic abnormalities.

Study	Design and population	Autoantibodies evaluated	Main capillaroscopic findings	Clinical implications
Cutolo et al., 2004 [16]	Cross-sectional study; 241 patients with systemic sclerosis and Raynaud’s phenomenon	Anti-Scl-70, anti-centromere antibodies	Anti-Scl-70 associated with active and late scleroderma patterns; no significant association for ACA	First evidence linking autoantibody profile with severity of microangiopathy

Koenig et al., 2008 [27]	Prospective cohort; 586 patients with Raynaud's phenomenon (20-year follow-up)	ACA, anti-Scl-70, anti-Th/To, anti-RNA polymerase III	Abnormal capillaroscopy and SSc-specific autoantibodies independently predicted progression to systemic sclerosis	Strong prognostic value of combined biomarkers
Sulli et al., 2013 [17]	Prospective longitudinal study; patients with systemic sclerosis	ANA, anti-Scl-70	Anti-Scl-70 associated with advanced microangiopathy; ANA-negative patients showed slower progression	Supports association between serology and vascular progression
Valentini et al., 2013 [19]	Prospective multicenter VEDOSS cohort	ACA, anti-Scl-70, other SSc-specific antibodies	Combined autoantibody positivity and abnormal capillaroscopy increased risk of progression to definite systemic sclerosis	Supports integrated serological and capillaroscopic risk stratification
Ingegnoli et al., 2013 (EUSTAR cohort) [18]	Multicenter observational cohort; 2,754 systemic sclerosis patients	SSc-specific autoantibodies	Late capillaroscopic pattern associated with severe disease and anti-Scl-70 positivity	Confirms link between advanced microangiopathy and severe phenotype
Hysa et al., 2023 [23]	Narrative review	ACA, anti-Scl-70, anti-RNP and others	Summarizes associations between autoantibodies, capillaroscopic patterns, and organ involvement	Comprehensive overview of serological-microvascular associations

Abbreviations: ACA, anti-centromere antibodies; ANA, antinuclear antibodies; EUSTAR, European Scleroderma Trials and Research; RNP, ribonucleoprotein; Scl-70, scleroderma-70; SSc, systemic sclerosis; VEDOSS, Very Early Diagnosis of Systemic Sclerosis.

In addition to the studies summarized above, our group evaluated a cohort of 19 patients with definite SSc in a study published in 2022 (1 male and 18 females) [29]. The previously reported association between advanced capillaroscopic abnormalities and anti-topoisomerase I positivity was confirmed [16,29]. Furthermore, anti-RNAP III antibodies were detected in patients both with and without RP, representing an observation that differs from previously published data [30]. Although these findings should be interpreted with caution because of the limited sample size, they support

the potential heterogeneity of anti-RNAP III-positive SSc and warrant further investigation of larger cohorts.

5. Other Systemic Sclerosis-Associated Autoantibodies

In addition to the three disease-specific autoantibodies included in the 2013 ACR/EULAR classification criteria, several other autoantibodies have been identified in patients with SSc. Although these antibodies are less prevalent, they may provide valuable information regarding disease phenotype, organ involvement, and prognosis. However, data concerning their association with nailfold capillaroscopic abnormalities remain limited. The principal characteristics of these antibodies are summarized in Table 4.

Table 4. Other systemic sclerosis-associated autoantibodies.

Autoantibody	Frequency in SSc	Main clinical associations	Reported capillaroscopic associations
Anti-Th/To	3–6%	Limited cutaneous SSc, pulmonary fibrosis, pulmonary arterial hypertension, possible renal involvement	Limited evidence; some studies suggest association with advanced microangiopathy and late scleroderma pattern
Anti-U3 RNP (fibrillarin)	4–10%	Younger age at onset, more severe internal organ involvement, pulmonary arterial hypertension, poorer prognosis	Insufficient and inconsistent data
Anti-Ku	<5%	Overlap syndromes, myositis, arthritis, joint contractures	No consistent capillaroscopic pattern established
Anti-PM/Scl (PM-Scl-75 and PM-Scl-100)	3–10%	SSc–myositis overlap syndrome, muscle involvement	Limited evidence available
Anti-Ro52 / Ro60	Variable frequency	Overlap syndromes, additional autoimmune features	No established specific capillaroscopic associations

Abbreviations: SSc, systemic sclerosis; PM/Scl, polymyositis/scleroderma; U3RNP, U3-ribonucleoprotein.

Anti-Th/To antibodies are directed against nucleolar antigens and are most frequently detected in patients with lcSSc. It is confirmed that anti-Th/To and anti-U3RNP antibodies can be predictors of less favorable prognosis with a higher frequency of organ involvement, such as pulmonary fibrosis, PAH, and malignant hypertension with renal crisis [31,32].

The prevalence of anti-Th/To antibodies has been estimated at approximately 3–6% among patients with SSc and are associated mainly with the limited type of disease [33]. Despite their association with lcSSc, anti-Th/To antibodies have been linked to a poor prognosis due to an increased risk of pulmonary fibrosis, PAH, and renal involvement [34]. Recent studies have also demonstrated a significant association between anti-Th/To positivity and advanced capillaroscopic abnormalities. Patients positive for anti-Th/To antibodies were more likely to exhibit a late scleroderma pattern, which was further associated with a higher prevalence of ILD [34]. These findings suggest that anti-Th/To antibodies may represent a useful marker of both microvascular and pulmonary disease progression.

Anti – fibrilarin or also known as anti-U3RNP antibodies, have been investigated for several decades and are recognized as markers of distinct clinical subsets of SSc [32]. Some studies have reported a higher prevalence among individuals of African ancestry and have associated these antibodies with younger age at disease onset, more severe internal organ involvement, and poorer overall prognosis [32]. Musculoskeletal manifestations and PAH appear to be particularly common in this subgroup. However, evidence regarding the relationship between anti-U3RNP antibodies and capillaroscopic abnormalities remains scarce, and further studies are needed to determine whether a characteristic microvascular phenotype exists.

Anti-Ku antibodies are detected only in a minority of patients with SSc and are more frequently encountered in overlap syndromes. Available evidence suggests a strong association with musculoskeletal manifestations, including inflammatory myopathy, arthritis, and joint contractures [35]. In contrast, vascular manifestations such as digital ulcers and telangiectasia appear to occur less frequently in anti-Ku-positive patients. Despite these clinical associations, the relationship between anti-Ku antibodies and nailfold capillaroscopic findings remains poorly understood, and no specific capillaroscopic pattern has yet been identified.

Several other autoantibodies have also been identified in patients with SSc, such as anti-PM/Scl (PM/Scl-100 and PM-Scl-75), and Ro52, but they are not strictly specific for this disease. They are frequently detected in overlap syndromes involving inflammatory myopathies, systemic lupus erythematosus, or other connective tissue diseases. The simultaneous presence of multiple antibodies in a single patient is rare [9,13,36]. Although they may contribute to clinical phenotyping and disease

classification, available data regarding their association with capillaroscopic abnormalities are currently insufficient to support definitive conclusions.

The identification of disease-specific antibodies has important clinical implications because it facilitates the classification of patients into more homogeneous subgroups and improves risk stratification. Autoantibody profiling may contribute to the prediction of disease course, organ involvement, and long-term outcomes, thereby supporting individualized management strategies.

One of the strongest pieces of evidence supporting the predictive value of autoantibodies and capillaroscopy derives from the landmark prospective study by Koenig et al. [27]. In this twenty-year cohort study, 586 patients with Raynaud's phenomenon were evaluated for SSc-specific autoantibodies and monitored using nailfold capillaroscopy. During follow-up, 74 patients (12.6%) developed definite SSc. The presence of enlarged capillaries, progressive capillary loss, and SSc-specific autoantibodies were identified as independent predictors of disease progression. Notably, nearly 80% of patients presenting with both abnormal capillaroscopy and at least one SSc-specific autoantibody eventually developed definite SSc [27].

Although data regarding the presence of autoantibodies before the onset of clinically overt disease remain limited, accumulating evidence suggests that anti-centromere, anti-topoisomerase I (anti-Scl-70), and anti-Th/Tho antibodies may be detectable years before the development of definite SSc; [9,13]. Furthermore, several studies have reported that anti-centromere, anti-Ro-52, anti-Ro60 antibodies may precede the appearance of the first clinical manifestation by many years, highlighting their potential value as predictive biomarkers [20,21].

Recent investigations have increasingly focused on the combined assessment of autoantibody profiles, capillaroscopic abnormalities, and organ involvement as a means of improving risk stratifications in patients with SSc. A recently published French study demonstrated that nailfold capillaroscopic abnormalities are strong predictors of severe progression of the disease in these patients, further emphasizing the central role of microangiopathy in the pathogenesis and clinical evolution of SSc [37].

Overall, current evidence supports the concept that autoantibody profiles and capillaroscopic findings represent biomarkers in SSc. Their combined assessment may facilitate earlier diagnosis, improve prognostic evaluation,

and contribute to the identification of patients at increased risk of progressive vascular and organ involvement.

6. Discussion

SSc is characterized by a dynamic interplay between immune dysregulation and progressive microvascular injury, in which capillary damage often precedes clinical organ involvement. The evidence summarized in this review supports the concept that nailfold capillaroscopy and disease-specific autoantibodies represent complementary biomarkers reflecting different but interconnected aspects of disease pathogenesis.

Among SSc-specific autoantibodies, anti-topoisomerase I antibodies (anti-Scl-70) shows the strongest and most consistent association with advanced capillaroscopic abnormalities, including active and late scleroderma patterns and severe capillary loss. These findings are supported by cross-sectional and longitudinal studies, as well as large cohort data from EUSTAR, and align with the well-established link between antitopoisomerase I (anti-Scl-70) positivity and severe internal organ involvement, particularly ILD.

In contrast, anti-centromere antibodies define a more indolent vascular phenotype. Although anticentromere antibody-positive patients frequently exhibit capillary dilatation and giant capillaries, available data do not consistently demonstrate progression to advanced microangiopathy, suggesting a distinct and slower vascular disease trajectory.

Evidence regarding anti-RNAP III antibodies remains insufficient. While these antibodies are associated with a rapidly progressive clinical phenotype, including diffuse skin involvement and renal crisis, their relationship with capillaroscopic evolution is not yet clearly defined and requires further prospective investigation.

Importantly, combined assessment of serological and capillaroscopic abnormalities provides superior predictive value compared with either modality alone. Data from Koenig et al. and the VEDOSS cohort by Valentini et al. demonstrate that patients presenting with both SSc-specific autoantibodies and abnormal nailfold capillaroscopy have a substantially increased risk of progression from RP to definite SSc. These observations reinforce the concept of an integrated immuno-vascular biomarker model for early disease identification.

Overall, the available evidence supports a hierarchical relationship between autoantibody profiles and patterns of microvascular damage, with antitopoisomerase I (anti-Scl-70) representing the strongest correlate of severe capillary injury, anticentromere antibodies defining a distinct vascular subset, and anti-RNAP III remaining incompletely characterized. Recent studies have further strengthened the prognostic value of nailfold capillaroscopy, demonstrating associations between advanced capillaroscopic abnormalities, anti-Th/To antibody positivity, interstitial lung disease, and severe disease progression over time. Further multicenter prospective studies integrating serological, capillaroscopic, and clinical data are needed to refine risk stratification models and improve early disease prediction.

An emerging area of interest in SSc research is the application of artificial intelligence (AI) and machine learning techniques to nailfold capillaroscopy. Recent advances in automated image analysis have demonstrated the potential of AI-based algorithms to identify and quantify capillary abnormalities, including giant capillaries, microhemorrhages, capillary loss, and neoangiogenesis, with high accuracy and reproducibility. These approaches may reduce interobserver variability and facilitate standardized assessment of microvascular damage across different centers. Furthermore, the integration of capillaroscopic images with clinical characteristics and autoantibody profiles may improve risk stratification and enable earlier identification of patients at increased risk for disease progression and organ involvement. Although these technologies remain under active investigation, AI-assisted capillaroscopy represents a promising tool for advancing precision medicine in SSc and may contribute to more individualized patient management in the future [38,39].

Recent advances in imaging technologies, digital nailfold capillaroscopy, serological profiling, and artificial intelligence-assisted image analysis are expected to further improve the understanding of SSc pathogenesis and progression. The integration of capillaroscopic findings with disease-specific autoantibody profiles may facilitate the identification of distinct disease subsets and improve prediction of organ involvement and clinical outcomes. Future multicenter prospective studies combining clinical, serological, and imaging data are required to clarify the complex interactions between immune dysregulation, microvascular damage, and fibrosis. Such an integrated approach may contribute to earlier diagnosis, more accurate risk stratification, and the development of personalized therapeutic strategies for patients with systemic sclerosis.

7. Conclusions

SSc is a heterogeneous autoimmune disease in which immune dysregulation and microvascular damage play a central role in disease pathogenesis and progression. The available evidence demonstrates that disease-specific autoantibodies and nailfold capillaroscopic abnormalities represent biomarkers with important diagnostic, prognostic, and risk stratification value.

Among the currently recognized autoantibodies, anti-topoisomerase I antibodies show the most consistent association with advanced capillaroscopic abnormalities and severe disease manifestations, whereas anti-centromere and anti-RNA polymerase III antibodies are associated with distinct clinical phenotypes and organ involvement. The combined assessment of autoantibody profiles and nailfold capillaroscopy improves the identification of patients at risk of progression from RP to definite SSc and facilitates earlier diagnosis and closer monitoring.

Despite significant advances in this field, the relationship between specific autoantibodies, microvascular damage, and organ involvement has not yet been fully elucidated. Further prospective multicenter studies are needed to clarify these associations and to establish standardized biomarkers for disease progression and prognosis.

Future approaches integrating serological biomarkers, nailfold capillaroscopic findings, and emerging artificial intelligence-based image analysis technologies may improve risk stratification and contribute to more personalized management of patients with systemic sclerosis.

Declarations

Author Contributions

Conceptualization: S.D, S.L; Methodology: S.D., S.L; Formal analysis: S.L; Investigation: S.D.; Writing—original draft: S.D.; Writing—review & editing: all authors. The authors used ChatGPT (OpenAI, San Francisco, CA, USA) to assist with language editing, manuscript organization, and preparation of summary tables. All literature searches, data verification, scientific interpretation, critical appraisal of the evidence, and final approval of the manuscript were performed by the authors. The authors assume full responsibility for the content of the manuscript.

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Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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