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Capillaroscopy in Systemic Autoimmune Rheumatic Diseases: A Clinical Tool Linking Diagnosis and Pathogenesis

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Introduction

Systemic autoimmune rheumatic diseases (SARDs) including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIMs) are multisystemic, potentially life-threatening autoimmune diseases. These diseases are associated with the highest frequency of disease-associated morbidity and mortality among rheumatic diseases, largely because their complex pathophysiology remains poorly and incompletely understood.[1,2] Mortality in SARDs is associated with profound vascular dysfunction ranging from cardiovascular disease to more discreet localized vascular complications including Raynaud's phenomenon (RP), digital ulcers, and pulmonary arterial hypertension (PAH). These vascular complications stem from damage to endothelial cells caused by immune complex deposition,[3] platelet activation,[4] autoantibodies that promote thrombosis (e.g., antiphospholipid antibodies),[5] and immune dysregulation.[6]

The relationship between endothelial cell dysfunction and SARDs was first recognized by Maurice Raynaud in the 19th-century, particularly in the context of localized digital ischemia and gangrene.[7] RP is a frequently-encountered

problem in clinical practice, with a prevalence in the general population ranging from approximately 5–18%.[7-10] While most cases of RP are not associated with SARDs, patients with SARDs commonly experience RP.[7,9] This underscores the importance of vasculopathy related to endothelial dysfunction in the pathogenesis of SARDs.

RP is the earliest presenting feature in up to 20% of patients with SARDs.[7] Indeed, greater than 95% of patients with SSc experience RP.[11] Patients with SLE, IIMs including anti-synthetase syndrome (ASyS), and Sjögren's disease are also commonly affected.[12] Hence, a closer evaluation for microvascular changes is paramount in the clinical assessment of patients with SARDs. This article will review how nailfold video capillaroscopy is emerging as a valuable point-of-care tool for diagnosis and risk stratification by providing a window into the underlying endothelial dysfunction observed in these conditions.

Microvascular Dysfunction in SARDs is Intimately Linked to Pathogenesis

To date, the triggers of immune dysregulation and vasculopathy in SARDs remain unknown, and the pathogenesis is likely multifactorial. Contributing risks include environmental factors (e.g., viral infections,[13] silicone implants,[14] and silica[15]), genetic and epigenetic factors (e.g., defective angiogenesis[16,17] and DNA methylation[1]), genomic instability/malignancies,[18-20] and ischemic injury.[21] These factors can damage the endothelium either directly or indirectly via aberrant angiogenesis and fibroblast activation, along with an exaggerated immune response.

One of the earliest indicators of aberrant immune dysregulation in patients with SARDs is a tendency toward releasing elevated type I (e.g., alpha and beta) and/or type III (e.g., lambda) interferons.[22] Interferons are known to contribute to disease progression in SARDs through various mechanisms, particularly those related to endothelial dysfunction.[23] They also directly inhibit the proliferation of endothelial cells, thereby promoting maladaptive vascular remodelling, which further exacerbates vascular dysfunction in these diseases. In patients with various SARDs, more severe manifestations are linked with interferon dysregulation.[24,25]

Interferon signals exert both direct and indirect pleiotropic effects on microvascular endothelial cells.[26] This is relevant, as impaired angiogenesis is one of the hallmark features of SARD-associated endothelial dysfunction.[16] Further, molecules associated with aberrant endothelial cell function, such as apelin, and the soluble receptor for advanced glycation end-products (sRAGE), are elevated in patients with SARDs.[27,28] The release of these molecules promotes endothelial cell damage through pro-inflammatory signals such as high mobility group box 1 (HMGB1).[28,29] This endothelial damage, in turn, potentiates thrombosis through platelet activation and immune cell recruitment.[4]

Upon recruitment, immune cells promote further endothelial cell damage through the release of inflammatory mediators (e.g., cytokines and immune complexes). For instance, specific cytokines such as IP-10 rapidly increase in response to interferon signals, and in turn activate other innate immune cells, including plasmacytoid and myeloid dendritic cells, to promote their differentiation.[30] These cells subsequently facilitate the development of antigen-specific immune responses, ultimately resulting in the formation of immune complexes. These complexes directly activate endothelial cells, and lead to complement activation. In patients with SSc-specific antibodies (i.e., anti-Scl70, anti-centromere, anti-RNA polymerase, and anti-Th/To), autoantibodies are embedded within immune complexes. These complexes can directly activate endothelial cells and promote the release of other inflammatory mediators linked with disease progression.[3] Hence, in patients with SARDs, particularly those with SSc-spectrum disorders, systemic microvasculopathy is associated with a repetitive deleterious cycle of endothelial cell damage, microvascular remodelling, aberrant activation of somatic cells, (e.g., fibroblasts) and immune cells. This cycle directly promotes inflammation and potentiates further organ damage and disease progression. Clinically, this is highlighted by the presence of enriched perivascular inflammatory cells in nearly all patients with SSc, SLE, and IIMs,[31-33] illustrating the intimate relationship between inflammation and vascular dysfunction (**Figure 1**).

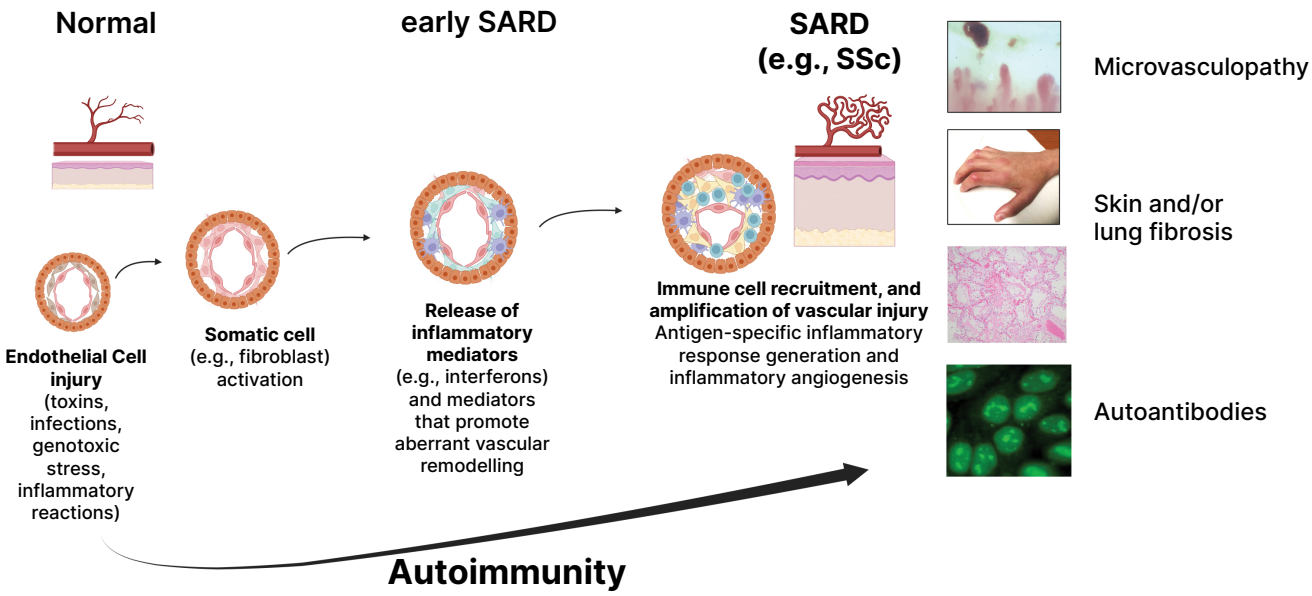

Figure 1. Simplistic overview for evolution of systemic autoimmune rheumatic diseases, (SARDs, particularly systemic sclerosis, SSc). Following vascular and Raynaud's-associated hypoxia-reperfusion injury, somatic cell activation ensues with associated release of inflammatory and vascular mediators. This results in disease amplification of inflammatory signals and disease progression. Nailfold video capillaroscopy is a point-of-care tool that can be utilized for directly visualizing SARD evolution; *created in BioRender*.

Nailfold Capillaroscopy: A Window for the Early Detection of SARDs and Their Complications

Systemic Sclerosis (SSc)

The progressive microvasculopathy observed in SSc patients is most clinically apparent in the distal nailfolds in the upper extremities. The most distal capillaries are directly exposed and positioned perpendicular to the nail bed, making them easily accessible for visualization with point-of-care tools in the clinic. This observation was first noted by Maricq and colleagues using widefield microscopy in the 1970s.[34,35] Since then, the presence of abnormal nailfold capillaries has been proposed as a useful indicator to distinguish idiopathic (primary) RP from RP due to SSc. This so-called "scleroderma pattern" is characterized by giant capillaries, microhemorrhages, and capillary disorganization/loss[36] (**Figure 2**). Individuals exhibiting a scleroderma pattern are much more likely to develop SSc than those without, particularly when SSc-specific autoantibodies are also present.[36-38] Conversely, patients with RP who lack both capillary abnormalities and seropositivity for SSc-specific autoantibodies rarely progress to develop SSc.[38] Thus, nailfold capillaroscopy serves as an indispensable tool for risk stratification of patients presenting with RP, and it is considered part of the standard-of-care in evaluating those with RP and a positive antinuclear antibody. Nailfold capillaroscopy can aid in differentiating primary RP from potentially life-threatening SARDs such as SSc. As a result, it has become an essential component of the clinical evaluation for those with RP.[7,39] Capillaroscopy has also been incorporated into the classification criteria for the very early diagnosis of systemic sclerosis (VEDOSS),[39,40] which may facilitate opportunities for early immunomodulation using antirheumatic medications.[39]

The clinical applications of capillaroscopy extend well beyond RP assessments. In patients with SSc, vascular remodelling parameters (particularly capillary loss) have been linked to disease progression including the development of digital ulcers,[41,42] skin fibrosis,[42] lung fibrosis,[43] and PAH.[42] Moreover, improvements in nailfold

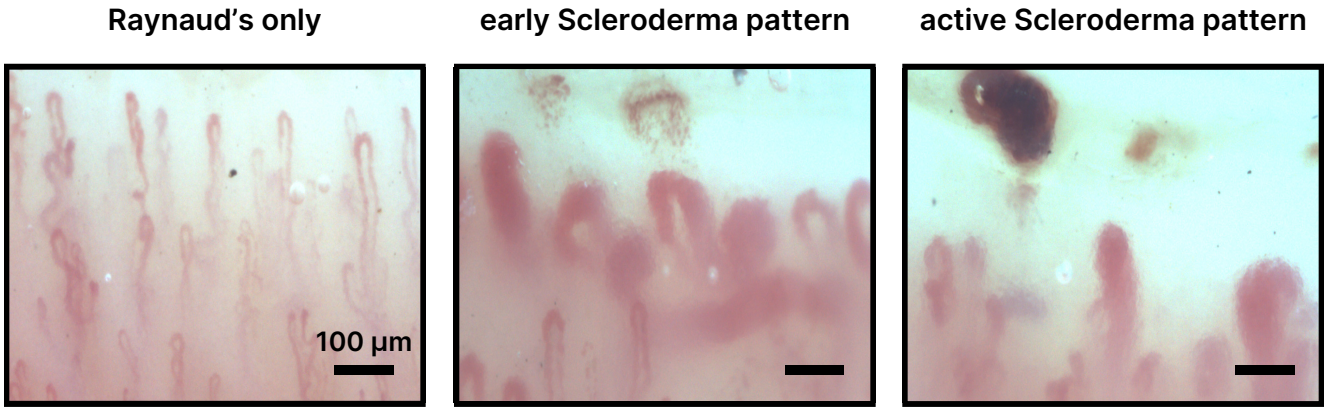

Figure 2. Representative nailfold video capillaroscopy images for a "scleroderma pattern". Images were collected using a DS Medica 2.0 device and a 200X lens. Note the presence of microhemorrhages, giant capillaries (more than 50 microns), and capillary disorganization/dropout with associated capillary loss that are more apparent in an "active scleroderma" pattern (**right**) compared to an "early scleroderma pattern" (**middle**); *courtesy of Roko P.A. Nikolic, MD, Maggie Larché, MBChB, PhD, MRCP (UK), and Mohammed Osman, MD, PhD, FRCPC.*

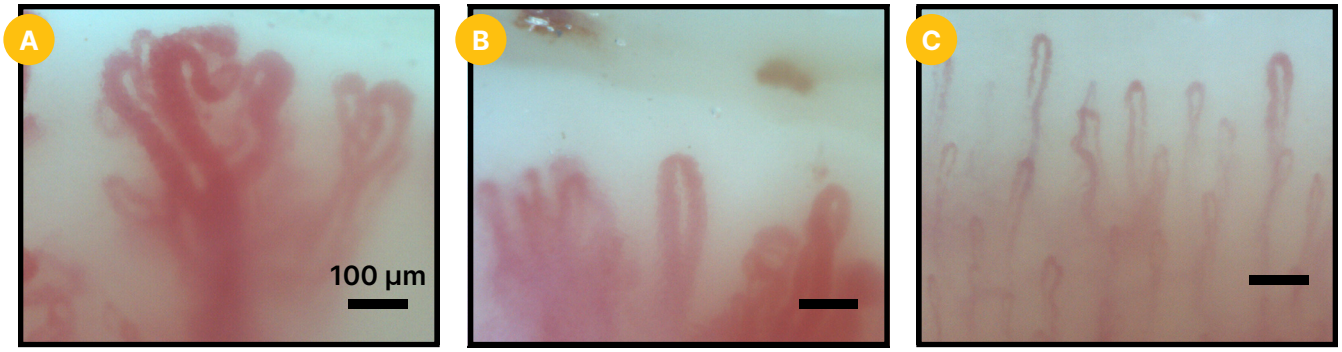

Figure 3. Representative capillary patterns in TIF-1-gamma positive dermatomyositis. Images were collected using a DS Medica 2.0 device and a 200X lens. Note the presence of bushy capillaries **(A)**, and scleroderma-like changes **(B)**. Also note the resolution of these capillary changes (from the same patient) following successful treatment using immunomodulation **(C)**; *courtesy of Roko P.A. Nikolic, MD, Maggie Larché, MBChB, PhD, MRCP (UK), and Mohammed Osman, MD, PhD, FRCPC.*

changes have been linked to the resolution of skin fibrosis in patients treated with autologous stem cell transplant[44] (**Figure 3**), highlighting the connection between nailfold capillary abnormalities and the dynamic disease evolution of SSc.

The sensitivity of capillaroscopy in predicting SSc is powerful and has been applied to other indications as well. Nailfold capillaroscopy can aid in differentiating sclerodermoid skin diseases that mimic SSc (e.g., pansclerotic morphea, eosinophilic fasciitis) from true SSc, as capillaroscopy usually appears normal in the former.[45] Importantly, some patients with morphea may also develop antinuclear antibodies, which can make the diagnosis without capillaroscopy more challenging.[46] Furthermore, the management of these scleroderma-mimicking conditions often relies upon corticosteroids.[46] However, this approach could be potentially harmful if the ultimate diagnosis is diffuse cutaneous SSc, as high doses of corticosteroids in such cases may be associated with the development of scleroderma renal crisis.[47]

Microvascular abnormalities observed in patients with SSc can also be detected in patients with other SARDs and offer prognostic value. Nailfold changes are more frequently observed in those with SARD-related interstitial lung disease than in those with interstitial pneumonia with autoimmune features or idiopathic pulmonary fibrosis.[48]

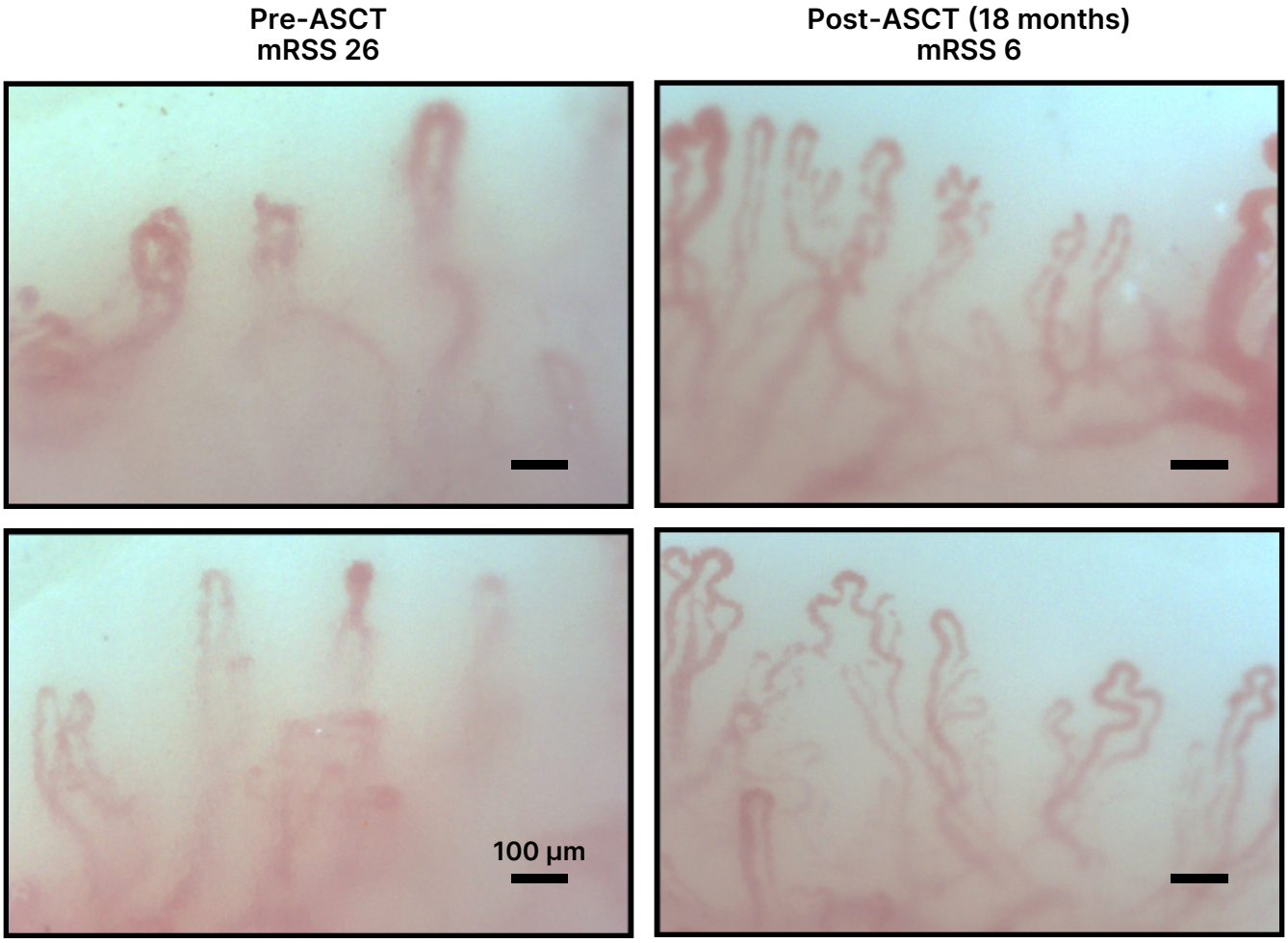

Figure 4. Capillary abnormalities in systemic sclerosis improve with autologous stem cell transplantation. Note improvement capillary density (and resolution of pericapillary edema) that correspond to marked improvement in skin fibrosis as measured using the modified Rodnan skin score (mRSS). Images were collected using a DS Medica 2.0 device and a 200X lens in a patient before autologous stem cell transplantation (ASCT), and approximately 18 months after transplantation; *courtesy of Roko P.A. Nikolic, MD, Maggie Larché, MBChB, PhD, MRCP (UK), and Mohammed Osman, MD, PhD, FRCPC.*

Idiopathic Inflammatory Myopathies: Dermatomyositis, Anti-synthetase Syndrome, and Juvenile Dermatomyositis

Diverse nailfold capillary changes can be observed in patients with IIMs – particularly those with dermatomyositis (DM) (**Figure 4**). These capillary changes range from "bushy capillaries" (reflecting profound vascular angiogenesis) to scleroderma-like changes (i.e., capillary dilation, giant capillaries, and microhemorrhages). Although these capillary changes are potentially similar to those seen in patients with SSc, the changes observed in patients with IIMs are dynamic and reversible.[49-51] The prevalence of nailfold capillary abnormalities in patients with IIMs is also quite variable. While one study identified capillary abnormalities in only 26.9% of patients with DM, a more recent study reported that 55.7% of all patients with pooled IIMs exhibited capillary changes.[50] Of note, capillary abnormalities are infrequently present in patients with acute necrotizing myositis.[52] Capillary abnormalities are frequently seen in patients who are seropositive for anti-MDA5 and anti-TIF1γ autoantibodies.[49,50,53] In one study, 87.5% of those seropositive for anti-MDA5 demonstrated these changes.[50] Additionally, changes may also be more frequently observed in those with Gottron's papules and the heliotrope sign,[50] and they correlate with skin and lung involvement.[51,54]

Nailfold changes in patients with DM are remarkably dynamic, correlating with overall disease activity and improving with immunosuppressive treatment.[50,51] In fact, microvascular changes may even normalize with the use of immunomodulators.[51] Capillary scores may correlate with interferon scores[49] and may also serve as prognostic indicators in those with IIM-associated ILD.[53] As a result, we and others have proposed that microvascular changes, particularly capillary density, may indeed be associated with global disease activity in DM.[49,51] This principle is not limited to adult patient populations. Indeed, capillary abnormalities are highly prevalent (greater than 80%) in pediatric patients with juvenile dermatomyositis (JDM).[55,56] Similar to adult DM, capillary density in JDM reflects overall disease activity and appears to respond to immunomodulation.[55,57]

Curiously, capillary abnormalities are not observed as frequently in patients with ASyS.[49,50] Nonetheless, patients with ASyS may develop giant (enlarged) capillaries associated with capillary disorganization, particularly when visceral involvement is apparent.[58] Thus, inflammatory angiogenesis may be an important contributor to the progression of lung fibrosis in IIMs and particularly in patients with RP, including those with ASyS and anti-MDA5 DM.

Systemic Lupus Erythematosus

The nailfold changes observed in patients with SLE are often termed "non-specific."[36,59] This means that while abnormal, these changes do not strictly fulfill the criteria defining the scleroderma-like pattern appreciable in those with systemic sclerosis.[36,41,60] Capillaroscopy in those with SLE may be associated with reduced capillary density, particularly when visceral organs are affected, as well as increased capillary tortuosity, corkscrew-shaped capillaries, microhemorrhages, and heterogeneity in capillary size.[59,61,62] One study reported that nailfold capillary abnormalities in those with SLE were significantly more common in those with RP, and were predictive of seropositivity for anti-U1-RNP and anticardiolipin antibodies.[61] Further, only 6% of those with SLE demonstrated "scleroderma-like" changes.[61] Hence, nailfold changes may be useful in discerning between the two SARDs in patients presenting with RP. Nailfold abnormalities correlate with disease activity and anti-dsDNA titers in patients with SLE.[59,63,64] They have also been suggested as predictors of SLE-associated ILD,[65] and the presence of normal capillaries can help reduce the likelihood of lupus nephritis.[66] Nonetheless, the potential relationship between nailfold abnormalities and organ involvement in SLE remains to be clarified.[59]

Other Autoimmune Rheumatic Diseases

Capillaroscopy is increasingly being used to assess patients with other autoimmune rheumatic diseases including rheumatoid arthritis, psoriatic arthritis,[67] and Sjögren's disease.[68] However, its role in assessing patients with these conditions remains less defined. Although uncommon, scleroderma-like nailfold changes can be observed in patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, where capillary abnormalities may similarly correlate with disease activity.[69]

Challenges Associated with Capillaroscopy: Standardization and Implementation

Despite the diagnostic and prognostic information available through nailfold video capillaroscopy for patients with SARDs, most clinicians have not yet incorporated this technique in routine clinical practice. As a result, international efforts have been made to standardize nailfold video capillaroscopy.[36] Further, newer devices, equipped with software that uses machine learning to semi-automatically identify abnormal capillaries, including detecting scleroderma-associated capillary changes, have been developed.[70] Newer and less expensive alternatives for nailfold video capillaroscopy have made capillary assessment much more accessible.[71] Introductory basic training in capillaroscopy is now available through the European Alliance of Associations for Rheumatology.[36] The significant diagnostic value of this technique has warranted myriad efforts to enhance its accessibility and standardization.

Conclusions and Future Directions

Nailfold capillaroscopy has emerged as an accessible and invaluable point-of-care tool for diagnosing, prognosticating, and managing patients with SARDs. By enabling a sensitive and direct assessment of the microvascular changes observed in patients with these conditions, capillaroscopy bridges the clinical manifestations of SARDs with their underlying pathophysiology. As a prognostic tool, capillaroscopy facilitates accurate differentiation between patients with primary RP who are at low risk for systemic complications, those with scleroderma-mimicking features, and those with RP that may indicate potentially life-threatening SARDs.[36-38,45,46] This differentiation aids in directing further investigation and follow-up. The utility of capillaroscopy in monitoring of SSc and IIM[44,51] holds promise for expanding its role in the tailored and personalized care of patients with these SARDs in the future. Further research may better characterize the utility of capillaroscopy in predicting outcomes for patients with SSc, SLE, and IIM, with respect to other systemic manifestations.

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M.O.: None declared.

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