

Review

Emerging Blood Biomarkers in Systemic Sclerosis: From Single Molecules to Biomarker-Based Patient Stratification

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Abstract

Background/Objectives: Systemic sclerosis (SSc) is a heterogeneous systemic autoimmune rheumatic disease characterized by immune dysregulation, vasculopathy, and fibrosis involving the skin and internal organs. Interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), and cardiac involvement remain major causes of morbidity and mortality, yet prediction of disease progression and therapeutic responsiveness remains difficult. **Methods:** This narrative review summarizes studies of circulating blood biomarkers in SSc, with emphasis on literature published since 2020 and on Japanese multicenter longitudinal cohort studies. Disease-specific autoantibodies were intentionally excluded from the main scope, and the review focuses on soluble biomarkers measurable in peripheral blood that reflect inflammation, endothelial injury, and fibrotic remodeling. **Results:** Multiple cytokines, chemokines, adhesion molecules, endothelial markers, extracellular vesicle-associated molecules, and extracellular matrix (ECM)-related molecules have been associated with disease activity, organ involvement, prognosis, and therapeutic response in SSc. Clinically established biomarkers such as KL-6 and surfactant protein-D (SP-D) for SSc-associated interstitial lung disease (ILD), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) for pulmonary arterial hypertension (PAH), are already used as adjunctive tools in routine clinical assessment, whereas many other candidate biomarkers, including interleukin (IL)-6, CCL2, CXCL8, CXCL4, intercellular adhesion molecule-1 (ICAM-1), CCL18, periostin, endostatin, endothelin-1, extracellular vesicle signatures, and ECM turnover markers remain at varying stages of clinical validation. In particular, Japanese multicenter longitudinal studies have demonstrated the prognostic significance of circulating chemokines and adhesion molecules in early SSc and, more recently, identified biomarker-based clusters associated with distinct pulmonary trajectories. Recent multidimensional proteomic and transcriptomic approaches further support biologically based patient stratification in SSc. **Conclusions:** Blood biomarkers may contribute to risk stratification, prediction of organ progression, and future precision medicine in SSc. Integrated biomarker signatures may better capture the biological heterogeneity of SSc than single biomarkers alone. However, most candidate biomarkers still require external validation, assay standardization, and demonstration of incremental value over conventional clinical variables before routine clinical implementation.

Keywords: systemic sclerosis; biomarker; cytokine; chemokine; fibrosis; interstitial lung disease; endothelial dysfunction; precision medicine



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1. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune rheumatic disease characterized by immune abnormalities, microvascular injury, and fibrosis involving the skin and internal organs. The clinical phenotype of SSc varies markedly among patients, ranging from relatively mild involvement to severe multisystem disease complicated by interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), cardiac dysfunction, or renal crisis. This heterogeneity represents one of the greatest challenges in clinical management and therapeutic development [1–7].

ILD develops in approximately half of patients with SSc and remains a leading cause of mortality. In addition, vascular complications such as PAH and digital ulcers substantially impair quality of life and prognosis. Early identification of patients at risk for progressive organ involvement is therefore critically important. However, clinical assessment alone often fails to accurately predict disease trajectories [1–7].

Although biomarkers obtained directly from affected organs or tissues may provide more precise information regarding local pathophysiology and organ-specific disease activity, such approaches are often invasive and difficult to apply routinely in clinical practice. In contrast, peripheral blood biomarkers can be obtained relatively easily and repeatedly, making them more practical for daily clinical assessment and longitudinal disease monitoring. Therefore, this review focuses specifically on circulating soluble biomarkers and related blood-derived molecular signatures in SSc.

Traditionally, disease-specific autoantibodies such as anti-topoisomerase I antibody and anticentromere antibody have been used for diagnosis and clinical classification. Nevertheless, autoantibodies generally reflect stable immunologic phenotypes rather than dynamic disease activity. Consequently, there has been growing interest in soluble circulating biomarkers capable of reflecting ongoing inflammation, endothelial activation, and fibrotic remodeling [8,9].

Over the last two decades, numerous cytokines, chemokines, adhesion molecules, growth factors, extracellular vesicle-associated molecules, and extracellular matrix (ECM)-related molecules have been investigated as candidate biomarkers in SSc. Initially, most studies focused on single molecules associated with disease activity or organ involvement. Subsequently, longitudinal cohort studies demonstrated prognostic significance of certain biomarkers. More recently, multidimensional approaches integrating multiple biomarkers and unsupervised clustering have emerged as promising strategies for identifying biologically distinct disease subsets.

Japanese multicenter cohort studies have made substantial contributions to this field. Early studies demonstrated associations between circulating chemokines and disease activity, while subsequent longitudinal analyses identified prognostic biomarkers for pulmonary decline and physical dysfunction. More recently, biomarker-based clustering approaches identified distinct pulmonary trajectories in early severe SSc, representing an important step toward biomarker-driven precision medicine [10–13].

This review summarizes advances in circulating soluble biomarkers in SSc, with particular emphasis on studies published since 2020 and on findings from Japanese longitudinal cohort studies. Unlike previous systematic reviews that focused mainly on individual biomarkers or SSc-ILD, this narrative review emphasizes the transition from single soluble biomarkers to integrated biomarker signatures and patient stratification, with particular attention to longitudinal evidence and translational limitations.

2. Literature Search Strategy

Literature for this narrative review was primarily identified through searches of PubMed and related databases using combinations of the terms “systemic sclerosis” and

“biomarker”. Particular emphasis was placed on studies published since 2020, although earlier landmark studies, especially longitudinal cohort studies from Japan, were also included when considered important for understanding the evolution of biomarker research in SSc. Priority was given to peer-reviewed clinical studies, translational investigations, systematic reviews, and recent review articles relevant to circulating blood biomarkers in SSc. Because this was not a systematic review, no formal risk-of-bias assessment, meta-analysis, or GRADE evaluation was performed. Therefore, the strength of evidence was interpreted qualitatively, with particular attention to study design, longitudinal validation, replication, and clinical applicability.

3. Pathophysiological Basis of Blood Biomarkers in SSc

The pathogenesis of SSc is complex and incompletely understood but is generally considered to involve three interrelated processes: immune dysregulation, endothelial dysfunction, and fibrosis. Blood biomarkers are thought to reflect these pathogenic pathways [1–9,14].

3.1. Immune Dysregulation

Immune activation is an early and central event in SSc. Both innate and adaptive immune responses contribute to disease progression. Activated monocytes/macrophages, T cells, and B cells infiltrate affected tissues and produce numerous inflammatory mediators including cytokines and chemokines [3,14].

Macrophages play particularly important roles in SSc fibrosis. Alternatively activated macrophages produce profibrotic mediators such as transforming growth factor-beta (TGF-beta), IL-6, and CCL18. T helper cell polarization is also altered in SSc, with contributions from Th2, Th17, and T follicular helper pathways [9,14].

Recent therapeutic studies have further strengthened the concept that B cells play central pathogenic roles in SSc. The DESIRES trial demonstrated that rituximab, a monoclonal antibody targeting CD20-positive B cells, significantly improved skin sclerosis in patients with SSc and showed favorable effects on pulmonary involvement [15]. In addition, emerging evidence suggests that CD19-targeted chimeric antigen receptor (CAR)-T cell therapy may represent a novel therapeutic strategy for severe refractory SSc. Recent case series demonstrated marked improvement in skin fibrosis and interstitial lung disease following CAR-T cell therapy, further supporting the pathogenic importance of B cells in SSc [16].

Type I interferon (IFN) signaling is increasingly recognized as another major immunologic pathway in SSc. IFN-inducible gene signatures have been identified in subsets of patients and are associated with inflammatory phenotypes and progressive disease [17]. Because these inflammatory pathways generate soluble mediators detectable in serum, circulating cytokines and chemokines may reflect ongoing disease activity [9,17].

3.2. Endothelial Dysfunction and Vasculopathy

Vascular injury is a hallmark of SSc and often precedes overt fibrosis. Endothelial cell activation and apoptosis lead to impaired angiogenesis, vascular remodeling, and tissue ischemia [3,14]. Activated endothelial cells express adhesion molecules such as intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule-1 (VCAM-1), and selectins, facilitating leukocyte recruitment into tissues. Platelet activation further amplifies vascular inflammation through release of chemokines and growth factors [11,12].

Although angiogenic mediators such as vascular endothelial growth factor (VEGF) are elevated in SSc, effective angiogenesis is paradoxically impaired, suggesting dysregulated vascular repair mechanisms. Recent clinical studies evaluating IL-8, VEGF, basic fibroblast

growth factor, and IFN- α further support the concept that angiogenic and inflammatory mediator profiles reflect vascular involvement and disease course in SSc [18].

Endoglin is a TGF- β co-receptor expressed on endothelial cells and involved in vascular remodeling. A systematic review highlighted soluble endoglin as a candidate endothelial biomarker in SSc, particularly in relation to PAH and vascular complications [19].

3.3. Fibrosis and Extracellular Matrix Remodeling

Fibrosis results from persistent activation of fibroblasts and myofibroblasts. In addition to resident fibroblasts, mesenchymal transition of endothelial cells, pericytes, epithelial cells, and other cellular sources have been proposed to contribute to myofibroblast accumulation in fibrotic diseases, including SSc [20]. Activated fibroblasts produce excessive collagen and ECM proteins, leading to progressive tissue stiffness and organ dysfunction [3,14,20].

TGF- β signaling represents a central profibrotic pathway in SSc. Additional mediators including IL-6, connective tissue growth factor, endothelin-1, and periostin also contribute to fibroblast activation [9,14,20]. ECM turnover generates measurable circulating biomarkers including collagen neoepitopes, matrix metalloproteinases (MMPs), and matricellular proteins. These molecules may directly reflect ongoing fibrotic activity [20,21].

4. Cytokines and Chemokines

4.1. IL-6 and Related Inflammatory Mediators

IL-6 is among the most extensively studied cytokines in SSc and is strongly implicated in inflammation and fibrosis. Elevated serum IL-6 levels are associated with diffuse cutaneous disease, higher modified Rodnan skin score (mRSS), inflammatory phenotypes, progressive skin fibrosis, and worse pulmonary outcomes [9,21]. IL-6 promotes fibroblast activation through JAK/STAT signaling and enhances collagen synthesis. It also contributes to B-cell activation and Th17 differentiation [9,14].

Emerging inflammatory biomarkers are also being investigated in SSc. Recently, soluble oncostatin M receptor was proposed as a potential diagnostic biomarker, suggesting possible involvement of oncostatin M signaling pathways in SSc-related inflammation and fibrosis [22].

The clinical importance of IL-6 was reinforced by clinical trials of tocilizumab, an anti-IL-6 receptor antibody. Biomarker analyses from the focuSSced trial suggested that IL-6-related inflammatory pathways are linked to progressive pulmonary fibrosis [21–23]. Tocilizumab also appeared to stabilize lung function in early SSc-ILD, further supporting the relevance of inflammatory biomarkers in identifying treatment-responsive phenotypes [23,24].

4.2. CCL2 (MCP-1)

CCL2 is a monocyte chemoattractant strongly implicated in SSc fibrosis. CCL2 recruits monocytes and macrophages into tissues and may directly promote fibroblast activation [9,10,14]. Serum CCL2 levels are elevated in SSc and are associated with ILD severity and skin fibrosis. Earlier Japanese cohort studies demonstrated that serum CCL2 levels correlated with disease activity and longitudinal pulmonary dysfunction [10,11]. Because macrophage-driven fibrosis is central to SSc pathogenesis, CCL2 remains one of the most biologically plausible profibrotic biomarkers [9–11].

4.3. CXCL8 (IL-8)

CXCL8 is a neutrophil-attracting chemokine associated with inflammatory and vascular activation [10,11,18]. Japanese longitudinal cohort studies demonstrated elevated CXCL8 levels in early SSc and identified baseline CXCL8 levels as predictors of subsequent

physical dysfunction [11]. These findings suggested that soluble inflammatory mediators may predict future disease progression rather than merely reflect current activity [11].

4.4. IFN-Related Chemokines and Type I Interferon Signaling

CXCL9 and CXCL10 are IFN-inducible chemokines associated with Th1-type inflammation and activation of type I IFN pathways. Elevated serum levels of these chemokines have been observed particularly in early inflammatory SSc and are associated with inflammatory disease activity and diffuse cutaneous involvement [10,11,17]. Accumulating evidence increasingly supports the importance of type I IFN signaling in the pathogenesis of SSc. IFN-inducible gene signatures and serum IFN scores have been associated with inflammatory phenotypes, progressive fibrosis, and biologically distinct disease subsets [17].

These findings suggest that IFN-related biomarkers may eventually contribute to molecular classification and biomarker-based precision medicine approaches in SSc. Furthermore, IFN-related pathways may represent potential therapeutic targets in inflammatory SSc phenotypes [17].

4.5. CXCL4 and Other Platelet-Derived Biomarkers

CXCL4 has emerged as one of the most promising biomarkers in SSc. Originally identified as a platelet-derived chemokine, CXCL4 is strongly associated with fibrosis and vascular disease [25–27]. High CXCL4 levels correlate with ILD progression, PAH, digital ulcers, and mortality. Experimental and translational studies suggest that CXCL4 may contribute to endothelial dysfunction, innate immune activation, and fibroblast activation [25–27]. Because CXCL4 appears closely linked to severe fibrotic phenotypes, it may represent both a biomarker and pathogenic mediator [25–27]. In addition to CXCL4 (also known as platelet factor 4, PF4), other platelet-derived mediators such as soluble CD40 ligand (sCD40L) have also been investigated as candidate biomarkers of vascular activation, although current evidence remains limited [28].

5. Adhesion Molecules and Endothelial Biomarkers

5.1. ICAM-1 and Selectins

Adhesion molecules play critical roles in leukocyte recruitment and endothelial activation [12]. A multicenter Japanese study demonstrated elevated serum ICAM-1, E-selectin, and P-selectin levels in patients with early SSc. Importantly, baseline ICAM-1 levels predicted subsequent decline in pulmonary function [12]. P-selectin levels were also associated with future disability progression, suggesting relationships between platelet/endothelial activation and systemic disease severity [12].

5.2. VEGF, Endostatin, and Angiogenic Mediators

VEGF is elevated in SSc despite defective angiogenesis. This paradox suggests dysregulated vascular repair mechanisms. VEGF levels have been associated with digital ulcers, PAH, and abnormal nailfold capillary findings, although its clinical utility as an isolated biomarker remains uncertain [18].

Recent meta-analytic evidence further supports the importance of angiogenesis-related biomarkers in SSc. Circulating endostatin, an endogenous anti-angiogenic glycoprotein, is significantly elevated in patients with SSc, particularly in those with digital ulcers and PAH. These findings suggest that endostatin may reflect impaired vascular repair and progressive vasculopathy in SSc [29].

5.3. Endothelin-1 and Endoglin

Endothelin-1 is a potent vasoconstrictor implicated in vascular remodeling and fibrosis [2]. Elevated endothelin-1 levels have been associated with PAH, digital ulcers, and pulmonary fibrosis. A recent systematic review and meta-analysis further confirmed significantly elevated circulating endothelin-1 levels in patients with SSc compared with healthy controls, supporting its role as a biomarker of vascular dysfunction and fibrosis [30].

Endoglin integrates vascular and profibrotic signaling pathways and may represent an important mechanistic biomarker. Elevated soluble endoglin levels have been associated with PAH and vascular complications in SSc [19].

6. Fibrosis and Extracellular Matrix Biomarkers

6.1. KL-6 and SP-D

KL-6 and SP-D are widely used biomarkers for SSc-associated ILD. In Japan, both biomarkers are routinely measured in clinical practice and are covered by the national health insurance system for the evaluation and monitoring of interstitial lung diseases. Elevated KL-6 reflects alveolar epithelial injury and correlates with high-resolution computed tomography abnormalities and pulmonary function impairment. Longitudinal cohort studies further demonstrated that elevated KL-6 levels were associated with subsequent decline in DLCO and progressive pulmonary dysfunction, supporting its prognostic utility in SSc-ILD [31].

Candidate serum biomarker studies have shown that KL-6, SP-D, CCL18, and related pneumoproteins are associated with ILD severity and progression, although their performance differs across cohorts and disease stages [32,33].

6.2. CCL18

CCL18 is produced mainly by alternatively activated macrophages and is strongly associated with pulmonary fibrosis [33,34]. Several studies identified elevated CCL18 levels as predictors of progressive ILD and mortality in SSc [33,34]. Because macrophage activation plays central roles in fibrosis, CCL18 may represent one of the most robust fibrosis-related biomarkers [33,34].

6.3. Periostin, IGFBP7, COMP, and Collagen Turnover Markers

Periostin is a matricellular protein induced by IL-4, IL-13, and TGF-beta signaling and has emerged as a candidate biomarker reflecting cutaneous and pulmonary fibrosis in SSc. Biomarker analyses from therapeutic trials further support its role as a fibrosis-related biomarker [21]. Serum periostin levels were positively correlated with mRSS, particularly in diffuse cutaneous SSc, and were associated with progressive skin sclerosis during longitudinal follow-up [35].

Insulin-like growth factor-binding protein (IGFBP) 7 has also emerged as a candidate fibrosis-related biomarker in SSc. Elevated serum IGFBP7 levels were associated with diffuse cutaneous disease, increased skin thickness, and interstitial lung disease, suggesting potential involvement in fibroblast activation and tissue remodeling [36].

Cartilage oligomeric matrix protein (COMP) and collagen neopeptides such as Pro-C3 reflect ECM remodeling and collagen synthesis. Recent studies demonstrated associations between these markers and progressive cutaneous and pulmonary fibrosis, suggesting that they may eventually allow direct monitoring of active fibrogenesis [21].

6.4. Matrix Metalloproteinases

MMPs regulate ECM degradation and remodeling. Altered levels of MMP-7 and MMP-12 have been associated with ILD severity and progressive fibrosis [31,37]. Recent

studies suggest that combined MMP/TIMP signatures may improve diagnostic accuracy for connective tissue disease-associated ILD. In particular, MMP-7, MMP-9, MMP-10, and MMP-12 were significantly elevated in SSc-ILD and may contribute to earlier identification of pulmonary involvement [37].

7. Biomarkers for Organ Involvement

Although many biomarkers discussed in the previous sections overlap across inflammatory, vascular, and fibrotic pathways, their relative clinical relevance may differ according to specific organ involvement. Therefore, this section summarizes biomarker profiles from the perspective of major organ complications in SSc.

7.1. Skin Fibrosis

Skin fibrosis remains a central clinical manifestation and therapeutic target in SSc. mRSS is widely used for assessment of severity, longitudinal progression, and therapeutic response of skin fibrosis. Several circulating biomarkers have been associated with the extent and progression of cutaneous involvement.

Elevated serum IL-6 levels have been associated with diffuse cutaneous involvement, higher mRSS, and inflammatory phenotypes [9,21]. CCL2 has also been linked to skin fibrosis and profibrotic macrophage activation [10,11].

Periostin has emerged as a promising biomarker reflecting cutaneous fibrosis. Serum periostin levels correlated positively with mRSS and progressive skin fibrosis, particularly in diffuse cutaneous SSc [35]. Similarly, IGFBP7 was associated with diffuse cutaneous disease and increased skin thickness [36].

ECM turnover markers including COMP and Pro-C3 may reflect active fibrogenesis in skin tissues and could potentially serve as biomarkers of ongoing cutaneous fibrosis [21].

7.2. Interstitial Lung Disease

ILD is the most important determinant of mortality in many SSc cohorts [5,6]. Multiple biomarkers have been associated with ILD severity or progression, including KL-6, SP-D, CCL18, IL-6, CCL2, CXCL4, ICAM-1, periostin, MMPs, and extracellular vesicle-associated biomarkers [21,31–40]. However, single biomarkers alone often show limited predictive accuracy [32,33,38]. Consequently, integrated biomarker approaches may provide superior prediction of pulmonary trajectories [13,32,38].

Recent studies have also highlighted extracellular vesicles (EVs) as emerging biomarkers in SSc-ILD. Increased circulating EV subpopulations, particularly ICAM1-positive EVs, were associated with progressive fibrosing ILD and independently predicted pulmonary progression during longitudinal follow-up [39].

International cohort studies have also provided important context for interpreting blood biomarkers in SSc-ILD. In the EUSTAR database, progressive ILD showed heterogeneous longitudinal patterns, emphasizing the need for biomarkers that can complement serial pulmonary function testing and clinical risk factors [41].

Analyses from the SENSICIS trial further demonstrated that patients with SSc-ILD remain at risk for lung function decline across a range of baseline fibrotic extents, supporting the need for broadly applicable prognostic tools [42].

In addition, international biomarker studies have shown that pneumoproteins, inflammatory mediators, endothelial biomarkers, and matrix remodeling markers, including KL-6, SP-D, CCL18, CXCL4, ICAM-1, endothelin-1, and matrix metalloproteinases, may provide prognostic information, although their performance varies across cohorts and requires further validation [32,38,43,44].

7.3. Pulmonary Hypertension

Biomarkers associated with PAH include BNP/NT-proBNP, endoglin, endothelin-1, endostatin, VEGF-related molecules, and EV-associated signatures. NT-proBNP is currently the most clinically established circulating biomarker for SSc-associated pulmonary arterial hypertension (PAH). Reflecting myocardial wall stress and right ventricular overload, elevated NT-proBNP levels are associated with disease severity, right ventricular dysfunction, and adverse prognosis. Importantly, NT-proBNP has been incorporated into established screening strategies, including the DETECT algorithm [45], and is widely used in routine clinical practice for risk assessment and longitudinal monitoring of SSc-PAH. In contrast, several other candidate vascular biomarkers, including endoglin, endostatin, and endothelin-1, remain investigational despite accumulating evidence supporting their potential clinical utility [2,19,29,30]. Recent longitudinal studies have further identified GDF-15 and PSP-D as promising candidate biomarkers for future development of SSc-associated PAH [46].

7.4. Cardiac Involvement

Cardiac involvement in SSc ranges from subclinical myocardial fibrosis to severe arrhythmias and heart failure. Candidate biomarkers include troponins, natriuretic peptides, inflammatory cytokines, and fibrosis markers [47,48]. Because early detection of cardiac involvement remains difficult, additional biomarker development is needed.

8. Japanese Longitudinal Cohort Studies in SSc Biomarker Research

Japanese multicenter longitudinal cohort studies have provided important insights into circulating biomarkers associated with disease progression and organ involvement in SSc [10–13]. Early studies demonstrated elevated serum levels of chemokines including CCL2, CXCL8, CXCL9, and CXCL10 in patients with SSc [10,11]. Subsequent longitudinal analyses demonstrated that baseline CXCL8 levels predicted future physical dysfunction in early SSc, establishing the prognostic significance of soluble inflammatory biomarkers [11].

Further studies investigated endothelial biomarkers including ICAM-1 and selectins. Baseline ICAM-1 levels predicted subsequent pulmonary decline, linking endothelial activation to progressive ILD [12]. In a recent multicenter Japanese cohort study, patients with early severe SSc were classified into three biomarker-defined clusters based on serum chemokine and adhesion molecule profiles using k-means clustering analysis [13].

Cluster 1 was characterized by elevated sICAM-1 and sE-selectin levels, whereas Cluster 2 showed elevated CCL2, CXCL8, and sP-selectin levels. Cluster 3 showed no distinctive biomarker pattern and served as the reference group. Importantly, these clusters demonstrated distinct pulmonary function trajectories. Cluster 1 showed impaired pulmonary function at baseline with only minimal further decline during follow-up, whereas Cluster 2 initially showed relatively preserved pulmonary function but demonstrated progressive decline over time. In contrast, pulmonary function remained relatively stable throughout the disease course in Cluster 3 [13].

These findings suggest that serum biomarker profiles may reflect biologically distinct inflammatory and vascular disease processes associated with different patterns of pulmonary progression in early severe SSc. This progression from single biomarkers to integrated clustering approaches represents a major conceptual advance in SSc biomarker research [10–13].

Because SSc is biologically and clinically heterogeneous, single biomarkers alone may not sufficiently capture complex disease phenotypes or differences across ethnic populations. Integrated multi-biomarker clustering approaches may therefore provide more robust stratification of patients by simultaneously reflecting multiple pathogenic

pathways, including inflammation, endothelial dysfunction, and fibrosis. Such approaches may also improve longitudinal prediction of organ progression beyond conventional single-marker analyses. Major Japanese longitudinal cohort studies and their principal biomarker findings are summarized in Table 1.

Table 1. Major Japanese Longitudinal Cohort Studies of Circulating Biomarkers in Systemic Sclerosis.

Study	Biomarkers Investigated	Main Findings	Clinical Implications
Hasegawa et al., Clin. Rheumatol. 2011 [10]	CCL2, CXCL8, CXCL9, CXCL10, and cytokines	Chemokines and cytokines were elevated and associated with disease activity.	Early evidence for soluble inflammatory biomarkers in Japanese SSc.
Hasegawa et al., Mod. Rheumatol. 2013 [11]	CCL2, CCL5, CXCL8, CXCL9, CXCL10	Baseline CXCL8 predicted future physical dysfunction.	Longitudinal prognostic biomarker study.
Hasegawa et al., PLoS ONE 2014 [12]	ICAM-1, E-selectin, L-selectin, P-selectin	Baseline ICAM-1 predicted subsequent pulmonary dysfunction; P-selectin was associated with disability.	Endothelial biomarkers linked to prognosis.
Uesugi-Uchida et al., Front. Immunol. 2026 [13]	Multi-biomarker clustering of chemokines and adhesion molecules	Three biomarker-defined clusters showed distinct pulmonary trajectories.	Prototype of biomarker-based precision medicine in early severe SSc.

Abbreviations: CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; ICAM-1, intercellular adhesion molecule-1; SSc, systemic sclerosis.

These Japanese longitudinal cohort studies should be interpreted as complementary to international cohort and trial-based evidence rather than as isolated findings. While Japanese studies have highlighted the prognostic significance of chemokines and adhesion molecules in early SSc, large international datasets such as EUSTAR and SENSICIS have emphasized the heterogeneity of SSc-ILD progression and the importance of integrating biomarkers with clinical variables, pulmonary function tests, HRCT findings, and treatment background [41,42]. Further cross-validation between Japanese and non-Asian cohorts will be essential to determine the generalizability of biomarker-based stratification.

9. Biomarker-Based Precision Medicine

Recent advances in machine learning and systems biology have accelerated development of biomarker-based precision medicine approaches [13,49,50]. Because SSc is biologically heterogeneous, patients with similar clinical phenotypes may have fundamentally different pathogenic pathways [1,13]. Molecular profiling may therefore allow identification of biologically distinct patient subsets with different prognoses and therapeutic responsiveness.

Integrative clustering analyses combining clinical and proteomic data have further strengthened the concept of biologically distinct SSc subsets. Dans-Caballero et al. identified two clinically and molecularly distinct clusters characterized by different patterns of organ involvement, autoantibody profiles, and circulating proteomic signatures associated with fibrosis, endothelial dysfunction, and inflammation [49]. Importantly, serum obtained from patients in the severe cluster induced profibrotic and inflammatory gene expression in dermal fibroblasts in vitro, supporting the biological relevance of molecular stratification approaches and suggesting that circulating molecular profiles may actively contribute to disease progression [49].

Transcriptome-integrated biomarker studies have identified soluble CD13 as a potential novel circulating biomarker in SSc. Elevated soluble CD13 levels were associated with inflammatory and immune-related transcriptomic signatures in peripheral blood, suggesting possible utility for molecular stratification and precision medicine approaches [50].

Extracellular vesicle-associated microRNA signatures may further improve molecular stratification in SSc. A recent study identified a four-miRNA extracellular vesicle signature associated with SSc-ILD and progressive profibrotic pathways [51].

Potential applications of integrated biomarker strategies include prediction of ILD progression, identification of inflammatory versus fibrotic phenotypes, therapeutic response prediction, and enrichment of clinical trial populations. Integration of circulating biomarkers with transcriptomics, proteomics, imaging, and clinical data may further improve disease stratification and individualized therapeutic approaches.

Representative circulating biomarkers in SSc, including their biological functions and associations with organ involvement and fibrosis, are summarized in Table 2. Potential clinical applications of circulating biomarkers and integrated biomarker-based strategies in SSc are summarized in Table 3.

Table 2. Representative Circulating Biomarkers in Systemic Sclerosis and Their Current Clinical Readiness.

Biomarker	Main Biological Role	Clinical Associations	Potential Utility	Clinical Readiness
IL-6 [9,21,23,24]	Inflammation; fibroblast activation	Skin fibrosis; ILD progression	Disease activity; therapeutic response	Advanced clinical validation
sOSMR [22]	Oncostatin M signaling	Diagnostic association	Emerging inflammatory biomarker	Experimental
CCL2 (MCP-1) [10,11]	Monocyte recruitment	Skin fibrosis; ILD	Prognostic biomarker	Emerging
CXCL8 (IL-8) [10,11,18]	Neutrophil recruitment	Physical dysfunction; vascular inflammation	Longitudinal prognosis	Emerging
CXCL9/CXCL10 [10,11,17]	IFN-related inflammation	Early inflammatory SSc	Immune profiling	Emerging
CXCL4 [25–27]	Platelet activation; DAMP-like activity	ILD progression; PAH; severe disease	High-risk phenotype	Advanced clinical validation
ICAM-1 [12,13]	Endothelial activation	Pulmonary decline	ILD prognosis	Emerging
E-selectin/P-selectin [12,13]	Endothelial/platelet activation	Vascular involvement; disability	Disease severity	Emerging
VEGF [18]	Angiogenesis	Digital ulcers; PAH	Vascular monitoring	Emerging
Endostatin [29]	Anti-angiogenic mediator	Digital ulcers; PAH	Vascular risk marker	Emerging
Endothelin-1 [30]	Vasoconstriction; vascular remodeling	PAH; fibrosis	Vascular dysfunction	Advanced clinical validation
Endoglin [19]	Vascular remodeling	PAH	Endothelial biomarker	Emerging
NT-proBNP [45]	Cardiac wall stress	PAH, right ventricular dysfunction	Screening and prognostic assessment of SSc-PAH	Established
KL-6 [31–33]	Alveolar injury	ILD severity; DLCO decline	Pulmonary monitoring	Established
SP-D [31,32]	Lung epithelial injury	ILD progression	ILD biomarker	Established
CCL18 [33,34]	Macrophage activation	Progressive ILD	Prognostic biomarker	Advanced clinical validation

Table 2. Cont.

Biomarker	Main Biological Role	Clinical Associations	Potential Utility	Clinical Readiness
Periostin [21,35]	Fibroblast activation	Skin sclerosis progression; ILD	Fibrotic activity	Emerging
IGFBP7 [36]	Fibrosis-related secreted protein	dcSSc; skin fibrosis; ILD	Emerging fibrosis biomarker	Experimental
COMP/Pro-C3 [21]	ECM remodeling; collagen synthesis	Skin and lung fibrosis	ECM turnover	Emerging
MMP/TIMP signatures [37,38]	Matrix remodeling	SSc-ILD	ILD detection	Emerging
EV/EV-miRNA signatures [39,51]	Cell-derived vesicle signaling	Progressive ILD	Molecular stratification	Experimental
Soluble CD13 [50]	Immune-related transcriptomic signal	Inflammatory phenotype	Precision medicine	Experimental

Clinical readiness was categorized according to the current level of external validation and routine clinical implementation. Established: routinely used in clinical practice or incorporated into clinical algorithms; Advanced clinical validation: supported by multiple independent cohorts; Emerging: promising but requiring further validation; Experimental: early-stage biomarkers with limited clinical evidence. Abbreviations: CCL, C-C motif chemokine ligand; COMP, cartilage oligomeric matrix protein; CXCL, C-X-C motif chemokine ligand; DAMP, damage-associated molecular pattern; dcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusing capacity for carbon monoxide; ECM, extracellular matrix; EV, extracellular vesicle; ICAM-1, intercellular adhesion molecule-1; IFN, interferon; IGFBP7, insulin-like growth factor-binding protein 7; IL, interleukin; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; MMP, matrix metalloproteinase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; Pro-C3, procollagen type III N-terminal propeptide; sOSMR, soluble oncostatin M receptor; SP-D, surfactant protein-D; TIMP, tissue inhibitor of metalloproteinase; VEGF, vascular endothelial growth factor. intercellular adhesion molecule-1; SSc, systemic sclerosis.

Table 3. Potential Clinical Applications of Circulating Biomarkers in Systemic Sclerosis.

Clinical Purpose	Candidate Biomarkers
Early inflammatory disease detection	IL-6, sOSMR, CXCL9, CXCL10, IFN score, soluble CD13 [10,11,17,21–24]
Monitoring skin fibrosis progression	IL-6, CCL2, periostin, IGFBP7, COMP/Pro-C3 [10,11,21,35,36,44]
Prediction of ILD progression	KL-6, SP-D, CCL18, ICAM-1, CXCL4, EVs, EV-miRNAs, MMP/TIMP signatures [12,25–27,31,39,43,51]
PAH screening and prognosis	NT-proBNP, endoglin, endothelin-1, endostatin [19,29,30,45,46]
Monitoring fibrosis activity	Periostin, IGFBP7, Pro-C3, COMP, MMPs [20,21,36–38]
Therapeutic response assessment	IL-6, CXCL4, ECM turnover markers [21,23,24,26]
Identification of high-risk phenotypes	Multi-biomarker clustering, EV signatures [13,39,49,51]
Precision medicine stratification	Integrated biomarker signatures, soluble CD13, EV-miRNA signatures [13,40,49–51]

Abbreviations: COMP, cartilage oligomeric matrix protein; ECM, extracellular matrix; EV, extracellular vesicle; IFN, interferon; IGFBP7, insulin-like growth factor-binding protein 7; IL, interleukin; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; MMP, matrix metalloproteinase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; Pro-C3, procollagen type III N-terminal propeptide; sOSMR, soluble oncostatin M receptor; SP-D, surfactant protein-D; TIMP, tissue inhibitor of metalloproteinase.

10. Challenges and Barriers to Clinical Translation

10.1. Limited Validation and Replication

Although numerous circulating biomarkers have been reported in SSc, most remain investigational. Only a limited number, such as KL-6, SP-D, and NT-proBNP, have achieved broad clinical familiarity, and even these markers are generally used as adjuncts rather than

stand-alone decision-making tools. Furthermore, although many candidate biomarkers have shown promising associations with disease activity, organ involvement, or prognosis, relatively few have undergone external validation in independent cohorts. Several biomarkers have also yielded inconsistent or conflicting results across studies, likely reflecting differences in patient populations, disease stage, treatment exposure, sample size, and analytical methodologies. Therefore, additional multicenter prospective studies and independent replication are required before most candidate biomarkers can be incorporated into routine clinical practice [43,44].

10.2. Pre-Analytical and Analytical Issues

Pre-analytical variables, including sample type, processing time, storage temperature, freeze–thaw cycles, and circadian or treatment-related variation, may substantially influence measured biomarker levels. In addition, differences among ELISA kits, multiplex platforms, and laboratory protocols limit direct comparison across studies [43].

10.3. Incremental Value over Standard Care

A key unresolved question is whether circulating biomarkers provide incremental predictive value beyond conventional clinical variables, including disease duration, mRSS, autoantibody status, baseline PFTs, HRCT extent, and echocardiographic findings. Future studies should report whether biomarker models improve discrimination, calibration, or reclassification compared with standard clinical assessment alone [44].

10.4. Generalizability Across Populations

Because genetic background, ethnicity, environmental factors, disease duration, and treatment exposure may influence biomarker profiles, findings from Japanese cohorts should be validated in independent international cohorts before generalization to non-Asian populations [41,42,44].

10.5. Cost-Effectiveness and Regulatory Issues

Clinical implementation will also require evidence of cost-effectiveness, regulatory acceptance, assay reproducibility, and clear demonstration that biomarker-guided decisions improve patient outcomes compared with current standard-of-care monitoring [43,44]. Unlike NT-proBNP, which has been widely adopted internationally, the routine clinical use of KL-6 and SP-D remains largely limited to Japan despite accumulating international evidence supporting their clinical utility [32,43].

11. Future Perspectives

Future biomarker research in SSc will likely focus on longitudinal multiomics integration, standardized assays, and AI-driven prediction models, and emerging biomarker platforms, including circulating microRNA signatures in whole blood, metabolomics, gut microbiome-derived biomarkers, single-cell RNA sequencing, spatial transcriptomics, and extracellular vesicle-associated molecular profiling [51–54]. These complementary approaches may reveal novel pathogenic pathways, improve molecular stratification, and facilitate the identification of new therapeutic targets [51–54].

Despite substantial advances, prediction of progressive SSc-ILD remains challenging. A recent systematic review and meta-analysis demonstrated robust associations of KL-6, SP-D, and IL-8 with SSc-ILD, but also highlighted the limited validation and prognostic consistency of many other proposed biomarkers [43]. A scoping review emphasized that few biomarkers consistently predict ILD progression, although KL-6 currently appears among the most reproducible prognostic biomarkers [44]. Future studies should determine

whether composite biomarker models integrating multiple pathogenic pathways outperform individual biomarkers in predicting organ progression and therapeutic response.

Another important future direction is biomarker-guided therapy selection. For example, inflammatory biomarker signatures may identify patients more likely to respond to IL-6 blockade or JAK inhibition, whereas fibrosis-dominant signatures may identify patients requiring antifibrotic therapy [21–24]. Ultimately, biomarker-driven precision medicine may eventually contribute to individualized therapeutic approaches, although no biomarker-guided treatment algorithm has yet been validated for routine SSc care.

12. Conclusions

Substantial progress has been made in identifying circulating blood biomarkers associated with inflammation, endothelial dysfunction, and fibrosis in SSc [8,9,13]. Recent advances have shifted the field from isolated biomarker analyses toward multidimensional biomarker profiling and biologically based patient stratification [13,40,51–53]. Findings from Japanese longitudinal cohort studies have also supported multidimensional biomarker stratification approaches in SSc [10–13].

At present, most circulating biomarkers in SSc should be regarded as complementary tools for research and risk stratification rather than replacements for established clinical assessment. Future multicenter studies should determine whether biomarker-based models improve prediction beyond conventional clinical variables and whether biomarker-guided management improves patient outcomes.

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