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Review

Lung Involvement in Systemic Sclerosis—From Pathogenesis to Prediction

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Abstract: Systemic sclerosis (SSc) is a rare, multifactorial autoimmune disease characterized by widespread vascular damage and fibrosis. Pulmonary involvement is a significant manifestation of SSc, contributing to considerable morbidity and mortality. Therefore, identifying reliable biomarkers is of the utmost importance. This review explores emerging biomarkers to enhance diagnostic accuracy, prognostic assessment, and disease monitoring in SSc lung involvement. We discuss recent findings in immunological biomarkers, inflammatory indicators, and other parameters that can function as potential diagnostic and prognostic tools. A comprehensive understanding of these biomarkers could result in earlier and more accurate detection of pulmonary complications in SSc, aiding in timely intervention. Furthermore, we explore the advances in disease monitoring through innovative biomarkers, focusing on their roles in disease activity and treatment response. Integrating these novel biomarkers into current clinical practice and therapeutic protocols through clinical trials can revolutionize the management of SSc-related lung disease, ultimately improving patient outcomes and quality of life.

Keywords: systemic sclerosis; SSc; scleroderma; pulmonary sclerosis; fibrosis; interstitial lung disease; pulmonary arterial hypertension; PAH

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1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue, affecting multiple systems and organs, generalized by increased fibrosis and vascular changes. It is characterized by functional and structural abnormalities of small blood vessels, skin and internal organ fibrosis, and autoantibody production [1].

It has the highest mortality rate among rheumatic diseases, even though survival rates have improved, particularly for those with diffuse cutaneous SSc (dcSSc). For individuals living with SSc, there is considerable uncertainty regarding their prognosis and the possibility of developing serious or life-altering symptoms. It is a rare disease, classified as an orphan disease, indicating a substantial need for medical attention [1].

Being an infrequent condition, with an annual incidence of 10–50 new cases per million people, SSc has a prevalence of 40–340 individuals per million, and there are differences in occurrence across various regions. Pulmonary involvement in SSc includes mainly

the development of pulmonary vascular diseases such as pulmonary artery hypertension (PAH), pulmonary venoocclusive disease (PVOD), interstitial lung disease (ILD), and increased susceptibility to lung neoplasms [2].

Interstitial changes are discoverable in up to 80% of SSc patients via high-resolution CT scans of the chest and in up to 90% of patients upon autopsy [2]. However, only about 30–40% will develop ILD that has clinical significance, which carries a 10-year mortality rate as high as 40%. While ILD becomes more common as SSc progresses, it typically manifests within the first five years following the initial non-Raynaud's symptoms. It is unlikely to appear more than 15 years postdiagnosis. The early appearance of SSc-ILD, especially within the first three years of diagnosis, is increasingly observed and may indicate a more severe disease progression [3]. Demographic factors linked to the development of ILD in SSc patients include sex (being male), African American ethnicity, and diffuse skin involvement. It is also more prevalent among those with nail fold capillary irregularities, digital ulcers, a longer duration of disease, and PAH identified through echocardiogram screening. A genetic predisposition to SSc-ILD has been established, with most risk associated with variations in the HLA region and genes involved in innate immunity, as well as B-cell and T-cell activation and signal transduction [3].

This current paper aims to review the available literature on the pathogenesis of lung involvement in SSc and potential diagnostic and therapeutic options. For this purpose, we performed a comprehensive search across multiple databases, including PubMed, Scopus, and Web of Science. The search period covered articles published from January 1950 to July 2024 to ensure the inclusion of recent and relevant studies. Boolean operators and keywords used in the search included the following: ("Systemic Sclerosis" OR "Scleroderma") AND ("Lung Involvement" OR "Pulmonary Manifestations" OR "Interstitial Lung Disease") AND ("Pathogenesis" OR "Mechanism" OR "Etiology") AND ("Prediction" OR "Prognosis" OR "Biomarkers"). The search aimed to identify original research articles, review papers, and clinical studies. The abstracts and titles were initially screened to exclude irrelevant studies, followed by a full-text review to ensure the inclusion of high-quality papers that directly addressed the topic. In total, 312 papers were retrieved, with 70 meeting the inclusion criteria for this review (Figure 1).

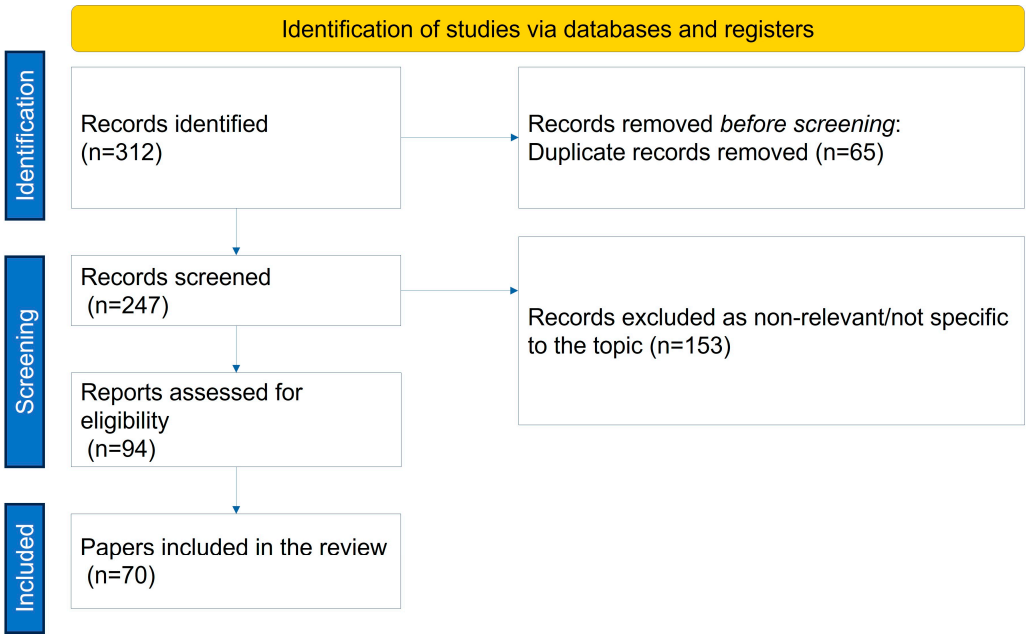

Figure 1. Identification, screening, and selection of papers to include.

2. Pathogenesis of Lung Involvement in SSc

2.1. Interstitial Lung Involvement

In SSc-ILD, the disruption of lung architecture and accumulation of a collagen-rich ECM results from interactions among epithelial, endothelial, and interstitial cells and components of the innate and adaptive immune systems, as Khanna et al. have shown [4].

ILD is commonly implicated with SSc, characterized by the gradual development of fibrosis and scarring of the lung parenchyma. Thickening of the alveolar walls, fibroblast proliferation, accumulation of ECM proteins and fibrosis within the alveolar and interstitial spaces are all pathological hallmarks of SSc-ILD. Histologically, this manifests as usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP), with NSIP being more common in SSc. The lung architecture is disrupted, affecting gas exchange and leading to hypoxia and, therefore, to pulmonary hypertension (PH), thus significantly impacting morbidity and mortality rates [5]. Honeycombing and traction bronchiectasis may develop as fibrosis progresses [6]. The early detection of ILD in SSc is crucial as it allows for interventions that aim to slow down or stop disease progression [7].

ILD-associated PH in SSc is a special entity in the lung involvement in SSc [8,9]. In SSc, PH could also develop as a consequence of hypoxia and/or lung diseases, mostly ILD (group 3 PH). It affects up to 31% of patients with clinically significant SSc-ILD and is related to increased mortality rates compared with SSc-ILD patients without PH [10,11]. The mechanism behind ILD-PH in SSc includes a shared pathophysiology concerning parenchymal and vascular remodeling, with endothelial injury and vascular dysfunction interacting with endothelial dysfunction, oxidative stress, altered immune pathways, perivascular fibrosis, or a genetic predisposition [12,13].

2.2. Mechanisms of Fibrosis in SSc

This pathological process begins with repetitive endothelial and epithelial cell injuries, which activate immune responses, recruit fibroblasts, and lead to their differentiation into myofibroblasts. These myofibroblasts accumulate ECM and contribute to fibrosis. Epithelial cells may undergo apoptosis or epithelial–mesenchymal transition (EMT), leading to further ECM production and resistance to apoptosis, which perpetuates fibrosis [4].

Denton et al. concluded that TGF-β plays a crucial role in fibrosis by promoting ECM accumulation and regulating immune responses. Injured cells secrete TGF-β, which recruits immune cells like macrophages that release more TGF-β, enhancing fibrotic processes [14]. Other cytokines, such as IL-4 and IL-13, produced by type 2 helper T cells and increased thrombin levels contribute to fibroblast proliferation and differentiation [15,16].

Moreover, according to Bhattacharyya et al., the Wnt/β-catenin pathway plays a role in fibroblast activation and tissue remodeling in lung fibrosis [17]. Moving forward, macrophages, essential for lung immunity, are also involved in fibrosis through M1 and M2 polarization. As presented by Khanna et al., M2 macrophages, characterized by markers like CD163 and CD204, accumulate in SSc patients and release fibrotic mediators such as chemokine (C-C motif) ligand 18 (CCL18). Altered macrophage–endothelial interactions can worsen fibrosis and vasculopathy [4]. According to Lafyatis, B lymphocytes also contribute to fibrosis by producing pro-inflammatory cytokines like IL-6, which promote fibrotic pathways and myofibroblast activation [15]. Finally, according to Murguganandam et al., elevated levels of biomarkers such as Krebs von den Lungen 6 (KL-6), surfactant protein D (SP-D), and CCL19 are associated with active SSc-ILD and its progression [18].

2.3. Vascular Abnormalities in SSc: Pathophysiology of Pulmonary Hypertension, Endothelial Cell Dysfunction, and Vascular Remodeling

As we stated above, the pathophysiology of lung involvement in SSc includes PAH, PVOD, and ILD, with marked susceptibility to lung neoplasms [19]. Changes in vasculature or lung interstitium could lead to the development of PH defined as a mean pulmonary arterial hypertension over 25 mm Hg. According to the updated classification of PH by the World Health Organization (WHO), PH is classified into five groups. SSc is most often

associated with group 1, pulmonary arterial hypertension (PAH); group 3, PH due to chronic lung diseases and/or hypoxia; and less commonly, group 2, PH due to left heart disease [10].

In SSc, PH could present as an isolated disease manifestation, as PAH (SSc-associated PAH or SSc-PAH), or in combination with ILD (PH-ILD) with the latter subtypes of PH having different prognosis in patients with SSc. Thus, in this review we will focus on PAH and ILD as the main and most serious pulmonary manifestations in SSc.

PAH is one of the primary outcomes of vascular disorders in SSc, along with PVOD [19]. The pathophysiology of SSc-PAH involves a complex interaction of vascular injury, fibrosis, and immune dysregulation [20]. Patients diagnosed with SSc exhibit the highest occurrence of PH group 1 among individuals with collagen vascular diseases. Patients with SSc-PAH also demonstrate a tendency for additional organ involvement, especially in the form of renal dysfunction and intrinsic heart disease, which may lead to end-stage organ failure [19]. This is evidenced by Mulkoju et al. stating that PAH is associated with increased early mortality and is the most prevalent cause of disease-related mortality in specific subtypes of SSc [21].

Various risk factors have been implicated with the development of PAH, including Raynaud's phenomenon, chronic disease, telangiectasia, menopause, older age, reduced diffusion capacity for carbon monoxide (DLco < 50%), DLco/alveolar volume < 70%, and an elevation in right ventricular systolic pressure > 2 mmHg/year [22]. Hemodynamic impairment in these patients is less severe than idiopathic PAH (IPAH). Still, they often exhibit more profound right ventricular dysfunction and higher N-terminal brain natriuretic peptide (NT-pro BNP) levels, indicating severe disease progression [4].

Endothelial cell (EC) dysfunction is pivotal, triggered by factors such as reactive oxygen species, cytokines, and autoantibodies. More specifically, this dysfunction leads to endothelial-to-mesenchymal transition (EndoMT), where ECs transform into myofibroblasts, contributing to ECM overproduction and vascular remodeling [18]. Furthermore, according to Bhattacharyya et al. [17], activated endothelial cells secrete endothelin-1, nitric oxide, and adhesion molecules, which result in vasoconstriction, tissue ischemia, and inflammation. Imbalanced cytokines including endothelial growth factor (VEGF), matrix metalloproteinase (MMP)-9, endothelin-1 (ET-1) and angiostatic factors [pentraxin 3 (PTX3), MMP-12, endostatin, angiostatin, semaphorin 3E (Sema3E), and Slit2], and impaired recruitment of endothelial progenitor cells (EPCs) inhibit proper angiogenesis, aggravating vascular destruction [17]. Doskaliuk et al. emphasize that endothelial cells decrease the presence of endothelial junctional proteins like occludin and vascular endothelial cadherin. Consequently, EndoMT cells lose their ability to act as a barrier, leading to increased plasma leakage and promoting vascular remodeling in PAH [23].

2.4. Immunological and Inflammatory Processes: Autoantibodies, Immune System Dysregulation, Cytokines, and Inflammatory Mediators

Autoantibodies are highly important to the pathogenesis of SSc, significantly influencing the development and progression of lung fibrosis and other organ complications [1]. The antibodies, such as antinuclear antibodies (ANAs), anti-centromere antibodies (ACAs), and anti-topoisomerase I (anti-Scl-70) antibodies, are indeed significant in diagnosing and monitoring SSc [22]. However, the correlation between these antibody levels and disease activity, particularly lung involvement, varies [24]. ANAs are found in SSc patients and are associated with various clinical manifestations.

While these antibodies are valuable in identifying subsets of SSc patients and predicting disease patterns, their levels do not always directly correlate with disease activity or severity. For example, anti-Scl-70 antibodies are associated with dcSSc and an increased risk of ILD, yet their presence or titer may not reflect the current activity or progression of ILD [22]. According to Muruganandam et al., the presence of anti-Scl-70 antibodies is mainly associated with a higher risk of developing ILD, affecting up to 85% of SSc patients, and is a leading cause of SSc-related mortality [20]. These autoantibodies contribute to

fibrosis by inducing endothelial and epithelial cell injury, which activates the immune system and recruits fibroblasts to the lung tissue. Similarly, ACAs are linked to limited cutaneous SSc (lcSSc) and a lower risk of severe ILD, but their titers do not necessarily correlate with pulmonary involvement [22]. In contrast, anti-Scl-70 antibodies correlate with dcSSc, and there is a higher likelihood of ILD, which is a major complication affecting the lungs [24].

Although some studies have shown that the presence of these antibodies can help predict the course and severity of the disease [22,24], understanding these correlations is crucial for an early diagnosis and targeted treatment, potentially improving patient outcomes by helping to provide a more personalized medical approach. This knowledge shows the importance of antibody testing in the management of SSc, particularly for monitoring lung involvement and guiding therapeutic decisions.

Furthermore, Bhattacharyya et al. [17] highlight the importance of biomarkers as therapeutic targets, with the potential for research-led advancements in patient care. A distinguishing feature of autoantibodies is their accuracy regarding the diagnosis of particular subsets of SSc, with titer measurements relating to disease severity and reproducibility of laboratory measurements. Furthermore, patients with SSc-ILD may present with unique autoantibodies not often associated with other autoimmune diseases [17]. In line with these, autoantibodies, such as anti-Scl-70, ACAs, and anti-RNA polymerase III (ARA), serve as key diagnostic and prognostic biomarkers in SSc [18].

The autoimmune nature of SSc is further evidenced by Bhattacharyya et al. through the presence of anti-fibroblast antibodies in up to 40% of patients, which stimulate IL-6 production and pro-fibrotic chemokines, enhancing fibroblast activation and collagen synthesis [17]. Similarly, antibodies against fibrillin 1 and platelet-derived growth factor receptors (PDGFRs) have been shown to promote collagen gene expression and myofibroblast differentiation via endogenous TGF-β signaling pathways. The involvement of these autoantibodies in the fibrotic process underscores their role in perpetuating the chronic inflammation and fibrosis seen in SSc-ILD. The simultaneous presence of different SSc-specific autoantibodies is rare but highlights the complexity of the autoimmune response in SSc [20]. Cytokines play a pivotal role in the pathogenesis of lung fibrosis in SSc, particularly in the development of ILD, which is a significant cause of morbidity and mortality in SSc patients [18].

As Murguganandam et al. pointed out, transforming growth factor-beta (TGF-β) is central to the fibrotic process in SSc, driving the excessive deposition of extracellular matrix (ECM) proteins, particularly collagen, which increases lung tissue stiffness and reduces lung compliance [20]. Additionally, cytokines such as interleukins (IL-1, IL-4, IL-6, IL-8, IL-10 IL-13, IL-16, IL-17, IL-18, IL-22, IL-32, and IL-35); the chemokines CCL, C-X-C motif (CXC), and C-X3-C motif chemokine ligand 1 (CX3CL1) (fractalkine); and growth differentiation factor 15 (GDF15) are implicated in the recruitment and activation of fibroblasts, further contributing to fibrosis. The involvement of cytokines and autoantibodies suggests the complex immune dysregulation in SSc and highlights potential therapeutic targets for mitigating lung fibrosis and improving patient outcomes [20].

The complex pathogenesis of lung involvement in SSc is presented in Figure 2.

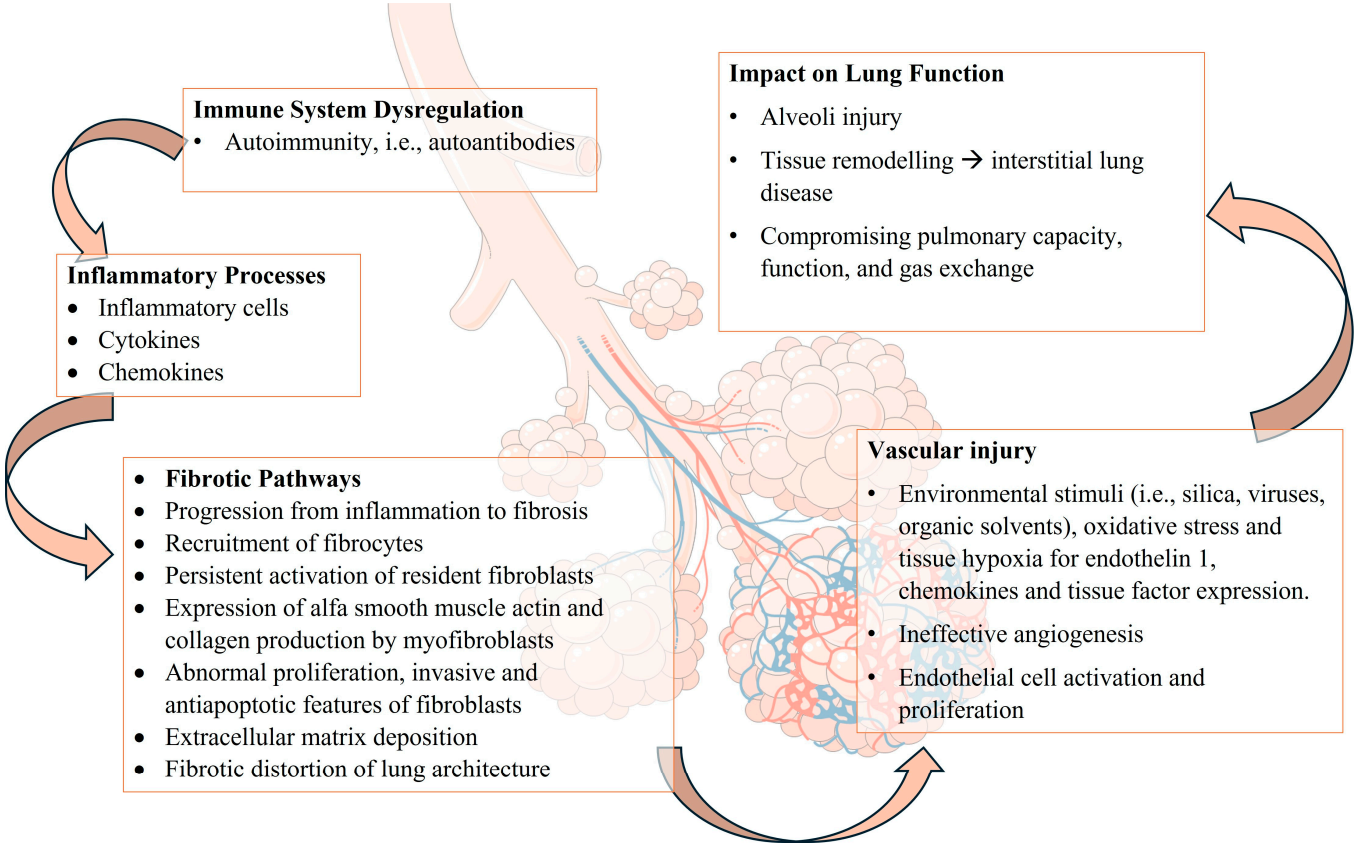

Figure 2. Pathogenesis of lung involvement in SSc is linked to the migration, activation, and proliferation of fibroblasts and differentiation into myofibroblasts. Autoreactive immune cells and produced antibodies and mediators (i.e., cytokines) further perpetuate the inflammation. When fibroblasts and myofibroblasts are persistently activated, they invade pulmonary tissue and produce collagen and extracellular matrix protein. Eventually, the excessive extracellular matrix protein remodels and distorts the lung architecture, leading to compromised lung function. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons BY 4.0 (https://creativecommons.org/licenses/by/4.0/; last accessed on 3 August 2024).

3. Clinical Manifestations and Diagnosis

3.1. Symptoms of Lung Involvement in SSc

When a patient with SSc presents with signs and symptoms referring to the chest, a variety of potential disorders should be considered. They include direct pulmonary involvement, indirect pulmonary complications, or a combination of both. Direct lung involvement can be subdivided into two common types: ILD and PAH [25]. Together, they account for around 60% of SSc-related deaths, with ILD being the leading cause of morbidity and mortality in SSc patients. SSc-induced PAH is most common in the lcSSc variant of the disease, while dcSSc is common in patients with ILD [19,26].

A considerable number of patients with SSc-ILD present with no specific symptoms, significantly when extrapulmonary manifestations of the disease limit their mobility. When symptoms are present, dyspnea, in exertion at first and eventually at rest; non-productive cough; and fatigue are most commonly reported. Patients with PAH can also present with hemoptysis, syncope, and symptoms of fluid retention. Perelas et al. note that the longer duration of the disease is associated with pulmonary involvement, specifically SSc-ILD [27].

3.2. Diagnostic Tools and Techniques

According to Solomon et al., up to 90% of patients will have interstitial abnormalities on high-resolution computed tomography (HRCT), while 40–70% will have pulmonary function test (PFT) changes [28]. HRCT is the standard modality for the non-invasive diagnosis of SSc-ILD. NSIP is the most common pattern detected in the scans of more than 80% of patients with SSc-ILD. This is characterized by peripheral ground-glass opacities, with an apical to basal gradient and possibly with subpleural spacing. The modality does have limitations, including the possibility of being normal in patients with PFT abnormalities or in patients with an abnormal chest auscultation (crackles) [28]. Despite the limitations, a normal HRCT at baseline can predict a low chance for the development of SSc-ILD, with around 85% of these patients having a normal scan at a mean follow-up of 5 years. PFTs are an essential non-invasive method for detecting pulmonary complications in the early stages.

Forced vital capacity and lung diffusing capacity for carbon monoxide (DLco) have been traditionally used to assess lung involvement in SSc. Spirometry and lung volumes show reasonable specificity but poor sensitivity to pulmonary fibrosis in SSc [29]. PFTs show a reduction in FVC in 40–75% of patients, with 15% having a severe reduction. Patients with minimal to no restriction had a 10-year survival rate of 87%, while patients with moderate and severe restriction had 75% and 58% 10-year survival rates, respectively. Functional vital capacity and DLco have been identified as adverse prognostic markers in SSc-related pulmonary injury. Almost all patients with pulmonary function test abnormalities will have a reduced DLco, with that being the most significant marker for poor outcomes and having a correlation with the extent of lung disease. Studies have indicated that DLco is preferable to spirometry in detecting lung involvement [29].

In the case of PAH, transthoracic echocardiography is the most widely used tool for screening. A plain CXR is the least sensitive test for evaluating PAH [30]. Still, it shows high specificity (up to 100% in one study), with findings including right pulmonary artery enlargement and loss of peripheral vasculature. Another valuable modality for the evaluation of patients with SSc is the use of biomarkers. ANAs are present in more than 90% of SSc patients and could be reliable biomarkers for diagnosis [30]. Additionally, several studies have suggested that TGF-β plays an essential role in the fibrotic process; therefore, it could be a potential biomarker for fibrosis development. Interleukin receptor-associated kinase-1 (IRAK-1), interferon regulatory factor (IRF5), connective tissue growth factor (CTGF), transducer and activator of transcription signal 4 (STAT4), and nucleotide-binding oligomerization domain (NOD)-like receptor containing a Pyrin domain 1 (NLRP1) have been reported to be implicated in SSc damage [21]. Genetic factors, including DRB1 alleles, have also been implicated. Several interleukins and chemokines like CCL18, CX3CL1, and CXCL4 can be elevated and have been associated with SSc-ILD [21].

3.3. Differential Diagnosis

Depending on the HRCT pattern, various differential diagnoses can be considered. That includes other CT diseases, drug-associated NSIP, interstitial pneumonia with autoimmune features, hypersensitivity pneumonitis, and idiopathic NSIP [31]. That is mainly in the early stage. The late fibrotic stage differential can include CT diseases, drug toxicity, chronic hypertensive pneumonitis, asbestosis, and idiopathic pulmonary fibrosis. SSc-ILD shares similarities with IPF, but differences can be observed. Under histological examination, a nonspecific interstitial pneumonia pattern is seen in SSc-ILD, while IPF is defined by usual interstitial pneumonia. A definite interstitial pneumonia honeycomb pattern is present in fewer than 10% of patients with SSc-ILD [31].

Figure 3 presents an overview of lung involvement in SSc, including clinical manifestations, diagnosis, prognosis, and follow-up.

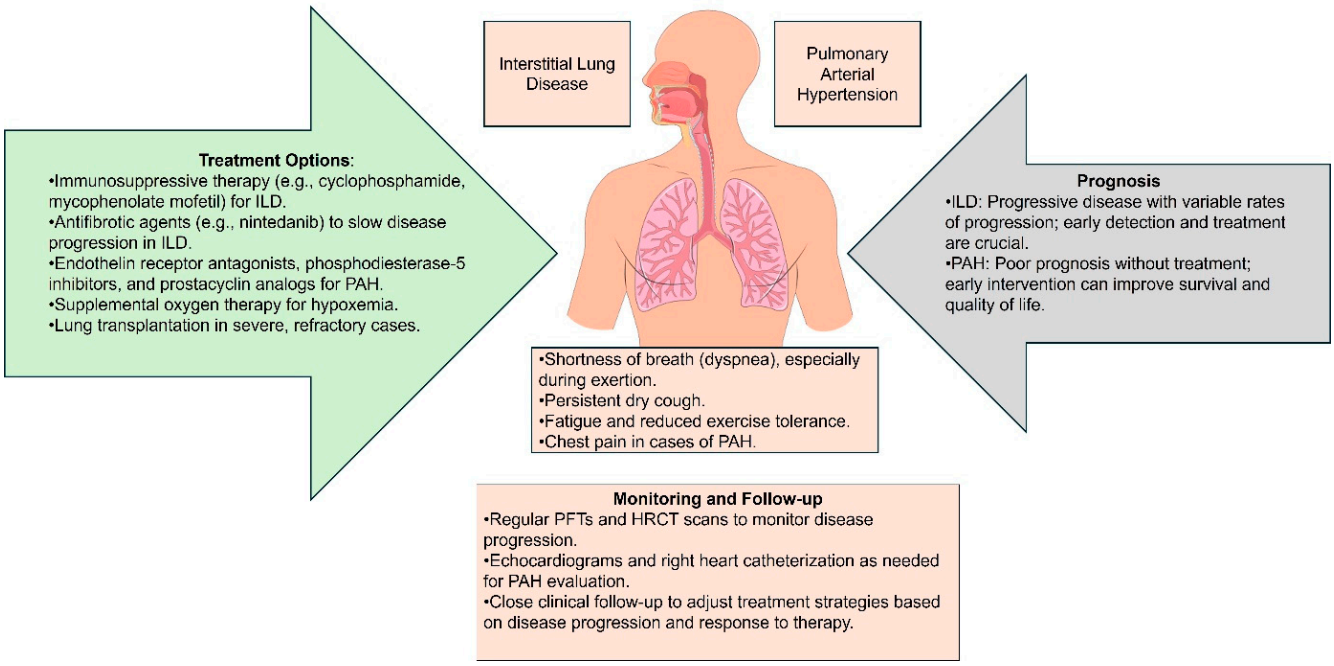

Figure 3. Interstitial lung disease and pulmonary arterial hypertension as lung involvement in SSc. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/; last accessed on 3 August 2024).

4. Prediction and Monitoring of Lung Involvement

4.1. Risk Factors and Predictive Models: Genetic Predisposition and Environmental and Lifestyle Factors

Lung involvement in the case of SSc typically affects the lung interstitium, in the context of ILD. The most common histopathological presentation of SSc-ILD is NSIP, which corresponds to the typical ground-glass pattern observed on lung CT [32]. Interestingly the UIP pattern, despite being consistent with "fibrotic" chest CT features of honeycombing and traction bronchiectasis, is less commonly seen in SSc-ILD. The highly variable course of SSc-ILD requires the use of strong prognostic predictors of severe and progressive disease with the aim of timely and precise clinical management. Genetic predictors in this context can act as discriminating factors for patients at higher risk for developing ILD while also offering predictive value to disease progression at the time of the initial disease diagnosis. Additionally, they can aid in risk stratification of the subgroup not included in the Goh staging system that does not meet the criterion of antecedent presence of ILD on HRCT [32].

The prevalence of ILD increases exponentially in individuals of Choctaw Native American, African, and Japanese descent when compared with a cohort of European descent. Simultaneously, the aforementioned ethnic groups exhibit an accelerated decline in lung function and worse overall survival rates when compared with European individuals [33].

Multiple HLA region associations have been made, with the HLA-DRB1 region playing a predominant role in the disease incidence among UK Caucasians, Spanish, and Black South African individuals. Conversely, the HLA-DQB1*0501 allele seems to be associated with the disease occurrence in Han Chinese [33].

Other genes implicated in SSc are shown to affect multiple aspects of innate immunity, as well as B- and T-lymphocyte activation processes. Some notable examples are single nucleotide polymorphisms (SNPs) in the genes of interferon regulatory factor 5 (IRF5), signal transducer and activator of transcription 4 (STAT4), and cell receptor CD3ζ (CD247) [33].

STAT4 is the transcription factor associated with the expression of type 1 interferons, IL-12 and IL-23. SNPs in the gene of IRF5 affect the transcription of interferon A and B, as well as other pro-inflammatory cytokines, and can thus alter the disease severity or even

impact a protective effect. At the same time, specific polymorphisms can have a synergistic effect, e.g., the cumulative effect of IRF5 SNP with specific STAT4 SNP, leading to increased ILD severity. Another possible genetic association is with gene CD226, which codes for DNAX accessory molecule 1 and is implicated in cell-mediated cytotoxicity of T and NK cells [33].

NLRP1 provides a platform for the assembly of the inflammasome forming that has been found to have an additive effect with specific SNPs of STAT4 and ILR5 genes [30], leading to promoting the processing and maturation of pro-IL-1β. Additionally, single nucleotide polymorphisms are present in NLRP1 (i.e., rs8182352 variant) with both anti-topoisomerase-positive and SSc-related fibrosing alveolitis [34].

The IRAK1 gene, located on the X chromosome, encodes a protein kinase whose function results in enhanced NFκ-B activity. Connective tissue growth factor (CTGF) drives the differentiation of myofibroblasts, therefore contributing to extracellular matrix deposition in tissues. Sato et al. have successfully demonstrated that serum levels of CTGF can predict the extent of pulmonary fibrosis in SSc-ILD [35]. The CD247 gene codes for the T-cell receptor T3 ζ chain that forms the T-cell receptor (TCR)/CD3 complex [36].

Activating mutations in the MUC5B (mucin 5B) gene and overexpression of the components involved in the Wnt pathway (e.g., β-catenin and MMP7) have been known to contribute to the pathogenesis of IPF. Still, they do not appear to play a role in ILD [4].

A posttranscriptional mechanism of gene expression regulation through targeting the messenger RNAs (mRNAs) includes the synthesis of microRNAs (miRNAs). miRNAs comprise a class of endogenous short noncoding RNA molecules that serve as negative regulators of the gene expression [16]. Functional studies have shown that miRNAs regulate critical fibrosis-related signaling pathways and molecules related to fibroblast hyperactivity and abnormal synthesis of ECM proteins, as well as SSc-related genes, thus playing an important role in the pathogenesis of fibrosis [16,37]. miRNAs have been shown to directly or indirectly participate in the fibrotic process by targeting the transforming growth factor (TGF)/Smad3 canonical signaling pathway and the connective tissue growth factor (CTGF), by affecting the epithelial-to-mesenchymal transition and inducing myofibroblast proliferation and resistance to apoptosis [16,38].

Environmental and lifestyle risk factors associated with SSc are presented in Table 1.

Table 1. Risk factors associated with SSc.

Group of Factors	Examples
Genetic	IRF5, STAT4, CD247, CD226, NLRP1, IRAK1, CTGF, HLA DRB1, HLA-DQB1
Environmental and lifestyle	Silica, silicone breast implants Vinyl chloride, trichloroethylene, benzene, toluene Bleomycin, L-5-hydroxytryptophan Rapeseed oil Epoxy resins Infectious: CMV, EBV, parvovirus B19, retroviruses Neoplastic: lung cancer, breast cancer, esophageal cancer, hematological malignancies

Environmental factors can be attributable to occupational exposures (e.g., silica and organic solvents); infectious agents (bacterial and viral); and non-occupational/non-infectious exposure to drugs, pesticides, and silicones. The pathogenetic mechanisms implicated in SSc include (1) immune tolerance interference, e.g., epigenetic modification by drugs; (2) immune system activation, e.g., vinyl chloride-mediated activation of CD8+ subsets and enhanced immunogenicity; and (3) molecular mimicry shared by many infectious triggers [39].

Some infectious agents studied for their contributions to SSc are parvovirus B19, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and retroviruses. Neoplastic and/or

paraneoplastic associations have been made with lung and breast cancer. As Maria et al. concluded, lung cancer appears to be linked with SSc-ILD in the presence of anti-Scl-70 Ab. On the other hand, the most commonly encountered cancers involve the breast, which in turn seems to be dependent on the presence of anti-RNA-PolIII Ab [40].

The sex predisposition of SSc for females follows the classic trend of most autoimmune diseases. This, subsequently, culminates in men preferentially presenting with an active and diffuse disease with an increased incidence of lung involvement, which may have a negative predictive value on survival. Truchetet et al. have also proposed that the failure of the physiological silencing of one of the two X-chromosomal copies in females can enhance autoantibody production. Another suggestion that focuses on the SNP of genes found on the X chromosome, such as IL13RA2, IRAK1, and FOXP3, may further elucidate the pathogenesis of SSc and explain the female-predominant nature of the disease [41].

4.2. Biomarkers for Early Detection: Emerging Biomarkers and Role of Autoantibodies in Prediction

The prediction of early pulmonary involvement in patients with SSc is a crucial aspect of the treatment strategy. Recent advances have been made in searching for serological or proteomic biomarkers for early detection of lung involvement in this subset of patients [42].

PAH is a severe complication in about 7–12% of SSc patients. A bare minimum for detecting PAH in SSc patients includes PFT with measurement of diffusion capacity of the lung for carbon monoxide (DLCO) and the systolic pulmonary arterial pressure on echocardiography. According to the DETECT protocol, a clinical examination, PFTs, cardiac examination, and serum biomarkers can be used with high sensitivity but relatively low specificity for PAH [42]. Biomarker research focuses on identifying several circulating or tissue-specific biomarkers whose concentrations could be used to predict PAH.

Natriuretic peptides are molecules released by the cardiac myocytes in response to ischemia, hypoxia, and ventricular wall stress. Atrial natriuretic peptide (ANP) and the more stable brain (B-type) natriuretic peptide are secreted in response to atrial or ventricular stretching, aiming for vasodilation and increased diuresis and natriuresis. In recent years, the N-terminal Pro-Brain natriuretic peptide (NT-proBNP) has been proven to be a preferable biomarker due to its longer half-life and higher stability and accuracy than BNP. NT-proBNP levels have been higher in SSc patients with PAH than those without PAH [43]. The change in NT-proBNP levels has shown a prognostic prediction in PAH at baseline and in the follow-up of the patients [44]. Of note is that levels of NT-proBNP could be elevated in SSc patients without PAH as a result of primary cardiac involvement.

Vascular Endothelial Growth Factor-A (VEGF-A) is an essential regulator of angiogenesis, promoting new angiogenesis, vascular permeability, and endothelial cell migration. Circulating levels of VEGF-A have been described in SSc patients, as well as in SSc-PAH patients, in correlation with the systemic pulmonary arterial pressure, DLCO, and MRC dyspnea score [45].

Growth Differentiation Factor-15 (GDF-15) plays a vital role in cell growth and differentiation. It is a cytokine member of the TGF-β superfamily, and its levels are higher in SSc-PAH patients compared with SSc patients without PAH and healthy volunteers with high diagnostic accuracy [46]. Serum levels of type I, II, and III interferon (IFN) are elevated in SSc-PAH, and an association exists between SSc-PAH and serum levels of interferon γ inducible protein 10 (IP10) [47,48].

Regarding the role of SSc-specific autoantibodies, there is no clear association between ANAs in PAH SSc patients. According to the literature, patients with anticentromere (ACA), CENP-A, and/or CENP-B are more prone to develop PAH but not ILD [49]. The frequency of ILD has been reported to be higher in SSc patients with anti-Th/To-positivity [50]. Antibodies against ET-1 receptor type A and angiotensin receptor type 1 have been found to be higher in PAH associated with connective tissue disease, and in particular, SSc, as well as with the development of digital ulceration in SSc [51].

4.3. Monitoring Disease Progression

Monitoring disease progression in SSc is crucial for preventing disease complications and reducing mortality rates. Inflammatory serum markers like C-reactive protein are helpful for the prediction of disease progression. Elevated serum levels of CRP have been identified as an independent predictor of PAH with a poor prognosis [52]. Monitoring serum uric acid is recommended for the detection of scleroderma-renal crisis, as well as being a predictor of PAH-related ventricular dysfunction [53].

According to the recommendations for evaluating and monitoring patients with PAH and CTD, asymptomatic SSc patients should undergo resting echocardiography as a screening, followed by annual screening with echocardiography, DLCO, and biomarkers. Right heart catheterization is recommended in all cases of suspected PAH associated with CTD [54]. According to the DETECT algorithm, patients with SSc and an increased risk of developing PAH should undergo a two-step screening (Figure 4).

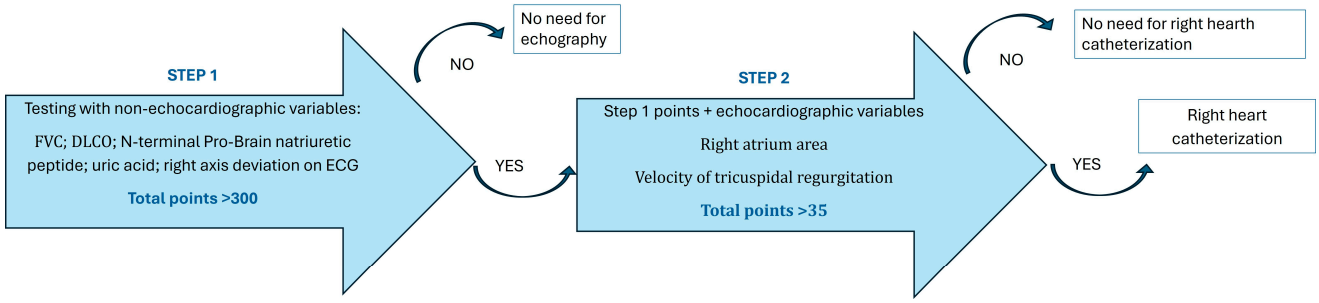

Figure 4. Algorithm for SSc management when the risk of PAH is high. FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; ACA, anticentromere antibodies.

5. Current and Emerging Therapies for SSc

5.1. Pharmacological Treatment

The approach to treating SSc and its effects on the lung is aimed at suppressing the three pathogenetically relevant processes inherent to disease progression: immune-mediated inflammation, fibrosis, and vasculopathy. Immunosuppressants receive the most attention given that they are, at a group level, indicated in virtually all patients from the time of the diagnosis [55].

In patients with predominantly skin disease, methotrexate is still considered the first treatment of choice, showing its moderately beneficial effect on inhibiting further skin thickening. Due to its anti-inflammatory and immunosuppressive effects, methotrexate has been used to manage mainly skin, joint, and muscle involvement in SSc. So far methotrexate is recommended for treating skin changes in patients with early diffuse SSc demonstrating efficacy in reducing skin fibrosis and improving skin scores [56]. However, its use in patients without lung involvement requires careful consideration. There is a concern that methotrexate could contribute to the development of lung fibrosis due to allergic, cytotoxic, or immunologic reactions, particularly in patients with pre-existing pulmonary symptoms or those at risk for pulmonary complications. The risk of methotrexate-induced lung fibrosis, although relatively low, needs to be weighed against its potential benefits. Clinical practice recommendations, based on current evidence, state that methotrexate may be used in early-stage SSc with skin involvement, provided that patients are closely monitored for any signs of lung involvement. Regular pulmonary assessments and imaging may be warranted to detect any early signs of lung fibrosis [56].

Cyclophosphamide and mycophenolate mofetil (MMF) serve as the following line of immunosuppressants, indicated either when the skin is pronouncedly affected or in the case of significantly affected internal organs, primarily the lung interstitium and the gastrointestinal tract [55].

The effect of these two immunosuppressants on progressive ILD was assessed in two randomized controlled trials: the Scleroderma Lung Studies (SLSs) 1 and 2. In the SLS1

study, oral cyclophosphamide was shown to be superior to a placebo in preventing decline in lung function tests [57].

In SLS2, MMF was shown to be non-inferior to cyclophosphamide in terms of efficacy, but it had a better tolerability profile. It is worth noting that the effect size of the treatment in both studies was modest at best, with a forced vital capacity (FVC) improvement of less than 3% predicted value in both the SLS1 and SLS2. This difference is in line with those observed in other studies. It indicates the expected benefits from the treatment: immunosuppression is intended to hamper further ILD progression rather than lead to a clinically meaningful improvement [58].

In the current therapeutic armamentarium, both cyclophosphamide and MMF are employed, and there is an increasing trend toward the use of MMF. The advantage of MMF is its more acceptable toxicity profile, making it suitable not only as an induction treatment option but also as a longer-term maintenance agent. On the other hand, cyclophosphamide is usually administered intravenously, circumventing the issue of adherence to treatment associated with oral MMF. Even though oral cyclophosphamide was employed in SLS1 and SLS2, the intravenous use of pulse cyclophosphamide (which has become a standard in most centers) is associated with a lower cumulative dose and, consequently, less toxicity [59].

Although azathioprine is not among the first immunosuppressive agents of choice, it can still be considered a maintenance option if MMF is not tolerated, is unavailable, or is contraindicated (such as in pregnancy) [60].

Among the biological treatment options for SSc, rituximab (RTX, an anti-CD20 monoclonal antibody) and tocilizumab (TCZ, a monoclonal antibody inhibiting the interleukin 6 receptor) have demonstrated their effects in clinical trials, primarily on the ILD component. They are used as a later treatment line after an inadequate response to a conventional immunosuppressive agent. The possibility of combining RTX and TCZ with MMF may be beneficial in selected patients, as well as a further addition of an antifibrotic agent [61]. In this recent meta-analysis of 20 studies, RTX has been shown to improve FVC by 4.49% at six months and by 7.03% at 12 months [61]. Even though these improvements seem numerically superior compared with other immunosuppressants, RTX was not superior to cyclophosphamide in its effect on FVC in the recently published RECITAL study conducted on patients with CTD-ILD [62].

Tocilizumab (TCZ) is a humanized anti-human IL-6 receptor antibody that binds to soluble and membrane-bound IL-6 receptors, and at detectable levels in the blood, TCZ is capable of almost completely blocking the transmembrane signaling of IL-6 [63]. TCZ is approved for use in the treatment of various immune-mediated diseases including rheumatoid arthritis (RA) and giant cell arteritis (GCA) [64]. The phase II faSScinate and phase III focuSSced trials evaluated the safety and efficacy of TCZ in patients with early active dcSSc. While the improvements in skin fibrosis were not statistically significant between the TCZ group and the placebo group, it was indicated that it might preserve lung function in patients with early SSc-ILD and elevated acute phase reactants. In 2021, it was approved by the FDA for use in patients with SSc-ILD based on the results of the focuSSced trial. More specifically, in the faSScinate trial, the difference in FVC between the placebo group and the TCZ group was 120 mL with a difference of 167 mL overall in the focuSSced one [65,66]. Collectively, the data from Khanna D et al. showed that the stabilization of lung function in patients receiving TCZ was consistent across all severity groups with SSc-ILD, showing that the effects of TCZ were observed in all subgroups.

Regarding safety, during the phase III study, 82 patients in the placebo groups had at least one adverse event, with the number in the TCZ group being 89 [66]. Only two of the TCZ group patients experienced cardiac disorders during the study compared with seven in the placebo group. Overall, no major differences in experienced adverse effects were observed between the two groups. Kuster S et al. [67] confirm the previously mentioned adverse effects and do not reveal significant new potential threats of TCZ during treatment.

Tocilizumab was approved for SSc-associated ILD based on the results of a randomized controlled trial, which did not meet its primary skin endpoint. The trial did show a

numerical improvement in the modified Rodnan skin score at week 48 in the tocilizumab group compared with the placebo (−6.1 vs. −4.4, respectively). Interestingly, the change in FVC at week 48 was only −0.4% in the tocilizumab group compared with −4.6% in the placebo group ($p = 0.002$). However, this finding was a priori not taken into account as significant due to the hierarchical structure of the study disregarding any results of secondary endpoint analyses in the context of the study not meeting the primary endpoint [66].

The role of glucocorticoids is not as prominent in SSc compared with other connective tissue diseases due to an increased risk of renal crisis associated with their use. However, glucocorticoids are still used in patients exhibiting features overlapping with other inflammatory rheumatic conditions, such as arthritis, myositis, and serositis [68]. Antifibrotic drugs are promising therapeutic options available for SSc. Nintedanib is the first and currently only antifibrotic agent approved for the treatment of SSc, used in the treatment of ILD. At the same time, it does not affect the skin. In the current treatment paradigm, it is being used in cases of progressive pulmonary fibrosis, usually as an add-on option following an inadequate effect of immunosuppressive treatment. Its approval is based on its rather modest efficacy demonstrated in the SENCSIS trial: an absolute difference in the FVC predicted value of 1.2% (equaling 46.4 mL) between the nintendanib add-on group and the standard of care group. On the other hand, 75.7% of patients on nintendanib experienced diarrhea even in the trial (compared with 31.6% in the control group) [68]. Pirfenidone is another antifibrotic agent already being used for the treatment of idiopathic pulmonary fibrosis. There is growing evidence that its use may also be of benefit to patients with progressive pulmonary fibrosis in the context of SSc [68].

Current treatment options for PAH include endothelin receptor antagonists, phosphodiesterase 5 (PDE5) inhibitors, prostaglandin analogs, and soluble guanylate cyclase agonists. Endothelin receptor blockade, PDE5 inhibitors, and iloprost have also been shown to control the symptoms of secondary Raynaud's phenomenon and digital ulcers associated with vasculopathy inherent to the disease. The therapeutic approach to PAH in patients with SSc is analogous to treating idiopathic PAH. The initialization of therapy with a single agent is reserved only for a low-risk patient profile. In contrast, most patients should be concomitantly started on dual treatment (usually an endothelin receptor antagonist and a PDE5 inhibitor) [69].

It is worth noting that the recent change in the definition of the cutoff value of increased pulmonary artery pressure from 25 mmHg to 20 mmHg (and 3 Wood units to 2 Wood units) should allow for better control of patients under risk of development of PAH-related complications and poor outcomes [70].

5.2. Non-Pharmacological Approaches

Oxygen therapy is used in patients with evidence of partial or global respiratory insufficiency in an acute setting of an ILD exacerbation or respiratory infection or the setting of severe later-stage ILD and/or SSc-associated PAH despite treatment with pharmacological agents. Oxygen treatment aims to prevent further deterioration of the patient's condition, mainly to prevent secondary (especially right-sided) heart failure, as well as to improve quality of life and mortality. Given the lack of direct evidence of using supplementary oxygen in patients with SSc, data on the expected benefits are derived from other more frequent conditions [71].

Although there are some recommendations regarding nutrition for preventing pulmonary fibrosis, such as low sodium (salt) intake and avoiding added sugars and saturated and trans fat, no specific nutrition and diet could really prevent lung involvement in SSc patients [72].

The use of hyperbaric oxygen has been described as an adjunctive add-on treatment of intractable ulcers due to severe vascular insufficiency in patients with SSc. Despite some authorities favoring such a treatment modality, its efficacy and potential safety issues have not been assessed in well-designed clinical trials [73].

Pulmonary rehabilitation is an important adjunctive treatment option that increases the patient's quality of life and improves exertional capacity. Despite the relatively well-documented role of pulmonary rehabilitation in patients with other lung diseases, the role of pulmonary rehabilitation in SSc still needs to be fully appreciated in well-designed clinical studies. An interesting aspect may be speech therapy, which has been shown to decrease the incidence of aspiration episodes associated with exacerbations of ILD [74].

A systematic review by Murphy et al. (2022), which included 15 randomized controlled trials and one prospective quasi-experimental study, revealed within-group improvements in intervention groups (most focused on hands/upper extremities, followed by multicomponent, orofacial, and directed self-management). However, the study's heterogenicity, interventions that focus on hand and upper extremity outcomes or are multicomponent, provides some support for rehabilitation in SSc [75].

5.3. Future Directions and Research for SSc Lung Complications

Various molecular targets have been explored through preclinical studies and clinical trials. These include the blockade of the costimulatory CD28-CD80/86 T-cell signal with abatacept and the blockade of CD19 and CD20 on cells of B lineage, as well as the inhibition of CCL24 (Chemokine C-C motif ligand 24), tumor necrosis factor-alpha, transforming growth factor–beta, B-cell activating factor (BAFF), LPA1 receptor (lysophosphatidic acid receptor 1), sGC (soluble guanylate cyclase), Janus kinases, interleukins 6 and 17, endothelin receptor, and autotaxin [76].

Despite the high number of potential therapeutic targets, the biology of SSc as a predominantly pro-fibrotic condition is the main limiting feature toward achieving improved outcomes. A modest therapeutic effect of immunosuppressive agents has illustrated that the disease is recognized at a late stage or that active inflammation should not be the primary therapeutic target. On the other hand, nintendanib has not demonstrated its antifibrotic property beyond the lung interstitium. The fact that there are several immunosuppressive agents and several agents targeting PAH but only one available agent targeting fibrosis reveals a highly unmet need for the control of fibrosis in SSc.

6. Conclusions

In conclusion, the complexity and high patient burden of SSc-related lung disease calls for a more thorough understanding of the underlying pathophysiological mechanisms, the standardization of biomarker evaluation, and their integration into clinical practice. Predictive models and biomarkers for lung involvement in SSc can significantly enhance early diagnosis, enable more personalized treatment strategies, and improve patient outcomes. Many SSc patients are stable over time; however, predicting the progression of the disease, based on different markers, etc., would be of utmost importance. By identifying high-risk individuals and monitoring disease progression more effectively, these predictive tools can guide clinical decision-making, potentially reducing lung damage and improving overall prognosis. We believe these advancements will contribute to more targeted and proactive approaches in managing SSc-related lung complications.

Overcoming the challenges around lung involvement in SSc would denote a new era of refined diagnostic and personalized treatment options, offering hope for improved outcomes in SSc patients with lung involvement. Collaboration between multidisciplinary teams, technological advances, and meticulous research endeavors are all prerequisites for the future improvement of patient care.

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