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Review

Pulmonary Involvement in Primary Sjögren's Syndrome: Interstitial Lung Disease Phenotypes and Diagnostic Challenges

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Abstract

Pulmonary involvement in primary Sjögren's syndrome (pSS) is common and exhibits significant clinical heterogeneity, particularly in cases where interstitial lung disease (pSS-ILD) develops. Reported variability in prevalence, radiologic phenotypes, and clinical outcomes indicates both underlying biological diversity and differences in classification criteria, case ascertainment, and diagnostic approaches. Pulmonary manifestations may be subclinical, and early interstitial abnormalities are frequently undetected due to the limited sensitivity of chest radiography. Presentations such as ILD-first or non-sicca onset, seronegative disease, and coexisting or mimicking conditions, including lymphoproliferative disorders and amyloidosis, increase the difficulty of diagnosis. High-resolution computed tomography (HRCT) demonstrates a wide range of patterns, including inflammatory, fibrotic, and mixed phenotypes, which often overlap and change over time. Reliance on pattern-based categorization may not adequately reflect the underlying pathobiology; for example, those with usual interstitial pneumonia (UIP)-like morphology have significant prognostic implications within the pSS spectrum. A structured, multidomain assessment that integrates symptoms, pulmonary function, and HRCT findings, ideally inside a multidisciplinary discussion (MDD), may boost diagnostic accuracy and risk stratification. Nevertheless, heterogeneity in definitions and reporting continues to impede comparability across patient cohorts. Additional research is necessary to standardize phenotyping frameworks and identify predictors of disease progression to inform individualized diagnostic and management strategies.

Keywords: primary Sjögren's syndrome; interstitial lung disease; high-resolution computed tomography; usual interstitial pneumonia; progressive pulmonary fibrosis; diagnostic challenges; subclinical disease; multidisciplinary assessment

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1. Introduction

Primary Sjögren's syndrome (pSS)-associated interstitial lung disease (ILD) represents a significant clinical challenge due to its heterogeneous manifestations and the potential for under-recognition, particularly in the absence of systematic evaluation strategies [1,2].

Primary Sjögren's syndrome is a systemic autoimmune disease characterized by clinically significant extraglandular manifestations, including pulmonary involvement [2,3]. Immune-mediated mechanisms, such as aberrant immune activation and dysregulated tissue repair and remodeling, contribute to pSS-related lung injury. These mechanisms

account for the varied clinical phenotypes, ranging from inflammation-predominant to fibrosing forms. Additionally, reported rates of pulmonary involvement in pSS vary widely across studies, likely due to differences in case ascertainment methods, including routine clinical evaluation and systematic screening [3].

This variation is not simply methodological; it carries direct clinical consequences. When assessment relies primarily on symptoms and chest radiography, a meaningful proportion of lung involvement is likely to go unrecognized. A prospective study demonstrated that HRCT is sensitive for detecting pulmonary involvement in pSS and can reveal both interstitial abnormalities and inflammatory bronchiolar changes that may not be evident on clinical evaluation [4]. Taken together, the results support a more thorough diagnostic strategy that combines complementary modalities, including pulmonary function testing and HRCT, rather than depending on any single element of the respiratory work-up [4].

In clinical practice, the combination of subclinical detection using HRCT and the considerable variability in reported prevalence across ascertainment strategies necessitates a more precise conceptualization of primary Sjögren's syndrome-associated interstitial lung disease (pSS-ILD) [5]. The pSS-ILD should be framed within a transparent, phenotypic approach that accounts for its frequent underdiagnosis and the need for improved detection strategies [6].

Pulmonary involvement is often identified late or incidentally, sometimes preceding the formal diagnosis of pSS. This pattern reflects both the high sensitivity of HRCT for detecting subclinical disease and the heterogeneity of current detection approaches, which contribute to wide variability in reported prevalence [2–5]. As a result, the true prevalence and clinicoradiological spectrum of pSS-ILD remain difficult to define, limiting cross-study comparability and complicating decisions regarding systematic respiratory assessment. These challenges underscore the need for standardized phenotyping and diagnostic pathways [6].

This review synthesizes the clinicoradiologic ILD phenotypes described in (pSS) and examines diagnostic challenges that contribute to under-recognition, with particular emphasis on subclinical disease and the impact of ascertainment strategies on reported cases of "pSS-ILD." The manuscript focuses on ILD associated with pSS and the factors influencing its clinical recognition, especially phenotyping and diagnostic pathways. It does not serve as a formal clinical guideline or systematic review; instead, it organizes the available evidence to clarify current gaps and highlight priorities for standardization in both research and clinical practice.

2. Methods

This narrative review was conducted using a focused literature search in PubMed. PubMed was the primary database used. The search covered publications from 1997 to January 2026.

Search strategy. We searched PubMed using a predefined query designed to capture interstitial lung disease (ILD) phenotypes and diagnostic challenges in primary Sjögren's syndrome (pSS). The search combined terms related to pSS, ILD, HRCT patterns, screening, seronegativity, and diagnostic complexity. A representative search strategy included:

("primary Sjögren*"[Title/Abstract] OR "Sjögren* syndrome"[Title/Abstract] OR "pSS"[Title/Abstract]) AND ("interstitial lung disease"[Title/Abstract] OR "ILD"[Title/Abstract] OR "interstitial pneumonia"[Title/Abstract] OR "pulmonary involvement"[Title/Abstract]) AND (("high-resolution computed tomography"[Title/Abstract] OR "HRCT"[Title/Abstract] OR "computed tomography"[Title/Abstract] OR "CT pattern"[Title/Abstract] OR "radiologic pattern"[Title/Abstract] OR "NSIP"[Title/Abstract] OR "UIP"[Title/Abstract] OR "LIP"[Title/

Abstract] OR "organizing pneumonia"[Title/Abstract] OR "OP"[Title/Abstract]) OR ("screening"[Title/Abstract] OR "subclinical"[Title/Abstract] OR "diagnostic"[Title/Abstract] OR "diagnostic challenge*"[Title/Abstract] OR "seronegative"[Title/Abstract] OR "occult"[Title/Abstract])). Study selection was performed independently by two reviewers.

The initial search identified a core set of publications relevant to ILD phenotypes and diagnostic challenges in pSS. Retrieval was subsequently expanded through reference list screening of key articles and major guidelines, citation tracking, and focused thematic searches addressing HRCT reproducibility, radiologic–pathologic correlation, and definitions of progression in connective-tissue-disease-associated ILD (CTD-ILD).

Eligibility and prioritization. English-language original studies (cohort, case-control, cross-sectional, and diagnostic) and comprehensive reviews were considered. Case series were included when they provided clinically relevant radiological or pathological insights, and selected case reports were incorporated when they illustrated atypical presentations or specific diagnostic challenges not captured in larger studies. Priority was given to studies reporting explicit HRCT pattern classification, clearly defined diagnostic pathways (including multimodal screening strategies), and clinically relevant outcomes or progression in pSS-ILD. Studies focusing exclusively on non-primary Sjögren's syndrome, non-ILD pulmonary manifestations without interstitial assessment, or non-human data were excluded unless they provided essential mechanistic insight.

This review was not a formal systematic review, and no quantitative synthesis was conducted. Rather, it aimed to synthesize available evidence and highlight methodological sources of heterogeneity across studies.

3. Scope and Definitions of pSS-ILD

The term "pSS-ILD" is widely used in the literature as an umbrella designation for primary Sjögren's syndrome-associated interstitial lung disease. However, substantial variability exists in how studies operationally define both pSS and ILD, including differences in pSS categorization frameworks [7], the evidentiary basis for establishing ILD (such as HRCT, pulmonary function testing, or histopathology), diagnostic thresholds, and the use of multidisciplinary discussion (MDD) [8]. Those methodological distinctions introduce heterogeneity in cohort assembly and limit comparability across studies [3]. For uniform consistency, the present review adopts the term "pSS-ILD," while stressing that its interpretation in any given study is determined by three key methodological choices—the classification of pSS [7], the ascertainment of ILD [8], and the ascertainment setting (systematic screening versus ILD-clinic-based cohorts) [3]—all of which can materially influence the phenotypes reported [3,8].

3.1. pSS Classification Criteria and Cross-Study Comparability

The comparability of studies involving pSS-ILD is influenced by the classification criteria applied to identify pSS. The 2002 American-European Consensus Group (AECG) criteria integrate patient-reported symptoms with objective findings, including ocular and oral symptoms, ocular signs, minor salivary gland histopathology, objective evidence of salivary gland involvement, and anti-SSA (Ro) and anti-SSB (La) antibodies [9]. For the classification of primary disease, defined as the absence of an associated condition, four of six criteria must be met, with at least one being histopathology or serology [9]. The AECG criteria also specify exclusion criteria, including prior head or neck radiotherapy, hepatitis C infection, sarcoidosis, amyloidosis, and graft-versus-host disease, to reduce misclassification from conditions that may present with sicca features or mimic pSS [9].

The 2016 ACR/EULAR criteria use a weighted scoring system to classify pSS [7]. Anti-SSA positivity and a labial salivary gland biopsy showing focal lymphocytic sialadeni-

tis each contribute 3 points, while the ocular staining score, Schirmer test, and unstimulated whole salivary flow each contribute 1 point. A total score of 4 or more meets the classification threshold [7]. Individuals are eligible if they have at least one symptom of ocular or oral dryness, or when clinical suspicion is supported by relevant systemic features. This approach is particularly useful when glandular symptoms are not the predominant manifestation [7].

These differences are clinically relevant for the identification and management of pSS-ILD. The AECG criteria incorporate symptomatic assessment, whereas the ACR/EULAR criteria emphasize serological markers, histopathology, and objective testing [7,9]. In cases where pulmonary involvement is the initial manifestation, the decision to suspect pSS is guided by sicca symptoms or systemic features, and by the availability of objective assessments such as anti-SSA testing, biopsy, or standardized measures, which can influence the classification and identification of pSS-ILD [7,9]. Additionally, the ACR/EULAR criteria exclude isolated anti-SSB antibodies, as their inclusion in earlier criteria may have resulted in increased misclassification [7,10].

Beyond rheumatologic classification criteria, contemporary ILD frameworks further shape the conceptualization and reporting of pSS-ILD. The updated international multidisciplinary classification of the interstitial pneumonias emphasizes morphologic pattern recognition, levels of diagnostic confidence, and the integration of clinical context within the MDD [8]. Accordingly, variability in the application of these ILD classification standards may compound differences introduced by pSS criteria alone, further affecting cohort composition and cross-study comparability. Taken together, differences in both rheumatologic classification criteria and ILD diagnostic frameworks contribute to substantial heterogeneity in the identification and characterization of pSS-ILD across studies [3,8].

The ACR/EULAR criteria demonstrate strong performance in external validation; however, their effectiveness and the types of cases identified may differ across populations and clinical environments. For example, a study involving Japanese patients compared ACR/EULAR with AECG criteria and reported sensitivity and specificity estimates, indicating that the selection of classification criteria can influence cohort composition and comparability across study populations [3,11].

Clearly specifying the pSS classification criteria employed, such as AECG, ACR/EULAR, or others, is essential. This selection determines patient inclusion and influences estimates of ILD prevalence, phenotype distributions, and prognostic outcomes.

3.2. Defining pSS-ILD: HRCT, PFTs, Histopathology, and MDD

A clear definition of pSS-ILD is essential for this review. In daily practice, ILD is usually diagnosed by HRCT and characterized radiologically as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), or lymphocytic interstitial pneumonia (LIP) [8]. Pulmonary function tests assess physiological impairment and support severity assessment, whereas histopathology is reserved for selected cases in which diagnostic uncertainty persists [12]. These terms describe dominant imaging morphologies and do not necessarily correspond to specific histopathologic diagnoses [2,8]. Modern ILD care focuses on integrating information from imaging, clinical context, autoimmunity lab tests, and pathology when needed, ideally through MDD [8,12].

In this review, we adopt a practical definition of pSS-ILD. ILD is considered present when HRCT demonstrates interstitial abnormalities based on their pattern and extent, with pulmonary function tests supporting disease characterization when available [12]. In cases of diagnostic uncertainty, including the underlying cause and level of confidence, final diagnostic decisions should be established through MDD [8,12].

Given the increasing emphasis on disease behavior, we also apply the framework of progressive pulmonary fibrosis (PPF) to describe clinically relevant disease evolution. According to the 2022 ATS/ERS/JRS/ALAT guideline, PPF in non-IPF ILDs is defined by the presence of at least two of the following within the previous year, in the absence of an alternative explanation: worsening respiratory symptoms; physiological progression (e.g., absolute decline in FVC $\geq$ 5% or DLCO $\geq$ 10%); and radiologic progression (e.g., increased traction bronchiectasis, new reticulation, or increased honeycombing) [13].

3.3. Study Design Effects on Reported pSS-ILD Phenotypes: Screening-Based Samples Versus ILD Clinic Cohorts

The pSS-ILD phenotypes reported across studies are strongly influenced by the setting and strategy used for case identification [14]. Cohorts derived from systematic respiratory screening may capture patients with mild or subclinical disease, whereas ILD-clinic-based cohorts may be enriched for symptomatic patients with more established or functionally significant pulmonary involvement [7].

Second, even within pSS, the diagnostic components in classification criteria differ between frameworks. The AECG criteria include salivary gland testing along with symptoms and signs [9]. In contrast, ACR/EULAR uses fewer weighted, measurable items and excludes isolated anti-SSB antibodies due to concerns about misclassification [7]. If access to minor salivary gland biopsy or standardized quantitative tests is inconsistent, the choice of criteria can change the sample. This can result in more seropositive or biopsy-positive profiles, or favor definitions based on symptoms, thereby directly affecting the clinical spectrum observed in studies [14,15].

The way ILD is defined and confirmed affects which HRCT patterns are most common. For example, a group of patients recruited from an ILD clinic and later diagnosed with pSS using serology or salivary gland biopsy may differ from a group from a rheumatology clinic that underwent systematic respiratory screening [3]. This issue is made more complex because ILD evaluation usually starts with the HRCT pattern, then is refined with clinical and lab data, including autoimmune serology, and may involve invasive procedures if the diagnosis or treatment is unclear [8,16]. Thus, comparing UIP and NSIP (or other patterns) involves more than only reporting the pattern distribution; it also depends on how ILD was identified, how patterns were assigned, and whether there was a central review or MDD [8,16].

To sum up, in this review, we use "pSS-ILD" to refer to ILD identified mainly by HRCT, based on pattern and extent, in patients with pSS, as classified by established criteria (AECG 2002 or ACR/EULAR 2016, as reported). When possible, we use the PPF framework to describe disease progression. Being clear about these definitions helps compare studies and better understand differences in prevalence, types, and outcomes across groups and clinical settings.

4. HRCT in Fibrosing ILD: Pattern-Based Interpretation and Pitfalls

HRCT plays a key role in diagnosing fibrosing ILD because it helps translate complex tissue changes into a standardized, pattern-based system [17]. This method works best when there is a clear, dominant pattern, but its accuracy decreases when fibrosing interstitial changes coexist with airway-centered or lymphoproliferative features, or when images reflect advanced fibrosis [17,18]. In these unclear cases, common misinterpretations include overdiagnosing UIP by confusing traction bronchiectasis or bronchiolectasis with honeycombing, failing to recognize subtle honeycombing, and diagnosing idiopathic pulmonary fibrosis (IPF) prematurely when HRCT suggests UIP but the clinical context indicates an alternative cause [16,17].

These diagnostic pitfalls reflect the complex and overlapping immune–fibrotic processes underlying pSS-ILD, in which HRCT patterns represent dominant morphological expressions rather than fixed biological entities [8,12]. A conceptual framework summarizing this dynamic spectrum, its progressive fibrosing trajectory over time, and its lymphoproliferative features is presented in Figure 1 [8,12,13].

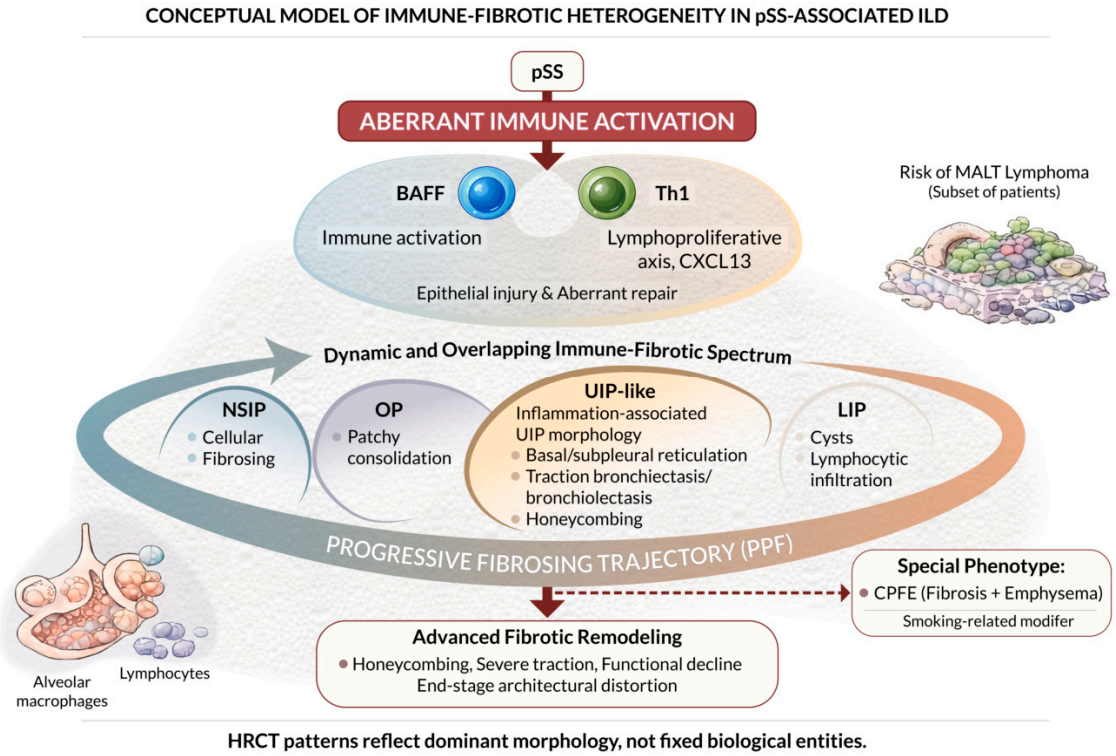


Figure 1. Conceptual model of immune–fibrotic heterogeneity in pSS-associated interstitial lung disease. Primary Sjögren's syndrome (pSS) drives aberrant immune activation and epithelial injury with dysregulated repair, generating a dynamic and overlapping immune fibrotic spectrum of HRCT phenotypes, including nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), inflammation-associated UIP-like morphology (biologically distinct from idiopathic pulmonary fibrosis), and lymphocytic interstitial pneumonia (LIP). The progressive fibrosing trajectory (PPF) is depicted as a longitudinal gradient that preferentially intensifies toward fibrosing NSIP and UIP-like patterns and may culminate in advanced fibrotic remodeling (end-stage architectural distortion). A lymphoproliferative axis links LIP to an increased risk of mucosa-associated lymphoid tissue (MALT) lymphoma in a subset of patients. Combined pulmonary fibrosis and emphysema (CPFE) is shown as a smoking-related modifier. HRCT patterns reflect dominant morphology rather than fixed biological entities.

4.1. Dominant Versus Mixed Patterns and Fibrosis Burden

Current practice starts by identifying the main HRCT pattern, such as typical UIP, probable UIP, indeterminate for UIP, or an alternative diagnosis. At the same time, fibrosis is characterized by its extent and severity, as reflected in features such as reticulation, traction bronchiectasis or bronchiolectasis, and honeycombing [17]. According to the Fleischner proposal, the main difference between typical and probable UIP is the presence of honeycombing. The key features include basal and subpleural reticulation with traction bronchiectasis or bronchiolectasis, in the absence of imaging signs suggesting an alternative cause [17].

In many ILDs associated with autoimmune disease, the dominant HRCT pattern may be accompanied by features of other interstitial or airway-centered processes, reflecting the underlying histopathologic heterogeneity [19,20]. In pSS, lung tissue findings are varied.

Even when interstitial pneumonia is the main feature, other interstitial patterns or airway abnormalities are frequently present, supporting the interpretation of HRCT findings as a composite of overlapping features rather than a single diagnostic entity [20].

In SSc-ILD, HRCT often shows a spectrum of patterns, with NSIP being the most common. However, radiologic and pathologic studies indicate that reticulation is not uniform. Different forms of reticulation, particularly traction reticulation, are associated with varying degrees of architectural distortion and fibrotic burden. Irregular reticulation with traction may suggest a UIP-like component, characterized by dense fibrosis and advanced architectural destruction, and may provide more informative risk stratification than simply categorizing the pattern as NSIP [21].

Figure 2 illustrates representative CT patterns in pSS-associated ILD, highlighting selected manifestations within the radiologic spectrum.

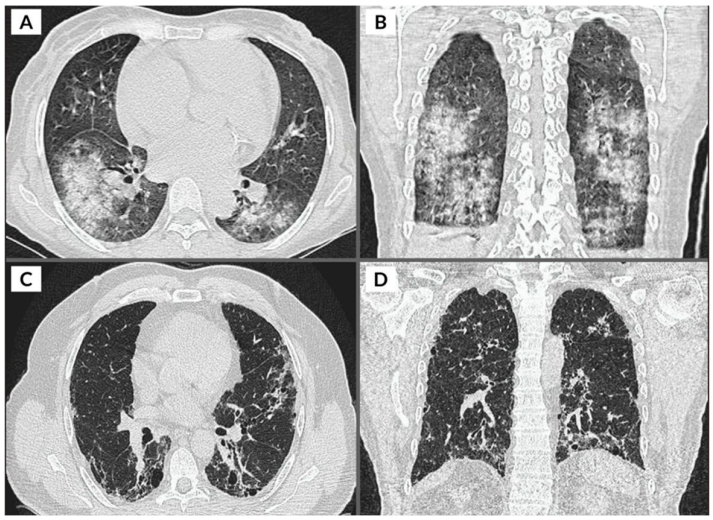


Figure 2. High-resolution CT patterns of interstitial lung disease (pSS-ILD). (**A**,**B**) Axial (**A**) and coronal (**B**) CT images demonstrating an organizing pneumonia (OP) pattern, characterized by bilateral, patchy areas of consolidation with a predominantly peripheral and peribronchovascular distribution. (**C**,**D**) Axial (**C**) and coronal (**D**) CT images demonstrating a usual interstitial pneumonia (UIP) pattern, showing basal and subpleural predominant reticulation, architectural distortion, and honeycombing, consistent with fibrotic interstitial lung disease.

Features such as traction bronchiectasis or bronchiolectasis also indicate the extent of fibrosis. These are considered key signs of fibrosis in UIP and help distinguish established structural fibrosis from ground-glass opacities. When ground-glass changes appear alongside reticulation and traction, they should be interpreted as part of the fibrosing process rather than as isolated inflammation [12,17].

In this context, peripheral clusters of traction bronchiectasis or bronchiolectasis may be mistaken for honeycombing, particularly in the lung bases. Diagnostic interpretation becomes more challenging when smoking-related changes result in the coexistence of fibrosis and emphysema. HRCT reports should explicitly describe the presence and extent of emphysema. Sequential image review and multiplanar reconstructions can improve differentiation between honeycombing and traction-related cystic changes [17].

4.2. HRCT Histopathology Concordance and Interobserver Variability

HRCT can support a working diagnosis; however, the literature identifies two major and distinct limitations: imperfect correlation with histopathology and interobserver variability in image interpretation, both of which can directly influence clinical decision making [16,17,22].

According to the Fleischner statement, the probable UIP category, defined by subpleural and basal reticulation with traction bronchiectasis or bronchiolectasis but no honeycombing, has a high likelihood (82–94%) of corresponding to histopathologic UIP on surgical lung biopsy, supporting its role as an intermediate category linking imaging and pathology [17].

The statement also notes the opposite can be true: histopathologic UIP may still be present even when HRCT findings are indeterminate or do not meet typical or probable criteria. Findings such as mosaic attenuation should not be used in isolation to exclude UIP. Instead, these features should prompt careful evaluation for alternative diagnoses, particularly hypersensitivity pneumonitis, rather than exclusion of UIP on imaging grounds alone [17].

The coexistence of different pulmonary processes can make radiologic-pathologic correlation more difficult. In pSS, the same imaging pattern may result from a combination of interstitial, airway-centered, and other pulmonary abnormalities rather than from a single disease process [12,20,23]. The main conditions that may mimic pSS-ILD are discussed in Section 6.4.

The challenge is further compounded by variability in image interpretation. In a study by Walsh et al., 112 observers classified HRCT scans using ATS/ERS/JRS/ALAT criteria and achieved only moderate agreement ($\kappa \approx 0.48$–0.52), with limited impact of reader experience on consistency [22]. This variability is clinically relevant because radiologic categorization often guides management decisions. In addition, distinguishing key features such as honeycombing can be difficult, particularly in the presence of emphysema or traction-related changes, further increasing diagnostic uncertainty [17].

According to the ATS/ERS classification of idiopathic interstitial pneumonias (IIPs), a case may be considered "unclassifiable" when available data are insufficient or when there is major discordance among clinical, radiologic, and histopathologic findings, including situations in which multiple patterns of lung injury coexist and cannot be reconciled into a single diagnostic entity [8,18]. Major discordance among clinical, radiologic, and histopathologic findings may render a case unclassifiable, underscoring the limits of HRCT as a stand-alone diagnostic tool [18]. The management of this diagnostic uncertainty is addressed in Section 4.3.

4.3. Limits of HRCT and Indications for MDD, BAL, and Biopsy

Additional diagnostic evaluation should be considered when clinical and HRCT findings do not provide sufficient confidence regarding the presence, cause, or dominant pulmonary process [17,24]. In patients without an established cause of ILD, indeterminate or alternative HRCT patterns may require further evaluation. However, in patients with established pSS, compatible HRCT abnormalities often support pSS-ILD without routine lung biopsy [13,16,17,25].

In connective-tissue-disease-associated ILD, including pSS-ILD, diagnostic confidence usually depends on integrating the clinical context with HRCT findings. Multidisciplinary discussion is most useful when the cause of ILD remains uncertain, when clinical and imaging findings are discordant, or when an alternative pulmonary process would materially change management [26]. BAL may help exclude infection, alveolar hemorrhage, diffuse alveolar damage, or organizing pneumonia, but it generally does not establish a specific chronic fibrotic pattern. Lung biopsy should be reserved for selected cases, including suspected malignancy or lymphoproliferative disease, atypical focal or infiltrative abnormalities, or persistent uncertainty in which histopathology is expected to influence treatment [8,26].

MDD plays a central role in this process. The ATS/ERS statement on IIPs emphasizes that both clinical and imaging data are required for diagnosis. Rather than replacing biopsy, MDD helps determine when tissue sampling is likely to provide additional diagnostic value beyond HRCT and when it may be avoided. Once a histopathologic pattern is identified, potential underlying causes such as hypersensitivity pneumonitis, CTD, or drug-induced injury should be reconsidered, supporting an integrated diagnostic approach [18].

5. ILD Phenotypes in Primary Sjögren's Syndrome

pSS-associated ILD presents with a wide spectrum of radiologic features, ranging from mild interstitial inflammation to advanced fibrosis and lymphoid proliferation [27]. Unlike idiopathic pulmonary fibrosis (IPF), in which the UIP pattern is relatively consistent and strongly predictive of disease behavior, pSS-ILD frequently exhibits overlapping patterns that may evolve over time [12,17,20]. Although radiologic patterns are often described as predominantly inflammatory or fibrotic, this distinction is not absolute, as most patterns include both components to varying degrees. Accordingly, these patterns are better interpreted along a continuum rather than as discrete categories. This underscores the importance of careful, context-driven interpretation of HRCT findings. While radiologic patterns contribute to disease phenotyping and may provide prognostic clues, they should not be interpreted in isolation, as disease severity and progression depend on the integration of fibrotic burden, physiological impairment, and longitudinal disease behavior [20,28].

5.1. Patterns with Predominant Fibrotic Features

NSIP is the most common fibrosing pattern found in pSS-ILD [20,24,29]. On HRCT, NSIP typically appears as ground glass opacities in the lower and peripheral lung regions, with fine reticulation and mild to moderate traction bronchiectasis or bronchiolectasis. The lung architecture is generally preserved, and honeycombing is absent or minimal [16,17]. These imaging features correlate with histopathology, which shows relatively uniform interstitial fibrosis with varying degrees of chronic inflammation. The cellular subtype of NSIP is characterized by more prominent ground glass opacities and less architectural distortion, whereas the fibrotic subtype shows increased reticulation and traction bronchiectasis [20,29].

Some patients have a UIP-like pattern, which on HRCT appears as irregular reticulation predominantly in the lower and peripheral lung regions, with traction bronchiectasis or bronchiolectasis and, in some cases, clear honeycombing [20,28,30]. Studies show that, while these features resemble UIP, in pSS they often coexist with findings less typical of IPF, such as residual ground glass opacities, signs of ongoing inflammation, and mixed patterns [20,24,28]. In both radiology and pathology, irregular reticulation with traction bronchiectasis reflects denser fibrosis and more advanced structural remodeling.

Distinguishing NSIP from a UIP-like pattern in pSS-ILD is important. UIP-like features are often associated with more severe functional impairment, a higher risk of fibrosing progression, and a worse prognosis in patients with pSS, although these outcomes are generally less severe than in IPF [29,31,32]. This difference reflects the underlying biological heterogeneity of pSS-ILD, in which fibrotic and inflammatory processes frequently coexist, in contrast to the more uniformly fibrotic nature of IPF [24,28]. Identifying this distinction also helps prevent the inappropriate application of diagnostic and therapeutic strategies designed for IPF to a disease with a different underlying biology [28].

5.2. Patterns with Prominent Inflammatory and Potentially Reversible Features

Patterns with a predominant inflammatory component are frequently observed in the radiologic spectrum of pSS-associated ILD [20,29,30]. OP can occur alone or in combination with NSIP [20,29]. On HRCT, OP typically presents as patchy areas of consolidation, often in the peripheral or peribronchovascular regions. These opacities may be migratory and are frequently associated with ground-glass attenuation and fine septal thickening. Air bronchograms and partial resolution on follow-up imaging are commonly observed [20].

When NSIP and OP coexist, this pattern generally reflects a predominance of inflammatory activity over established fibrosis and may be associated with increased systemic immune activity and distinct clinical profiles [20,29,30,33]. These patients often show a more favorable response to corticosteroids or immunosuppressive therapy, with potential for structural improvement, as suggested by the inflammatory nature of these patterns [20,29]. Recognizing NSIP–OP overlap is therefore essential to avoid misclassification as irreversible fibrotic disease, particularly given the frequent identification of mixed and inflammatory patterns in pSS-ILD cohorts [20,30,31].

5.3. Cystic and Lymphocytic Phenotypes

A distinctive manifestation of pSS-ILD is the cystic–lymphocytic phenotype, most commonly associated with interstitial pneumonia (LIP) [20,30,34], although LIP is reported less frequently in cohort studies than other pSS-ILD patterns [31]. On HRCT, this phenotype is characterized by multiple thin-walled cysts of varying size and distribution, often accompanied by diffuse ground-glass opacities, centrilobular nodules, septal thickening, and abnormalities along the bronchovascular bundles [20,34]. These findings reflect lymphocytic infiltration of the pulmonary interstitium and peribronchovascular regions.

Because cystic and nodular findings may also occur in pulmonary conditions other than ILD, atypical, persistent, or enlarging lesions require targeted differential evaluation, as discussed in Section 6.4 [23,34].

5.4. Less Common Phenotypes

Some less frequently recognized phenotypes include combined pulmonary fibrosis and emphysema (CPFE), mixed unclassifiable patterns, and advanced disease with major structural damage [35]. On HRCT, CPFE appears as centrilobular and paraseptal emphysema in the upper lobes together with basal fibrosis. This combination can make the assessment of disease severity difficult, as lung volumes may appear relatively preserved despite markedly impaired gas exchange [35].

These forms are clinically important because they are more challenging to diagnose, are associated with a higher risk of pulmonary hypertension, and often result in worse functional and survival outcomes [35–37]. Recognizing these phenotypes underscores the importance of careful HRCT interpretation and integration of findings within a multidisciplinary framework, particularly in the context of heterogeneous ILD presentations [20,35].

6. Diagnostic Challenges in pSS-ILD

As previously discussed, pSS-associated ILD remains frequently underdiagnosed, which contributes to diagnostic delay in clinical practice. Several factors account for this challenge. Subclinical disease or nonspecific respiratory symptoms may not prompt early evaluation [38,39], and there is often overreliance on chest radiography despite its limited sensitivity for detecting early interstitial changes [40]. In addition, ILD-first presentations, sometimes referred to as “occult pSS,” may delay recognition of the underlying autoimmune disease [41,42]. Seronegativity for anti-SSA and anti-SSB antibodies can further complicate the diagnostic process, leading to premature exclusion of pSS in the work-

up [43]. Moreover, conditions that may mimic ILD in this context, such as pulmonary lymphoma or amyloidosis, can divert attention from the correct diagnosis and require careful differentiation [44].

Because no single parameter adequately reflects disease progression, current approaches recommend integrating clinical symptoms, pulmonary function tests, and imaging findings to monitor disease course and guide management decisions, ideally within a multidimensional and longitudinal framework [45–48].

6.1. Subclinical Disease and Limitations of Symptoms and Chest Radiography

A key diagnostic challenge lies in the poor correlation between respiratory symptoms, chest radiography, and early interstitial injury. In pSS, lung involvement may occur even in the absence of overt symptoms, and studies suggest that pulmonary abnormalities, including interstitial inflammation and small-airway disease, are more prevalent than clinically apparent [24,31,38]. Even among patients with established pSS-ILD, respiratory symptoms may be absent or subtle, limiting early clinical suspicion [24].

Chest radiography further contributes to diagnostic limitations due to its low sensitivity for detecting early interstitial changes [40,49]. In contrast, HRCT is significantly more sensitive for identifying early lung abnormalities. For example, in asymptomatic patients with normal chest radiographs, HRCT has been shown to detect abnormalities in up to 65% of cases (24 out of 37), underscoring the limitations of conventional imaging in early disease detection [5].

6.2. ILD-First Presentations and Non-Sicca pSS: Diagnostic Clues and Delay

ILD may precede the recognition of pSS, particularly in patients with mild or absent sicca symptoms, leading to initial classification as idiopathic disease. In the study by Auteri et al., 46% of patients with previously unrecognized Sjögren's syndrome in an IPAF/ILD setting were diagnosed with ILD before Sjögren's syndrome, with a median interval of 15 months between diagnoses [41,42]. Similar findings have been reported in other cohorts; for example, a multicenter study found that ILD preceded pSS in 15 of 25 cases [31].

This presentation is more frequent in non-sicca phenotypes. In a case-control study, approximately 41% of patients initially presented with pulmonary symptoms, whereas only 20% reported sicca symptoms at disease onset, with a mean diagnostic interval of 15.8 months [30,50]. In practice, these patients are often first evaluated by pulmonologists and categorized as idiopathic ILD or IPAF, frequently without systematic assessment for Sjögren's-related autoimmunity or glandular dysfunction [51,52].

In patients presenting with ILD as the initial manifestation, particularly in unclassifiable ILD or IPAF, evaluation for features suggestive of underlying pSS is warranted. Relevant clinical clues include the Raynaud phenomenon, inflammatory arthralgia or arthritis, cutaneous vasculitis (e.g., purpura), parotid gland enlargement, and peripheral neuropathy [38,52,53]. Among these, the Raynaud phenomenon has been associated with a higher prevalence of lung involvement in pSS (60.53% vs. 17.29%) [51,54].

In patients newly evaluated for ILD, an IPAF-based approach may facilitate the identification of underlying connective tissue disease. IPAF is defined by the presence of interstitial pneumonia on HRCT or lung biopsy, exclusion of alternative causes, and features from at least two domains: clinical, serologic, or morphologic [53]. These include autoantibodies such as anti-SSA and anti-SSB, as well as characteristic morphologic patterns, including NSIP, OP, LIP, or overlap patterns [52,53].

In clinical practice, a focused sicca history and physical examination should be performed, together with extended serologic testing and assessment of glandular function

when indicated. When clinical or HRCT findings raise suspicion of underlying pSS, early referral to rheumatology should be considered to facilitate multidisciplinary evaluation [52].

6.3. Serology and Seronegative pSS: Implications for Case Definition

A clinically relevant seronegative subgroup of pSS exists in which patients lack classic autoantibodies, particularly in the context of ILD-dominant presentations [42,55]. In pSS-ILD cohorts, substantial seronegativity has been reported, including negativity for anti-SSA and anti-SSB [55]. Within the IPAF/ILD spectrum of "occult Sjögren's syndrome," anti-SSA and anti-SSB negativity has been described in approximately 79% and 85% of cases, respectively [41]. These findings are consistent with current IPAF frameworks, which recognize that autoimmune disease may be clinically and serologically incomplete at presentation [50,53].

In this review, "seronegative pSS" refers to cases with negative anti-SSA/SSB serology, with or without ANA or RF, in which diagnosis relies on objective evidence of glandular dysfunction or histopathology [7,55]. When clinical suspicion persists despite negative serology, minor salivary gland biopsy (MSGB) and objective ocular or oral tests become essential components of the diagnostic work-up [7,42]. Indeed, Auteri et al. demonstrated that pSS can still be diagnosed in seronegative ILD patients when MSGB shows focal lymphocytic sialadenitis [41]. This framework is particularly relevant in patients with HRCT patterns commonly associated with autoimmune disease within the IPAF spectrum, such as NSIP, OP, LIP, or overlap patterns [41,53].

6.4. Differential Diagnosis and Mimics: Lymphoproliferative Disease, Amyloidosis, Infection, Drug Toxicity, and Overlap Syndromes

The differential diagnosis of pSS-associated ILD includes a range of conditions with overlapping clinical and radiologic features [56,57]. Lymphoproliferative disorders are particularly relevant, as pSS is associated with an increased risk of lymphoma (approximately 5–18%), with pulmonary involvement reported in a subset of cases (~6%), as described by Lee et al. Mucosa-associated lymphoid tissue (MALT) lymphoma is the most frequent subtype and may present on imaging as pulmonary nodules, areas of consolidation, or mass-like lesions [38,44,56–59]. HRCT may demonstrate air trapping on expiratory imaging, reflecting concomitant small-airway involvement and contributing to the spectrum of radiologic findings [38,57,58].

Pulmonary MALT lymphoma in Sjögren's syndrome shows a variable clinical presentation. In one study, approximately one-third of cases were identified incidentally in asymptomatic patients, whereas cough and dyspnea were the most common symptoms when present [44,60]. In pSS cohorts, differentiation between lymphoproliferative disease and benign or indeterminate lesions often requires histopathologic confirmation, with the choice between transbronchial and surgical biopsy guided by clinical and radiologic features [36,44].

Pulmonary amyloidosis can look like pSS-ILD [61,62]. Patients with tracheobronchial or parenchymal involvement may have a long-lasting cough and shortness of breath. HRCT might show nodules, ground-glass opacities, septal thickening, cysts, or calcifications. These outcomes can resemble LIP and other ILD patterns, so histopathologic confirmation is often needed [62,63]. Lee et al. recommend bronchoscopy with biopsy if amyloidosis is suspected, particularly in patients with persistent respiratory symptoms, and suggest bronchoalveolar lavage or bronchoscopy to exclude infection when clinically indicated [38].

A structured diagnostic algorithm incorporating these principles is presented in Figure 3.

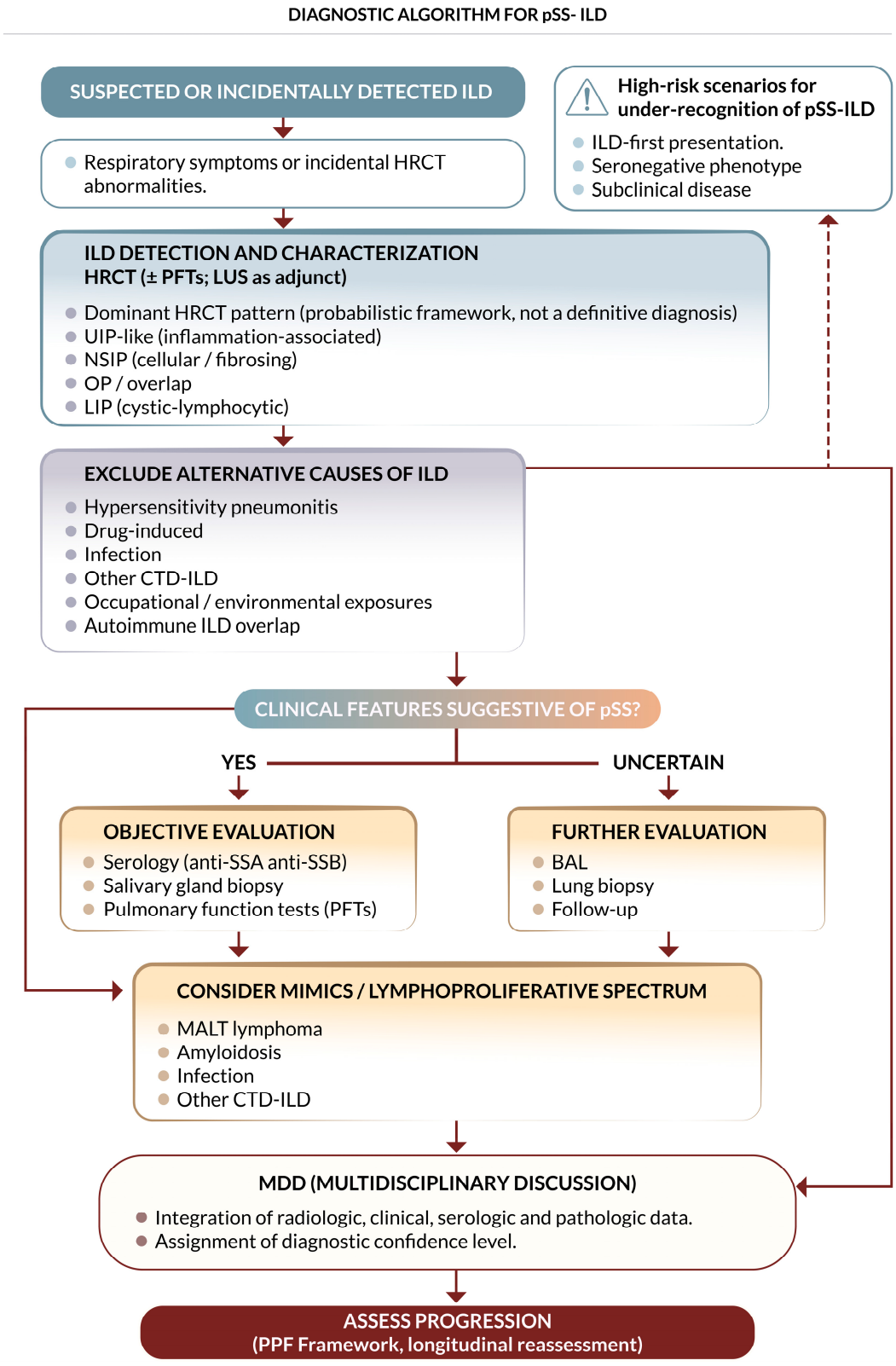


Figure 3. Diagnostic algorithm for primary Sjögren's syndrome–associated interstitial lung disease (pSS-ILD). The algorithm outlines a structured approach to evaluating suspected or incidentally detected ILD in the context of pSS. Initial assessment includes clinical presentation and imaging abnormalities, with high-resolution computed tomography (HRCT) serving as the reference standard for pattern characterization. HRCT patterns, such as usual interstitial pneumonia (UIP)-like, nonspecific

interstitial pneumonia (NSIP), organizing pneumonia (OP), and lymphocytic interstitial pneumonia (LIP), are interpreted as probabilistic frameworks rather than definitive diagnoses. The algorithm emphasizes the importance of excluding alternative causes of ILD and recognizing high-risk scenarios for under-recognition, including ILD-first presentations, seronegative phenotypes, and subclinical disease. When features suggestive of pSS are present, further evaluation includes serologic testing (anti-SSA/SSB antibodies), minor salivary gland biopsy, and pulmonary function tests. In cases of diagnostic uncertainty, additional investigations such as bronchoalveolar lavage (BAL), lung biopsy, or longitudinal follow-up may be required. Consideration of mimicking conditions, including mucosa-associated lymphoid tissue (MALT) lymphoma, amyloidosis, infection, and other connective tissue disease-associated ILDs, is essential. Final diagnostic integration and confidence assessment are achieved through multidisciplinary discussion (MDD). A longitudinal evaluation using the progressive pulmonary fibrosis (PPF) framework is recommended to assess disease progression over time. HRCT patterns inform disease characterization but do not establish diagnosis.

7. Prognosis and Disease Trajectories in pSS-ILD

In pSS-ILD, a single HRCT pattern alone does not fully determine prognosis. While certain imaging patterns, particularly a classic UIP pattern, have been associated with a higher likelihood of disease progression, outcomes cannot be inferred from morphology alone. HRCT remains essential for diagnosis and initial assessment; however, prognosis depends on the integration of fibrotic burden, physiological impairment, host characteristics, and especially longitudinal disease behavior [63]. Accordingly, current approaches emphasize dynamic assessment using measurable changes over time rather than reliance on static imaging patterns [63].

7.1. Prognostic Determinants: Fibrosis Burden, DLCO/FVC, Age, and Smoking

In fibrotic ILDs like pSS-ILD, both the amount and severity of fibrosis are important for predicting outcomes [64]. More fibrosis often leads to worse survival and a higher risk of functional decline, especially when scarring is more severe than reversible inflammation [65]. Accordingly, radiologic pattern labels should not be used in isolation, and prognostic assessment requires integration of imaging findings with physiological measures and longitudinal disease evolution [66,67].

Physiological measures offer a clear and practical way to assess risk. Baseline FVC and DLCO show the overall impact of the disease [68], but tracking changes in these values over time provides even more useful information. DLCO is often used as a marker for both lung tissue damage and blood vessel involvement, and lower DLCO values are linked to worse outcomes in connective-tissue-disease-related ILD [68,69]. FVC is also important for monitoring and is a key part of how progressive fibrosing disease is defined, as it is reliable and correlates with important clinical outcomes. The same HRCT pattern can be linked to very different physiological risk profiles, so it is important to consider both the severity of functional impairment and changes over time when making prognostic decisions [69].

Host factors affect prognosis. Older patients usually have worse outcomes in UIP-spectrum disease, likely because they have less physiological reserve and more comorbidities [70–72]. Smoking history, which is frequently associated with idiopathic pulmonary fibrosis (IPF), can also worsen pSS-ILD by causing lung injury and making repair more difficult. Smoking is often associated with emphysema, which may complicate lung function assessment and increase breathlessness and gas exchange problems [73,74]. These results indicate that the prognosis in pSS-ILD should be assessed based on different factors, including the extent of fibrosis, physiological impairment, and patient vulnerability.

7.2. Progressive Pulmonary Fibrosis: Evidence in pSS-ILD and Remaining Uncertainties

Recognizing PPF has changed our knowledge of non-IPF ILDs, showing that some cases get worse even with standard treatment. In pSS-ILD, research and specialist views show that some patients keep progressing, with worsening symptoms, declining function, and changes on imaging, sometimes even when using immunosuppressive therapy [75]. This has important clinical consequences because it challenges the notion that autoimmune-associated ILD is always driven by inflammation or responds well to treatment. It also shows the need for regular, structured monitoring over time [76].

However, research on pSS-ILD is still limited because most studies are retrospective, have small sample sizes, use different definitions of progression, and vary in treatment and follow-up. Fibrotic types, such as UIP and fibrotic NSIP, have been associated with a higher risk [77], but more prospective studies focused on pSS are needed to determine how frequently PPF occurs, identify early warning signs, and understand how inflammation leads to fibrosis [78]. These gaps make it harder to assess risk early, determine the optimal timing of treatment, and build accurate predictive models for pSS-ILD. As new guidelines define progression based on symptoms, function, and imaging, consistently applying these standards in pSS-ILD will be important for better reporting and research comparisons [79].

7.3. UIP in pSS Versus IPF: Prognostic and Management Implications

Although UIP morphology is often associated with a poor prognosis, its prognostic significance depends on the clinical context. In CTD-ILD, including pSS-ILD, research shows that the impact of UIP on prognosis can differ [46]. When comparing biopsy-proven UIP in pSS (UIP/pSS) to UIP in IPF (UIP/IPF), there are differences in pathology, imaging, and outcomes [28,80]. Histologically, UIP/pSS usually shows greater inflammation and immune cell clusters, such as lymphoplasmacytic infiltration and lymphoid follicles with germinal centres, and fewer fibroblastic foci [28,76,78,80]. On imaging, mediastinal lymphadenopathy and bronchial wall thickening are more common in UIP/pSS [28,58]. These differences are important in practice because they are linked to reports of a better prognosis in UIP/pSS compared to UIP/IPF, and some patients, especially early in the disease, may have a better chance of short-term stabilization. These differences have important clinical consequences. First, seeing a UIP pattern on HRCT in a patient with pSS should not automatically lead to a diagnosis of IPF, as this could result in incorrect advice and missed treatment options. Second, it is important to consider clinical features, autoantibody results, detailed HRCT findings, and, when possible, histopathology, because UIP/pSS can look similar to UIP/IPF on scans or under the microscope but may have a different cause and course [79]. Finally, differences between UIP/pSS and UIP/IPF support patient management based on disease progression over time, rather than solely on the UIP label [80,81]. Focusing on disease behaviour rather than the HRCT label helps guide prognosis and treatment decisions for each patient.

8. Discussion

pSS-ILD represents a clinically significant yet conceptually complex entity [1,64]. This variability has important implications for disease characterization, influencing reported prevalence, patient selection, and interpretation of outcomes [6,9,10,20]. In this context, the term “pSS-ILD” is used inconsistently in the literature, referring both to a clinical entity and to study-defined populations [75]. Most available evidence derives from retrospective studies with small sample sizes, heterogeneous treatment strategies, and variable follow-up intervals [25,75]. These issues make it hard to draw strong conclusions about how the disease changes over time [25,75]. Even though more studies now use systems that consider multiple aspects of progression [13], comparisons across cohorts remain lim-

ited by differences in HRCT interpretation, thresholds for clinically meaningful change, and definitions of progression [13,22,45,46].

HRCT terms are important for clinical decisions, but different doctors may interpret scans differently [22], and the match between imaging and biopsy results is not always exact, especially for UIP [20,76]. A scan labeled as 'probable UIP' often matches UIP on biopsy, but UIP can also be found when the scan is unclear [17,22]. These observations underscore that HRCT patterns function as probabilistic frameworks rather than definitive diagnostic endpoints [20,78].

Variability in the application of multidisciplinary discussions (MDDs) may influence the characterization of radiologic patterns and the reported prevalence of pSS-associated ILD across studies [18,38]. In addition, differences in study design and inclusion criteria, particularly those focused on sicca symptoms or serologic profiles, may shape patient selection and contribute to heterogeneity in reported cohorts [41,43,55]. These factors highlight the impact of methodological variability on disease characterization and limit comparability across studies.

Radiologic patterns nonetheless provide relevant prognostic stratification within this multidimensional framework [25,27,33]. NSIP is the most common [20,25], whereas a UIP-like pattern is generally associated with more advanced disease and a higher risk of fibrotic progression, although typically less aggressive than idiopathic pulmonary fibrosis [28,29,32,79,80]. These observations support the role of HRCT patterns as one component of prognostic assessment, to be interpreted alongside functional impairment and longitudinal evolution [13,45,46].

The cystic–lymphocytic pattern not only describes the appearance of ILD but may also signal an increased risk of lymphoproliferative disease in pSS [44,58,61,62]. The overlapping radiologic features of benign and malignant processes necessitate structured longitudinal follow-up and, when clinically indicated, histopathologic confirmation [44,57,58].

Delays in diagnosis are common when ILD is the first sign of disease [30,31,41]. Patients may be labeled as having idiopathic ILD or IPAF and not fully checked for Sjögren's syndrome if they do not have obvious systemic symptoms [41,50,53]. If they also lack typical antibodies, it becomes even harder to recognize and may lead to misdiagnosis as an idiopathic disease [41,43,55].

Misclassification can happen when a UIP pattern on HRCT is assumed to mean idiopathic pulmonary fibrosis in patients who already have pSS [28,76,78]. Even if the imaging meets UIP/IPF criteria, the disease process and course may differ [28,76]. Studies show that UIP in pSS can have unique features, such as lymph node enlargement and thickened bronchial walls, and could at times lead to better outcomes than IPF [28,58,79].

To best predict outcomes in pSS-ILD, doctors should consider HRCT patterns, the extent of fibrosis, lung function, and how these change over time [13,45,46]. Age, smoking, and emphysema also affect how the disease is understood [35,73,80]. Collectively, these considerations argue against a purely pattern-based interpretation of pSS-ILD and support a dynamic, progression-oriented framework that integrates radiologic phenotype and immune context [13,45,81]. An additional component of this multidimensional assessment is pulmonary hypertension, including both pulmonary arterial hypertension and ILD-associated pulmonary hypertension, which may further worsen functional status and clinical outcomes in selected patients [82].

9. Conclusions

pSS-ILD represents a heterogeneous entity in which variability in definitions and diagnostic approaches continues to influence reported prevalence, imaging characterization, and clinical outcomes. HRCT remains the cornerstone for identifying pulmonary

involvement and defining radiologic phenotypes. So far, research has been limited by inconsistent definitions, mostly small, retrospective studies, varying follow-up times, and irregular use of standard imaging and assessment tools. To identify cases earlier, use a stepwise approach that entails HRCT imaging, clinical context, and objective tests for Sjögren's, especially when suspicion remains. Going forward, we need consistent definitions and prospective studies that use standardized methods to improve comparisons and strengthen prognostic estimates.

10. Future Directions

Although pulmonary involvement in pSS is increasingly recognized; however, the diagnosis and management of pSS-ILD remain challenging. Subsequent research should integrate radiologic and pathologic data, mainly in patients with a UIP-like pattern, to distinguish inflammation-driven disease from irreversible fibrosis. Large, prospective studies using HRCT, tissue analysis, and longitudinal assessment of lung function are necessary to develop robust risk prediction models. Identifying reliable biomarkers that predict progression to PPF is also essential; for example, KL-6, chemokine profiles, and specific autoantibodies should be evaluated in long-term studies alongside cutting-edge imaging modalities and artificial intelligence tools to facilitate earlier identification of high-risk patients. For therapeutic development, well-defined pSS-ILD cohorts are required to determine the optimal use of immunomodulatory, antifibrotic, or combination therapies. Due to the heterogeneity of radiologic patterns, future treatment strategies should be adjusted to specific patient subtypes rather than depending solely on approaches established for idiopathic pulmonary fibrosis (IPF). The development of standardized MDD frameworks for connective tissue disease-related ILD may enhance diagnostic consistency and facilitate earlier, individualized care.

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Abbreviations

The following abbreviations are used in this manuscript:

ACR	American College of Rheumatology
AECG	American–European Consensus Group
ALAT	Latin American Thoracic Association
ANA	Antinuclear antibody
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
CHEST	American College of Chest Physicians
CPFE	Combined pulmonary fibrosis and emphysema
CT	Computed tomography

CTD	Connective tissue disease
CTD-ILD	Connective-tissue-disease-associated interstitial lung disease
DLCO	Diffusing capacity of the lung for carbon monoxide
ERS	European Respiratory Society
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
ILD	Interstitial lung disease
IIPs	Idiopathic interstitial pneumonias
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
KL-6	Krebs von den Lungen-6
LIP	Lymphocytic interstitial pneumonia
LUS	Lung ultrasound
MALT	Mucosa-associated lymphoid tissue
MDD	Multidisciplinary discussion
MSGB	Minor salivary gland biopsy
NSIP	Nonspecific interstitial pneumonia
OP	Organizing pneumonia
PPF	Progressive pulmonary fibrosis
pSS	Primary Sjögren's syndrome
pSS-ILD	Primary Sjögren's syndrome-associated interstitial lung disease
RF	Rheumatoid factor
UIP	Usual interstitial pneumonia
anti-SSA	Anti-Sjögren's syndrome-related antigen A antibody
anti-SSB	Anti-Sjögren's syndrome-related antigen B antibody

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