Pulmonary Involvement in Systemic Lupus Erythematosus: Challenges in Clinical Practice

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Abstract:
Pulmonary involvement in systemic lupus erythematosus (SLE) represents a clinically significant and often underrecognized manifestation that substantially contributes to morbidity and mortality. Lung involvement in SLE may affect the pleura, lung parenchyma, pulmonary vasculature, and respiratory musculature, presenting with a wide spectrum of clinical patterns ranging from asymptomatic findings to life-threatening conditions. The heterogeneity of pulmonary manifestations and their frequently nonspecific presentation pose major diagnostic challenges and often lead to delayed recognition. Advances in imaging techniques and pulmonary function testing have improved detection; however, accurate diagnosis requires a comprehensive and multidisciplinary approach. Management remains challenging due to the lack of standardized, disease-specific treatment guidelines and the variable response to immunosuppressive and targeted therapies. Early identification of pulmonary involvement and timely initiation of appropriate treatment are essential to prevent irreversible lung damage and improve long-term outcomes in patients with SLE. This review summarizes current knowledge on clinical patterns, diagnostic challenges, and management strategies of SLE-related pulmonary disease.

Keywords: *Systemic lupus erythematosus; Pulmonary involvement; Interstitial lung disease; Pleuritis; Pulmonary arterial hypertension; Diagnostic challenges; Treatment strategies*

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder characterized by a highly heterogeneous clinical course and complex immunopathogenesis. The development of SLE is influenced by the interaction of genetic susceptibility, environmental triggers, and dysregulation of both innate and adaptive immune responses [1]. Owing to this complexity, the disease may manifest with a broad clinical spectrum, ranging from mild mucocutaneous involvement to severe, life-threatening damage of vital organs.

Among the various organ systems affected, the respiratory system represents a clinically important yet often underrecognized target of SLE-related pathology. Pulmonary involvement may affect any anatomical compartment of the respiratory tract and can occur at different stages of the disease, displaying variable severity. Although the precise molecular mechanisms responsible for lung involvement in SLE have not been fully elucidated, persistent inflammation and immune dysregulation are considered central pathogenic drivers [2]. Elevated levels of pro-inflammatory cytokines, including interleukin-6, interleukin-1, interleukin-8, tumor necrosis factor-α, and type I interferons, together with circulating immune complexes, contribute to pulmonary inflammation, vascular injury, and progressive tissue remodeling that may culminate in fibrosis [3].

Immune cells play a pivotal role in mediating lung damage in SLE. The inflammatory microenvironment within pulmonary tissue promotes the recruitment and activation of neutrophils, monocytes, macrophages, and lymphocyte subsets. T lymphocytes contribute to lung injury through the secretion of pro-inflammatory cytokines and by enhancing B-cell activation, while B cells promote autoantibody production and immune complex deposition within pulmonary structures [4]. Neutrophils further exacerbate inflammation through neutrophil extracellular trap formation, exposing nuclear antigens and amplifying autoimmune responses. Activated macrophages perpetuate tissue damage by releasing inflammatory mediators and profibrotic factors, thereby linking immune activation to chronic structural lung injury [5].

Clinically, respiratory manifestations of SLE may present in acute or chronic forms and are frequently nonspecific, including symptoms such as cough, dyspnea, and pleuritic chest pain.

Importantly, pulmonary involvement may also remain clinically silent and be detected only through imaging studies or functional assessments. Pulmonary manifestations can be classified as primary, directly related to immune-mediated damage caused by SLE; secondary, resulting from other systemic complications of the disease; or associated with comorbid conditions such as infections or malignancies [6], [7]. Primary pulmonary involvement encompasses a wide range of entities, including pleuritis, interstitial pneumonitis, pulmonary arterial hypertension, diffuse alveolar hemorrhage, obliterative bronchiolitis, and shrinking lung syndrome.

The reported prevalence of pulmonary manifestations in SLE varies considerably across studies due to differences in diagnostic criteria and patient populations. Pleural involvement is the most frequently observed manifestation, while parenchymal and vascular complications occur less commonly but are often associated with significant morbidity and mortality. In particular, conditions such as diffuse alveolar hemorrhage and acute interstitial pneumonitis are rare but potentially fatal, underscoring the prognostic importance of early recognition. Even chronic forms, such as interstitial lung disease, although infrequent, negatively affect long-term survival and quality of life [8].

Methodology

Clinical Patterns and Classification of Pulmonary Involvement in Systemic Lupus Erythematosus

Pulmonary involvement in systemic lupus erythematosus represents a heterogeneous group of clinical entities that vary widely in terms of anatomical localization, severity, and clinical course. This diversity reflects the complex immunopathological mechanisms underlying the disease and poses significant challenges for timely diagnosis and clinical management. Lung involvement in SLE may occur at any stage of the disease and can manifest as an isolated finding or in association with multisystem activity.

From a clinical perspective, pulmonary manifestations in SLE are commonly classified into primary, secondary, and comorbid forms. Primary pulmonary involvement arises directly from immune-mediated injury attributable to SLE itself, whereas secondary manifestations develop as a consequence of other systemic complications, such as renal failure, nephrotic syndrome, or cardiac dysfunction Comorbid pulmonary conditions, including infections, malignancies, and overlapping respiratory diseases, may further complicate the clinical picture and obscure the attribution of symptoms to lupus-related pathology.

Primary pulmonary manifestations can be further categorized according to the anatomical compartment involved. Pleural disease constitutes the most frequently observed form of lung involvement in SLE and typically presents as pleuritis with or without pleural effusion. Although pleural manifestations are often associated with active systemic disease, they may range from asymptomatic effusions to severe pleuritic pain and respiratory compromise.

Result and Discussion

The high prevalence of pleural involvement underscores its diagnostic relevance, yet its nonspecific presentation often necessitates careful exclusion of alternative etiologies.

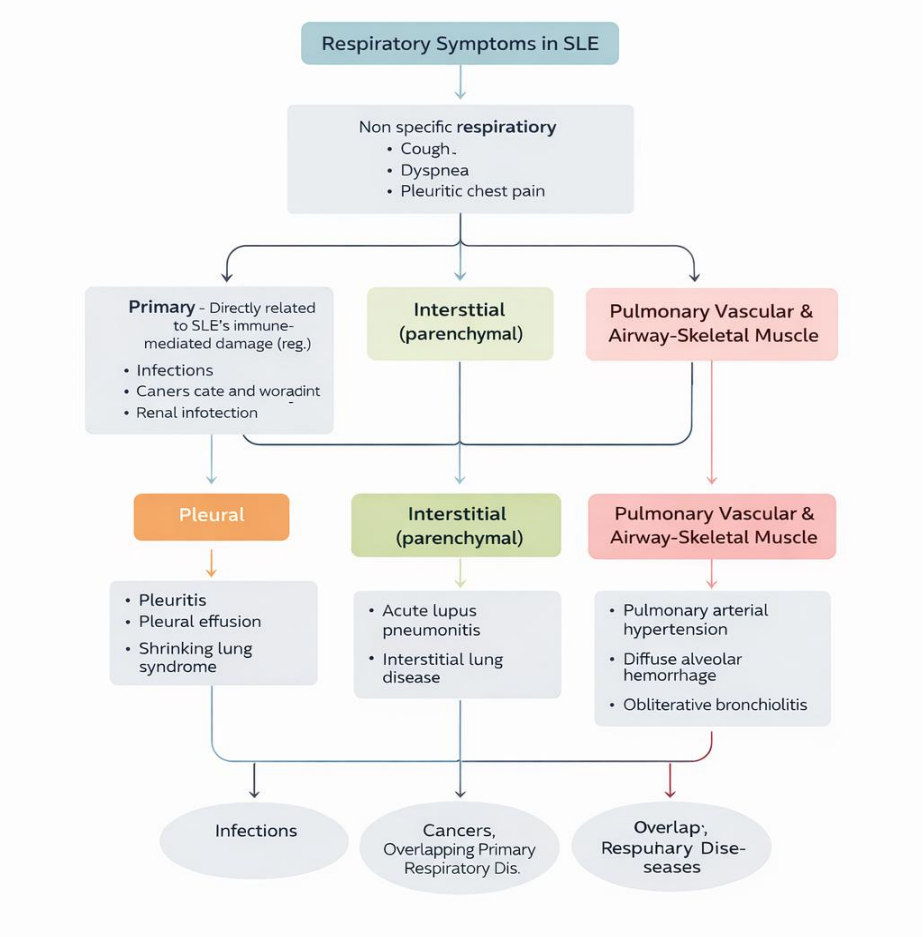


Figure 1. Clinical patterns and classification of pulmonary involvement in systemic lupus erythematosus.

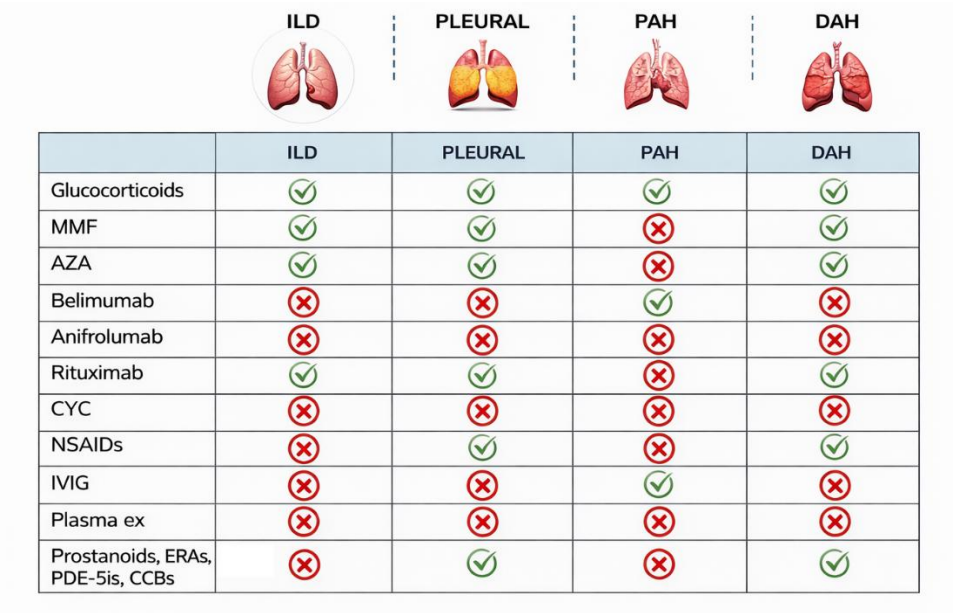
Parenchymal lung involvement is less common but clinically significant due to its potential association with high morbidity and mortality. Acute presentations, such as acute lupus pneumonitis and diffuse alveolar hemorrhage, are rare but represent medical emergencies. These conditions are characterized by rapid clinical deterioration, severe hypoxemia, and a high risk of fatal outcomes if not promptly recognized and treated [9]. Chronic parenchymal involvement, most commonly in the form of interstitial lung disease, typically follows a more indolent course but may lead to progressive respiratory impairment and reduced long-term survival.

Pulmonary vascular involvement in SLE primarily manifests as pulmonary arterial hypertension, a condition associated with poor prognosis and substantial functional limitation. Its insidious onset and nonspecific early symptoms frequently result in delayed diagnosis [10]. Similarly, rare entities such as shrinking lung syndrome and obliterative bronchiolitis are often underdiagnosed due to their low prevalence and overlapping clinical features with other pulmonary disorders.

An important characteristic of pulmonary involvement in SLE is the frequent discrepancy between structural abnormalities and clinical symptoms. Many patients remain asymptomatic despite radiological or functional evidence of lung disease, while others present with nonspecific respiratory complaints that may mimic infectious or cardiovascular conditions [11]. This clinical ambiguity contributes to diagnostic delays and highlights the need for heightened clinical awareness and systematic evaluation strategies.

The reported prevalence of individual pulmonary manifestations varies considerably across studies, reflecting differences in study design, diagnostic criteria, and patient populations. Nevertheless, available data consistently indicate that pulmonary involvement is a major contributor to disease burden

and adverse outcomes in SLE [12]. Acute forms are associated with particularly high mortality rates, while chronic manifestations negatively affect quality of life and long-term prognosis.



	ILD	PLEURAL	PAH	DAH
Glucocorticoids	✓	✓	✓	✓
MMF	✓	✓	✗	✓
AZA	✓	✓	✗	✓
Belimumab	✗	✗	✓	✗
Anifrolumab	✗	✗	✗	✗
Rituximab	✓	✓	✗	✓
CYC	✗	✗	✗	✗
NSAIDs	✗	✓	✗	✓
IVIG	✗	✗	✓	✗
Plasma ex	✗	✗	✗	✗
Prostanoids, ERAs, PDE-5is, CCBs	✗	✓	✗	✓

Figure 2. Treatment strategies for pulmonary involvement in systemic lupus erythematosus.

Diagnostic Approach to Pulmonary Manifestations in Systemic Lupus Erythematosus

The diagnosis of pulmonary involvement in systemic lupus erythematosus remains a significant challenge in clinical practice due to the heterogeneity of clinical manifestations, frequent overlap with non-lupus conditions, and the often-subclinical nature of lung disease [13]. Respiratory complications may arise at any stage of SLE and can occur independently of overall disease activity, further complicating timely recognition and accurate attribution.

One of the principal diagnostic difficulties lies in the nonspecific presentation of respiratory symptoms. Clinical features such as cough, dyspnea, chest discomfort, and reduced exercise tolerance are common in SLE patients but lack diagnostic specificity, as they may reflect infectious processes, cardiovascular disease, drug-related toxicity, or pulmonary embolism. Moreover, a substantial proportion of patients exhibit radiological or functional abnormalities in the absence of overt respiratory symptoms, leading to underdiagnosis or delayed identification of pulmonary involvement [14].

Table 1. Summary of Diagnostic Tools for Pulmonary Involvement in Systemic Lupus Erythematosus.

Diagnostic tool	Key findings	Clinical value	Limitations / comments
Chest X-ray (CXR)	May reveal pleural effusion, consolidation, or diffuse infiltrates depending on disease pattern	First-line imaging tool; useful for initial assessment	Low sensitivity in early or subclinical disease

Computed Tomography (HRCT)	Interstitial septal thickening, ground-glass opacities, parenchymal bands	Most sensitive method for early detection and characterization of lung involvement	Radiation exposure; limited availability in some settings
Pulmonary Function Tests (PFT)	Reduced DLCO; restrictive ventilatory pattern	Useful for detecting subclinical pulmonary involvement and follow-up	Normal results do not exclude early disease
Bronchoalveolar Lavage (BAL)	Neutrophil predominance in acute inflammation; hemosiderin-laden macrophages in DAH	Helps exclude infection and supports diagnosis of DAH	Invasive; not suitable for routine screening
Lung Biopsy	Fibrosis, immune complex deposition, alveolar damage	Definitive diagnosis in unclear cases	High risk; reserved for selected patients
FDG-PET	Increased uptake in inflammatory pulmonary lesions	Potential marker of disease activity	Limited availability; high cost
Dynamic MRI	Reduced diaphragmatic motion	Useful in suspected shrinking lung syndrome	Limited diagnostic scope

Clinical assessment should therefore be systematic and incorporate a careful evaluation of symptom onset, disease activity, serological markers, and the presence of extrapulmonary manifestations. Acute respiratory deterioration in SLE patients warrants urgent investigation, as life-threatening entities such as acute lupus pneumonitis or diffuse alveolar hemorrhage may progress rapidly and require immediate intervention. Conversely, chronic pulmonary involvement, particularly interstitial lung disease or pulmonary arterial hypertension, often follows an insidious course and may remain unrecognized until advanced stages.

Imaging plays a central role in the diagnostic workup of SLE-related lung disease. Chest radiography is typically the first-line modality due to its accessibility; however, its sensitivity is limited, especially in early or mild disease. High-resolution computed tomography has emerged as the most informative imaging technique for detecting both acute and chronic pulmonary abnormalities. HRCT

allows detailed visualization of parenchymal, pleural, and vascular changes and is particularly valuable for identifying interstitial lung disease, ground-glass opacities, and subtle structural alterations that may not be evident on conventional radiographs.

Pulmonary function testing provides complementary information and is especially useful for detecting subclinical disease. A reduction in diffusing capacity for carbon monoxide is the most frequently observed functional abnormality and may precede radiological changes. Restrictive ventilatory patterns further support the presence of interstitial involvement, although normal pulmonary function tests do not exclude early lung disease. Serial assessment may therefore be required to monitor disease progression and therapeutic response.

In selected cases, invasive diagnostic procedures are necessary to clarify the underlying pathology. Bronchoalveolar lavage is primarily employed to exclude infection and to support the diagnosis of diffuse alveolar hemorrhage, particularly in patients presenting with acute respiratory failure and unexplained anemia. Lung biopsy is reserved for cases with inconclusive clinical and radiological findings, given its associated morbidity, and is generally limited to situations in which diagnostic uncertainty significantly affects management decisions .

Another major diagnostic challenge is the differentiation between primary lupus-related pulmonary involvement and secondary or comorbid conditions. Immunosuppressive therapy predisposes SLE patients to respiratory infections that may closely mimic inflammatory lung manifestations, both clinically and radiologically. Similarly, drug-induced lung injury and thromboembolic disease must be carefully considered in the differential diagnosis. This overlap underscores the importance of a multidisciplinary approach involving rheumatologists, pulmonologists, radiologists, and, when necessary, intensivists.

Management and Treatment Challenges of Pulmonary Involvement in Systemic Lupus Erythematosus

The management of pulmonary involvement in systemic lupus erythematosus remains challenging due to the heterogeneity of clinical manifestations, the variable severity of lung disease, and the limited availability of evidence-based, disease-specific therapeutic guidelines. Treatment strategies are largely extrapolated from clinical experience, small observational studies, and therapeutic approaches used for severe manifestations of SLE affecting other organ systems. As a result, therapeutic decision-making often requires individualization based on clinical presentation, disease activity, and comorbid conditions .

A fundamental challenge in clinical management is the timely initiation of appropriate therapy. Mild pulmonary manifestations, particularly pleural involvement, may respond adequately to nonsteroidal anti-inflammatory drugs and low-dose corticosteroids. However, prolonged use of these agents is limited by potential adverse effects, including gastrointestinal toxicity and renal impairment, which are of particular concern in patients with concomitant lupus nephritis. Consequently, escalation to immunomodulatory therapy is frequently required in patients with persistent or recurrent disease.

Corticosteroids remain the cornerstone of treatment for moderate to severe pulmonary involvement in SLE. High-dose systemic corticosteroids are commonly employed in acute, life-threatening conditions such as acute lupus pneumonitis and diffuse alveolar hemorrhage. Despite their effectiveness in controlling inflammation, corticosteroids are associated with significant short- and long-term complications, including infection risk, osteoporosis, and metabolic disturbances. Balancing therapeutic benefit against cumulative toxicity represents a persistent management dilemma, especially in patients requiring repeated or prolonged courses.

Immunosuppressive agents, including mycophenolate mofetil, azathioprine, and cyclophosphamide, are widely used as steroid-sparing therapies and for the treatment of severe pulmonary manifestations. Mycophenolate mofetil and azathioprine are often preferred for chronic interstitial lung disease due to their more favorable safety profiles, whereas cyclophosphamide is generally reserved for rapidly progressive or refractory cases [15]. Nevertheless, robust comparative data

evaluating the efficacy of these agents specifically in SLE-related lung disease are lacking, and treatment responses remain unpredictable. The presence of chronic interstitial lung damage highlights the therapeutic challenges encountered in advanced stages of SLE-related pulmonary disease, where structural remodeling may reduce responsiveness to conventional treatment (Figure 3).

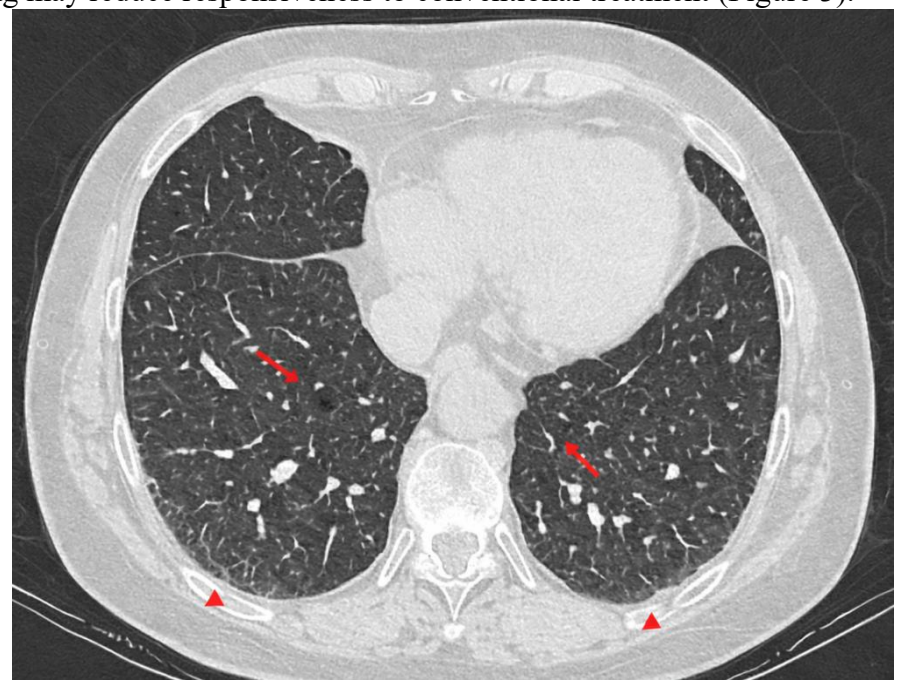


Figure 3. High-resolution computed tomography features of chronic interstitial lung involvement in systemic lupus erythematosus.

The emergence of biologic therapies has expanded the therapeutic landscape, yet their role in pulmonary involvement of SLE is not fully defined. Agents targeting B-cell activity, such as belimumab and rituximab, have shown variable efficacy across different pulmonary phenotypes. While some studies report clinical improvement in pleural disease and diffuse alveolar hemorrhage, responses in interstitial lung disease and pulmonary arterial hypertension are inconsistent. The absence of large randomized controlled trials limits definitive conclusions regarding patient selection and optimal treatment duration.

Management of pulmonary arterial hypertension in SLE presents additional complexity, as treatment often requires a combination of immunosuppressive therapy and pulmonary vasodilators. Endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin analogues, and calcium channel blockers are used to improve hemodynamics and functional capacity. However, delayed diagnosis and the presence of coexisting parenchymal lung disease frequently compromise treatment outcomes.

Supportive and adjunctive therapies play a critical role in comprehensive management. Oxygen supplementation, pulmonary rehabilitation, infection prophylaxis, and careful monitoring for drug-related toxicity are essential components of patient care. In selected cases, advanced interventions such as plasmapheresis or intravenous immunoglobulin therapy may be considered, particularly in refractory diffuse alveolar hemorrhage, although supporting evidence remains limited.

Conclusion

Pulmonary involvement in systemic lupus erythematosus represents a heterogeneous and clinically significant manifestation that contributes substantially to morbidity and mortality. Lung involvement may affect multiple anatomical compartments and often presents with nonspecific or subclinical features, leading to delayed diagnosis and underestimation of disease severity.

The variability of clinical patterns and the overlap with infectious, cardiovascular, and drug-related conditions pose major diagnostic challenges. Although imaging techniques and pulmonary

function testing have improved detection, accurate diagnosis requires a systematic and multidisciplinary approach.

Management remains complex due to the absence of standardized, disease-specific treatment algorithms. Therapeutic decisions are largely individualized and influenced by disease phenotype, severity, and comorbidities. Early recognition and timely intervention are therefore essential to prevent irreversible lung damage and improve long-term outcomes in patients with systemic lupus erythematosus.

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