

Pulmonary Manifestations of Systemic Lupus Erythematosus Among Adults in Aseer Region, Saudi Arabia

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Background: Nearly half of the Systemic lupus erythematosus (SLE) patients develop lung involvement. The study assessed the extent of pulmonary involvement among SLE patients and to identify the associated factors in the population.

Methodology: This retrospective cohort study was conducted at Aseer Hospital and Khamis Myshat Hospital in the Southern region of Saudi Arabia. The study spanned from January 1, 2016, to June 3, 2023. Patient inclusion criteria encompassed individuals who received a definitive diagnosis and classification as per American College of Rheumatology criteria, while patients under 18 years of age and those with mixed connective tissue diseases were excluded.

Results: A total of 247 participants were included. 41.7% (n=103) aged 41 years and older, 95.1% (n = 235) were females. Around 10.10% had diabetes mellitus and 17.00% had hypertension and hypothyroidism. Lupus Nephritis was in 15.40%. Chest involvement was reported in 21.9%, in the form of pleuritis (6.10%), pleural effusion (4.00%), and lupus pneumonitis (4.00%), interstitial lung disease (4.00%), pulmonary embolism (3.60%) of individuals, and pulmonary hemorrhage (2.80%). The respiratory symptoms reported by SLE were; dyspnea, cough, and chest pain each having a prevalence of around 18.0%. Palpitations have a relatively high occurrence at 13.80%. Meanwhile, hemoptysis (blood coughing) has a lower prevalence of 1.20%, and fever is reported at 2.80%. Having chronic kidney disease and hypertension were significantly associated with having pulmonary involvement; ($\chi^2=3.308$, $p=0.027$) and ($\chi^2=7.782$, Fisher's $p=0.002$) respectively. The seropositivity for antiphospholipid Abs, anti-CCP, and anti-dsDNA were significantly associated with pulmonary involvement ($\chi^2=3.239$, $p=0.049$), ($\chi^2=4.621$, Fisher's $p=0.023$), and ($\chi^2=8.248$, $p=0.010$) respectively.

Conclusion: The study found that 21.9% of SLE patients experience chest involvement, with varying degrees of pulmonary symptoms. Factors such as chronic kidney disease, hypertension, antiphospholipid antibodies, Anti-CCP positivity, and seropositivity for Anti-dsDNA were found to be significant associations with lung involvement, contributing to our understanding of SLE.

Keywords: Systemic lupus erythematosus, pulmonary manifestation, Anti-dsDNA antibodies, ANA

Introduction

Systemic lupus erythematosus is a chronic autoimmune illness characterized by a variety of clinical and immunological abnormalities.¹ SLE-related complications can affect all compartments of the lungs and include pleuritis, interstitial lung disease (ILD), alveolar hemorrhage, shrinking lung syndrome (SLS), pulmonary hypertension (PH), airways disease, and thromboembolic disease.² Clinicians awareness of SLE-related pulmonary symptoms and the development of more

sensitive techniques capturing lung involvement have led to the realization that subclinical lung involvement occurs more frequently than clinically discernible involvement.^{3,4}

Clinical evaluations of SLE patients should usually include a comprehensive examination for respiratory problems.^{4,5} Some asymptomatic patients may present with incidental findings of abnormal chest imaging or lung function tests.⁶ Serological indications such as elevated erythrocyte sedimentation rate (ESR), low complement, and increased double-stranded DNA (dsDNA) antibody titers, urge further need to evaluate whether the new respiratory symptoms are caused by lupus.^{7,8}

It has been reported that around 20 to 90% of SLE patients develop the lung involvement.^{7,9} However, it has lately been proposed that this figure is closer to 50–70%.¹⁰ Older age and anti-RNP antibodies are predictors of progression to earlier irreversible lung damage.¹¹ The pulmonary manifestations of SLE related mortality varies depending on the type and level of lung involvement observed.¹² Chronic lung disease associated with SLE can have a negative impact on the well-being, physical performance, and quality of life of patients.¹³ Respiratory manifestations can be acute or chronic, primary (directly caused by the disease) or secondary (due to concomitant complications such as infections). Interestingly, acute manifestations may be associated with generalized lupus disease activity, while chronic complications may progress independently to general disease activity.¹⁴ Respiratory manifestations of SLE are associated with a variable mortality rate, depending to the type of involvement, its extension, and the presence of comorbidities.¹³ Therefore, the assessment and treatment of lung involvement in patients with SLE should be performed promptly. CXR, HRCT, and PFT are recommended as diagnostic work-up. Moreover, exact diagnostic criteria for lung involvement in SLE remain elusive. Thus, more attention should be paid to the active surveillance and management of pulmonary manifestations of SLE.¹⁵

The existing clinical and therapeutic trial data specifically focused on respiratory manifestations of SLE are scarce. The current study hypothesized that the prevalence of pulmonary involvement among patients with SLE is significantly high, with a tendency toward severe complications. The objective of this study was to assess the extent of pulmonary involvement among SLE patients and to identify the factors that are associated with the occurrence and severity of such involvement. Understanding these factors is essential to providing comprehensive care to patients with SLE, as it can help identify those at higher risk and potentially guide interventions to mitigate severe complications.

Methods

Study Design and Patient Selection

This retrospective cohort study was conducted at Aseer Hospital and Khamis Myshat Hospital in the Southern region of Saudi Arabia. The study spanned from January 1, 2016, to June 3, 2023. Patient inclusion criteria encompassed individuals who received a definitive diagnosis and classification according to the American College of Rheumatology criteria, while patients under 18 years of age and those with mixed connective tissue diseases were excluded.

Data Collection

Demographic information, including age, gender, nationality, and chronic diseases, was systematically extracted from patient records. Patients were asked about the duration of SLE suffering in parallel with the collection of the following laboratory data; Serum complement (C3 and C4), antiphospholipid antibodies (Antiphospholipid, ACL Ab), Anti-CCP (Cyclic Citrullinated Peptide) Antibodies; Anti-Smith Antibodies; Rheumatoid factor; Anti-dsDNA Antibodies (Anti-double-stranded DNA): Anti-dsDNA antibodies are highly specific to SLE and are often linked to lupus nephritis, a kidney complication of SLE.

Assessment of pulmonary manifestations: chest symptoms were recorded and two senior radiologists independently reviewed chest radiographs and high-resolution computed tomography (HRCT) scans to reach diagnosis consensus. Pulmonary manifestations were meticulously documented, which included pleural thickening/effusion, pericardial effusion, pneumonia, pneumonitis, interstitial lung disease, bronchiectasis, diaphragmatic dysfunction, pulmonary embolism (PE), adult respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage (DAH), cryptogenic organizing pneumonia (COP) and pulmonary edema.

Statistical Analysis

Statistical analysis was carried out using R software version 4.2. Categorical variables were expressed as frequencies and percentages. The chi-square test was used to determine if there is a significant association between categorical variables. The Fisher's Exact Test was used to determine the significance of the association between two categorical variables if the assumption of the Chi square test was violated. Phi coefficient of association was used to determine the strength and direction of association between two binary (dichotomous) variables for the 2*2 table. Cramer's V was used to measure the association between two categorical variables in a contingency table more than 2*2. We set the p-value below 0.05 to be statistically significant.

Ethical Approval

To maintain ethical standards, the research diligently sought approval (IRB log No: REC-07-08-2022) from the Directorate of Health Affairs, Aseer Region Research Ethics Committee, and Ministry of Health Saudi Arabia. Throughout the research process, the principles outlined in the Helsinki Declaration were strictly followed.

Results

Table 1 summarizes the key demographic characteristics of a sample of 247 people. The age distribution of the sample reveals a significant prevalence of people 41 years of age and older (41.7%). The gender makeup is highly biased toward women (95.1%). Nationality data show that nearly all participants are Saudi, with one single Indian. A considerable proportion of patients (61.9%) reported having other comorbid diseases, while 38.1% did not.

Figure 1a and **b** depicts the linked comorbid medical disorders in SLE patients. Among this group, the prevalence rates of associated conditions were as follows, 15.40% for Lupus nephritis, 0.40% for autoimmune hemolytic anemia (AIHA), 4.50% for pulmonary embolism (PE), 6.10% for chronic kidney disease (CKD), 6.50% for rheumatoid arthritis (RA), and 8.90% for deep vein thrombosis (DVT). The prevalence of comorbidities was as follows, 1.20% for bronchial asthma (BA), 10.10% for diabetes mellitus (DM), 17.00% for hypertension, and 17.00% for hypothyroidism.

In total, 21.9% of SLE reported chest involvement. **Figure 2** shows the pattern of pulmonary involvement; pleuritis, affected 6.10% of individuals, pleural effusion was present in 4.00% of cases, lupus pneumonitis, affected 4.00% of individuals, interstitial lung disease affected 4.00% of cases, pulmonary embolism was reported in 3.60% of individuals, and pulmonary hemorrhage, was reported among 2.80%. The respiratory symptoms reported by SLE were as follows; dyspnea (shortness of breath), cough, and chest pain each have a prevalence of around 18.0%. Palpitations have

Table 1 Sociodemographic Characteristics of the Studied Population

Studied variables Overall (N=247)		N (%)
Age	Less than 20 years old	14 (5.7%)
	30–21 years	61 (24.7%)
	40–31 years	69 (27.9%)
	41 years and older	103 (41.7%)
Gender	Female	235 (95.1%)
	Male	12 (4.9%)
Nationality	Indian	1 (0.4%)
	Saudi	246 (99.6%)
Does suffer from other comorbid diseases	No	94 (38.1%)
	Yes	153 (61.9%)

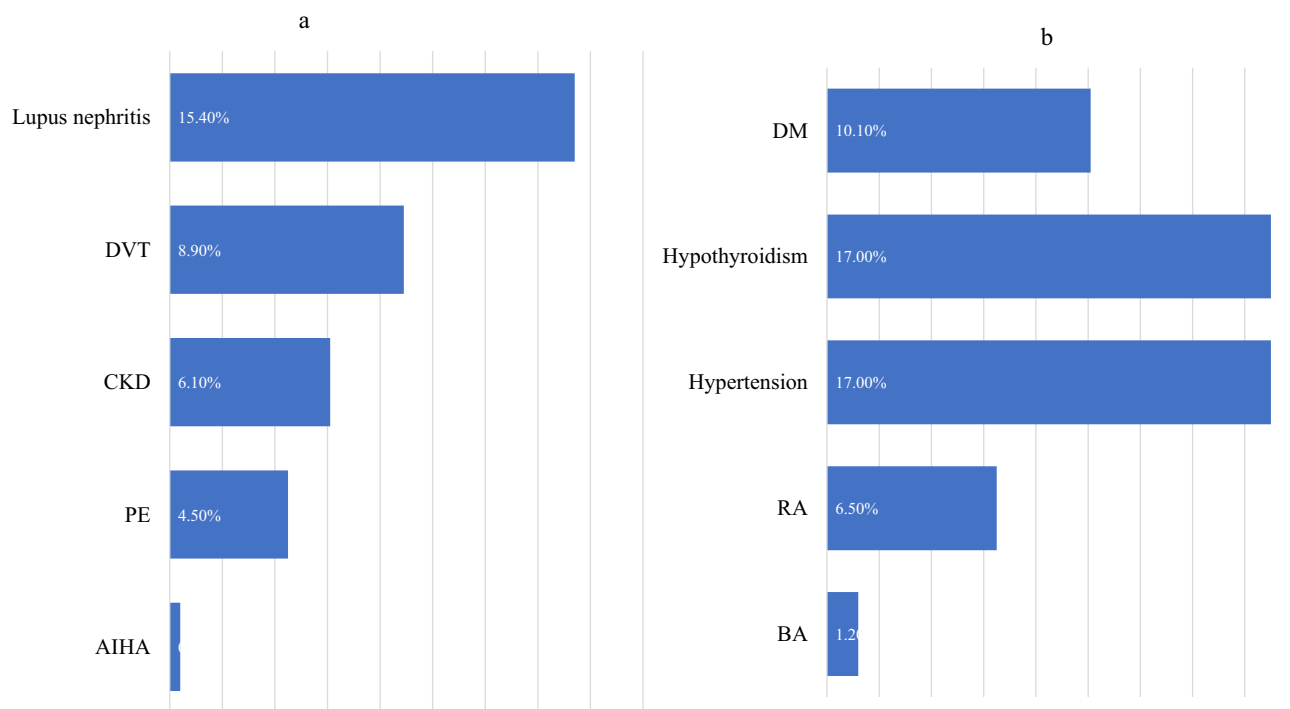


Figure 1 (a and b) shows the associated comorbidities associated with SLE.

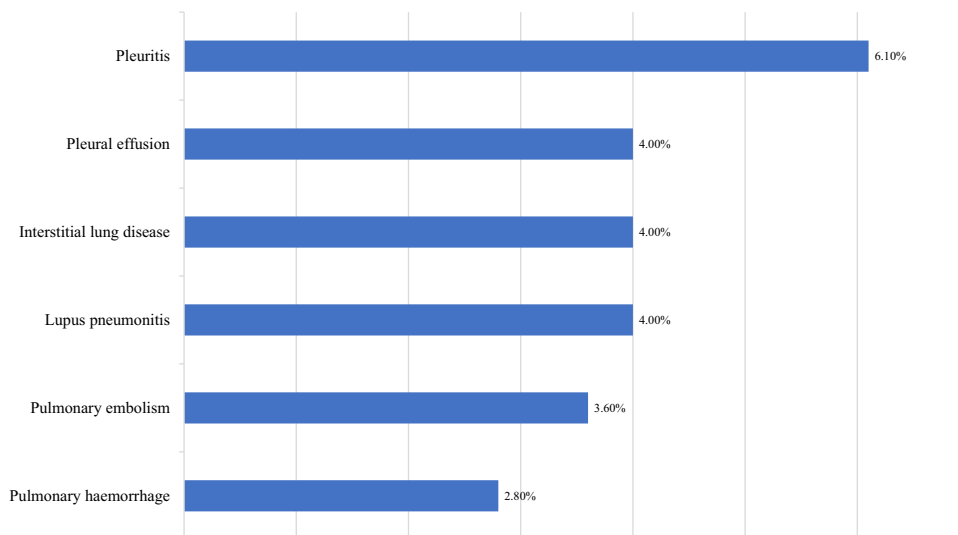


Figure 2 Pattern of pulmonary involvement among patients with SLE.

a relatively high occurrence at 13.80%. Meanwhile, hemoptysis (blood coughing) has a lower prevalence of 1.20%. (Figure 3)

Table 2 shows the characteristics of the individuals who had suffered from SLE. Regarding the duration of their SLE experience, 15.4% had experienced the condition for less than 3 years, 42.9% for a period of 3 to 6 years, 25.9% for 6 to 12 years, and 15.8% for more than 12 years. In terms of laboratory findings, serum complement was found to be positive in 3.2% of cases, antiphospholipid in 0.8%, ACL Ab in 4.5%, anti-CCP in 2.4%, anti-Smith in 1.2%, and rheumatoid factor in 17.4%. Additionally, C3 exhibited high levels in 4.5%, low levels in 24.3%, and was negative in 71.3% of cases.

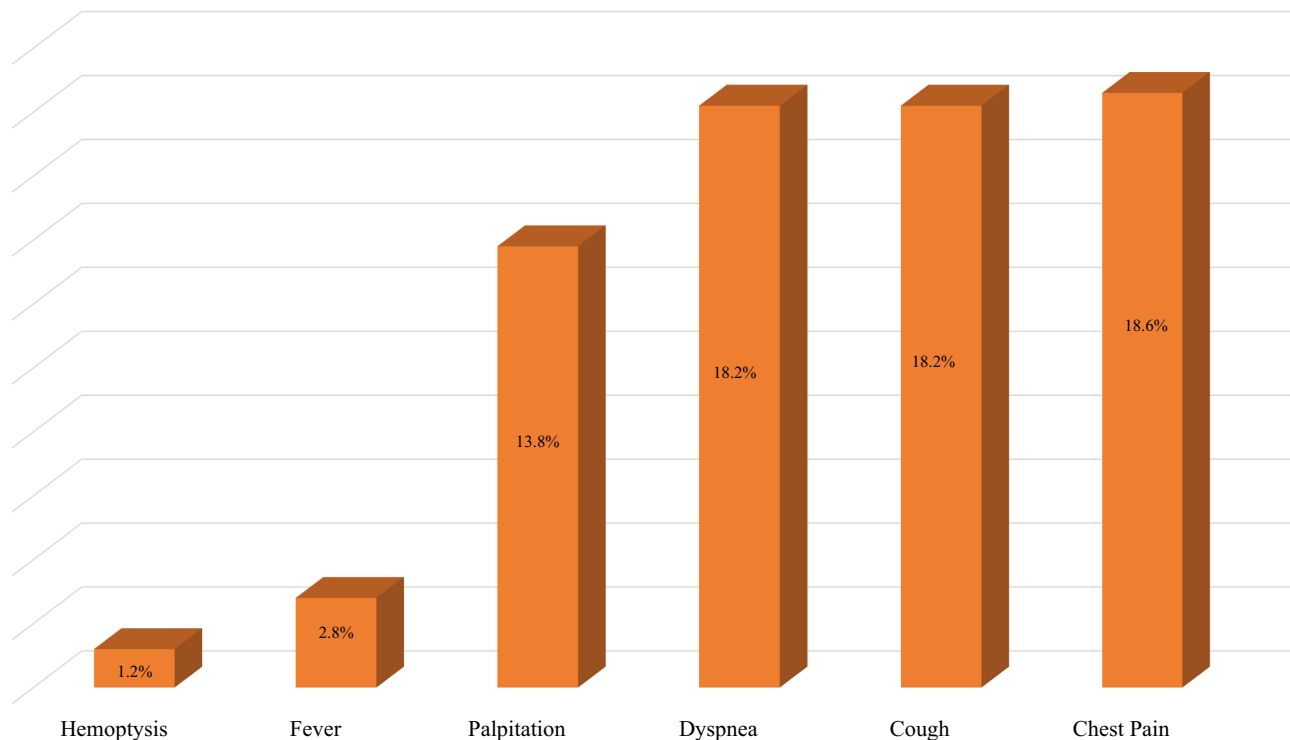


Figure 3 The respiratory symptoms that presented with systemic lupus erythematosus.

Similarly, C4 was observed to be high in 5.3%, low in 18.6%, and negative in 76.1% of cases. Lastly, anti-dsDNA was detected as positive in 47.0% of cases.

Table 3 shows the variables that were significantly associated with lung involvement among patients with SLE. Having CKD was significantly associated with having pulmonary involvement; ($p=0.027$). Similarly, hypertension was significantly associated with pulmonary involvement, ($p=0.002$). The seropositivity for antiphospholipid Abs was

Table 2 Characteristics and Laboratory Profiles of Past Systemic Lupus Erythematosus Patients

SLE Characteristics	Overall (N=247)	N (%)
How long have you been suffering from SLE	Less than 3 years	38 (15.4%)
	3 years - 6 years	106 (42.9%)
	6 years - 12 years	64 (25.9%)
	More than 12 years	39 (15.8%)
Serum complement	Positive	8 (3.2%)
Antiphospholipid	Positive	2 (0.8%)
ACL Ab	Positive	11 (4.5%)
Anti-CCP	Positive	6 (2.4%)
Anti-smith	Positive	3 (1.2%)
Rheumatoid factor	Positive	43 (17.4%)
C3	High C3	11 (4.5%)
	Low C3	60 (24.3%)
	Negative	176 (71.3%)
C4	High C4	13 (5.3%)
	Low C4	46 (18.6%)
	Negative	188 (76.1%)
Anti dsDNA	Positive	116 (47.0%)

Table 3 Factors Associated with the Development of Pulmonary Involvement

Studied Variables		Total		Pulmonary Involvement				Test Statistics
				No		Yes		
		N	%	N	%	n	%	
Duration of SLE	Less than 3 years	38	15.4	35	92.1	3	7.9	p=0.052
	4–6 years	106	42.9	80	75.5	26	24.5	
	7–12 years	64	25.9	51	79.7	13	21.3	
	More than 12 years	39	15.9	26	66.6	13	33.4	
Age	Less than 20 years	14	5.7	11	78.6	3	21.4	p=0.266
	30–21 years	61	24.7	42	68.9	19	31.1	
	40–31 years	69	27.9	57	82.6	12	17.4	
	41 years and older	103	41.7	82	79.6	21	20.4	
Gender	Female	235	95.1	184	78.3	51	21.7	p=0.474
	Male	12	4.9	8	66.7	4	33.3	
Hypothyroidism	No	205	83	155	75.6	50	24.4	p=0.102
	Yes	42	17	37	88.1	5	11.9	
Lupus nephritis	No	209	84.6	159	76.1	50	23.9	p=0.202
	Yes	38	15.4	33	86.8	5	13.2	
CKD	No	232	93.9	177	76.3	55	23.7	p=0.027
	Yes	15	6.1	15	100.0	0	0.0	
Hypertension	No	205	83	152	74.1	53	25.9	p=0.002
	Yes	42	17	40	95.2	2	4.8	
DM	No	222	89.9	170	76.6	52	23.4	p=0.309
	Yes	25	10.1	22	88.0	3	12.0	
Antiphospholipid	Negative	245	99.2	192	78.4	53	21.6	p=0.049
	Positive	2	0.8	0	0.0	2	100.0	
ACL Ab	Negative	236	95.5	190	80.5	46	19.5	$\chi^2=20.124 \cdot df=1 \cdot \phi=0.309 \cdot$ Fisher's p=0.0001
	Positive	11	4.5	2	18.2	9	81.8	
Anti-CCP	Negative	241	97.6	190	78.8	51	21.2	p=0.023
	Positive	6	2.4	2	33.3	4	66.7	
Antids DNA	Equivocal 10–15	12	4.9	7	58.3	5	41.7	p=0.010
	Negative <10 IU/mL	129	52.2	109	84.5	20	15.5	
	Positive >15 IU/mL	106	42.9	76	71.7	30	28.3	

significantly associated with pulmonary involvement ($p=0.049$). Similarly, anti-CCP and antacids-DNA seropositivity were significantly associated with pulmonary involvement ($\chi^2=4.621$, Fisher's $p=0.023$), and ($p=0.010$) respectively.

Discussion

In this retrospective study, we aimed to assess the prevalence of pulmonary involvement among SLE. The study found that 21.9% of SLE patients reported chest involvement, with pulmonary involvement varying among cases. Respiratory symptoms included dyspnea, cough, chest pain, palpitations, hemoptysis, and fever. These data provide insight into the prevalence of these symptoms, which are crucial for medical evaluation and diagnosis. Variables that were significantly associated with lung involvement among patients with SLE- were having CKD or hypertension, antiphospholipid Abs, Anti-CCP, and Antids-DNA seropositivity.

Incidence of Pulmonary Complications

In this study, more than one-fifth of patients with SLE had pulmonary involvement. The most reported affection was pleurisy. A similar study conducted in Saudi Arabia based on reviewing records over 10 years involving 184 patients with SLE in the Western Region found that lung manifestations were common in 33% of patients with pulmonary involvement.⁵ Approximately half of SLE patients have lung involvement, and 4–5% present with pulmonary symptoms.^{16,17} We found that the most common

findings were pleural effusion, consolidation, and atelectasis. Similarly, previous studies reported that the most frequent intrathoracic condition in SLE is pleuritis, which manifests as chest discomfort, cough, dyspnea, and pleural effusion.^{14,17}

The most favorable thoracic location involves the pleura and ranges from an asymptomatic manifestation to pleuritic pain present in around half of the patients.¹⁷ The pathologic evidence of pleural fibrosis or pleuritis reported is 50–93%, and pleural effusion in chest radiologic studies is 16–50%.¹⁷ Swigris et al¹⁸ observed that the entire pulmonary system or any of its components can be damaged in SLE. Several markers, such as higher systemic type 1 interferon (IFN) levels, circulating immune complexes (IC), and neutrophils, are associated with SLE. They appear to play a critical role in promoting lung inflammation, fibrosis, and tissue destruction.¹⁹

Duration of the SLE

We found that there was no significant association between the duration of the disease and the incidence of pulmonary complications. Pulmonary abnormalities were significantly higher within the first five years after SLE diagnosis in the study by Alamoudi et al. However, neither disease duration nor Lupus Nephritis was associated with increased risk.⁵ However, neither disease duration nor LN was associated with increased risk. The study highlights the importance of identifying risk factors for lung involvement in SLE patients.

Disease Complications, Activity, and Autoantibodies

We observed a significant association between having CKD or hypertension and the occurrence of pulmonary lung disease. Antids DNA was also associated with the incidence of pulmonary diseases. Similarly, Alamoudi et al⁵ found that low complement levels, high Anti-dsDNA levels, and disease activity were all found to be significantly associated with HRCT findings. Furthermore, the presence of pleural effusion, pneumonia, and ground glass attenuation was found to be significantly associated with disease activity. Anti-CCP is not common in SLE and usually indicates an overlap with Rheumatoid arthritis. Interestingly, positive Anti CCP -SLE patients had an increased incidence of lung disease. Whether it's related to CCP -MUC5B promotor variant and other genetics linked to lung disease in Rheumatoid arthritis or it's simply a serological marker and a risk factor for lung involvement in SLE, we need more studies with a larger sample size to explore the risk and association.²⁰

Strengths and Limitations

This study encountered several limitations. Firstly, due to its retrospective nature, there is a possibility that certain patient information may have been overlooked, despite the meticulous efforts of the authors to document all relevant details. It is important to note that some data related to specific diagnoses were extracted from patient records, making it impossible to entirely rule out diagnostic errors, especially for closely related conditions. However, this study had many strengths. It was conducted in more than one center, which may reduce the risk of bias in the study's findings. Furthermore, the sample size was considered sufficient for this study, and the cohort likely consisted of individuals with similar backgrounds, with more than 99% of Saudi nationality.

Conclusions

The study revealed that 21.9% of SLE patients reported experiencing chest involvement, with varying degrees of pulmonary manifestations observed between cases. The respiratory symptoms reported included dyspnea, cough, chest pain, palpitations, hemoptysis, and fever. The prevalence of these symptoms within the SLE population is of significant importance for medical evaluation and diagnostic considerations. In particular, certain variables displayed significant associations with lung involvement among SLE patients, including the presence of CKD or hypertension, the presence of antiphospholipid antibodies, anti-CCP positivity, and seropositivity for Anti-dsDNA. These results provide valuable insights into factors linked to pulmonary involvement in SLE patients and contribute to our understanding of this complex autoimmune condition.

Patient Privacy Protection Statement

We desensitized all the data that can be used to identify patients' personal information, such as their names, hospitalization IDs, and telephone numbers, to protect the privacy of patients.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author upon reasonable request.

Statement of Ethics

The study protocol has been reviewed and approved by the Directorate of Health Affairs, Aseer Region Ethics Committee, and Saudi Ministry of Health. Informed consent was obtained from all individuals participating in the study. The patients' privacy and personal identity information were well protected. The protocol of the study is compliant with Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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