J MEDICINE 2026; 27: 78-85

Original Article

Chest X-ray Abnormalities of Patients with Systemic Lupus Erythematosus Presenting with Cough and its Association with Disease Activity

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Abstract

Objective: *To assess the pattern of chest x-ray abnormalities and their relationships with disease activity in systemic lupus erythematosus (SLE) patients with cough.*

Methods: *This cross-sectional study was conducted at Bangladesh Medical University's Department of Rheumatology, Dhaka, Bangladesh. Patients with SLE who reported cough of any duration were enrolled using the 2019 American College of Rheumatology/ European League Against Rheumatism classification criteria. Clinical history, physical examination findings, chest x-ray, relevant lab tests and the SELENA-SLEDAI score were documented. Subjects were divided into groups based on the presence of chest x-ray abnormality. Multiple logistic regression (backward elimination) was used to identify the factors associated with chest x-ray abnormalities.*

Results: *Eighty cases (74 females and 6 males) with a mean age of 29.2 were recruited. Forty patients had abnormalities in their chest X-rays. Common X-ray abnormalities were cardiomegaly (35%), pleural effusion (27.5%), consolidation (15%), inhomogeneous opacities (22%), reticulonodular shadows (17.5%), pulmonary cavitary lesion (5%) and miliary mottling (2.5%). Shortness of breath, abnormal breath sounds and added sounds were also more marked in these patients. In contrast, those with normal X-ray chest (n=40) had signs and symptoms of upper respiratory tract inflammations only. X-ray abnormalities were associated with low body mass index, increased anti-double-stranded DNA, erythrocyte sedimentation rate, C-reactive protein, low hemoglobin and lymphopenia (all* P *<0.05). X-ray abnormalities were independently associated with a high disease activity score and a high erythrocyte sedimentation rate.*

Conclusions: *Conventional chest x-ray abnormalities were associated with higher disease activity among patients with SLE presenting with cough.*

Keywords: *Systemic Lupus Erythematosus (SLE), Cough, Chest X ray, Disease Activity, Bangladesh.*

DOI: *https://doi.org/10.3329/jom.v27i2.92265*

Received: *11-04-2026;* ***Accepted:*** *20-06-2026*

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Introduction

Systemic lupus erythematosus (SLE) is a multifactorial disease of autoimmune etiology that mainly affects women of childbearing age.[1] It can involve all the body systems with a broad spectrum of symptoms. Involvement of the cardio-respiratory system is quite common, for which they seek medical attention at their initial presentation or any stage of disease progression.[1]

SLE can affect every part of the respiratory system, including lung parenchyma, pleura, pulmonary vessels and diaphragm. The prevalence of pulmonary involvement in SLE varies from 20% to 90%, depending on the criteria used to define it.[3] Myocardial involvement affects approximately 3-9% and pericardial effusion was detected in 11-54% of patients during the disease course.[4] The presentations were diverse, with overlapping symptoms.

Cough is a common symptom and can be present in more than 50% of respiratory and cardiac cases.[5,6] Proper history and clinical examinations can help determine the etiology. Numerous tests can be performed to accurately assess a cough, such as a chest x-ray, sputum analysis, high-resolution CT scan (HRCT), broncho-alveolar lavage analysis, spirometry, echocardiogram, etc. An initial, noninvasive, affordable and widely accessible investigation is a chest x-ray. It can provide a key indicator of the pattern of cardio-respiratory involvement and can direct more costly and invasive investigations.

The common chest X-ray manifestations in SLE patients are pleural effusion, lupus pneumonitis, pneumonia, interstitial lung disease, shrinking lung syndrome, pericardial effusion, pulmonary hypertension and pulmonary edema.[7,8] Chest X-ray usually gives no information in other conditions like acute epiglottitis, laryngitis, tracheitis, crico-arytenoiditis, vocal cord paralysis, etc., which had also been reported in SLE cases.[9]

Abnormal chest x-rays were found in about 40% of SLE patients who presented themselves with cough.[6] However, when a chest x-ray shows an abnormality, it points out definitive cardio-pulmonary, pleural, or pericardial involvement, which may manifest as an active disease, secondary infection, or a disease process in another organ or a treatment complication. Association with SLE disease activity may be helpful in clinical decision-making. In some studies, pulmonary involvement in high-resolution CT scan (HRCT) of SLE patients was found to be associated with SLE disease activity, low complement (C3 and C4) levels and high anti-double stranded (ds) DNA levels[7] and serum markers.[10]

Despite chest X-rays being limited in diagnosing various cardiopulmonary conditions, it is the cheapest and simplest method to evaluate patients with common symptoms like cough in a resource-poor setting. This study aimed to get a primary hint for diverse etiologies causing cough in SLE patients, their clinical characteristics and radiographic presentation and their association with disease activity and serum markers.

Methods

Study design and patient enrollment: This cross-sectional study was conducted in the inpatient and outpatient rheumatology clinics of Bangabandhu Sheikh Mujib Medical University (BSMMU), currently Bangladesh Medical University (BMU), Dhaka, Bangladesh, from July 2020 to August 2021. Eighty cases with SLE, as per ACR/EULAR classification criteria 2019,[11] who presented with cough were enrolled consecutively after getting the informed written consent. Consent was taken from the parents or legal guardians of the subjects under the age of 18. Subjects with overlap syndrome and known or suspected COVID-19 pneumonia were excluded from the study.

***Data collection*:**

Demographic data, age, sex, and duration of disease were recorded. History of cough, shortness of breath, fever, chest pain, rhinorrhea, and sore throat were taken. Physical examinations for general, respiratory, and cardiac systems were done. Complete blood count (CBC), ESR, CRP, complements C3, C4, anti-ds- DNA, urine routine microscopic examination (R/E), and X-ray chest posterior anterior (P/A) view were done for all patients. Anti-dsDNA antibody was measured using the enzyme-linked immunosorbent assay (ELISA) method in the Department of Microbiology BMU. It was considered positive when>30 U/L and strongly positive when > 90 U/L. C3 and C4 were measured by nephelometry (normal values 0.9–1.8 and 0.1–0.4 g/l, respectively). A questionnaire including SELENA-SLEDAI (Safety of Estrogens in Systemic Lupus Erythematosus National Assessment and Systemic Lupus Erythematosus Disease Activity Index) score was filled in for every patient. In SELENA-SLEDAI, the symptoms, signs, laboratory tests, and physician's assessment for each of the nine organ systems are given in a weighted score and summed up at the time of the visit or in the preceding ten days. The maximum theoretical score is 105; flares are graded as no flare ≤3, mild to moderate flare 4-12, and severe flare >12. A senior radiologist reviewed all X-ray films for the findings suggestive of pleural effusion/thickening, pneumonic consolidation, inhomogeneous opacities, reticulo-nodular shadows, pulmonary cavitation,

cardiomegaly or pericardial effusion, elevation of the diaphragm etc.

Statistical analysis:

Data was analyzed using SPSS version 23 (Statistical Package for Social Sciences) software. The enrolled subjects with chest X-ray abnormalities were compared with those with no abnormalities in demographic, laboratory, and clinical variables. Descriptive data were expressed as numbers and percentages. The chi-square and Fisher exact tests were used to find associations between qualitative variables. Means of quantitative variables were compared by independent sample t-test. All variables were analyzed by multiple logistic regression (backward elimination) to identify the independent factors associated with chest x-ray abnormalities. *P*-value < 0.05 was considered significant.

Operational definition

Radiological definitions of chest X-ray abnormalities were considered according to Sutton D [4] and from the literature search.

Pleural effusion was defined as homogenous opacity spread upwards, obscuring the lung base with a well-defined, concave upper edge, which obscures the diaphragmatic shadow. *Pleural thickening* may present as dense pleural shadowing or blunting of the costophrenic angle. *Consolidation* is homogenous lung opacification limited by fissures when air replacement occurs by fluid or solid material in one or more acini. The affected lobes retain normal volume and often show air bronchograms. *Miliary shadows are small discrete nodules 1-2 mm in diameter* distributed throughout both lungs. These nodules may enlarge and coalesce. *Reticular shadowing* appears as a fine, irregular network of lines surrounding a filled lung. *Reticulonodular shadowing* is considered where nodules are less than 1cm in diameter, ill-defined, and irregular in outline. *A cavitating lesion is a gas-filled space surrounded by a complete wall that* is 3 mm or greater in thickness. *Inhomogeneous opacity* usually describes pneumonitis by nonspecific infections/ inflammation in one or both lung fields. *Cardiomegaly* is traditionally defined as an increase in the cardiothoracic ratio to be > 0.5 on a PA film. To calculate the thoracic ratio, the width of the cardiac silhouette is divided by the width of the entire thoracic cage. In most patients, the right hemidiaphragm is higher than the left. On inspiration, the domes of the diaphragms are at the level of the sixth rib anteriorly and at or below the tenth rib posteriorly. A difference greater than 3 cm in height is considered as an *elevated hemi diaphragm*. *Pulmonary edema* often appears as upper lobe pulmonary venous diversion (stag's antler sign) peri-bronchial cuffing and perihilar haze, septal (Kerley) lines, thickening of interlobar fissures, features of air space opacification classically in a batwing distribution.[13]

A pericardial fluid of >200 ml is usually required to become radiographically visible *Pericardial effusion*. Radiographic signs include globular enlargement of the cardiac shadow, giving a water bottle configuration where the lung field remains normal or oligemic.[14]

Results

One hundred and twenty-three patients were screened for enrollment, and 43 were excluded according to exclusion criteria. Among the remaining 80 SLE patients, 92.5% were female, aged 13 to 56 years. Forty subjects presented with abnormal X-ray findings compared with those with normal X-rays. There was no significant difference in age, sex, and disease duration between the two groups except for low BMI (*P*<0.01) (Table 1)

Table 1: Characteristics of patients of systemic lupus erythematosus by normal and abnormal X-ray findings

Socio-demographic characteristic	Total n=80	X-ray abnormal n=40, n (%)	X-ray normal n=40 n (%)	*P value*
Age (year)	29.2±10.2	29.9±11.3	28.5±9.1	0.52*
Sex number (%)				
Female	74 (92.5)	36(91.1)	38(95.6)	0.67†
Male	6 (7.5)	4(8.9)	2(4.4)	
Body mass index (kg/m^2)	21.7±4.6	20.5±4.8	22.9±4.1	0.01*
Duration of disease (year)	4.3±5.3	4.0±4.9	4.6±5.7	0.61*

*t-test, † Fisher's exact test

While individuals with normal CXR had much more throat inflammation, rhinorrhea, and the common cold, patients with abnormal chest x-rays had significantly more shortness of breath, irregular breath sounds, additional sounds, and symptoms of pulmonary hypertension. (Table 2). Major chest x-ray abnormalities were depicted in detail. (Figure 1). Among the patients with normal chest x-rays, more commonly diagnosed cases are common cold, upper airway cough syndrome, and bronchial asthma with its cough variant form (with the presence of self or family history of asthma). The patient who had pleuritic chest pain and dry cough was diagnosed with pleurisy when a pleural rub was found on her chest examination (Table 3). Sputum cultures were found

Table 2: Cardio-respiratory manifestations found in systemic lupus erythematosus patients presented with cough

Clinical characteristic	Total n=80 (%)	X-ray abnormal n=40 (%)	X-ray normal n= 40 (%)	*P*
Duration of cough				
<3 weeks	48 (60.0)	22 (55.0)	26 (65.0)	0.64 $^{\alpha}$
3 weeks - 8 weeks	12 (15.0)	7 (17.5)	5 (12.5)	
> 8 weeks	20 (25.0)	11 (27.5)	9 (22.5)	
Character of cough				
Dry	49 (61.2)	23 (57.5)	26 (65.0)	0.64 $^{\alpha}$
Productive	31(38.7)	17 (42.5)	14(35.0)	
Shortness of breath	33 (41.2)	23 (57.5)	10 (25.0)	0.00 $^{\alpha}$
Chest pain	15 (18.7)	10 (25.0)	5 (12.5)	0.13 $^{£}$
Rhinorrhea	25 (31.2)	5 (12.5)	20 (50.0)	0.00 $^{£}$
Throat inflammation	6 (7.5)	0	6 (15.0)	0.03 $^{£}$
Paranasal sinus tenderness	3 (3.7)	0	3 (7.5)	0.24 $^{£}$
Breath sound*				
Vesicular	51(63.7)	24 (60.0)	27 (67.5)	
Vesicular with prolonged expiration	16 (20.0)	3 (7.5)	13 (32.5)	
Bronchial	4 (5.0)	4 (10.0)	0	
Diminished	9 (11.3)	9 (22.5)	0	
Added sound**				
Rhonchi	8 (10.0)	0	8 (20.0)	
End inspiratory crepitation	9 (11.2)	7 (17.5)	2 (5.0)	
Coarse crepitation	8 (10.0)	8 (20.0)	0	
Localized crepitation	12 (15.0)	12 (30.0)	0	
Loud pulmonary component of second heart sound §	7 (8.7)	6 (15.0)	1 (2.5)	0.03 $^{£}$

$^{£}$ Fisher exact test, $^{\alpha}$Chi-square test

*Vesicular breath sound denotes normal character, vesicular with prolong expiration occurs due to airway obstruction, bronchial breath sound occurs in consolidation. In pleural effusion or collapse breath sound may remain diminished.

**Polyphonic Ronchi are found in Bronchial asthma or Chronic obstructive airway disease, end inspiratory crackles denotes Diffuse parenchymal lung disease, coarse or localized crepitations usually found in pneumonitis or bronchiectasis.

§The loud pulmonary component of second heart sound denotes pulmonary hypertension.

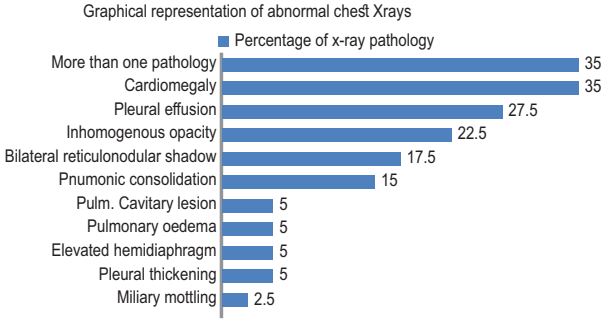

Figure 1. Graphical presentation (%) of abnormal radiological findings on chest X-rays (n=40)

positive in a few cases who had consolidation or inhomogeneous opacity on chest x-ray (klebsiella seven and pseudomonal one). Echocardiography was done in selected patients according to x-ray findings. Dilated cardiomyopathy and pericardial effusion were found in isolation or combination. HRCT was done to evaluate reticulonodular shadows and inhomogeneous opacities. Pleural fluid studies were done in patients with pleural effusion. No organism was found in exudative fluids. The diagnosis was occasionally confirmed by seeing the response to treatment.

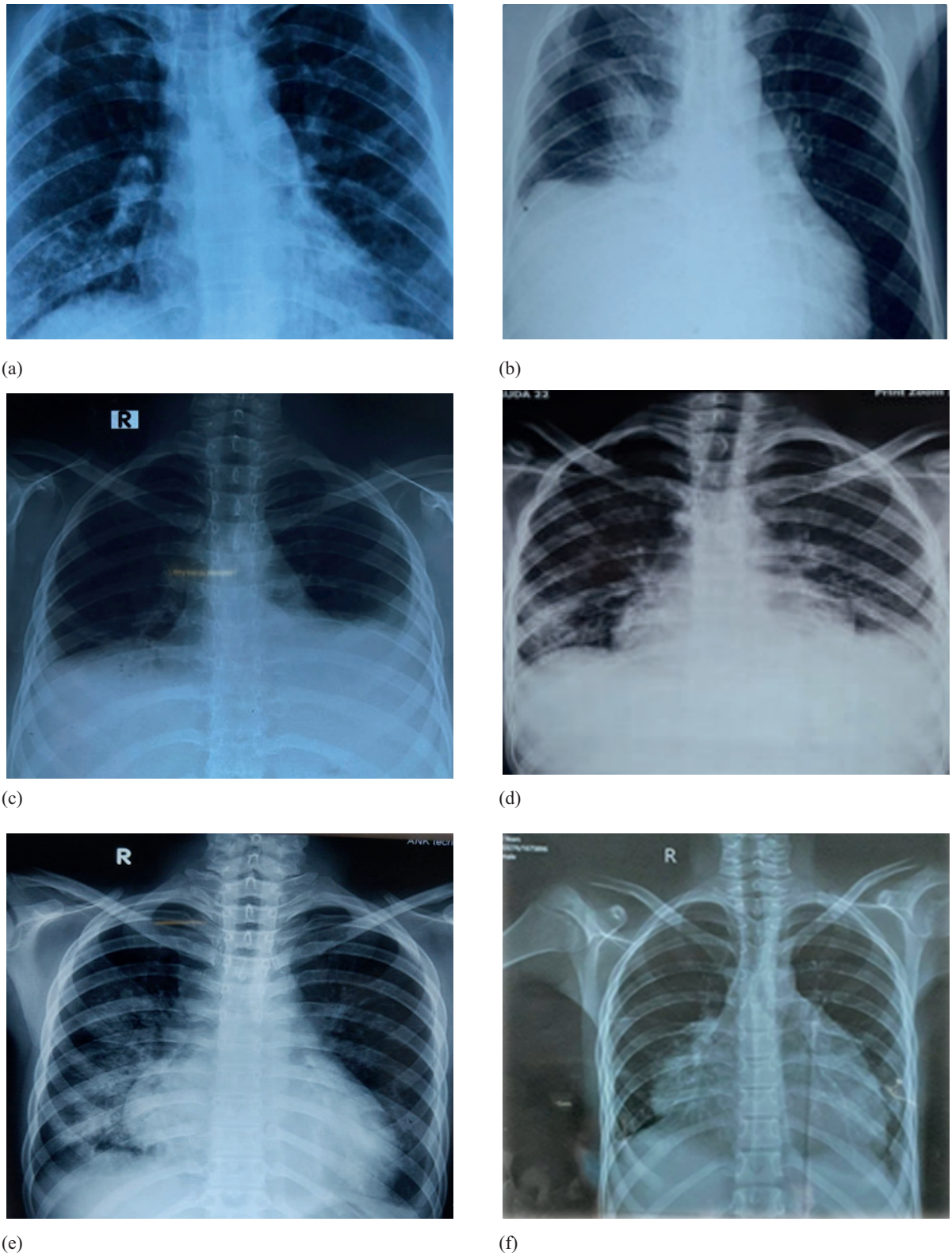

Figure 2: Abnormal chest x-rays of patients with SLE *a. reticulonodular inhomogeneous opacities picture; b. elevated right hemidiaphragm with prominent pulmonary vasculatures; c. bilateral pleural effusion picture; d. cardiomegaly with right left-sided pleural effusion; e. globular cardiac shadow (pericardial effusion); f. globular cardiac shadow with right sided consolidation.*

The common manifestations of SLE like mucocutaneous involvement, musculoskeletal symptoms, constitutional features, ascites, and some laboratory parameters like low hemoglobin, lymphopenia, raised ESR and/or CRP, high mean and strongly positive anti-ds-DNA were more frequent in chest abnormal x-ray group (Table 4). The disease activity index SELENA SLEDAI score and high ESR were independent factors associated with the chest x-ray abnormalities in multivariate logistic regression analysis (Table 5).

Table 3: *Possible clinical diagnosis of the patients with normal chest x-ray*

Diagnosis	n=40 (%)
Common cold	18 (22.5)
Upper airway cough syndrome	9 (11.3)
Asthma	7 (8.8)
Cough variant asthma	5 (6.3)
Pleurisy	1 (2.5)

Table 4: Clinical manifestations related to systemic lupus erythematosus with chest x-rays

Clinical and laboratory characteristics	Total (n=80)	X-ray abnormal (n=40)	X-ray normal (n=40)	*P* value
		number (%)		
Musculoskeletal	38 (47.5)	26 (65.0)	12 (30.0)	0.00$^{\alpha}$
Constitutional feature	32 (40.0)	22(55.0)	10(25.0)	0.00$^{\alpha}$
Mucocutaneous	30 (37.5)	18 (45.0)	12 (30.0)	0.16$^{\alpha}$
Anemia	27 (33.7)	19 (47.5)	8 (20.0)	0.00 $^{£}$
Lupus nephritis	27 (33.7)	16 (40.0)	11 (27.5)	0.17$^{\alpha}$
Ascites	12 (15.0)	9 (22.5)	3 (7.5)	0.05$^{£}$
Neuropsychiatric manifestation	6 (7.5)	4 (10.0)	2 (5.0)	0.34$^{£}$
High disease activitySELENA SLEDAI>12	27(33.7)	21 (52.5%)	6 (15%)	0.00$^{\alpha}$
Lymphopenia<1000/cmm	26 (32.5)	18 (45.0)	8 (20.0)	0.02$^{\alpha}$
Complement 3	40(50.0)	23 (57.5)	17 (42.5)	0.11$^{\alpha}$
Complement 4	15 (18.8)	9 (22.5)	6 (15.0)	0.45$^{\alpha}$
Strongly positive Anti ds-DNA >90 u/L	44 (55)	27 (67.5)	17 (42.5)	0.02$^{\alpha}$
	(Mean± Standard Deviation)			
SELENA SLEDAI	8.5±6.9	11.4±6.6	5.7±5.9	0.00$^{\beta}$
Hemoglobin	10.37±1.97	9.87±1.91	10.87±1.92	0.02§
Eryrhrocyte SedimentationRate	54.13±34.89	66.0±39.3	42.5±25.5	0.01$^{\beta}$
C-Reactive Protein	28.12±41.9	40.5±45.4	16.5±34.9	0.00$^{\beta}$
Anti-ds-DNA	96.38±76.80	114.8±75.4	77.9±74.6	0.03§

$^{\alpha}$Chi-square test, $^{£}$ Fisher exact test, $^{\beta}$Mann Whitney U test, § Independent t test

Table 5: *Multivariate logistic regression analysis of all independent variables for identification of factors associated with abnormal chest x-rays*

Variables	Odds Ratio (95% confidence interval)	*P*-value
SELENA SLEDAI	1.17 (1.04 – 1.32)	0.00
Erythrocyte sedimentation rate	1.02 (1.00 – 1.05)	0.02
Age of the participant	1.07 (0.99 - 1.16)	0.05

Discussion

Cardiorespiratory involvement in systemic lupus erythematosus (SLE) is not as well-known as the mucocutaneous, musculoskeletal, and renal symptoms, even though it happens often. We studied SLE patients with coughs primarily using chest X-rays in our resource-constrained setting. Females made up 92.5% of the participants in this study, with a mean age of 29.2±10.2 years. These findings matched those of an Indian study in which 92% of the patients were female.[15] Another study at the same center discovered

a mean age of 29.1±8.7 years.[6] Patients who had x-ray anomalies had significantly reduced BMI (P=0.01). In SLE patients, there was an inverse relationship between changes in body mass index and disease activity.[16]

14 (35%) of x-rays revealed cardiomegaly, 11 (27.5%) pleural effusions, and 2 (5%) raised hemi diaphragms. These findings were virtually identical to those of a previous study conducted in France, in which pleural effusion was found in 24.5% of patients, pericardial effusion was found in 22.6% of patients, and elevated hemidiaphragm was found in 4.9% of patients. A significant relationship between the presence of pleural and pericardial effusions was noted. In our study, 14 (35%) cases had a combination of two or more pathologies, with cardiomegaly, which includes pericardial effusion and dilated cardiomyopathies, with pleural effusion being the most common.[17] Parallel to prior research, our study did not identify pleural effusion as the predominant manifestation. This is because pleural effusion typically does not cause coughing and often remains asymptomatic[18] and we took the SLE patients with cough.

Making a firm clinical diagnosis is difficult due to the variety and overlap of cardio-respiratory symptoms and signs. Most studies have found that clinical examinations' sensitivity and reliability could be better to fair.[19] We conducted a pertinent history and physical examination. Acute cough was present in 48 (60%) of 80 SLE patients, while the remainder had chronic cough. The study by Azad et al. was dissimilar to our findings, in which 83% of SLE patients exhibited chronic cough. Asthma (47%) and postnasal drips (28%) were identified as the leading and second most prevalent causes of cough in their series.[8] We took both inpatient and outpatient patients, whereas they only took outpatients.

Possible immunological similarities between allergies and autoimmune illness can be used to explain the relationship between atopic conditions and SLE in individuals. In a Taiwanese study, the incidence rate of asthma was 2.61 times higher in the SLE group than in the non-SLE cohort. [5] In our study, asthma and cough variant asthma were suspected based on history and physical examination, but confirmation by spirometry or methacholine challenge test was not feasible.

Patients in our series who had abnormal X-rays reported musculoskeletal problems (65%) more frequently than other SLE symptoms. 80% of the patients with pleuro-pulmonary involvement had arthritis, according to Narváez et al.[21] We did not find a substantial correlation between lupus nephritis and pulmonary symptoms, but they did. Bivariate analysis revealed that subjects with anomalies on the chest x-ray had significant lymphopenia, high ESR, CRP, disease activity, and anti-ds DNA levels (all P<0.05). In China, the correlation between parenchymal lesions with high ESR and pleural/pericardial lesions with positive CRP was reported in SLE patients with chest CT findings [10]. The association between lymphopenia and lupus nephritis was reported in another study.[22] High disease activity, anti-ds DNA, and low complement were reported to be associated with pulmonary involvement in HRCT, according to Alamoudi et al.[7] High disease activity and high ESR were independently linked in the current study to cardio-pulmonary involvement that led to x-ray abnormalities. Further research is warranted, given the connection between x-ray abnormalities and lymphopenia and CRP.

In many cases, our study was limited by a need for more resources and diagnostic assays to confirm the diagnosis of cough. A single-center study did not disclose the full scope of cardiopulmonary involvement in Bangladeshi SLE patients.

Modern people are accustomed to using newer, more expensive equipment, which is scarce in resource-poor rural areas. Modernizing and making older ones, like chest X-rays, more accessible will help more people. Conventional X-rays are safe and provide immediate information that doctors can easily analyze. A meticulous review of chest X-rays can reveal SLE patients' cardiopulmonary involvement, which often correlates with the disease severity. Data are reproducible and can be used for serial evaluation, follow-up, therapy response monitoring, and disease prognosis in clinical and research settings.

Conclusion

Cough is a common symptom in cardio-respiratory involvement of SLE. When a cough is evident in SLE patients with clinical or laboratory indicators of high disease activity, it is more economical to perform a chest x-ray to establish a preliminary diagnosis and to guide additional testing and therapy.

Conflict of interest: We do not have any conflict of interest.

Funding: Bangladesh Medical University.

Ethical clearance was taken from Institutional Review Board, Bangladesh Medical University. BMU/2020/6986, Dated 09/07/2020.

Acknowledgements

Rafia Afrose conceptualized the study, designed it, developed the data collection tool, collected data, and wrote the manuscript. Syed Atiqul Haq guided the research. Md Kamrul Hasan Sajib and Momotaz Begum collected data

and participated in manuscript writing. Rafia Afrose and Rabeya Akhter Ferdousi read the radiographs and reviewed literature. Mohammad Mostafa Zaman guided the data analysis, interpreted the findings, and critically reviewed the manuscript. All authors approved the last version of the manuscript.

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