LESIONS OF RESPIRATORY SYSTEM IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CHARACTERISTICS AND PREVALENCE; CHARACTERISTICS OF THE PREVALENCE OF SYNTROPIC COMORBID LESIONS, THEIR RELATIONSHIP WITH THE AGE OF PATIENTS, DISEASE DURATION AND THE SEVERITY OF RESPIRATORY FAILURE

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DOI: https://doi.org/10.31435/rsglobal_ws/30062020/7107

ARTICLE INFO

Received: 15 April 2020
Accepted: 07 June 2020
Published: 30 June 2020

KEYWORDS

systemic lupus erythematosus, lesions of respiratory system, characteristics, prevalence.

ABSTRACT

Introduction. The respiratory system lesions in patients with systemic lupus erythematosus have not been properly addressed by both clinicians and scientists yet, since the progression of these lesions is often asymptomatic.

Objective. To identify and determine the nature and prevalence of respiratory system lesions in patients with systemic lupus erythematosus; to distinguish syntropic comorbid lesions, to determine their prevalence and their relationship with the age of patients, disease duration, and the severity of respiratory failure.

Materials and methods. 370 patients (331 women and 39 men) with SLE were enrolled. They underwent comprehensive examinations and were stratified by age, duration, and the activity of SLE. The obtained data were processed in Microsoft Excel by means of descriptive statistics, $\chi 2$ test, and z-test for comparisons of two proportions; the relationships were considered to be statistically significant when $p < 0.05$.

Results. 67.57% of patients with SLE had respiratory system lesions. Pneumosclerosis, pulmonary hypertension, pneumonitis, and pulmonary fibrosis were found to be syntropic comorbid lesions, i.e. pathogenetically associated with SLE. The prevalence of syntropic comorbid respiratory system lesions in patients with systemic lupus erythematosus depends on the age of patients, duration of the disease, and the severity of respiratory failure. Pneumosclerosis is more prevalent in elderly patients and patients with the SLE duration of more than 6 years. It was the cause of respiratory failure in 43.02% of patients; the condition was of the first degree of severity. Pulmonary hypertension is more prevalent in elderly patients and patients with the SLE duration of less than one year. It led to respiratory failure in 16.13% of patients; the respiratory failure was predominantly mild. Pneumonitis is more prevalent in young patients and patients with SLE duration of more than 10 years. It led to respiratory failure in 52.00% of patients, while 64.10% out of them had degree I respiratory failure. Pulmonary fibrosis is more prevalent in elderly patients and patients with the SLE duration of 1-5 years. It led to respiratory failure in 62.50% of patients, while 80.00% out of them had the first degree of this condition).

Citation: Ulyana Abrahamovych, Orest Abrahamovych, Roman Dutka, Marta Farmaha, Olha Romaniuk. (2020) Lesions of Respiratory System in Patients with Systemic Lupus Erythematosus: Characteristics and Prevalence; Characteristics of the Prevalence of Syntropic Comorbid Lesions, Their Relationship with the Age of Patients, Disease Duration and the Severity of Respiratory Failure. *World Science.* 6(58), Vol.2. doi: 10.31435/rsglobal_ws/30062020/7107

Introduction. All components of the respiratory system, namely, upper respiratory tract, pulmonary parenchyma, pulmonary vascular system, pleura, and respiratory muscles, in more than half of patients with systemic lupus erythematosus (SLE) are known [3, 7] to be involved in the pathological process. Its progression, while often asymptomatic [2, 4, 7], not infrequently suddenly acquires negative dynamics, and lesions of the respiratory system may become the cause of death [1, 5-8]. However, this issue has not been addressed properly by clinicians yet.

Objective. To identify and determine the nature and prevalence of respiratory system lesions in patients with systemic lupus erythematosus; to distinguish syntropic comorbid lesions, to determine their prevalence and their relationship with the age of patients, disease duration, and severity of respiratory failure.

Materials and methods. Having obtained written consents to participate in comprehensive examinations in accordance with the principles of Helsinki Human Rights Declaration, Council of Europe Convention on Human Rights and Biomedicine, the relevant laws of Ukraine and other international instruments, after stratification by the presence of SLE, we randomly enrolled 370 patients – 331 women (89.46%) and 39 men (10.54%). The patients were diagnosed with SLE in accordance with the Order of the Ministry for Health of Ukraine No. 676 of October 12, 2006 "On the Approval of Protocols for the Provision of Medical Care under the Rheumatology Specialty", recommendations of the European League against Rheumatism (2010) and American College of Rheumatology (2010, 2012). All patients had received treatment in 2010-2018 at the Rheumatology Department of Lviv Regional Clinical Hospital, the clinical base of the Departments of Internal Medicine No. 1 and No. 2 of the Danylo Halytskyi Lviv National Medical University.

The patients were stratified by age according to the classification of the World Health Organization (2015) into three groups – young age group (aged 18 to 44 years, 204 patients), middle age group (aged 45 to 59 years, 153 patients) and old age group (aged 60 to 75 years, 13 patients). They were also stratified into four groups by the duration of SLE (less than one year (21 patients), 1-5 years (133 patients), 5-10 years (78 patients) and more than 10 years (138 patients)) and into five groups by the SLE activity assessment, namely, SLEDAI scores (seven patients with inactive SLE (SLEDAI = 0), 61 patients with the mild activity of SLE (SLEDAI = 1 to 5), 158 patients with the moderate activity of SLE (SLEDAI = 6 to 10), 104 patients with the high activity of SLE (SLEDAI = 11 to 19), and 40 patients with the very high activity of SLE (SLEDAI ≥ 20)).

The patients had undergone comprehensive clinical-laboratory and instrumental examinations of respiratory system lesions in accordance with the Order of the Ministry of Health No. 128 of March 19, 2007 "On the Approval of Protocols for the Provision of Medical Care under the Pulmonology Specialty", as amended by Orders of the Ministry of Health of Ukraine – No. 555 of June 27, 2013, and No. 868 of October 8, 2013. We considered passport information, patients' complaints, anamneses of the disease and their lives obtained through a comprehensive objective examination, as well as the results of additional laboratory and instrumental examinations. The latter included echocardiography (Samsung H-60 ultrasound scanner (South Korea)), chest radiography (Chirospecta-2 and Chirana radiography systems (Czech Republic and Slovakia)), spirometry (Vitalograph ALPHA spirometer (Mexico)).

The research was conducted in *two phases.* At the *first step* of the *first phase,* all patients were diagnosed with specific respiratory system lesions to determine their nature and prevalence. At the *second step* of the *first phase*, we identified those lesions that were pathogenetically associated with SLE, i.e. were syntropic comorbid lesions, if their prevalence rose significantly with the increase in

SLE activity. In the *second phase*, we determined the relationship between the prevalence of syntropic comorbid respiratory system lesions and the age of patients (*first step*), disease duration (*second step)* and the severity of respiratory failure (*third step*).

The obtained data were processed in Microsoft Excel by means of descriptive statistics, $\chi 2$ test, and z-test for comparisons of two proportions; the relationships were considered to be statistically significant when $p < 0.05$.

Results. According to the results obtained in the *first step of the first stage*, 250 patients with SLE (67.57% of all examined) had respiratory system lesions. Pneumosclerosis was the most prevalent type of lesions, since it was detected in 179 patients (49.31%). Other respiratory system lesions had the following prevalence: pulmonary hypertension was detected in 62 patients (22.55%), pneumonitis – in 75 patients (20.49%), pulmonary fibrosis – in 40 patients (11.02%), chronic obstructive bronchitis – in 14 patients (3.79%), pulmonary emphysema – in eleven patients (2.98%), chronic non-obstructive bronchitis – in seven patients (1.90%), bronchial asthma – in six patients (1.63%), and allergic rhinitis – in two patients (0.54%).

Thus, 67.57% of patients with SLE had lesions of the respiratory system: the most prevalent type of lesions was pneumosclerosis, the least prevalent type of lesions was allergic rhinitis.

The first phase consisted of *two consecutive steps* where the *first step* was to determine the prevalence of all the respiratory system lesions in patients with SLE, and the *second step* was to determine relationships between disease activity and prevalence of those lesions with a view to identifying lesions that were pathogenetically associated with SLE, i.e. syntropic comorbid lesions.

The results of the *second step* are presented in Table 1. This step dealt with the relationships between the prevalence of the respiratory system lesions and SLE activity. It allowed us to identify lesions that were pathogenetically associated with SLE, i.e. syntropic comorbid lesions.

Table 1. Prevalence of Respiratory System Lesions in Patients with Systemic Lupus Erythematosus and Their Relationship with SLE Activity

No.	Respiratory system lesions	Patients with SLE, no activity according to SLEDAI, n = 7		Patients with SLE, mild activity according to SLEDAI, n = 61		Patients with SLE, moderate activity according to SLEDAI, n = 158		Patients with SLE, high activity according to SLEDAI, n = 104		Patients with SLE, very high activity according to SLEDAI, n = 40	
		n	%	n	%	n	%	n	%	n	%
1	Pneumosclerosis	0	0.00	26	44.83	n = 155		n = 103		23	57.50
						73	47.10	57	55.34		
2	Pulmonary hypertension	n = 3		n = 41		n = 115		n = 7 8		n = 38	
		0	0.00	6	14.63	29	25.22	12	15 , 39	15	39.47
3	Pneumonitis	1	14.29	7	11.48	n = 155		n = 103		14	35.00
						28	18.06	25	24.27		
4	Pulmonary fibrosis	1	14.29	n = 58		n = 155		n = 103		10	25.00
				7	12.07	12	7.74	10	9.71		
5	Chronic obstructive bronchitis	0	0.00	2	3.28	9	5.70	n = 103		2	5.00
								1	0.97		
6	Pulmonary emphysema	0	0.00	2	3.28	4	2.53	n = 103		4	10.00
								1	0.97		
7	Chronic non-obstructive bronchitis	0	0.00	2	3.28	3	1.90	n = 103		0	0.00
								2	1.94		
8	Bronchial asthma	0	0.00	1	1.64	2	1.27	n = 103		2	5.00
9	Allergic rhinitis	0	0.00	0	0.00	0	0.00	n = 103		0	0.00
								2	1.94		
								1	0.97		

There were no individuals with pneumosclerosis among patients with inactive SLE (0.00%). However, this type of lesions was detected in 26 patients with the mild activity of SLE (44.83%), in 73 patients with the moderate activity of SLE (47.10%), in 57 patients with the hight activity of SLE (55.34%), and 23 patients with the very high activity of SLE (57.50%). There was a significant relationship between the prevalence of pneumosclerosis and SLE activity ($\chi2 = 10.15$, $p = 0.04$).

Patients with inactive SLE had no pulmonary hypertension (0.00%). However, this type of lesions was detected in six patients with the mild activity of SLE (14.63%), in 29 patients with the moderate activity of SLE (25.28%), in twelve patients with the high activity of SLE (15.39%) and 15 patients with the very high activity of SLE (39.47%). We found a statistically significant relationship between the prevalence of pulmonary hypertension and SLE activity ($\chi2 = 11.34$, $p = 0.02$).

Pneumonitis was detected in one patient with inactive SLE (14.29%), in seven patients with the mild activity of SLE (11.48%), in 28 patients with the moderate activity of SLE (18.06%), in 25 patients with the high activity of SLE (24.27%), and 14 patients with the very high activity of SLE (35.00%). The prevalence of pneumonitis depended on the activity of SLE, their relationship was statistically significant ($\chi2 = 9.84$, $p = 0.04$).

Pulmonary fibrosis was detected in one patient with inactive SLE (14.29%), in seven patients with the mild activity of SLE (12.07%), in twelve patients with the moderate activity of SLE (7.74%), in ten patients with the high activity of SLE (9.71%), and ten patients with the very high activity of SLE (25.00%). The prevalence of pulmonary fibrosis depended on the activity of SLE, their relationship was statistically significant ($\chi2 = 9.99$, $p = 0.04$).

Chronic obstructive bronchitis was detected in two patients with the mild activity of SLE (3.28%), in nine patients with the moderate activity of SLE (5.70%), in one patient with the high activity of SLE (0.97%), and two patients with the very high activity of SLE (5.00%). There was no statistically confirmed relationship between the prevalence of chronic obstructive bronchitis and the SLE activity ($\chi2 = 4.30$, $p > 0.05$).

Patients with inactive SLE had no pulmonary emphysema (0.00%). However, it was detected in two patients with the mild activity of SLE (3.28%), in four patients with the moderate activity of SLE (2.53%), in one patient with the high activity of SLE (0.97%), and four patients with the very high activity of SLE (10.00%). We did not found a statistically significant relationship between the prevalence of pulmonary emphysema and the SLE activity ($\chi2 = 8.60$, $p > 0.05$).

We detected isolated cases of chronic non-obstructive bronchitis in almost every group of patients: in two patients with the mild activity of SLE (3.28%), in three patients with the moderate activity of SLE (1.90%), and two patients with the high activity of SLE (1.94%). There were no cases of chronic non-obstructive bronchitis in patients with inactive SLE and the very high activity of SLE. There was no statistically significant relationship between the prevalence of chronic non-obstructive bronchitis and the SLE activity ($\chi2 = 1.54$, $p > 0.05$).

Bronchial asthma was detected in one patient with the mild activity of SLE (1.64%), in two patients with the moderate activity of SLE of II degree (1.27%), in one patient with the high activity of SLE (0.97%), and two patients with the very high activity of SLE (5.00%). There was no statistically significant relationship between the prevalence of bronchial asthma and the SLE activity ($\chi2 = 3.37$, $p > 0.05$).

Allergic rhinitis was detected in only two patients with the high activity of SLE (1.94%). Patients with inactive SLE and with the mild, moderate, and very high activity of SLE did not have allergic rhinitis. There was no relationship between the prevalence of this type of lesions and the SLE activity ($\chi2 = 5.19$, $p > 0.05$).

On the basis of these results, we concluded that pneumosclerosis, pulmonary hypertension, pneumonitis, and pulmonary fibrosis, in contrast to other types of lesions (chronic obstructive bronchitis, pulmonary emphysema, chronic non-obstructive bronchitis, bronchial asthma, allergic rhinitis), because of the statistically significant relationships between their prevalence and disease activity, were pathogenetically associated with SLE.

Thus, 67.57% of patients with SLE had respiratory system lesions. We concluded that pneumosclerosis, pulmonary hypertension, pneumonitis, and pulmonary fibrosis should be regarded as syntropic comorbid lesions. All other respiratory system lesions should be regarded as co-occurring comorbid lesions.

These findings emphasized the need to determine the prevalence characteristics for the respiratory system lesions that were pathogenetically associated with SLE, i.e. syntropic comorbid lesions (*the second phase*), as well as relationships between their prevalence and the age of patients (*the first step*), the SLE duration (*the second step*), and the severity of respiratory failure (*the third step).*

The results of the *first step of the second phase* are presented in Table 2.

Table 2. Prevalence Characteristics for the Respiratory System Lesions in Combination with the Age of Patients with Systemic Lupus Erythematosus

No.	Respiratory system lesions	Patients with Systemic Lupus Erythematosus							
		Young age group, n = 204				Middle age group, n = 152		Old age group, n = 13	
		Young age group I, n = 42		Young age group II, n = 162					
		n	%	n	%	n	%	n	%
1	Pneumosclerosis	22	52.58	n = 157		73 #	48.02	12 * ^	92.31
				72	45.86				
2	Pulmonary hypertension	n = 33		n = 120		n = 114		n = 8	
		5	15.15	16	13.33	34 #	29.83	7 ^ * #	87.50
3	Pneumonitis	10	23.81	n = 160		26	17.11	1	7.69
				38	23.75				
4	Pulmonary fibrosis	1	2.38	n = 157		26 * #	17.11	4 * #	30.78
				9	5.73				

Notes:
* - statistically significant difference in the number of cases in the young age group I (p <0,05);
# - statistically significant difference in the number of cases in young age group II (p <0,05);
^ - statistically significant difference in the number of cases in the middle age group (p <0,05).

Pneumosclerosis was more prevalent in the old age group of patients (twelve patients, 92.31%). It was also detected in almost half of patients in the young age group I, i.e. patients aged 18 to 24 years (22 patients, (52.58%)), young age II group, i.e. patients aged 25 to 44 years (72 patients, (45.86%)), and in middle age group (73 patients, (48.02%)).

Pulmonary hypertension was significantly more prevalent in the old age group of patients. There were only five cases (15.16%) of it in young age group I. However, it was detected in 16 patients (13.33%) of the young age II group, in 34 patients (29.83%) of the middle age group, and seven patients (87.50%) of the old age group.

Ten patients (23.81%) of the young age I group were diagnosed with pneumonitis. It had almost the same prevalence rate in the young age II group (38 patients, 23.75%). Pneumonitis was also detected in 26 patients of the middle age group (17.11%). This type of lesions was less prevalent in the old age group of patients (1 patient, 7.69%).

The prevalence rate of pulmonary fibrosis rose with the age of patients. It was significantly more prevalent in the old age group of patients (four patients, 30.78%), slightly less prevalent in the middle age group of patients (26 patients, 17.11%). Pulmonary fibrosis was the least prevalent in the young age II group (nine patients, 5.73%) and the young age I group (one patient, 2.38 %).

According to our findings, pneumosclerosis may be detected in almost every elderly patient with SLE, in other age groups pneumosclerosis may be detected in almost half of patients. Pulmonary hypertension is more prevalent in elderly patients with SLE, it is rare in young patients. Pneumonitis is more prevalent in young patients with SLE; it is very rare in middle-aged and elderly patients. The prevalence rate of pulmonary fibrosis rises with the age of patients.

The results of the *second step of the second phase* are presented in Table 3.

The prevalence of pneumosclerosis rose with the increases in the duration of SLE. It was more prevalent in patients with the SLE duration of 6-10 years (43 patients, 55.13%) and with the SLE duration of more than 10 years (71 patients, 51.83%). It was also detected in 58 patients with the SLE duration of 1-5 years and seven patients with the SLE duration of less than one year (44.96% and 36.84%, respectively).

Table 3. Prevalence Characteristics for the Respiratory System Lesions in Combination with the Duration of Systemic Lupus Erythematosus

No.	Respiratory system lesions	Duration of Systemic Lupus Erythematosus							
		Less than 1 year, n = 19		1-5 years, n = 132		6-10 years, n = 78		More than 10 years, n = 138	
		N	%	N	%	N	%	N	%
1	Pneumosclerosis	7	36.84	n = 129 58	44.96	43	55.13	71	51.83
2	Pulmonary hypertension	n = 9		n = 102		n = 66		n = 98	
		3	33.33	22	21.57	11	16.67	26	26.53
3	Pneumonitis	3	15.79	19	14.30	15	19.23	58 #	27.76
4	Pulmonary fibrosis	1	5.26	n = 129 21	16.28	1 #	1.28	17 ^	12.41

Notes:
* - statistically significant difference in the number of cases in patients with the SLE duration of less than one year ($p < 0.05$);
# - statistically significant difference in the number of cases in patients with the SLE duration of 1-5 years ($p < 0.05$);
^ - statistically significant difference in the number of cases in patients with the SLE duration of 6-10 years ($p < 0.05$).

Pulmonary hypertension had the following prevalence: in patients with the SLE duration of less than one year – three cases (33.33%), in patients with the SLE duration of 1-5 years – 22 cases (21.57%), in patients with the SLE duration of 6-10 years – eleven cases (16.67%), and in patients with the SLE duration of more than 10 years – 26 cases (26.53%).

Pneumonitis was more prevalent in patients with the SLE duration of more than 10 years (58 patients, 27.76%). This type of lesions had almost similar prevalence rates in other groups: it was detected in three patients with the SLE duration of less than one year (15.79%), in 19 patients with the SLE duration of 1-5 years (14.30%), and 15 patients with the SLE duration of 6-10 years (19.23%).

Pulmonary fibrosis was more prevalent in patients with the SLE duration of 1-5 years (21 patients, 16.28%). The prevalence rate was lower in patients with the SLE duration of 10 or more years (17 patients, 12.41%). Pulmonary fibrosis was also detected in one patient with the SLE duration of less than one year (5.26%) and in one patient with the SLE duration of 6-10 years (1.28%).

We found that pneumosclerosis was more prevalent in patients with the SLE duration of more than 6 years, pulmonary hypertension was more prevalent in patients with the SLE duration of less than one year, pneumonitis was more prevalent in patients with the SLE duration of more than 10 years, and pulmonary fibrosis - in patients with the SLE duration of 1-5 years.

The purpose of the last, *third step of the second phase* was to determine relationships between the prevalence of syntropic comorbid lesions of the respiratory system and the severity of respiratory failure. Pneumosclerosis induced respiratory failure in 77 patients (43.02%); 60 out of 77 patients (77.92%) had degree I respiratory failure, and 17 out of 77 patients (22.08%) had degree II respiratory failure.

Functional class I asymptomatic pulmonary hypertension (functional classes according to the classification of the World Health Organization, 1998) was detected in 52 patients with SLE (83.87%). Functional class II pulmonary hypertension was detected in nine patients (17.31%) who had minor physical limitations. Functional class III pulmonary hypertension was detected in one patient (1.92%) whose physical activity had to be moderately restricted.

Pneumonitis-induced respiratory failure was detected in 29 patients (52.00%) Degree I respiratory failure was detected in 25 out of 29 patients (64.10%), while degree II respiratory failure was detected in 14 out of 29 patients (35.90%).

Respiratory failure induced by pulmonary fibrosis was detected in 25 patients (62.50%). 20 out of 25 patients (80.00%) had degree I respiratory failure, while 5 out of 25 patients (20.00%) had degree II respiratory failure.

We found that almost half of patients with pneumosclerosis had manifestations of respiratory failure, and degree I respiratory failure prevailed among them. Most pulmonary hypertension cases

were of functional class I. We also found that more than half of patients with pulmonary fibrosis, as well as with pneumonitis, had manifestations of respiratory failure; in most cases, the respiratory failure was of the first degree of severity.

Thus, respiratory system lesions had their own prevalence characteristics. Pneumosclerosis was more prevalent in elderly patients and patients with the SLE duration of more than 6 years. It led in 43.02% of cases to respiratory failure. In its turn, respiratory failure induced by pneumosclerosis in a quarter of cases was of the second degree of severity, and in other patients – of the first degree. Pulmonary hypertension was more prevalent in elderly patients and patients with the SLE duration of less than one year. It was asymptomatic in four out of five patients (functional class I). Pneumonitis was more prevalent in young patients and patients with the SLE duration of more than 10 years. It led in half of the cases to respiratory failure (in 2/3 of cases – to the degree I respiratory failure, while in 1/3 of cases – to the degree II respiratory failure). Pulmonary fibrosis was more prevalent in elderly patients and people with the SLE duration of 1-5 years. It led in more than half of cases to respiratory failure. (in 4/5 of cases – to the degree I respiratory failure, in 1/5 of cases – to the degree II respiratory failure).

Conclusions. 1. 67.57% of patients with SLE had respiratory system lesions. Pneumosclerosis, pulmonary hypertension, pneumonitis, and pulmonary fibrosis are lesions that are syntropic comorbid, i.e. pathogenetically associated with SLE;

2. The prevalence of syntropic comorbid respiratory lesions in patients with systemic lupus erythematosus depends on the age of patients, disease duration, and the severity of respiratory failure: pneumosclerosis is more prevalent in elderly patients and patients with the SLE duration of more than 6 years. It was the cause of respiratory failure in 43.02% of patients, while the respiratory failure was predominantly of the first degree of severity. Pulmonary hypertension is more prevalent in elderly patients and patients with the SLE duration of less than one year. It led to respiratory failure in 16.13% of patients; the respiratory failure was predominantly of the first degree of severity. Pneumonitis is more prevalent in young patients and patients with the SLE duration of more than 10 years. It led to respiratory failure in 52.00% of patients, while 64.10% out of them had the degree I respiratory failure. Pulmonary fibrosis is more prevalent in elderly patients and patients with the SLE duration of 1-5 years. It led to respiratory failure in 62.50% of patients, while 80.00% out of them had the degree I respiratory failure.

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