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PAPER

Pleuropulmonary involvement in patients with systemic lupus erythematosus from a Latin American inception cohort (GLADEL)

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Objectives: The objectives of this study were to examine the demographic and clinical features associated with the occurrence of pleuropulmonary manifestations, the predictive factors of their occurrence and their impact on mortality in systemic lupus erythematosus (SLE) patients. **Materials and methods:** The association of pleuropulmonary manifestations with demographic and clinical features, the predictive factors of their occurrence and their impact on mortality were examined in GLADEL patients by appropriate univariable and multivariable analyses. **Results:** At least one pleuropulmonary manifestation occurred in 421 of the 1480 SLE patients (28.4%), pleurisy being the most frequent (24.0%). Age at SLE onset ≥30 years (OR 1.42; 95% CI 1.10–1.83), the presence of lower respiratory tract infection (OR 3.19; 95% CI 2.05–4.96), non-ischemic heart disease (OR 3.17; 95% CI 2.41–4.18), ischemic heart disease (OR 3.39; 95% CI 2.08–5.54), systemic (OR 2.00; 95% CI 1.37–2.91), ocular (OR 1.58; 95% CI 1.16–2.14) and renal manifestations (OR 1.44; 95% CI 1.09–1.83) were associated with pleuropulmonary manifestations, whereas cutaneous manifestations were negatively associated (OR 0.47; 95% CI 0.29–0.76). Non-ischemic heart disease (HR 2.24; 95% CI 1.63–3.09), SDI scores ≥1 (OR 1.54; 95% CI 1.10–2.17) and anti-La antibody positivity (OR 2.51; 95% CI 1.39–4.57) independently predicted their subsequent occurrence. Cutaneous manifestations were protective of the subsequent occurrence of pleuropulmonary manifestations (HR 0.62; 95% CI 0.43–0.90). Pleuropulmonary manifestations independently contributed a decreased survival (HR: 2.79 95% CI 1.80–4.31). **Conclusion:** Pleuropulmonary manifestations are frequent in SLE, particularly pleuritis. Older age, respiratory tract infection, cardiac, systemic and renal involvement were associated with them, whereas cutaneous manifestations were negatively associated. Cardiac compromise, SDI scores ≥1 and anti-La positivity at disease onset were predictive of their subsequent occurrence, whereas cutaneous manifestations were protective. They independently contributed to a decreased survival in these patients. *Lupus* (2017) **26,** 1368–1377.

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Introduction

Pulmonary involvement in patients with systemic lupus erythematosus (SLE) was first described by Osler in 1904[1] and has been reported to occur in 30.0–90.0% of the patients studied;[2–5] this wide range probably relates to the diverse methods used to define it (clinical manifestations, images or autopsy findings) and the different characteristics of the patients studied. It should be also noted that the respiratory system is more commonly affected in SLE than in any other systemic autoimmune disease and that all its components may be affected.[6]

Some pleuropulmonary manifestations have a chronic course; that is the case for pleuritis, chronic interstitial pneumonitis and the shrinking lung syndrome.[4,7–10] Others have an acute presentation, are often quite serious and may have a catastrophic outcome; that is the case for acute pneumonitis, pulmonary hypertension and alveolar hemorrhage.[2,11–14] Some patients may have more than one form of pleuropulmonary involvement during the course of their disease. Furthermore, it is also important to consider that pulmonary manifestations may have a direct impact on mortality and that lung infections are a major cause of death in patients with SLE.[6,15–17]

The aim of the present study was to investigate the occurrence of pleuropulmonary manifestations, the demographic and clinical features associated with them, the predictive factors of their occurrence and their impact on mortality in patients from the multicenter Latin American SLE cohort GLADEL (***G**rupo **L**atino **A**mericano **D**e **E**studio del **L**upus*).

Materials and methods

GLADEL is an observational inception cohort study that includes patients from 34 centers with expertise in the diagnosis and management of SLE from nine Latin American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela). Patients were recruited into the cohort with a recent (less than 2 years) diagnosis of SLE based on clinical and laboratory features, and the expertise of the investigator; fulfillment of four 1982 American College of Rheumatology (ACR) SLE criteria was not mandatory at enrollment although over time nearly all patients had fulfilled these criteria.

All centers used ARTHROS as a common database to collect data. ARTHROS 6.0 is a user-friendly Microsoft Excel-compatible database developed for this study using a Windows platform, Visual Basic language and Microsoft Access. The database included socioeconomic, demographic and clinical characteristics, treatment features and commonly available laboratory tests. Visits took place every six months and comprised history, physical examination and standard laboratory tests; specific auto-antibodies were performed at each participating center if clinically indicated. Ethnicity was defined according to the parents' and all four grandparents' self-reported ethnicity. The following ethnic groups were considered: Caucasian (individuals with all white European ancestors), Mestizo (individuals born in Latin America who had both Amerindian and white ancestors), African-Latin American (ALA) (individuals born in Latin America with at least one African ancestor whether other ancestors were white or not) and other. Socioeconomic status was evaluated using the Graffar index.[18]

Pleuropulmonary involvement was defined as the presence of one or more of the following manifestations: pleuritis, pneumonitis, pulmonary arterial hypertension, shrinking lung syndrome, pulmonary fibrosis, pulmonary hemorrhage, pulmonary thrombosis and lung infarction.

Other clinical manifestations were defined as per the ACR criteria with the exception of non-ischemic heart disease, which included pericarditis, endocarditis and myocarditis; ischemic heart disease was considered separately and included myocardial infarction, angina and coronary artery bypass surgery. In order to assess disease activity, the SLE Disease Activity Index (SLEDAI) was used while the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) was used to assess damage. For these analyses, the mean SLEDAI over time and the SDI obtained at first and last visits were used; items corresponding to pleuropulmonary involvement were excluded from both instruments. Regarding treatments, the use corticosteroids, intravenous methylprednisolone, antimalarials, methotrexate, azathioprine, cyclophosphamide, non-steroidal anti-inflammatory

drugs and anticoagulants at any time of follow-up was evaluated.

Patients who missed a study visit for a year and who could not be contacted by telephone, mail or postal services were considered lost to follow-up.

The local ethics committee of each center approved the protocol; informed consent was obtained from all patients.

Statistical analyses

Continuous variables were expressed as means (and standard deviations [SD]) if normally distributed, and medians (and interquartile ranges) if not. Categorical variables were expressed as percentages. The association between variables from the different domains and the presence of pleuropulmonary manifestations regardless of when they occurred was assessed by Pearson Chi-squared or Fisher's tests. Odds ratios (ORs) and 95% confidence intervals (CIs) were derived from univariable logistic regressions. Variables with a $p \leq 0.05$ in these analyses were included in a multivariable logistic regression. In alternative univariable and multivariable Cox regression analyses, factors predictive of the subsequent occurrence of pleuropulmonary manifestations were examined; for these analyses, clinical manifestations and laboratory parameters present prior to the diagnosis of SLE and the first SDI obtained were included. Patients who exhibited pleuropulmonary manifestations before the diagnosis of SLE were excluded from these analyses. In addition, the association between specific pleuropulmonary manifestations and either ischemic or non-ischemic heart disease was also examined; when possible multivariable analyses were also performed.

As noted, immunological tests were not available in all patients. For example, antinuclear antibodies (ANA) and anti-dsDNA antibodies as well as serum complement levels were not available in about 15% of patients; however, these proportions were comparable in patients with and without pleuropulmonary manifestations, so that, all patients were included in the analyses. On the other hand, anti-RNP, anti-Sm, anti-La, anti-Ro and anti-cardiolipin antibodies were not available in about 50% of patients. Given that these percentages were not comparable in those with and without pleuropulmonary manifestations, imputation analyses were performed. Thus, two opposite scenarios were created by imputing the missing data as either positive or negative; if the results remained unchanged in the univariable analyses despite data replacement, these data were included in the multivariate analysis, otherwise they were not. The lupus anticoagulant and anti-β_2 glycoprotein I antibodies were performed in less than 50% of the patients and were excluded from further analyses.

To determine the independent contribution of the presence of pleuropulmonary manifestations to mortality a multivariable Cox regression analysis was done. The following variables considered candidates for inclusion were: age, gender, ethnicity and socio-economic status, pulmonary infection, renal manifestations, cardiac involvement, SLEDAI and SDI scores. Pleuropulmonary manifestations was considered a time-dependent variable.

The SPSS, version 19 (Chicago, Illinois, USA) was used for all analyses.

Results

Of the 1480 patients included in the GLADEL cohort, 90.0% ($n = 1330$) were female; their mean (SD) ages at disease onset and at diagnosis were 28.0 (12.0) and 29.5 (12.3) years, respectively. The mean (SD) follow-up time was 51.2 (27.5) months. In terms of demographic characteristics, 43.6% ($n = 645$) of the patients were Mestizo, 40.9% ($n = 606$) were Caucasian, 12.6% ($n = 186$) African-Latin American and 2.9% ($n = 43$) Other. The socio-economic status was low in 60.9% ($n = 901$), medium in 28.8% ($n = 427$) and high in 10.3% ($n = 152$).

At least one pleuropulmonary manifestation was present in 28.4% ($n = 421$) of the patients; 59.8% ($n = 252$) of them occurred before the diagnosis of SLE. The most common manifestation was pleurisy, which occurred in 24.0% ($n = 354$) of the patients, followed by all the others, each one occurring in less than 5.0% of the patients: pneumonitis 2.3% ($n = 34$), pulmonary hypertension 2.2% ($n = 32$), shrinking lung syndrome 1.6% ($n = 23$), pulmonary fibrosis 1.4% ($n = 21$), pulmonary thrombosis 1.4% ($n = 20$), pulmonary hemorrhage 1.1% ($n = 16$) and lung infarction 0.3% ($n = 5$).

Features associated with the occurrence of pleuropulmonary manifestations

Univariable analyses

As shown in Table 1, patients exhibiting pleuropulmonary manifestations at any time during the course of the disease were older at disease onset (29.4 ± 13 years vs 27.5 ± 11.6 years; $p < 0.001$), and exhibited more frequently an SDI score ≥ 1 (77.2% vs 61.7%; $p < 0.001$), systemic (includes:

Table 1 Demographic and clinical features as a function of the presence of pleuropulmonary involvement at any time during the disease course in lupus patients from the GLADEL cohort

	With pleuropulmonary involvement (n = 421)	*Without pleuropulmonary involvement (n = 1059)*	*Univariable analyses*		*Multivariable analyses*[b]	
			OR (95% CI)[a]	p *value*[a]	*OR (95% CI)*	p *value*
Gender, female, %	372 (88.4)	958 (90.5)	0.80 (0.56–1.15)	0.253		
Age at SLE onset ≥30 yr, %	180 (42.8)	381 (36.0)	1.33 (1.06–1.67)	0.012	1.42 (1.10–1.83)	0.006
Ethnic groups, %						
White	182 (43.2)	424 (40)	Reference	Reference		
Mestizo	172 (40.9)	473 (44.7)	0.85 (0.67–1.08)	0.187		
Afro-Latin-American	52 (12.4)	134 (12.7)	0.90 (0.63–1.30)	0.587		
Other	15 (3.6)	28 (2.6)	1.25 (0.62–2.39)	0.505		
Socioeconomic status, %						
High	36 (8.6)	116 (11.0)	Reference	Reference		
Middle	113 (26.8)	314 (29.7)	1.16 (0.75–1.78)	0.501		
Low	272 (64.6)	629 (59.4)	1.39 (0.93–2.08)	0.104		
Clinical manifestations, %						
Systemic	379 (90.0)	838 (79.1)	2.38 (1.67–3.38)	<0.001	2.00 (1.37–2.91)	<0.001
Musculoskeletal	391 (92.9)	984 (92.9)	0.99 (0.64–1.54)	0.973		
Ocular	100 (23.8)	159 (15.0)	1.76 (1.33–2.33)	<0.001	1.58 (1.16–2.14)	0.003
Cutaneous	381 (90.5)	1006 (95.0)	0.50 (0.32–0.76)	0.002	0.47 (0.29–0.76)	0.002
Non-ischemic heart disease	276 (65.6)	408 (38.5)	3.04 (2.40–3.85)	<0.001	3.17 (2.41–4.18)	<0.001
Ischemic heart disease	39 (9.3)	51 (4.8)	2.02 (1.31–3.11)	0.002	3.39 (2.08–5.54)	<0.001
Renal	300 (71.3)	576 (54.4)	2.10 (1.63–2.65)	<0.001	1.44 (1.09–1.83)	0.017
Neurological	177 (42.0)	348 (32.9)	1.48 (1.17–1.87)	0.001		
Hematologic	355 (84.3)	813 (76.8)	1.63 (1.21–2.19)	0.001		
Lower respiratory tract infection	61 (14.5)	40 (3.8)	4.31 (2.85–6.55)	<0.001	3.19 (2.05–4.96)	<0.001
SDI ≥ 1	325 (77.2)	653 (61.7)	2.10 (1.62–2.73)	<0.001		
Mean SLEDAI ≥ 4	261 (62.0)	598 (56.5)	1.26 (0.99–1.58)	0.050		
Immunological laboratory, %						
ANA positivity	399 (99.0)	994 (97.8)	2.21 (0.76–6.45)	0.192		
Anti-dsDNA antibodies positivity	300 (79.8)	591 (69.9)	1.70 (1.27–2.27)	0.001		
Anti-RNP antibodies positivity	113 (59.8)	209 (51.0)	1.43 (1.01–2.03)	0.050		
Anti-Sm antibodies positivity	119 (54.6)	231 (48.0)	1.30 (0.94–1.80)	0.122		
Anti-Ro antibodies positivity	114 (55.9)	229 (49.1)	1.31 (0.94–1.82)	0.110		
Anti-La antibodies positivity	70 (36.6)	121 (28.2)	1.47 (1.03–2.11)	0.031		
Hypocomplementemia	275 (74.7)	581 (65.3)	1.57 (1.20–2.07)	<0.001		
IgG Anticardiolipin antibodies positivity	134 (54.7)	229 (46.3)	1.40 (1.03–1.91)	0.030		
IgM Anticardiolipin antibodies positivity	78 (38.2)	176 (38.4)	0.99 (0.71–1.39)	1.000		
Medications, %						
Corticosteroids	406 (96.4)	986 (93.1)	2.00 (1.14–3.53)	0.012		
Intravenous methylprednisolone	171 (40.6)	261 (24.6)	2.09 (1.65–2.66)	0.013		
Antimalarials	342 (81.2)	872 (82.3)	0.92 (0.69–1.24)	0.611		
Methotrexate	50 (11.9)	125 (11.8)	1.00 (0.71–1.43)	1.000		
Azathioprine	146 (31.3)	321 (30.3)	1.21 (0.96–1.55)	0.107		
Cyclophosphamide	17 (4.0)	31 (2.9)	1.39 (0.76–2.55)	0.336		
Non-steroidal anti-inflammatory drugs	186 (44.2)	438 (41.4)	1.12 (0.89–1.41)	0.325		
Anticoagulants	47 (11.2)	66 (6.2)	1.90 (1.28–2.80)	0.006		

SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (lung manifestation excluded); SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.
[a]Univariable analyses.
[b]Multivariable analyses, only variables associated with the presence of pleuropulmonary manifestations are shown.

fever, weight loss, asthenia, fatigue, anorexia, adenopathy) (90.0% vs 79.1%; $p < 0.001$), renal (71.3% vs 54.4%; $p < 0.001$), neurological (42.0% vs 32.9%; $p = 0.001$), hematologic (84.3% vs 76.8%; $p = 0.001$) and ocular manifestations (23.8% vs 15.0%; $p < 0.001$), non-ischemic heart disease (65.5% vs 38.5%; $p < 0.001$), ischemic heart disease (9.3% vs 4.8%; $p = 0.002$), and lower respiratory tract infection (14.5% vs 3.8%; $p < 0.001$); cutaneous manifestations, on the other hand, occurred less frequently among patients with pleuropulmonary involvement (90.5% vs 95.0%; $p = 0.002$). A higher frequency of positive anti-dsDNA antibodies (79.8% vs 69.9%; $p = 0.001$), hypocomplementemia (74.7% vs 65.3%; $p < 0.001$) and more frequent use of corticosteroids

(96.4% vs 93.1%, $p = 0.012$) were observed in patients with pleuropulmonary manifestations than in those without them. There were no differences in the frequency of pleuropulmonary manifestations among the different ethnic groups.

The frequency of anti-RNP, anti-La and anticardiolipin IgG antibodies positivity was higher in patients with pleuropulmonary manifestations, but statistical significance was not retained after data imputation.

Multivariable analyses

The variables independently associated with the presence of pleuropulmonary manifestations are noted in Table 1. They were age at SLE onset $\geq$30 years (OR 1.42; 95% CI 1.10–1.83), presence of lower respiratory tract infection (OR 3.19; 95% CI 2.05–4.96), non-ischemic heart disease (OR 3.17; 95% CI 2.41–4.18), Ischemic heart disease (OR 3.39; 95% CI 2.08–5.54), systemic (OR 2.00; 95% CI 1.37–2.91), ocular (OR 1.58; 95% CI 1.16–2.14) and renal manifestations (OR 1.44; 95% CI 1.09–1.83); cutaneous manifestations were, on the other hand, negatively associated with their occurrence (OR 0.47; 95% CI 0.29–0.76).

Factors predictive of pleuropulmonary manifestations

Table 2 depicts frequency, OR and 95% CI of the clinical and laboratory characteristics occurring prior to the diagnosis of SLE associated with the subsequent occurrence of pleuropulmonary manifestations. Within the clinical features, the presence of non-ischemic heart disease (OR 2.89; 95% CI 1.73–4.86), lower respiratory tract infection (OR 3.66; 95% CI 1.06–12.67), as well as the first SDI $\geq$ 1 (OR 1.87; 95% CI 1.30–2.71) were associated with the development of pleuropulmonary manifestations, whereas cutaneous manifestations were negatively associated with their occurrence (OR 0.46; 95% CI 0.34–0.64). Anti-La antibody positivity was associated with the development of pleuropulmonary manifestations (OR 4.40; 95% CI 1.99–9.72) and this association persisted whether the missing values were imputed as positive or negative. The same did not occur with anti-Ro antibody positivity since the initial association (OR 2.53; 95% CI 1.15–5.58) did not remain as such after the imputation of missing values. The variables remaining significant in the corresponding multivariable

Table 2 Risk factors associated with the development of pleuropulmonary manifestations according to clinical and laboratory characteristics present on or before or shortly after the diagnosis of Lupus in patients[a] from the GLADEL cohort

	With pleuropulmonary involvement (n = *169*)[α]	*Without pleuropulmonary involvement* (n = *1060*)[α]	*Univariable analyses*		*Multivariable analyses*[c]	
			OR (95% CI)[b]	p *value*[b]	*HR (95% CI)*	p *value*
Clinical manifestations, %						
Systemic	107 (63.1)	682 (64.3)	0.97 (0.69–1.36)	0.863		
Musculoskeletal	141 (83.9)	929 (87.6)	0.73 (0.47–1.56)	0.214		
Ocular	13 (7.7)	67 (6.3)	1.24 (0.67–2.30)	0.500		
Cutaneous	133 (79.2)	939 (88.6)	0.46 (0.34–0.64)	0.002	0.62 (0.43–0.90)	0.012
Non-ischemic heart disease	23 (13.7)	55 (5.2)	2.89 (1.73–4.86)	<0.001	2.24 (1.63–3.09)	<0.001
Ischemic heart disease	2 (1.2)	22 (2.1)	0.57 (0.13–2.44)	0.762		
Renal	67 (39.9)	343 (32.4)	1.39 (0.99–1.94)	0.064		
Neurological	23 (13.7)	145 (13.7)	1.00 (0.62–1.60)	1.000		
Hematologic	81 (48.2)	563 (53.1)	0.82 (0.59–1.14)	0.245		
Lower respiratory tract infection	4 (2.4)	7 (0.7)	3.66 (1.06–12.67)	0.051		
SDI $\geq$ 1	49 (29.2)	191 (18.0)	1.87 (1.30–2.71)	0.001	1.54 (1.10–2.17)	0.012
Immunological laboratory, %						
ANA positivity	114 (96.6)	860 (97.3)	0.79 (0.27–2.33)	0.562		
Anti-dsDNA antibodies positivity	61 (73.5)	405 (65.6)	1.45 (0.86–2.43)	0.174		
Anti-RNP antibodies positivity	22 (61.1)	117 (46.6)	1.80 (0.88–3.68)	0.112		
Anti-Sm antibodies positivity	26 (57.8)	154 (49.8)	1.38 (0.73–2.59)	0.342		
Anti-Ro antibodies positivity	21 (67.7)	126 (45.3)	2.53 (1.15–5.58)	0.022		
Anti-La antibodies positivity	17 (58.6)	63 (24.3)	4.40 (1.99–9.72)	<0.001	2.51 (1.39–4.57)	0.002
Hypocomplementemia	49 (65.3)	331 (58.6)	1.33 (0.80–2.21)	0.317		
IgG anticardiolipin antibodies positivity	14 (56.0)	110 (50.9)	1.23 (0.53–2.82)	0.677		
IgM anticardiolipin antibodies positivity	8 (34.8)	75 (38.9)	0.84 (0.34–2.07)	0.822		

SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (lung manifestation excluded).
[a]Patients with pleuropulmonary manifestations before diagnosis were excluded.
[b]Univariable analyses.
[c]Multivariable analyses (Cox regression), only variables associated with the risk of development of pleuropulmonary manifestations are shown.
[α]Total *n* are different in the evaluation of immune laboratory.

model are also depicted in Table 2. The alternative Cox regressions were overall consistent with the primary analyses; non-ischemic heart disease (HR 2.24; 95% CI 1.63–3.09), SDI > 1 (HR 1.54; 95% CI 1.10–2.17) and anti-La antibody positivity (HR 2.51; 95% CI 1.39–4.57) were independently associated with the subsequent occurrence of pleuropulmonary manifestations, whereas cutaneous manifestations (HR 0.62; 95% CI 0.43–0.90) were negatively associated with their occurrence.

Specific pleuropulmonary manifestations: univariable and multivariable analyses

Ischemic and non-ischemic heart disease were associated with the occurrence of pleurisy (OR 2.99; 95% CI 2.33–3.82 and OR 1.99; 95% CI 1.28–2.09, respectively), whereas only ischemic heart disease was associated with pulmonary hypertension (OR 6.60; 95% CI 2.96–14.73) and non-ischemic heart disease with pneumonitis (OR 2.48; 95% CI 1.20–5.13). The associations between ischemic and non-ischemic heart disease with pulmonary hemorrhage, shrinking lung and pulmonary fibrosis were non-significant. The association between ischemic and non-ischemic heart disease and pleurisy persisted in the multivariable analyses. Because of the relatively small number of events, multivariable analyses for the other manifestations (pulmonary hypertension and pneumonitis) were not performed. These data are shown in Tables 1 and 2 of the Online Appendix, respectively.

Mortality

Fifty-two (12.4%) patients with pleuropulmonary manifestations versus 38 (3.6%) patients without them, died over the follow-up period. As noted in Table 3, the mortality rate varied in relation to the presence of pleural manifestations (10.1%), or pulmonary manifestations alone (14.9%) or both (pleural and pulmonary) (21.4%).

After adjusting for known confounders in the multivariable Cox regression model pleuropulmonary manifestations remained a risk factor for diminished survival (HR: 2.79 (95% CI 1.80–4.31), $p < 0.001$) (Table 4).

Table 3 Mortality as a function of the presence of pleuropulmonary involvement in lupus patients from the GLADEL cohort

Pleuropulmonary involvement	n *(total)*	*Deceased* n	*%*	p
No	1059	38	3.6	<0.001
Pleural only	298	30	10.1	
Pulmonary only	67	10	14.9	
Pleural and pulmonary	56	12	21.4	

Table 4 Cox regression of predictors of mortality in lupus patients from the GLADEL cohort

	HR	*95% CI*	p
Pleuropulmonary manifestations	2.79	1.80–4.31	<0.001
Age at diagnosis (≥60)	4.45	1.92–10.27	<0.001
SDI > 1	4.19	2.65–6.63	<0.001
Pulmonary infections	3.23	1.93–5.39	<0.001
SLEDAI > 3	3.01	1.87–4.83	<0.001

SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.
Other variables included in the analysis: age, gender, ethnicity, pulmonary infection, renal manifestations, cardiac involvement.

Discussion

In this large cohort of Latin American SLE patients, pleuropulmonary manifestations were present in approximately one third of them, being pleural involvement the most frequent manifestation. Non-ischemic heart disease, SDI > 1 and anti-La antibody positivity at diagnosis or early on the disease course were predictive of their subsequent occurrence whereas cutaneous manifestations were negatively associated. Furthermore, pleuropulmonary manifestations contributed independently of other factors to a significantly decreased survival among those affected with them.

Twenty-eight percent of the patients presented with at least one pleuropulmonary manifestation some time during the course of the disease, and more than half of them occurred before SLE diagnosis, which is somewhat less than reported by other authors (30–90%). As noted, this variability is probably explained by the characteristics of the patients studied (early disease) and the methodology used to ascertain them; for example, we performed imaging and functional studies only if clinically indicated.[2–5]

The clinical manifestations associated with respiratory system involvement in SLE may vary depending on the structure affected, which in turn may be caused by different pathophysiological mechanisms; these include fibrotic parenchymal changes, deposit of circulating immune complexes

(supported by the presence of IgG, anti-DNA antibodies and complement in biopsies), vasculitis and thromboembolism.[5,19] In our study, pleural involvement was the most common feature (24.0%) which was higher than reported in the Eurolupus project (16.0%) and in asymptomatic patients from China (12.0%),[20] but lower than the reported in other clinical (between 30.0% and 50.0%) and autopsy studies (up to 90.0%).[3–5,7,8]

Of the parenchymal manifestations, the most commonly observed was pneumonitis (2.4%). This is consistent with observations from patients enrolled in clinical trials in which investigators have reported a frequency between 1.0% and 4.0%[20] with a mortality rate of up to 50.0%.[21] However, in many cases of fatal lupus pneumonitis other etiologies such as infections and aspiration also play a role as demonstrated in autopsy studies.[4,5]

Pulmonary arterial hypertension was present in 2.2% of the study population. In a study from Birmingham-UK that included 288 patients who underwent echocardiography for the detection of pulmonary hypertension, this was observed in 4.2%.[22] By contrast, in another study in which 544 patients were evaluated only if pulmonary arterial hypertension was suspected in clinical grounds, pulmonary arterial hypertension was confirmed in 1.8% of them.[23] In yet another study of 786 patients with SLE from Singapore primary pulmonary hypertension was identified in 3.0%.[24] This frequency is much higher that estimates reported for the general population of about 15 per 1 million inhabitants according to a French study.[25]

The shrinking lung syndrome, was observed in 1.6% of our patients, which is higher than previously reported (0.6–1.0%) by some investigators.[26] However, when diaphragmatic function has been systemically evaluated, the shrinking lung syndrome has been found to be present in over 20.0% of the patients.[27,28] Pulmonary fibrosis was observed in 1.4% of our patients, which is similar to what has been found in patients enrolled in clinical trials and lower than what has been observed in autopsy studies (13.0%),[4,9] and greater than what has been observed in the general population. In fact, in the US and Europe the prevalence of pulmonary fibrosis it is estimated to be between 1.25 to 63 per 100,000 population according on the definitions used.[29–30]

Pulmonary thrombosis and pulmonary infarction were found in 1.2% and 0.3% of the patients, respectively which is lower than the 7.8% of thromboembolism reported in an autopsy study of 90 patients.[5] As to pulmonary infarction, it was observed in 0.8% of 700 hospitalized patients and it was associated with the antiphospholipid syndrome,[32] whereas, its prevalence was 0.6% in the LUMINA (for **Lu**pus in **Mi**norities: **Na**ture vs Nurture) cohort.[33] Pulmonary embolism in patients with SLE entails a higher risk of pulmonary infarction (67%) when it is associated with antiphospholipid antibodies than the general risk observed in those subjects without SLE.[32]

Pulmonary hemorrhage occurred in 1.4% of our patients which is consistent with what has been described by other authors (1.6%),[34] and markedly lower than the frequency observed in studies performed in either hospitalized patients (3.7–6.0%)[12,35,36] or in an autopsy study (25.0%).[5] In most cases, pulmonary hemorrhage coexists with cardiac compromise or concomitant infections[4,37] and can lead to impaired respiratory function.[38]

Infections in general are common in lupus as these patients tend to be immunosuppressed as a consequence of the disease and the therapies used for it. The respiratory system is the most common infection site; infections there tend to be associated with significant morbidity and mortality.[39] Respiratory infections have been reported to be more frequent among patients with pleuropulmonary manifestations than on those without them in a study from Spain that included 284 lupus patients. In fact, in that study respiratory infections also predisposed to the occurrence of pleuropulmonary manifestations, closing a vicious circle; furthermore, according to this study, having lung involvement predisposes patients to the development of major infections in lupus.[40] Finally, it has been postulated that a respiratory infection is the common denominator which may lead to interstitial lung disease, alveolar damage which may manifest as alveolar hemorrhage or involvement of the arterial wall leading to pulmonary arterial hypertension.[41,42]

A strong association between pleuropulmonary manifestations (pleurisy, pneumonitis and pulmonary arterial hypertension) and non-ischemic and ischemic heart disease was observed; of these manifestations, an individual regression could be examined only for pleurisy owing to the relative small number of events for the other manifestations. It is tempting to speculate that there is common underlying pathophysiological mechanism for these associations but no conclusive data to the effect can be provided. Perhaps and increased frequency of anticardiolipin antibodies in patients with pulmonary arterial hypertension and ischemic heart disease could be the underlying explanation but we could not corroborate this.[43–45]

Previous investigations have documented a relationship between anticardiolipin antibodies (aCL), anti-RNP, anti-Ro and anti-Sm antibodies[24,45–47] with pleuropulmonary manifestations but we could not corroborate these associations.

As to the factors predictive of the subsequent occurrence of pleuropulmonary manifestations, cardiac compromise was consistently identified as a predictor which has been previously reported only in autopsy studies. The same was the case for an SDI ≥ 1; this is consistent with a 1996 study in which the damage index correlated with changes in the pulmonary function as measured by spirometry in patients with SLE.[10]

In contrast, cutaneous manifestations were shown to consistently protect against the occurrence of pleuropulmonary manifestations as had been previously reported in the LUMINA cohort[33] and in a study of more than 1000 patients from the USA in which the presence of discoid lupus was associated with a lower incidence of pleuritis.[48]

Our study also corroborates the fact that pleuropulmonary manifestations independently contribute to a diminished survival.[17,49]

Our study has some limitations. First, pleuropulmonary manifestations were not systematically evaluated but diagnosed by each patient's attending physician based on the presence of suggestive clinical manifestations. Second, not all patients fulfilled the ACR SLE classification criteria and thus their inclusion could have impacted the results; however, nearly all patients met ≥ 4 criteria at some point over their disease course. Third, auto-antibodies were not available in all patients, and had not been obtained at a central laboratory or at the time pleuropulmonary manifestations occurred. Fourth, we had not collected data on smoking habits; thus, the possible role of tobacco use on the occurrence of these manifestations could not be examined. Despite these limitations, our work reveals what happens in the usual medical practice and as such it contributes to our knowledge about these manifestations.

In conclusion, pleuropulmonary manifestations are relatively frequent in patients with lupus, they occur early in the course of the disease and these manifestations may impact on the patients' long-term outcome (mortality). Patients with active disease, those with non-ischemic heart disease and who are anti-La positive tend to be predisposed to their occurrence, while patients with cutaneous manifestations tend not to be predisposed to their occurrence.

On behalf of GLADEL

The following participants are members of GLADEL, have incorporated at least 20 patients into the database with adequate follow-up and in particular provided data related to elderly onset SLE.

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