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Original article

Primary cardiac disease in systemic lupus erythematosus patients: protective and risk factors—data from a multi-ethnic Latin American cohort

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Abstract

Objectives. The aim of this study was to assess the cumulative incidence, risk and protective factors and impact on mortality of primary cardiac disease in SLE patients (disease duration $\leqslant$2 years) from a multi-ethnic, international, longitudinal inception cohort (34 centres, 9 Latin American countries).

Methods. Risk and protective factors of primary cardiac disease (pericarditis, myocarditis, endocarditis, arrhythmias and/or valvular abnormalities) were evaluated.

Results. Of 1437 patients, 202 (14.1%) developed one or more manifestations: 164 pericarditis, 35 valvulopathy, 23 arrhythmias, 7 myocarditis and 1 endocarditis at follow-up; 77 of these patients also had an episode of primary cardiac disease at or before recruitment. In the multivariable parsimonious model, African/Latin American ethnicity [odds ratio (OR) 1.80, 95% CI 1.13, 2.86], primary cardiac disease at or before recruitment (OR 6.56, 95% CI 4.56, 9.43) and first SLICC/ACR Damage Index for SLE assessment (OR 1.31, 95% CI 1.14, 1.50) were risk factors for the subsequent occurrence of primary cardiac disease. CNS involvement (OR 0.44, 95% CI 0.25, 0.75) and antimalarial treatment (OR 0.62, 95% CI 0.44, 0.89) at or before recruitment were negatively associated with the occurrence of primary cardiac disease risk. Primary cardiac disease was not independently associated with mortality.

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CLINICAL SCIENCE

Conclusion. Primary cardiac disease occurred in 14.1% of SLE patients of the Grupo Latino Americano de Estudio de Lupus cohort and pericarditis was its most frequent manifestation. African origin and lupus damage were found to be risk factors, while CNS involvement at or before recruitment and antimalarial treatment were protective. Primary cardiac disease had no impact on mortality.

Key words: systemic lupus erythematosus, cardiac disease, antimalarials, mortality, survival.

Introduction

SLE is an autoimmune disease characterized by heterogeneous clinical manifestations, organ involvement and varied outcomes, probably related to a combination of ethnic, genetic, hormonal and environmental factors. Damage in the cardiovascular system, associated either with the activity and severity of the disease or with the detrimental effects of medications (e.g. corticosteroids) has been increasingly recognized in SLE patients over the past few years, while the autoimmune involvement of the cardiovascular system has taken a secondary place. It is known, however, that the endocardium, myocardium, pericardium, valves, conduction system and vessels can be targeted by the autoimmune process [1–5].

The prevalence of cardiovascular involvement in SLE has been reported with variable frequency in the literature, probably due to the criteria used to identify cases and the time during the disease course when the patients were studied. In fact, cardiovascular involvement, called carditis, was described in almost all SLE patients in autopsy studies of the 1950 s, when it was not uncommon to succumb to the disease; recent echocardiographic studies, on the other hand, have described a frequency of 57% [2–6]. This sort of cardiovascular involvement, presumably resulting from autoimmune mechanisms, is called primary cardiac disease, which has a distinct pathophysiological mechanism from the cardiovascular involvement associated with previous therapies or the disease itself as defined in the SLICC Damage Index (SDI) [1]. Despite difficulties in distinguishing between them, we decided to examine the cumulative incidence of primary cardiac disease, the risk and protective factors associated with its presence as well as its potential role in mortality in patients from the multi-ethnic Latin America cohort of SLE patients [Grupo Latino Americano de Estudio de Lupus (GLADEL) or Latin American Group for the Study of Lupus] cohort [7]. We hypothesized that primary cardiac disease is associated with non-Caucasian ethnicity, lower socio-economic status and more active and severe disease, whereas antimalarials may have a protective effect, and that primary cardiac disease has a negative impact on mortality.

Patients and methods

As previously described, patients were those participating in GLADEL, a multi-ethnic, international, longitudinal inception cohort study conducted in 34 centres with expertise in the diagnosis and management of SLE [7], and distributed among nine Latin American countries (Argentina, Brazil, Chile, Colombia, Cuba, Guatemala, Mexico, Peru and Venezuela) with a recent SLE diagnosis ($\leqslant$2 years). Fulfilment of four of the 1982 ACR SLE criteria [8] at the time of diagnosis was not mandatory and the diagnosis of SLE was based on clinical and laboratory features and the expertise of the investigator. The study was performed according with the Declaration of Helsinki for the conduct of research in humans and following local institutional review board regulations. Informed consent was obtained from all patients across all centres. The data analysis presented here is part of the GLADEL study and is therefore covered by the GLADEL ethical approval and patient consent. Every group used ARTHROS as a common database to collect data. All GLADEL investigators were trained in data collection and entry and on the proper utilization of the ARTHROS program. ARTHROS 6.0 is a user-friendly database program using a Windows platform. Data included socio-economic, demographic and clinical characteristics, treatment features and laboratory tests.

Socio-economic and demographic data were recorded only at the first visit. The clinical, laboratory and therapeutic patients' characteristics were evaluated at disease onset and during its course (cumulative incidence) by performing study visits every 6 months; however, events occurring during non-scheduled visits were also recorded in the database. Co-morbidities such as diabetes, infections, hypercholesterolaemia and hypertriglyceridaemia were registered at the first visit and then subsequently. Laboratory studies were performed at each participating centre using standard techniques. Corticosteroids were recorded as either oral prednisone or equivalent (low $<$20 mg/day, medium 20–60 mg/day, and high $>$60 mg/day) or i.v. (pulse methylprednisolone).

Disease activity was assessed with the SLEDAI [9] at entry into the cohort and at every follow-up visit. Not all patients were recruited into the GLADEL cohort at the time of diagnosis, although the great majority was. In those patients recruited after the diagnosis of SLE, the SLEDAI was scored at the time of the recruitment visit.

Damage was assessed with the SDI [10, 11] at entry into the cohort if patients had a disease duration of 6 months and at every follow-up visit in all patients. For the purpose of these analyses, all socio-economic, demographic, clinical and therapeutic manifestations were those occurring on or before the diagnosis of SLE, except for damage, which was when it was first recorded. The items from

the cardiovascular domain were excluded from the SDI for these analyses.

Primary cardiac disease was defined as the presence of one or more of the following manifestations: pericarditis, myocarditis, endocarditis, arrhythmias and/or valvular abnormalities presumably resulting from autoimmune mechanisms. Cardiac manifestations were determined based on the physician's judgment and defined as clinically detectable in the context of SLE activity and having excluded other possible aetiologies such as infections or damage as per the SDI as their cause. Each GLADEL study visit captures cumulative data up to the day of the visit, therefore events occurring between visits were properly identified and recorded.

Angina, myocardial infarction and coronary artery bypass surgery are components of the damage index and thus they were excluded within the primary cardiac disease category. Likewise, cases of ischaemic cardiovascular disease occurring in the 5 years of follow-up were considered in the damage index and not included in the analyses. Patients failing to return for a study visit within 1 year and who failed to be contacted through social services, by telephone or by mail were considered lost to follow-up.

Statistical analyses

The socio-economic, demographic and baseline clinical and therapeutic characteristics of SLE patients with and without primary cardiac disease occurring over the course of follow-up were examined by a series of univariable logistic regressions, as appropriate. A P-value $\leqslant 0.15$ was arbitrarily chosen for variables to be included in a multivariable logistic regression model. Primary cardiac disease at follow-up was the dependent variable in these analyses. This allowed examining time-dependent events, particularly the use of medications at or before the diagnosis of lupus. In contrast, primary cardiac disease occurring at or before the diagnosis of lupus was considered an independent variable. To improve the precision of the estimates, a reduced or parsimonious model was performed. The median follow-up time was determined using the reverse Kaplan–Meier estimator [12]. In a second set of analyses, the role of primary cardiac disease as a risk factor for mortality was examined by Cox multivariable regression analyses. Variables known to affect this outcome were included in this regression.

Results

Between 1997 and 2005, 1480 SLE patients were recruited into the GLADEL cohort, with 65 fulfilling fewer than four ACR classification criteria. For this study, patients from the ethnic group other ($n = 43$) were excluded, resulting in a total of 1437 patients. This other category included Asian and purely Amerindian patients, as well as patients whose ethnic origin had not been determined. Therefore there were 645 Mestizo (individuals of mixed European and Amerindian ethnic background), 606 Caucasian and 186 African–Latin American patients.

SLE patients in this cohort had a mean age at disease onset of 28.0 years (S.D. 12.1) and at disease diagnosis of 29.5 years (S.D. 12.3). Median time from the first clinical manifestation attributable to disease to the definitive SLE diagnosis was 5.9 months and the median duration of follow-up was 57.2 months.

Two hundred and two (14.1%) of the 1437 SLE patients developed primary cardiac disease over the course of follow-up; 77 of these patients also had one episode of primary cardiac disease at or before diagnosis. The main manifestations of primary cardiac disease over the disease course were pericarditis in 164 patients (81.2%), valvular heart disease in 35 (17.3%), arrhythmias in 23 (11.4%), myocarditis in 7 (3.5%) and non-infectious endocarditis in 1 (0.5%). There were overlapping manifestations in some patients.

Univariable analyses

Table 1 depicts the odds ratios (ORs) and 95% CIs for the socio-economic, demographic, clinical, laboratory and treatment features. There was an increased risk of primary cardiac disease occurrence in patients of African–Latin American ethnicity (OR 1.82, 95% CI 1.18, 2.80, $P = 0.0065$), but not in those of Mestizo origin, and also in those from the lower socio-economic group (OR 1.80, 95% CI 1.01, 3.21, $P = 0.0475$).

Within the clinical features, the presence of primary cardiac disease (OR 7.07, 95% CI 4.98, 10.4, $P < 0.0001$) and of lung involvement (OR 4.74, 95% CI 2.28, 9.64, $P < 0.0001$) at or before recruitment was associated with the subsequent occurrence of primary cardiac disease. Positive anti-dsDNA (OR 1.68, 95% CI 1.05, 2.70, $P = 0.0309$) and anti-La antibodies (OR 2.36, 95% CI 1.27, 4.39, $P = 0.0066$), low C3 levels (OR 2.38, 95% CI 1.43, 3.95, $P = 0.0009$), higher disease activity as measured by the SLEDAI (OR 1.02, 95% CI 1.01, 1.04, $P = 0.0349$) as well as greater damage as measured by the SDI (OR 1.30, 95% CI 1.15, 1.47, $P = 0.0002$) were also associated with the occurrence of primary cardiac disease. Regarding therapy, the use of low doses of corticosteroids (prednisone or equivalent) (OR 0.63, 95% CI 0.42, 0.96, $P = 0.0331$) and antimalarials (OR 0.49, 95% CI 0.35, 0.69, $P < 0.0001$) was negatively associated with the occurrence of primary cardiac disease.

Importantly, sex, age at disease onset, medical insurance coverage, education and marital status were not associated with an increased risk of primary cardiac disease. Likewise, general, musculoskeletal, skin, renal and/or haematological manifestations and APS and positivity for ANA, anti-Sm, anti-RNP and/or anti-Ro antibodies at SLE diagnosis were not associated with an increased risk of primary cardiac disease.

Multivariable analyses

Of note, 261 patients could not be included because of missing data for one or more of the explanatory variables. The variables independently associated with primary cardiac disease occurring over the course of follow-up in our patients by multivariable logistic regression analyses are

Table 1 Risk of developing primary cardiac disease according to sociodemographic, clinical and treatment characteristics at or before recruitment

Characteristic	OR	95% CI	*P*-value
Sex, female	0.91	0.57, 1.49	0.7380
Age	0.99	0.78, 1.01	0.1695
Ethnic group			
Caucasian	Reference group		
Mestizo	1.13	0.82, 1.58	0.4566
ALA	1.82	1.18, 2.80	0.0065
Years of education			
>12	Reference group		
0–7	1.14	0.76, 1.17	0.5229
8–12	0.91	0.62, 1.84	0.6345
Socio-economic status			
High	Reference group		
Middle	1.32	0.71, 2.47	0.3813
Low	1.80	1.01, 3.21	0.0475
Marital status			
Married	Reference group		
Single	1.11	0.82, 1.51	0.4932
Widow/divorced	1.34	0.63, 2.84	0.4478
Clinical manifestations			
General	1.14	0.82, 1.60	0.4286
Musculoskeletal	0.87	0.56, 1.40	0.5365
Cutaneous	0.68	0.46, 1.02	0.0463
Pulmonary	4.74	2.28, 9.64	<0.0001
Primary cardiac disease	7.07	4.98, 10.4	<0.0001
Renal disease	1.24	0.89, 1.67	0.2042
CNS	0.70	0.41, 1.14	0.1496
Haematological	0.83	0.61, 1.13	0.2109
Disease activity (SLEDAI)	1.02	1.01, 1.04	0.0349
SLICC/ACR DI first recorded	1.30	1.15, 1.47	0.0002
Immunological features			
ANA ($n = 1183$)	1.11	0.39, 3.21	0.8435
Anti-dsDNA antibodies ($n = 847$)	1.68	1.05, 2.70	0.0309
Anti-phospholipid antibodies ($n = 442$)	0.86	0.48, 1.54	0.6146
Anti-Sm antibodies ($n = 428$)	1.55	0.89, 2.67	0.1186
Anti-RNP antibodies ($n = 339$)	1.18	0.63, 2.23	0.6088
Anti-Ro antibodies ($n = 376$)	1.43	0.79, 2.57	0.2371
Anti-La antibodies ($n = 346$)	2.36	1.27, 4.39	0.0066
Low C3 ($n = 650$)	2.38	1.43, 3.95	0.0009
Low C4 ($n = 638$)	1.45	0.89, 2.37	0.1383
Co-morbidities			
Infections	0.84	0.48, 1.47	0.5350
Hypercholesterolaemia ($n = 93$)	1.46	0.36, 5.93	0.5976
Hypertriglyceridaemia ($n = 201$)	0.50	0.21, 1.18	0.1112
Treatments			
Corticosteroids[a]			
None	Reference group		
Low dose (<20 mg/day)	0.63	0.42, 0.96	0.0331
Medium dose (20–60 mg/day)	0.85	0.58, 1.25	0.4122
High dose (>60 mg/day)	0.69	0.45, 1.07	0.0981
Methylprednisolone pulse therapy	1.48	0.90, 2.43	0.1271
Any antimalarial[b]	0.49	0.35, 0.69	<0.0001
AZA	0.72	0.32, 1.59	0.4116
i.v. CYC	0.96	0.47, 1.98	0.9208
Haemodialysis	0.94	0.21, 4.20	0.9368

OR: odds ratio; ALA: African–Latin American; DI: Damage Index. [a]Prednisone or equivalent. [b]Chloroquine and/or HCQ.

TABLE 2 Characteristics associated with the occurrence of primary cardiac disease during the disease course by multiple variable logistic regression analysis

Characteristic	Full model			Reduced model		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Ethnic group						
Mestizo *vs* Caucasian	0.92	0.61, 1.39	0.7042	1.16	0.81, 1.66	0.4132
ALA *vs* Caucasian	1.79	1.06, 3.01	0.0298	1.80	1.13, 2.86	0.0133
Socio-economic status						
Low *vs* high	2.33	1.01, 5.37	0.0465			
Middle *vs* high	2.26	0.95, 5.37	0.0637			
Clinical manifestations						
Pulmonary involvement	1.83	0.79, 4.28	0.1614			
Primary cardiac disease	6.59	4.32, 10.06	<0.0001	6.56	4.56, 9.43	<0.0001
CNS compromise	0.52	0.29, 0.94	0.0302	0.44	0.25, 0.75	0.0028
Cutaneous	1.01	0.62, 1.65	0.9704			
SLEDAI first recorded	0.99	0.97, 1.02	0.5892			
SLICC DI first recorded	1.32	1.11, 1.56	0.0015	1.31	1.14, 1.50	0.0002
Treatments						
Oral corticosteroids[a]						
No corticosteroids	Reference group					
Low dose (<20 mg/day)	0.95	0.55, 1.64	0.8612			
Medium dose (20–60 mg/day)	0.81	0.51, 1.31	0.3898			
High dose (>60 mg/day)	0.68	0.40, 1.17	0.1684			
Methylprednisolone pulse therapy	1.08	0.58, 1.199	0.8103			
Antimalarials	0.66	0.43, 1.03	0.0657	0.62	0.44, 0.89	0.0093

OR: odds ratio; ALA: African–Latin American; DI: Damage Index. [a]Prednisone or equivalent.

depicted in Table 2. In the parsimonious or reduced model African–Latin American ethnicity (OR 1.80, 95% CI 1.13, 2.86, $P = 0.0133$), primary cardiac disease at or before recruitment (OR 6.56, 95% CI 4.56, 9.43, $P < 0.0001$) and damage (first recorded) (OR 1.31, 95% CI 1.14, 1.50, $P = 0.0002$) were associated with the occurrence of primary cardiac disease, whereas treatment with antimalarials was negatively associated with its occurrence (OR 0.62, 95% CI 0.44, 0.89, $P = 0.0093$). Likewise, CNS involvement at or before recruitment was negatively associated with the occurrence of primary cardiac disease (OR 0.44, 95% CI 0.25, 0.75, $P = 0.0028$).

Mortality

Patients with primary cardiac disease had a higher mortality rate (34/202, 16.8%) than those without (50/1245, 4.0%) (OR 4.80, 95% CI 3.01, 7.63). However, after adjusting for variables known to affect this outcome (sex, age at lupus diagnosis, education level, medical insurance, SDI (excluding cardiovascular domain items), SLEDAI at diagnosis, infections, renal disease and antimalarial treatment, primary cardiac disease was not retained in the multivariable Cox proportional regression model (hazard ratio 1.26, 95% CI 0.65, 2.43, $P = 0.49$).

Discussion

Cardiovascular involvement is considered a severe manifestation of all diseases and SLE is certainly no exception. Widely variable cumulative incidence rates of cardiovascular disease in lupus have been reported in the literature, probably related to different inclusion criteria in previous studies [1]. For this reason, in the present study only cardiac manifestations intimately related to the autoimmune process in lupus were considered, rather than those associated with damage resulting either from chronic inflammation or medication. Taking these into consideration, we found that primary cardiac disease occurred in 14% of the SLE patients of the GLADEL cohort over a median follow-up time of nearly 5 years.

The most remarkable observation of the present study was the recognition that the use of antimalarials had a protective effect over the later occurrence of primary cardiac disease. This finding extends the list of beneficial effects of antimalarials in lupus, including disease activity, flares, overall damage, renal survival and mortality [13–18]. In fact, a previous study from our group demonstrated that antimalarials had a protective effect on SLE survival, possibly in a time-dependent manner. A significant reduction in the production of IFN-α and TNF-α as a result of the inhibition of Toll-like receptors has been demonstrated in SLE patients treated with HCQ, and this has been suggested as an important mechanism explaining most of the beneficial effects of HCQ [13, 19].

As expected, some disease characteristics emerged as risk factors for the development of primary cardiac disease, including African ancestry, low socio-economic status, concomitant pulmonary involvement and primary

cardiac disease at or before recruitment. In fact, patients of African descent in North America, Colombia, the Caribbean Islands and the United Kingdom are known to have more severe disease activity and worse long-term outcomes, which is concordant with our findings [16, 20–23]. However, we were surprised by the fact that we did not find an association between primary cardiac disease and Mestizo ethnicity, given that these individuals, whether in our cohort or in North American cohorts, which include a large contingent of patients from this ethnic/racial group, experience a disease phenotypically resembling that observed in patients of African descent [24, 25]. Because patients of Asian and purely Amerindian ancestry were very few, we excluded them from the analyses, so we cannot state whether patients from these ethnic groups are either protected or at risk of developing primary cardiac disease.

Disease activity at recruitment, pulmonary involvement and damage were also initially identified as risk factors for the occurrence of primary cardiac disease over time. However, neither disease activity nor pulmonary compromise were retained in the multivariable analyses and were not examined further (specific type of pulmonary involvement). Nevertheless, in the univariable analyses there was an association between the presence of anti-dsDNA antibodies and low complement levels, in particular the C3 fraction, laboratory parameters that reflect active disease and autoimmune tissue injury and primary cardiac disease [26, 27]. As to the clinical manifestations, having primary cardiac disease early in the course of lupus was predictive of the occurrence of primary cardiac disease. On the other hand, CNS involvement appeared to be protective of its occurrence, which seems counterintuitive. This may reflect the diverse pathophysiological mosaic of this complex disease or the heterogeneity of the manifestations included within this category. In fact, small numbers for the different manifestations included did not allow us to examine them individually in the multivariable analyses. However, the only one that appears to have contributed to this apparent counterintuitive result is the presence of cranial nerve involvement (data not shown). Damage *per se* at the first evaluation was retained in the multivariable model as an independent risk factor for the occurrence of primary cardiovascular disease, which may relate to the presence of persistent disease activity in these patients and also demonstrates the severity of the disease these patients experience [28].

The most frequent manifestation of primary cardiac disease was pericarditis, which occurred in 81.2% of patients with primary cardiac disease and in 11.4% of the entire GLADEL SLE population. The cumulative incidence of pericarditis in the GLADEL cohort is comparable to data reported for other cohorts [29, 30]. Pericarditis is a well-recognized manifestation of SLE, and in fact is considered a component in all the activity indices currently used. Moreover, its presence at disease onset may have allowed early recognition of the disease, shortening the time between symptom onset and diagnosis, prompting the implementation of proper treatment. Probably because most lupus patients with pericarditis fully recover, we could not demonstrate any impact of having primary cardiac disease on mortality after adjusting for known confounding factors. Valvular heart disease, myocarditis and arrhythmias occurred less frequently in our cohort. This could be related to the fact that most of our patients only underwent a more detailed cardiovascular evaluation if it was clinically indicated rather than it being systematically performed. Actually, the low sensitivity of cardiac auscultation compared with two-dimensional transthoracic echocardiographic examination to detect valvular heart disease has already been demonstrated [2]. Conduction disorders in adult SLE patients are seldom described and almost always relate to active inflammatory disease that responds to immunosuppressive treatment. They are also associated with a poor prognosis, suggesting the importance of screening for these abnormalities in lupus patients [31, 32]. A recent study demonstrated the association of high SLE activity and cardiac involvement, supporting the systematic evaluation of these patients with sensitive tools like electrocardiography with QT interval dispersion evaluation [33]. In our patients, myocarditis was uncommon and less frequent than in patients from other cohorts, including those from LUMINA, a multi-ethnic US cohort, in which clinical myocarditis occurred in 10.7% of patients and was related to African American ethnicity, disease activity, damage and mortality [34]. Subclinical myocardial involvement associated with SLE activity has been described, and in a longitudinal study using MRI its association with mortality was demonstrated [35–37]. In a recent communication, a good correlation between cardiac MRI and histopathological findings was described. Furthermore, the distinction between viral and autoimmune myocarditis (frequently subclinical) can be made using this imaging modality [38]. Even though the use of immunosuppressive treatment in some SLE cardiac manifestations like myocarditis remains controversial, we want to stress that low doses of corticosteroid had a possible protective effect and its use may ameliorate the long-term effects of these manifestations [39].

Our study has some limitations. First, there was not a systematic cardiac evaluation of all GLADEL patients, so subclinical cases may have not been recognized. Second, complete ascertainment of all laboratory variables could not be performed, which prompted us to exclude some possible important risk factors from the multivariable analyses. Third, ethnic/racial group was determined by self-report and identification of the patients' ancestors rather than by ascertaining the ancestral genetic background [40–42]. Finally, it can be argued that some of our patients ($n = 65$) never fulfilled the ACR classification criteria for lupus and thus their inclusion could have impacted in the data presented. Given this, we repeated the analyses excluding these 65 patients and the results were remarkably similar (data not shown), which reaffirms our conclusions. Moreover, now that the SLICC group has redefined SLE, these patients probably would have been classified as lupus, making this a point of less importance [43, 44].

The study has some remarkable strengths, including the size of the cohort; its multinational, multicentre and multi-ethnic features; its inception nature and an adequate follow-up time.

We thus conclude that primary cardiac disease in lupus can occur at any time during its course. Patients of African ancestry with cardiac involvement at recruitment and having already experienced some damage are at increased risk of developing primary cardiac disease. On the other hand, the use of antimalarials seems beneficial to minimize the occurrence of primary cardiac disease. Even though we did not demonstrate a direct impact of primary cardiac disease on mortality, primary cardiac disease should be systematically investigated by non-invasive and sensitive diagnostic tests and treated appropriately.

Rheumatology key messages

- Primary cardiac disease occurred in 14% of Grupo Latino Americano de Estudio de Lupus patients, with pericarditis being the most frequent manifestation.
- African ancestry, cardiac involvement at SLE diagnosis and damage (first recorded) were risk factors for primary cardiac disease occurrence.

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Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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