

Original article

Hydroxychloroquine is associated with a lower risk of polyautoimmunity: data from the RELESSER Registry

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Abstract

Objectives. This article estimates the frequency of polyautoimmunity and associated factors in a large retrospective cohort of patients with SLE.

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Methods. RELESSER (Spanish Society of Rheumatology Lupus Registry) is a nationwide multicentre, hospital-based registry of SLE patients. This is a cross-sectional study. The main variable was polyautoimmunity, which was defined as the co-occurrence of SLE and another autoimmune disease, such as autoimmune thyroiditis, RA, scleroderma, inflammatory myopathy and MCTD. We also recorded the presence of multiple autoimmune syndrome, secondary SS, secondary APS and a family history of autoimmune disease. Multiple logistic regression analysis was performed to investigate possible risk factors for polyautoimmunity.

Results. Of the 3679 patients who fulfilled the criteria for SLE, 502 (13.6%) had polyautoimmunity. The most frequent types were autoimmune thyroiditis (7.9%), other systemic autoimmune diseases (6.2%), secondary SS (14.1%) and secondary APS (13.7%). Multiple autoimmune syndrome accounted for 10.2% of all cases of polyautoimmunity. A family history was recorded in 11.8%. According to the multivariate analysis, the factors associated with polyautoimmunity were female sex [odds ratio (95% CI), 1.72 (1.07, 2.72)], RP [1.63 (1.29, 2.05)], interstitial lung disease [3.35 (1.84, 6.01)], Jaccoud arthropathy [1.92 (1.40, 2.63)], anti-Ro/SSA and/or anti-La/SSB autoantibodies [2.03 (1.55, 2.67)], anti-RNP antibodies [1.48 (1.16, 1.90)], MTX [1.67 (1.26, 2.18)] and antimalarial drugs [0.50 (0.38, 0.67)].

Conclusion. Patients with SLE frequently present polyautoimmunity. We observed clinical and analytical characteristics associated with polyautoimmunity. Our finding that antimalarial drugs protected against polyautoimmunity should be verified in future studies.

Key words: polyautoimmunity, systemic lupus erythematosus, multiple autoimmune syndrome

Rheumatology key messages

- Antimalarial drugs could delay the development of polyautoimmunity in SLE patients. Anti-Ro/SSA, anti-La/SSB and anti-RNP antibodies were independently associated with polyautoimmunity in SLE patients.
- Polyautoimmunity in SLE patients was associated with Jaccoud arthropathy, RP and interstitial lung disease.

Introduction

SLE is a systemic autoimmune rheumatic disease (SARD) that can affect any tissue and lead to a wide range of clinical manifestations that are shared by other inflammatory diseases [1]. Polyautoimmunity is the co-occurrence of more than one well-defined autoimmune disease in the same patient. The co-occurrence of three or more autoimmune diseases is known as multiple autoimmune syndrome (MAS), which is an extreme phenotype of polyautoimmunity. Patients with SLE often present with autoimmune thyroiditis, SS, RA, autoimmune hepatitis or APS [2]. Overlap syndrome is defined as the co-occurrence of manifestations of several recognized and diagnostically confirmed autoimmune diseases in the same patient [3], although this area remains open to debate [4]. One example would be MCTD, which shares clinical characteristics with SLE, SSc, PM/DM and RA. Patients with this condition also have high ANA titres (anti-RNP), and their main symptoms are polyarthritis, hand oedema, RP, sclerodactyly, myositis and oesophageal hypomotility [5]. The subject of whether this disease is a separate entity or a transitional syndrome remains controversial [6]. The main objections are as follows: (i) patients can progress to another well-defined SARD; (ii) anti-RNP antibodies are not exclusive to this condition, and the most typical clinical manifestations of MCTD co-occur with other antibodies;

and (iii) there are no widely accepted classification criteria [7, 8].

Both polyautoimmunity and overlap syndromes, together with familial aggregation of autoimmune diseases, represent phenotypic expressions of an identical or similar genotype and of 'immune tautology'. Study of some of the characteristics of patients with SLE, polyautoimmunity and overlap syndromes (epidemiology, familial coaggregation, shared pathophysiology, genetic factors and similar treatments) has revealed no clear distinction between phenotypic subgroups [4, 9, 10]; therefore, it would be interesting to know how polyautoimmunity affects patients with SLE. Increased knowledge would provide us with information on the frequency and clinical characteristics of the condition and pave the way for new lines of research into the clinical significance of and mechanisms involved in autoimmunity.

The aims of the present study were as follows: (i) to investigate the prevalence of polyautoimmunity and MAS in a large cohort of patients with SLE in Spain; (ii) to describe the characteristics of subphenotypes; and (iii) to identify factors associated with polyautoimmunity in patients with SLE.

Methods

RELESSER Registry

We performed a retrospective evaluation of all adult patients in the RELESSER Registry (Spanish Society of

Rheumatology Lupus Registry) to determine the prevalence of polyautoimmunity and MAS in patients with SLE.

The RELESSER Registry is a nationwide multicentre, hospital-based registry involving a cross-sectional stage designed by the Systemic Autoimmune Diseases Working Group of the Spanish Society of Rheumatology [11]. The methodologic and general characteristics of the RELESSER Registry have been published elsewhere [12, 13]. The registry includes cumulative clinical data for patients with SLE in clinical settings. The Research Unit of the Spanish Society of Rheumatology was the coordinating centre and was responsible for providing expert methodological support at all stages of the project, monitoring the study, and identifying and resolving inconsistencies.

Written commitment was obtained from all investigators prior to participation. The study was approved by the Ethics Committee at Dr Negrín University Hospital, Gran Canaria, Spain, and then by the institutional research review boards at all participating centres. Informed consent was obtained from the patients. The study was conducted in accordance with the Declaration of Helsinki.

Study population

We selected adult patients with SLE defined according to the 1997 criteria of the ACR [14]. All patients had been attended and followed at any one of 45 Spanish rheumatology teaching centres with experience in the treatment of SLE. Patients were widely and homogeneously distributed throughout Spain in order to prevent selection bias.

Outcomes and definitions

Main outcome

Patients were considered to have polyautoimmunity when they simultaneously fulfilled the classification criteria for SLE classified according to the ACR 1997 criteria [14] and another autoimmune disease, such as autoimmune thyroiditis (abnormal thyroid function with antithyroid antibodies), MCTD according to the criteria of Alarcón-Segovia and Cardiel [15], other autoimmune diseases such as RA according to the criteria of the ACR [16], SSc [17] and inflammatory myopathy [18]. MAS was defined as the co-occurrence of SLE and at least two other autoimmune diseases (see above).

Other outcomes

We also recorded whether patients had secondary SS according to the criteria of the 2002 American-European Consensus Group [19], APS according to the Sydney criteria [20] or a family history (first- or second-degree) of SARD. However, these forms were not counted as polyautoimmunity but as secondary syndromes.

We also recorded demographic, clinical, analytical and treatment data. Demographic and clinical variables included age (in years), sex, comorbidities included in the Charlson index [21], date of onset of the disease

(date the patient first fulfilled four or more ACR or SLE criteria), duration of the disease (calculated from diagnosis to the most recent visit or death, if applicable), and all of the parameters covered in the ACR and SLE classification criteria. Analytical data were assessed in the local laboratory. We recorded all present or past drugs and the reasons for interrupting them, nonpharmacological treatments and mortality. At the last visit, we retrospectively recorded the activity index Safety of Oestrogens in Lupus Erythematosus: National Assessment-SLEDAI [22], the damage index SLICC/ACR Damage Index [23] and the Katz severity index [24].

Statistical analysis

We performed a descriptive analysis of the clinical, epidemiological, autoimmune and therapeutic characteristics of all patients with SLE with or without polyautoimmunity. Qualitative variables were expressed as absolute numbers and percentages; quantitative variables were expressed as mean (s.d.) or median [interquartile range (IQR)], as applicable.

The χ^2 and an ANOVA or Kruskal-Wallis test (depending on normality) were performed to compare the main characteristics between four groups of patients: (i) patients with SLE and no other autoimmune disease; (ii) patients with a family history of SLE; (iii) patients with autoimmune thyroiditis; and (iv) patients with another SARD. Survival was analysed based on Kaplan-Meier curves in order to compare time on antimalarial drugs in patients with SLE with and without polyautoimmunity or positive antibody titres. Finally, a binary logistic regression analysis was performed (dependent variable: polyautoimmunity) to explore variables associated with polyautoimmunity identified in the bivariate analysis and/or of clinical interest. Multicollinearity of independent variables was verified using the Pearson correlation coefficient ($r > 0.4$). The analysis was performed using Rcomander.

Results

Of the 4037 patients with SLE recruited in RELESSER-TRANS, 3679 (91.1%) fulfilled four or more ACR criteria for SLE. Most patients were women (90.3%) and white (93.1%), and the median (IQR) age was 44.0 (35.0–56.0) years.

Polyautoimmunity

A total of 502 of the 3679 (13.6%) patients with SLE had polyautoimmunity, and 51 (1.4%) had MAS. Most patients with polyautoimmunity were white women (94.4%) with long-term disease. The most common clinical manifestations in patients with polyautoimmunity were arthritis, cutaneous abnormalities and RP. Most patients (99%) had positive ANA titres, with a predominance of anti-DNA, anti-Ro and anti-RNP antibodies. As for treatment, the vast majority had received CS and antimalarial drugs at some time during the course of

their disease. Table 1 shows a comparison of the results for the whole SLE group ($n = 3679$) and the polyautoimmunity and SLE patients ($n = 502$).

The autoimmune diseases most commonly associated with SLE were autoimmune thyroiditis [289/3679 (7.9%)] and other autoimmune diseases [227/3679 (6.2%)].

In the latter group, 97/3679 (2.6%) had MCTD and 130/3679 (3.5%) had RA, SSc or inflammatory myopathy. A total of 517/3679 (14.1%) patients had secondary SS and 505/3679 (13.7%) had secondary APS. A family history of SARD was recorded in 433 patients (11.8%) with SLE.

TABLE 1 Characteristics of whole SLE group ($n = 3679$) with the polyautoimmunity and SLE patients ($n = 502$)

Variable	Whole SLE group ($n = 3679$)	Polyautoimmunity ($n = 502$)	P-value
Epidemiological characteristics			
Sex (female), n (%)	3315 (90.3)	473 (94.4)	0.001
Age at SLE diagnosis (years), mean (s.d.)	34.6 (14.6)	36.7 (14.2)	0.220
Age at the time of inclusion (years), mean (s.d.)	46.2 (14.8)	48.8 (14.6)	0.189
Disease duration (months), median (IQR)	165.4 (82.0–234.0)	162.0 (83.0–243.0)	0.159
Family history ^a , n (%)	433 (16.0)	60 (15.7)	0.902
Clinical manifestations			
SS, n (%)	517 (14.4)	127 (25.7)	<0.001
APS, n (%)	505 (13.9)	74 (14.9)	0.486
Malar rash, n (%)	2004 (55.2)	253 (50.8)	0.100
Discoid lupus, n (%)	753 (21.0)	94 (19.1)	0.265
Photosensitivity, n (%)	2172 (60.8)	293 (59.7)	0.569
Ulcer, n (%)	1645 (46.1)	218 (44.4)	0.414
Arthritis, n (%)	2827 (77.9)	393 (79.4)	0.415
Jaccoud arthropathy, n (%)	363 (10.0)	90 (18.1)	0.005
Pleuritis, n (%)	826 (23.0)	105 (21.3)	0.357
Pericarditis, n (%)	579 (16.1)	86 (17.3)	0.404
Neurologic ^b , n (%)	331 (9.1)	45 (9.1)	0.989
Hematologic ^c , n (%)	2371 (66.0)	320 (64.9)	0.568
RP, n (%)	1200 (33.9)	226 (45.8)	<0.001
Nephritis, n (%)	1101 (30.6)	131 (26.5)	0.035
Proteinuria, n (%)	1170 (32.2)	132 (26.6)	0.013
Interstitial lung disease, n (%)	73 (2.0)	25 (5.0)	0.010
Pulmonary hypertension, n (%)	8 (2.4)	17 (3.4)	0.157
Antibody profile			
ANA, n (%)	3637 (99.1)	497 (99.0)	0.892
Anti-dsDNA antibody positivity, n (%)	2629 (73.3)	350 (71.0)	0.208
Anti-Sm antibody positivity, n (%)	737 (21.2)	110 (22.8)	0.337
Anti-RNP antibody positivity, n (%)	891 (25.2)	164 (34.1)	<0.001
Anti-Ro antibody positivity, n (%)	1350 (36.0)	193 (39.9)	0.099
Anti-La antibody positivity, n (%)	690 (18.8)	104 (21.4)	0.117
LA, n (%)	638 (23.9)	70 (20.3)	0.114
aCL positivity, n (%)	759 (20.6)	96 (19.1)	0.678
Anti-beta 2 glycoprotein 1 positivity, n (%)	442 (12.0)	59 (11.8)	0.802
Severity indexes			
SLICC-ACR, median (IQR)	1.1 (0.0–2.0)	1.0 (0.0–2.0)	0.108
Katz index, median (IQR)	2.5 (1.0–3.0)	2.0 (1.0–3.0)	0.915
Mortality, n (%)	211 (6.6)	43 (8.4)	0.124
Treatment			
Glucocorticoids, n (%)	3112 (88.9)	439 (91.1)	0.224
MTX, n (%)	579 (16.6)	120 (24.7)	<0.001
Antimalarials, n (%)	2899 (83.3)	369 (76.7)	<0.001
Time on antimalarials (months), median (IQR)	123 (62.0–204.0)	113.0 (50.0–192.0)	
AZA, n (%)	1143 (33.0)	173 (36.0)	0.129
CYC, n (%)	780 (22.5)	95 (19.7)	0.126
Mycophenolate, n (%)	525 (15.2)	60 (12.4)	0.075
Rituximab, n (%)	227 (6.5)	44 (9.1)	0.170
Immunoglobulin, n (%)	154 (4.5)	23 (4.8)	0.721

^aFamily history: family history of systemic autoimmune rheumatic disease. ^bNeurologic: seizure and psychosis.

^cHematologic: haemolytic anaemia, leukopenia and thrombocytopenia. IQR: interquartile range.

Characteristics of the subtypes of polyautoimmunity

Table 2 shows the characteristics of the various subgroups associated with polyautoimmunity compared with patients with SLE who did not have polyautoimmunity. As shown, almost all differences were concentrated in patients with polyautoimmunity associated with another SARD, whereas patients with autoimmune thyroiditis or a family history of SARD had similar characteristics to patients with SLE but not polyautoimmunity.

Female sex was generally more frequent in all polyautoimmunity subphenotypes, whereas age and duration of SLE were higher in patients with polyautoimmunity and associated SARDs. However, other epidemiological characteristics such as race and smoking did not differ significantly between groups. As for clinical manifestations, patients with polyautoimmunity and another SARD less frequently had photosensitivity, malar rash, proteinuria and kidney disease. However, Jaccoud arthropathy, RP, interstitial lung disease, pulmonary hypertension and secondary SS were much more common.

The abovementioned associations were observed in patients with MAS as an extreme subphenotype of polyautoimmunity, although the association was stronger: they were all women (100%), had a lower frequency of kidney disease (16.0 vs 31.3%; $P = 0.024$), and had double the number of cases with secondary SS [n (%) = 51.0 vs 12.6; $P < 0.00$], RP (87.8 vs 31.9; $P < 0.001$), interstitial lung disease (6.0 vs 1.5; $P < 0.001$) and Jaccoud arthropathy (28.0 vs 8.7; $P < 0.001$), with respect to patients with SLE but no polyautoimmunity.

Polyautoimmunity was associated with anti-Ro/SSA antibodies ($P = 0.012$), and MAS was associated with anti-RNP antibodies ($P < 0.001$). Other antibodies such as aPL did not differ significantly between groups. As for treatment, patients with polyautoimmunity, including those with MAS, more commonly received MTX ($P < 0.001$), AZA ($P = 0.019$) and rituximab ($P = 0.043$). However, they took antimalarial agents less frequently ($P < 0.001$) or for less time [median (IQR): 56.6 (31.2–179.3) vs 185.9 (27.5–294.0) months; $P < 0.001$] (Fig. 1). Similarly, less exposure to antimalarial drugs was associated with a greater frequency of positive anti-Ro and anti-La titres [median (IQR): 157.0 (101.2–212.7) vs 240.0 (187.3–292.6) months; $P = 0.003$].

Multivariate analysis

The results of the multivariate analysis in Table 3 show that polyautoimmunity was associated with female sex, Jaccoud arthropathy, RP, interstitial lung disease, and positive titres for anti-Ro/SSA, anti-La/SSB and anti-RNP antibodies. Similarly, patients with polyautoimmunity were 67% more likely to be treated with MTX and 50% less likely to receive antimalarial drugs. However, variables of severity such as mortality or damage were not associated with polyautoimmunity.

Discussion

Classic systemic autoimmune diseases are characterized by very heterogeneous clinical phenotypes and by the fact that they share clinical manifestations and pathogenic mechanisms. This clinical and aetiological-pathogenic overlap has been referred to by some authors as ‘autoimmune tautology’ [25]. The best clinical evidence of this tautology arises from the co-occurrence of several autoimmune diseases in the same patient (i.e. polyautoimmunity), the progression from one phenotype to another during the clinical course (e.g. progression from MCTD to lupus) or the presence of overlap syndromes (e.g. antisynthetase syndrome) [26, 27]. In accordance with this perspective, we found the prevalence of polyautoimmunity to be 14% in patients with SLE and <2% in MAS. These percentages are lower than those reported by Rojas-Villarraga *et al.* [25, 28], who found a greater prevalence of polyautoimmunity in patients with SLE (around 40%) and of MAS (5.1%). The difference arises from the fact that the authors considered SS and APS to be independent entities and not secondary disorders. While this approach has recently been supported by other authors [29, 30], in the present study we adopted a traditional approach and treated them as being secondary to SLE. However, aside from this consideration, the percentages reported by these authors for SS and APS syndrome were similar to ours. In addition, the results of our multivariate model remained unchanged irrespective of which approach was used.

As for diseases associated with SLE, autoimmune thyroiditis was as frequent in the present study as the other SARDs together, although its importance in the clinical and epidemiological characteristics of the patients was negligible. Autoimmune thyroiditis is the most prevalent autoimmune disease in the general population [25, 31]. Although their aetiology is still poorly understood, genetic, immunological, hormonal and environmental factors are major predisposing and triggering factors [32].

The finding that polyautoimmunity has higher female representation than SLE is probably driven by the high prevalence of thyroid autoimmunity, which has a much higher female predominance than lupus, on the order of 30–40:1 vs 9:1 [33]. Female sex is also associated with a greater frequency of MAS, which was recorded in 100% of cases in the present study. While this finding could be biased owing to the composition of the RELESSER Registry itself (90% are women), it has been reported in other studies and attributed to hormones, genetics [34] and gender-related lifestyle [35].

Rojas-Villarraga *et al.* [28] also highlighted that a family history of autoimmune disease was a key risk factor for polyautoimmunity. While this observation has been reported in other autoimmune diseases [36–39], we were unable to confirm it in our study, not even when SS and APS were considered as not being secondary to SLE.

Anti-Ro/SSA and anti-La/SSB antibodies are associated with SS, SLE and neonatal lupus. In the present

TABLE 2 Characteristics of the different phenotypes of patients with SLE

Variable	Phenotype				P-value
	SLE ≥ 4 criteria ^a (n = 3177)	SLE + family history of systemic autoimmune disease (n = 433)	SLE + systemic autoimmune thyroiditis (n = 289)	SLE + other SARD (n = 227)	
Epidemiological characteristics					
Sex (female), n (%)	2842 (89.6)	402 (92.8)	275 (95.5)	212 (94.0)	0.006
Age at SLE diagnosis (years), mean (s.d.)	34.6 (14.6)	31.3 (13.5)	36.1 (13.8)	37.7 (14.6)	0.051
Age at the time of inclusion (years), mean (s.d.)	42.2 (13.8)	47.0 (14.1)	51.3 (14.8)	46.2 (14.8)	0.010
Disease duration (months), median (IQR)	148.0 (82.0–234.0)	144.0 (81.0–231.0)	143.0 (69.0–233.0)	180.5 (106.5–259.2)	0.001
Clinical manifestations					
Malar rash, n (%)	1751 (55.9)	254 (59.1)	156 (54.5)	102 (44.9)	0.013
Discoid lupus, n (%)	659 (21.3)	94 (22.1)	61 (21.6)	35 (15.6)	0.161
Photosensitivity, n (%)	1879 (61.0)	264 (62.9)	181 (64.9)	121 (53.3)	0.023
Oral ulcers, n (%)	1427 (46.4)	224 (52.8)	123 (43.5)	101 (45.5)	0.348
Arthritis, n (%)	2434 (77.7)	338 (79.5)	218 (77.0)	187 (82.7)	0.179
Jaccoud arthropathy, n (%)	315 (9.9)	46 (10.7)	22 (7.7)	72 (31.9)	<0.001
Pleuritis, n (%)	721 (23.2)	88 (20.9)	57 (20.2)	49 (21.7)	0.532
Pericarditis, n (%)	493 (15.9)	70 (16.6)	47 (16.5)	40 (17.7)	0.476
Proteinuria, n (%)	1001 (32.2)	126 (29.6)	87 (30.4)	45 (20.1)	0.011
Neurologic ^b , n (%)	286 (9.1)	44 (10.3)	20 (7.5)	26 (11.0)	0.500
Hematologic ^c , n (%)	2031 (65.5)	277 (64.9)	182 (64.3)	134 (60.3)	0.985
SS, n (%)	390 (12.6)	54 (12.7)	62 (21.9)	72 (31.9)	<0.001
APS, n (%)	431 (13.7)	65 (15.2)	43 (15.0)	34 (15.2)	0.843
RP, n (%)	974 (31.9)	159 (37.0)	88 (31.1)	148 (66.4)	<0.001
Nephritis, n (%)	970 (31.3)	124 (28.9)	79 (27.7)	51 (23.0)	0.133
Interstitial lung disease, n (%)	48 (1.5)	10 (2.3)	2 (0.7)	23 (10.2)	<0.001
Pulmonary hypertension, n (%)	71 (2.3)	13 (3.1)	5 (1.7)	11 (4.9)	<0.001
Antibody profile					
ANA, n (%)	3140 (99.1)	428 (99.1)	288 (99.7)	223 (98.2)	0.356
Anti-dsDNA antibody positivity, n (%)	2279 (73.7)	320 (76.4)	206 (73.0)	154 (68.4)	0.050
Anti-Sm antibody positivity, n (%)	627 (21.0)	108 (26.4)	58 (21.2)	56 (25.6)	0.435
Anti-RNP antibody positivity, n (%)	727 (23.8)	114 (27.3)	55 (20.2)	117 (52.5)	<0.001
Anti-Ro antibody positivity, n (%)	1210 (38.1)	185 (44.7)	111 (40.4)	90 (41.5)	0.179
Anti-La antibody positivity, n (%)	586 (18.4)	96 (23.1)	63 (22.9)	43 (19.3)	0.057
aCL positivity, n (%)	728 (25.1)	117 (26.3)	70 (24.6)	48 (22.0)	0.518
Anti-beta 2 glycoprotein 1 positivity, n (%)	270 (14.2)	56 (12.5)	30 (15.0)	13 (11.0)	0.166
LA, n (%)	568 (24.4)	94 (27.4)	42 (20.1)	27 (22.5)	0.255
Treatment					
Antimalarials, n (%)	2530 (84.3)	356 (86.0)	231 (83.4)	151 (69.0)	<0.001
Time on antimalarials (months), median (IQR)	60.0 (25.0–120.0)	58.0 (27.5–109.5)	48.0 (22.5–79.5)	36.0 (13.2–108.0)	0.008
MTX, n (%)	459 (15.3)	81 (19.8)	48 (17.1)	76 (34.9)	<0.001
AZA, n (%)	970 (32.5)	135 (32.8)	82 (29.7)	95 (44.0)	0.001
CYC, n (%)	685 (22.9)	85 (20.9)	52 (18.7)	44 (20.2)	0.339
Mycophenolate, n (%)	465 (15.7)	80 (19.7)	40 (14.3)	20 (9.2)	0.145
Rituximab, n (%)	183 (6.1)	31 (7.6)	22 (7.9)	23 (10.6)	0.038
Immunoglobulins, n (%)	131 (4.4)	22 (5.4)	18 (6.5)	5 (2.3)	0.210

The P-value is generated based on the χ^2 test, ANOVA or Kruskal–Wallis test (depending on normality). ^aSLE ≥ 4 criteria without polyautoimmunity. ^bNeurologic: seizure and psychosis. ^cHematologic: haemolytic anaemia, leukopenia and thrombocytopenia. SARD: systemic autoimmune rheumatic disease; IQR: interquartile range.

Fig. 1 Kaplan–Meier survival estimates

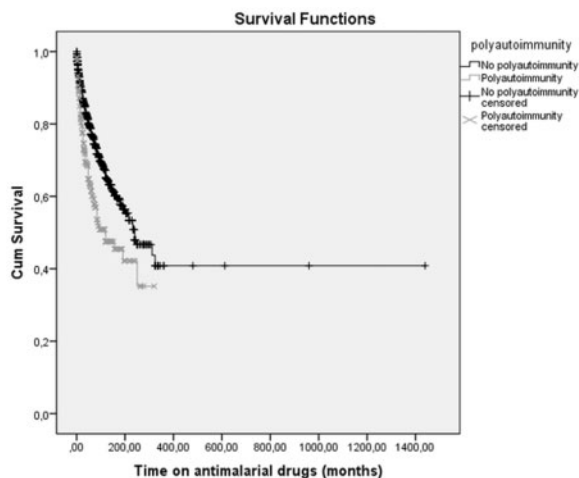


TABLE 3 Binary logistic regression analysis of the characteristics associated with polyautoimmunity in patients with SLE

Predictor	OR (95% CI)	P-value
Female sex	1.721 (1.074, 2.729)	0.024
RP	1.630 (1.292, 2.056)	<0.001
Interstitial lung disease	3.350 (1.840, 6.009)	<0.001
Anti-RNP positivity	1.486 (1.163, 1.900)	0.002
Anti-Ro and/or anti-La antibody positivity	2.039 (1.555, 2.673)	<0.001
Jaccoud arthropathy	1.921 (1.402, 2.634)	<0.001
Antimalarials	0.509 (0.384, 0.675)	<0.001
MTX	1.666 (1.268, 2.189)	<0.001

Nagelkerke $R^2 = 0.122$. Variables included: sex, age at the time of RELESSER-TRANS inclusion, duration of disease, proteinuria, anti-Ro and anti-La antibodies, RP, interstitial lung disease, anti-RNP, use of MTX, use of antimalarial treatment, Jaccoud arthropathy, mortality, SLICC-ACR. Dependent variable: polyautoimmunity. OR: odds ratio; RELESSER-TRANS: Spanish Society of Rheumatology Lupus Registry, cross-sectional phase.

study, these autoantibodies were also independently associated with polyautoimmunity. Despite the fact that this finding has been reported in studies that consider SS to be a separate entity [28, 29], we found that the association persisted even with autoimmune diseases other than this syndrome, such as autoimmune thyroiditis, RA, scleroderma, MCTD and inflammatory myositis. Other authors found that polyautoimmunity was more frequent in patients with SSc and positive anti-Ro titres [40]. The association between these antibodies and polyautoimmunity could be explained by the process known as 'epitope spreading', in which an immune

response is modified over time and the changes are associated with changes in the clinical picture [41, 42].

Another interesting aspect of the determinants of poly-autoimmunity is their influence on prognosis. While patients with polyautoimmunity in the present study less frequently had nephritis, our multivariate analysis showed that they were three times more likely to have interstitial lung disease and twice as likely to have Jaccoud arthropathy and RP. Interstitial lung disease and RP have been reported to be more frequent in patients with SLE and overlapping SS, SSc and MCTD [43, 44]. Our data confirm this observation. Jaccoud arthropathy is sometimes observed in patients with long-term SLE and is associated with disability. SLE has previously been reported to overlap with antisynthetase syndrome, RP and scleroderma [45], in addition to MCTD [46]. In all cases, as in our study, this clinical problem was associated with long-term disease and inflammation of the joints and tendons, which was sometimes subclinical [47]. Rojas-Villarraga *et al.* [28] found that joint involvement was a risk factor associated with polyautoimmunity and reported that patients with SLE and joint involvement were twice as likely to develop polyautoimmunity as patients with SLE without arthritis.

Lastly, a key aspect of systemic autoimmune diseases as a specific group is that they share similar therapies. Therefore, a detailed knowledge of the aetiology and pathogenesis of polyautoimmunity could enable the development of new therapeutic targets in these diseases. In this sense, we found that patients with polyautoimmunity were almost 50% less likely to receive antimalarial drugs and that patients who took these drugs did so for shorter periods. While the design of our study does not allow us to establish causality, this finding leads us to take two aspects into consideration. First, antimalarial drugs have a wide range of beneficial effects in patients with SLE and other autoimmune diseases (e.g. SS, DM). A particularly interesting effect for us is that patients with incomplete lupus (i.e. fewer than four criteria) treated with HCQ take longer to develop SLE than those who do not receive the drug [48]. Second, antimalarial agents are less frequently indicated in patients with polyautoimmunity, owing to the poorer response or the presence of manifestations such as Jaccoud arthropathy that lead physicians to prefer other drugs, such as MTX. Nevertheless, MTX seems less likely, because antimalarial drugs are the agents of choice for treatment of joint manifestations and because they tend to be used in combination with other drugs, even in severe complications [49]. Unfortunately, the relationship between polyautoimmunity and treatments received in SLE, as well as in other systemic autoimmune diseases, has not been as well studied as other aetiological, epidemiological and clinical-analytical factors.

Although polyautoimmunity has been addressed from various angles by a small number of authors, our study analyses a large number of patients, serves to validate current knowledge and provides data on a predominantly white Spanish population. However, our study is

subject to the methodological limitations that are inherent to all cross-sectional analyses of national registries. Over 40 centres throughout Spain participated in the registry. Since there was no centralized laboratory, the accuracy of the serological data may have been affected. It is also limited by the fact that most of the comorbid autoimmune diseases were not collected exhaustively or independently. Nevertheless, the diseases we did record account for 90% of those diseases that are commonly associated with patients who have SLE.

In conclusion, polyautoimmunity in the present cohort of patients with SLE was not uncommon and was associated with female sex, manifestations of poor prognosis (interstitial lung disease, Jaccoud arthropathy and RP), and specific antibody profiles (anti-Ro/SSA, anti-La/SSB and anti-RNP). Patients received more immunosuppressants and fewer antimalarial drugs. While this finding has to be confirmed, the lower frequency of antimalarial drugs in patients with polyautoimmunity suggests that these agents could have a protective effect against polyautoimmunity.

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