# Clinical and serological associations of autoantibodies in patients with systemic lupus erythematosus

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## ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the formation of antigen–antibody complexes which trigger an immune response. We investigate certain autoantibodies including nucleosome, double-stranded DNA (dsDNA), Smith, ribonucleoprotein, and Sjögren's syndrome-related antigens, and examine their associations with disease activity, damage accrual, and SLE-related clinical and serological manifestations in patients with SLE. We conducted a cross-sectional study with a total 293 patients (90.4% female, mean age 46.87±12.94 years) and used the Systemic Lupus Erythematosus Disease Activity Index 2000 and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) to evaluate disease activity and disease-related damage, respectively. Systemic Lupus Erythematosus Disease Activity Index scores were significantly higher in anti-nucleosome-positive (3.87±2.72 vs 2.52±2.76, p=0.004) and anti-dsDNA-positive (3.08±2.91 vs 2.04±2.48, p=0.010) patients compared with patients without these antibodies. SDI scores were also significantly higher in anti-nucleosome-positive patients (1.61±1.99 vs 0.89±1.06, p=0.004). The presence of antinucleosome (p=0.019) and anti-dsDNA antibodies (p=0.001) both correlated significantly with the incidence of nephritis; anti-La antibodies were associated with arthritis (p=0.022), and we also observed a relationship between the presence of antinucleosome antibodies and leukopenia (p=0.011). Patients with antinucleosome or anti-dsDNA antibodies had a higher disease activity and were likely to have nephritis. Antinucleosome was also associated with more damage accrual. A greater understanding of these autoantibodies could lead to the development of new approaches to more accurate assessments of SLE.

## Significance of this study

### What is already known about this subject?

- Certain autoantibodies detectable in some patients with systemic lupus erythematosus (SLE) might be responsible for the disease's wide range of clinical manifestations and may be used to predict disease subsets and prognosis.
- Anti-double-stranded DNA (dsDNA) and anti-nucleosome antibodies have been proposed as relevant markers of SLE prognosis whereas anti-Smith and anti-ribonucleoprotein antibodies have been linked to organ-specific damage.
- The potential association between autoantibodies and SLE-related clinical outcomes in patients with SLE has been controversial.

### What are the new findings?

- The frequency of anti-DNA positive result was significantly decreased in late-onset SLE patients when compared with that found in early-onset SLE patients (62.2% vs 77.1%, p=0.006).
- Systemic Lupus Erythematosus Disease Activity Index scores were significantly higher in anti-nucleosome-positive (3.87±2.72 vs 2.52±2.76, p=0.004) and anti-dsDNA-positive patients (3.08±2.91 vs 2.04±2.48, p=0.010) compared with patients without these antibodies. The presence of antinucleosome (p=0.019) and anti-dsDNA antibodies (p=0.001) both correlated significantly with the incidence of nephritis.
- Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index scores were also significantly higher in anti-nucleosome-positive patients (1.61±1.99 vs 0.89±1.06, p=0.004).

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the presence of a broad and heterogeneous group of

## Significance of this study

**How might these results change the focus of research or clinical practice?**

- Patients with SLE with anti-nucleosome or anti-dsDNA antibodies had a higher disease activity and were likely to have nephritis, reinforcing the potential of these antibodies as biomarkers of active lupus.
- An association between antinucleosome and damage accrual has been demonstrated. In clinical practice, these autoantibodies might help determine the follow-up in SLE.
- Serum autoantibodies are potentially helpful markers with a prognostic value that can be used to categorize patients and predict the course of the disease.

autoantibodies that recognize several cellular components, leading to the formation of antigen–antibody complexes which trigger an immune response.[1] SLE is a chronic inflammatory disease with a wide spectrum of clinical manifestations because of its effects on multiple organs.[2] Due to its complex nature, we still lack a clear understanding of the disease's underlying mechanisms.

It has been suggested that certain autoantibodies detectable in some patients with SLE are responsible for the disease's wide range of clinical manifestations and may be used to predict disease subsets and prognosis.[3] Nucleosomes are considered to be determinants factors in SLE as they induce a T-cell-mediated response in the hapten carrier-like system to increase production of several autoantibodies.[1] A positive correlation has been reported between antinucleosome antibodies and disease activity[4 5] and the severity of renal compromise in SLE.[5 6] Anti-double-stranded DNA (anti-dsDNA) has also traditionally been used as a diagnostic marker, but since anti-dsDNA positivity is associated with other rheumatic and inflammatory conditions besides the clinical manifestations of SLE, it is only considered for use as a complementary diagnostic tool.[7] Anti-dsDNA antibodies have been linked to lupus nephritis and the risk of renal flare.[8–12] Furthermore, anti-Smith (Sm) antibodies are highly specific for SLE,[13 14] but their pathogenic role and contribution to the disease remain unclear. Some authors have reported that anti-Sm antibodies are associated with disease activity[12 15 16] and clinical features, including renal,[16] neurological, and hematological disorders and vasculitis,[17] whereas others did not observe any association.[11 18] Antiribonucleoprotein (RNP) antibodies can be found in patients with SLE, but they are also frequently observed in mixed connective tissue disease.[19] Although the limited number of studies have reported contradictory results, anti-RNP antibodies have been associated with renal involvement,[16] photosensitivity,[11] and disease activity.[12] Finally, the pathogenic mechanisms attributed to anti-Sjögren's syndrome-related antigen antibodies in SLE are ill-defined since some authors have found an association between anti-Ro and disease activity,[12] while others have not.[1 11 18]

Due to the potential pathophysiological significance of autoantibodies in SLE, previous studies have addressed their potential association with SLE-related clinical outcomes. Anti-dsDNA and antinucleosome antibodies are the most studied and have been proposed as relevant markers of SLE prognosis. However, there is growing interest in other antibodies that have been linked to organ-specific damage in previous studies, such as anti-Sm and anti-RNP. Current evidence is limited and includes apparently contradictory findings. In this context, the present study aimed to investigate certain autoantibodies including nucleosome, dsDNA, RNP, Sm, Ro, and La, and to examine their possible associations with disease activity, damage accrual, and SLE-related clinical and serological manifestations in patients with SLE.

## METHODS

### Study population

A cross-sectional study was conducted among a population of patients with SLE recruited in the Andalusia region of Spain. All patients met the SLE revised criteria of the American College of Rheumatology or Systemic Lupus Erythematosus International Collaborating Clinics Group criteria.[14 20] The exclusion criteria were pregnancy, cerebrovascular disease, ischemic heart disease, active infections, major trauma or surgery in the previous 6 months, serum creatinine of ≥1.5 mg/dL and the presence of other autoimmune and/or chronic diseases not related with the main disease (ie, type 1 diabetes, multiple sclerosis rheumatoid arthritis, and cancer). A total of 293 patients with SLE met the inclusion criteria and were included in the study after giving written informed consent (90.4% female, mean age 46.87±12.94 years). Subjects' medical history including medication usage and cumulative clinical manifestations of the SLE was obtained during an in-person medical consultation. Similar to previous studies,[21] in the present study we used age 50 years and older to define late-onset SLE in our population.

### Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) assessment

The activity of the disease was assessed with the SLEDAI 2000.[22] SLEDAI is a list of 24 items, 16 of which are clinical items and 8 are laboratory results. Disease-related organ damage was assessed by using the SDI.[23] This instrument has been developed to assess irreversible damage in patients with SLE, independently of its cause.[24] Clinical manifestations of SLE including arthritis, facial rash, discoid lupus, oral mucosal ulceration, photosensitivity, hemolytic anemia, leukopenia, thrombocytopenia, neurologic disorders, nephritis and serositis were also examined.

### Laboratory measurements

Venous blood samples were collected between 07:30 and 10:00 after an overnight fast and then centrifuged for 15 min to obtain serum. The serum was analyzed immediately to obtain the biochemical variables including white blood cell, lymphocyte count, hemoglobin, platelet count, erythrocyte sedimentation rate (ESR), serum albumin, aspartate transaminase and alanine transaminase (ALT) determined by standard laboratory methods. Immunoturbidimetric assays (Beckman Coulter AU System CRP Latex reagent) were used to determine high-sensitivity C reactive protein (hs-CRP) levels in a Beckman Coulter analyzer (AU5800 Analyzer; Beckman

Coulter, California, USA). Homocysteine (Hcy) serum levels were measured with an enzymatic colorimetric assay using the Axis-Shield Liquid Stable 2-Part Homocysteine Reagent (Axis-Shield Diagnostics, Dundee, UK) in a Beckman Coulter analyser (AU680, Beckman Coulter). Serum samples were obtained to determine quantitatively human complement components C3 and C4 by immunoturbidimetric assay (Beckman Coulter AU System CRP Latex reagent) using a Beckman Coulter analyzer (AU5800 Analyzer, Beckman Coulter). EliA ENA assays for detecting autoantibodies against nucleosome, dsDNA, Sm, RNP, Ro, and La were performed using the respective EliA ENA kits (Phadia AB) on a Phadia 250 instrument (Phadia AB). Serum samples were added to the instrument where they were diluted 1:10 and added to antigen-coated wells. After incubation and washing, monoclonal g-chain-specific anti-human IgG conjugated with β-galactosidase was added to the wells. Development solution (0.01% 4-methylumbelliferyl-β-D-galactoside) was then applied and the reaction was terminated by adding a stop solution (4% sodium carbonate). All procedures were conducted as indicated in the manufacturer's instructions. Results were calculated automatically by the instrument; the ratio of test sample response to calibrator of >1 was positive, 0.7–1.0 equivocal and less than 0.7 negative.

### Statistical analysis

SPSS Statistics V.21.0 was used for all analyses. Continuous variables were presented as mean±SD and categorical variables as frequencies and percentages. The Kolmogorov-Smirnov test was used to verify data distribution normality. Percentages were compared using the $\chi^2$ test. Analysis of covariance was used to analyze differences clinical SLE disease activity and laboratory variables according to the presence of autoantibodies after adjusting for age, gender, time since diagnosis and smoking. Logistic regression analysis of clinical manifestations of SLE was used to estimate ORs for the presence or absence of autoantibodies after adjusting for covariates. P values of <0.05 were considered statistically significant.

## RESULTS

Table 1 shows the descriptive characteristics and clinical manifestations of the study cohort. Most patients were women (90.4%), and the population had a mean age of 46.87±12.94 years. The mean time since diagnosis of SLE was 9.12±6.58 years. Patients presented low to moderate disease activity (mean SLEDAI score of 2.77±2.83) and a very low damage index (mean SDI score of 1.00±1.25). According to their medical records, 79.4% of patients were taking antimalarial drugs, 36.8% immunosuppressants, and 39.2% corticosteroids. More than half of the patients had arthritis (55.6%), facial rash (53.8%), oral mucosal ulceration (52.0%), photosensitivity (67.7%), or leukopenia (60.2%).

The frequency of autoantibodies in patients with SLE according to sex and onset of the disease is shown in table 2. No statistically significant differences in the frequency of antinucleosome, anti-dsDNA, anti-Sm, anti-RNP and anti-La were found. However, a women-related increased frequency of anti-Ro positivity was observed (39.0% in women vs 17.9% in men, p=0.027). In relation to onset of the disease, in our study population the prevalence of late-onset SLE was 38.7%. Note that the frequency of anti-DNA positive result was significantly decreased in patients with late-onset SLE when compared with that found in patients with early-onset SLE (62.2% vs 77.1%, p=0.006).

Table 3 shows the clinical disease activity and laboratory data in relation to autoantibody phenotype. Patients were divided into two groups according to antibody positivity. The antibody rates in our study cohort were as follows: anti-nucleosome (11.2%), anti-dsDNA (71.6%), anti-Sm (11.9%), anti-RNP (10.2%), anti-Ro (37.0%), and anti-La (9.2%). SLEDAI scores were significantly higher in patients who were positive for antinucleosome (3.87±2.72

**Table 1** Descriptive characteristics and clinical manifestations of the study population

| Characteristics | Total (n=264) |
|---|---|
| Female | 265 (90.4) |
| Age (years) | 46.87 (12.94) |
| Time since diagnosis (years) | 9.12 (6.58) |
| Smoking | 67 (22.9) |
| Clinical activity | |
| SLEDAI score | 2.77±2.83 |
| SDI score | 1.00±1.25 |
| Laboratory data | |
| WBC (/µL) | 5709.86±2242.28 |
| Lymphocyte (/µL) | 1629.91±757.93 |
| Hemoglobin (/µL) | 13.89±6.61 |
| Platelet (x1000 /µL) | 226.44±70.64 |
| ESR (mm/h) | 19.24±15.50 |
| hs-CRP (mg/dL) | 3.23±4.89 |
| Hcy (µmol/L) | 12.44±7.25 |
| Albumin (g/dL) | 4.08±0.37 |
| AST (IU/L) | 23.71±10.80 |
| ALT (IU/L) | 19.69±9.47 |
| Complement C3 level (mg/dL) | 109.23±28.01 |
| Complement C4 level (mg/dL) | 22.80±16.69 |
| Medication used | |
| Antimalarial use | 231 (79.4) |
| Immunosuppressor use | 107 (36.8) |
| Corticoid use | 114 (39.2) |
| Clinical manifestations | |
| Arthritis | 155 (55.6) |
| Facial rash | 150 (53.8) |
| Discoid lupus | 37 (13.3) |
| Mucosal ulceration | 145 (52.0) |
| Photosensitivity | 189 (67.7) |
| Hemolytic anemia | 19 (6.8) |
| Leukopenia | 168 (60.2) |
| Thrombocytopenia | 41 (14.7) |
| Neurological | 37 (13.3) |
| Nephritis | 73 (26.2) |
| Serositis | 36 (12.9) |

Data are expressed as mean and frequency and percentage.
ALT, alanine transaminase; AST, aspartate transaminase; ESR, erythrocyte sedimentation rate; Hcy, homocysteine; hs-CRP, high-sensitivity C reactive protein; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; WBC, white blood cell.

**Table 2** Antinuclear antibodies in patients with SLE stratified according to sex and onset of the disease

| Total | Total N (%) | Sex | | | Onset of the disease | | |
|---|---|---|---|---|---|---|---|
| | | Women, n (%) | Men, n (%) | P value | Early onset <50 years, n (%) | Late onset 50 years, n (%) | P value |
| Nucleosome | 31 (11.2) | 30 (12.0) | 1 (3.7) | 0.406 | 18 (10.5) | 13 (12.1) | 0.406 |
| dsDNA (+) | 204 (71.3) | 183 (70.9) | 21 (75.0) | 0.651 | 135 (77.1) | 69 (62.2) | **0.006** |
| Sm (+) | 35 (12.0) | 32 (12.2) | 3 (10.7) | 0.822 | 22 (12.4) | 13 (11.5) | 0.827 |
| RNP (+) | 30 (10.6) | 28 (10.6) | 2 (7.1) | 0.801 | 22 (12.3) | 8 (7.1) | 0.257 |
| Ro (+) | 108 (37) | 103 (39.0) | 5 (17.9) | **0.027** | 61 (34.1) | 47 (41.6) | 0.195 |
| La (+) | 27 (9.2) | 27 (10.2) | – | 0.076 | 13 (7.3) | 14 (12.4) | 0.141 |

Data are expressed as frequency and percentage.
Bold values denote statistical significance (p<0.05).
dsDNA, double-stranded DNA; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; Sm, Smith.

vs 2.52±2.76, p=0.004) and anti-dsDNA (3.08±2.91 vs 2.04±2.48, p=0.010) antibodies compared with those without these antibodies. SDI scores were also significantly higher in anti-nucleosome-positive patients (1.61±1.99 vs 0.89±1.06, p=0.004). Unexpectedly, anti-Ro-positive patients had lower damage accrual scores (0.84±1.16 vs 1.10±1.30, p=0.028).

Regarding laboratory data, patients with antinucleosome (25.60±18.86 vs 18.33±14.61, p=0.039), anti-dsDNA (20.74±16.94 vs 15.53±10.71, p=0.015), anti-RNP (27.06±18.40 vs 18.22±14.84, p=0.008) and anti-Ro antibodies (21.57±16.26 vs 17.84±14.90, p=0.042) had a significantly higher ESR compared with equivalent antibody-negative patients. Patients with anti-dsDNA (3.61±5.50 vs 2.37±2.82, p=0.030) and anti-La antibodies (5.34±10.40 vs 3.03±3.93, p=0.017) also had significantly greater hs-CRP concentrations. Subjects with anti-RNP antibodies had significantly higher levels of ALT (24.66±10.74 vs 19.20±9.23, p=0.018) and a lower lymphocyte count (1314.93±569.46 vs 1666.15±769.33, p=0.023). In the same line, the presence of anti-dsDNA antibodies was associated with lower albumin concentrations (4.04±0.35 vs 4.14±0.40, p=0.027) and patients with anti-La antibodies had significantly lower levels of complement C3 (100.26±25–26 vs 110.15±28.16, p=0.045). Contrary to expectations, anti-La antibodies correlated significantly with a higher platelet count (258.55±68.78 vs 223.16±70.13, p=0.014) after adjusting for covariates, and patients with anti-Ro antibodies had significantly higher albumin concentrations (4.14±0.36 vs 4.04±0.38, p=0.034). Furthermore, the presence of anti-dsDNA antibodies was associated with lower Hcy levels (11.74±4.69 vs 14.18±11.18, p=0.023).

Table 4 shows the prevalence of clinical manifestations with respect to autoantibody phenotype. Arthritis correlated significantly with the presence of anti-La antibodies after adjusting for covariates (p=0.022). Nephritis was significantly associated with the presence of antinucleosome (p=0.019) and anti-dsDNA antibodies (p=0.001). We also observed a relationship between the presence of leukopenia and antinucleosome antibodies (p=0.011). Note that the prevalence of facial rash was significantly lower in patients with antinucleosome antibodies (p=0.036).

## DISCUSSION

The detection of autoantibodies is considered a defining feature in the diagnosis of SLE.[25] Therefore, it is increasingly important that we unravel the potential clinical significance of autoantibodies to assist in the development of novel biological therapeutic approaches to SLE.[26] In the current study, we investigated certain autoantibodies and examined their possible associations with disease activity, damage accrual, and SLE-related clinical and serological manifestations in patients with SLE. The results indicate that those patients with antinucleosome and anti-dsDNA antibodies had a higher disease activity and were more likely to have nephritis. Additionally, antinucleosome antibodies were associated with a higher damage accrual; anti-La were linked to arthritis; and we observed a relationship between antinucleosome antibodies and leukopenia. The present study confirms previously reported associations between autoantibodies and clinical manifestations in patients with SLE, but also presents some peculiar relationships in Spanish Caucasian patients.

As for the autoantibody profile, the total prevalence of antinucleosome (11.2%) and anti-RNP (10.2%) in our study was considerably lower than the proportion found in previous research.[1 4 11 27 28] This discrepancy could be explained by differences in ethnicity and clinical condition, since important variances in the prevalence of autoantibodies have been described in SLE, depending on ethnicity.[29] Indeed, it is notable that patients in our study presented a low to moderate disease activity (mean SLEDAI score of 2.77±2.83) and a very low damage index (mean SDI score of 1.00±1.25). In line with our findings, anti-dsDNA antibodies have previously been reported in 43%–92% of patients with SLE.[11 27 30 31] The observed prevalence of anti-Sm antibodies ranges from 15% to 55.5%,[15 17 27] which is slightly higher than our data (11.9%). In accordance with the results presented here, a prevalence of 36%–64% and 8%–33.6% has been reported for anti-Ro and anti-La, respectively.[1 11 27] Furthermore, the discrepancy between the frequency of positive results among different studies might be due to the autoantibody detection methods used. Regarding the frequency of autoantibodies according to sex, in our population from Southern Spain, we found a women-related increased frequency of anti-Ro positivity. Interestingly, in an epidemiological study from Northwestern Spain, lower frequency of anti-Ro (13.0 vs 31.5%, p=0.08) was also observed in men when compared with women.[32] Likewise, previous studies have reported a lower prevalence of anti-Ro antibodies in men.[33 34] In relation to onset of the disease, we found that the frequency of anti-DNA positive result was significantly decreased in patients with late-onset SLE when compared with that found in patients with

**Table 3** Clinical SLE disease activity and laboratory data in relation to autoantibody phenotype

| | Nucleosome (+) (n=31) | Nucleosome (–) (n=247) | P value | dsDNA (+) (n=204) | dsDNA (–) (n=82) | P value | Sm (+) (n=35) | Sm (–) (n=256) | P value | RNP (+) (n=31) | RNP (–) (n=261) | P value | Ro (+) (n=108) | Ro (–) (n=184) | P value | La (+) (n=27) | La (–) (n=265) | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinical activity | | | | | | | | | | | | | | | | | | |
| SLEDAI score | 3.87±2.72 | 2.52±2.76 | **0.004** | 3.08±2.91 | 2.04±2.48 | **0.010** | 3.14±2.76 | 2.73±2.84 | 0.449 | 3.63±3.05 | 2.69±2.80 | 0.149 | 2.60±2.73 | 2.87±2.89 | 0.453 | 2.89±2.57 | 2.76±2.86 | 0.852 |
| SDI score | 1.61±1.99 | 0.89±1.06 | **0.004** | 1.03±1.32 | 0.93±1.09 | 0.162 | 1.28±1.54 | 0.97±1.21 | 0.123 | 1.26±1.55 | 0.98±1.22 | 0.278 | 0.84±1.16 | 1.10±1.30 | **0.028** | 1.07±1.35 | 1.00±1.25 | 0.927 |
| Laboratory data | | | | | | | | | | | | | | | | | | |
| WBC (/µL) | 5577.22±1723.92 | 5689.36±2210.66 | 0.806 | 5814.12±2204.76 | 5507.53±2350.52 | 0.315 | 5663.05±2141.01 | 5708.07±2260.52 | 0.924 | 5383.79±1526.57 | 5738.30±2308.64 | 0.455 | 5372.88±2001.31 | 5907.97±2355.39 | 0.095 | 5321.92±2076.00 | 5748.21±2258.12 | 0.441 |
| Lymphocyte (/µL) | 1702.35±708.69 | 1628.45±764.86 | 0.777 | 1624.28±793.94 | 1634.46±667.69 | 0.868 | 1471.58±701.36 | 1651.70±764.15 | 0.197 | 1314.93±569.46 | 1666.15±769.33 | **0.023** | 1530.43±671.79 | 1689.25±800.91 | 0.087 | 1495.11±521.38 | 1644.24±778.26 | 0.335 |
| Hemoglobin (/µL) | 13.08±1.45 | 14.02±7.17 | 0.797 | 13.89±7.83 | 13.89±1.04 | 0.989 | 13.62±1.41 | 13.93±7.04 | 0.794 | 13.06±1.25 | 13.99±6.97 | 0.788 | 13.40±1.22 | 14.18±8.28 | 0.362 | 13.12±1.16 | 13.97±6.92 | 0.589 |
| Platelet (×1000 /µL) | 228.19±54.85 | 226.00±72.81 | 0.998 | 226.43±71.48 | 226.59±70.12 | 0.644 | 211.97±58.12 | 227.76±71.41 | 0.195 | 224.20±58.87 | 226.05±71.32 | 0.090 | 232.79±68.57 | 222.69±71.75 | 0.146 | 258.55±68.78 | 223.16±70.13 | **0.014** |
| ESR (mm/ hour) | 25.60±18.86 | 18.33±14.61 | **0.039** | 20.74±16.94 | 15.53±10.71 | **0.015** | 21.37±18.75 | 18.85±14.96 | 0.340 | 27.06±18.40 | 18.22±14.84 | **0.008** | 21.57±16.26 | 17.84±14.90 | **0.042** | 23.34±17.33 | 18.83±15.28 | 0.177 |
| hs-CRP (mg/ dL) | 4.11±3.72 | 3.20±5.08 | 0.078 | 3.61±5.50 | 2.37±2.82 | **0.030** | 3.21±4.92 | 3.25±4.90 | 0.938 | 4.12±5.59 | 3.14±4.81 | 0.556 | 3.44±6.14 | 3.11±3.99 | 0.415 | 5.34±10.40 | 3.03±3.93 | **0.017** |
| Hcy (µmol/L) | 11.65±3.36 | 12.65±7.76 | 0.584 | 11.74±4.69 | 14.18±11.18 | **0.023** | 11.80±4.09 | 12.54±7.58 | 0.642 | 12.57±4.34 | 12.44±7.52 | 0.886 | 12.41±5.62 | 12.46±8.08 | 0.955 | 13.69±9.49 | 12.32±7.91 | 0.348 |
| Albumin (g/dL) | 3.98±0.40 | 4.09±0.37 | 0.498 | 4.04±0.35 | 4.14±0.40 | **0.027** | 4.04±0.37 | 4.08±0.37 | 0.596 | 3.98±0.34 | 4.09±0.38 | 0.229 | 4.14±0.36 | 4.04±0.38 | **0.034** | 4.06±0.47 | 4.08±0.36 | 0.917 |
| AST (IU/L) | 21.94±8.35 | 23.57±11.09 | 0.820 | 24.03±10.87 | 22.65±10.65 | 0.407 | 23.46±8.30 | 23.74±11.05 | 0.838 | 27.69±9.86 | 23.29±10.84 | 0.088 | 22.38±6.34 | 24.60±12.92 | 0.237 | 23.41±9.31 | 23.74±10.96 | 0.920 |
| ALT (IU/L) | 20.52±8.20 | 19.28±9.43 | 0.535 | 19.20±8.90 | 20.33±10.39 | 0.440 | 20.52±10.46 | 19.60±9.38 | 0.468 | 24.66±10.74 | 19.20±9.23 | **0.018** | 19.20±6.65 | 19.95±10.67 | 0.933 | 21.29±7.53 | 19.54±9.64 | 0.356 |
| Complement C3 level (mg/ dL) | 111.98±34.98 | 108.89±26.69 | 0.536 | 107.30±29.44 | 113.81±23.36 | 0.196 | 109.45±31.33 | 109.16±27.64 | 0.896 | 109.06±32.70 | 109.21±27.54 | 0.871 | 109.36±27.59 | 109.16±28.33 | 0.606 | 100.26±25–26 | 110.15±28.16 | **0.045** |
| Complement C4 level (mg/ dL) | 22.88±15.93 | 22.91±17.16 | 0.996 | 22.63±18.86 | 22.88±9.28 | 0.970 | 20.42±9.98 | 23.11±17.42 | 0.407 | 22.77±9.79 | 22.79±17.35 | 0.982 | 24.08±20.99 | 22.05±13.53 | 0.371 | 21.64±10.12 | 22.92±17.23 | 0.726 |

Data are expressed as mean and range.
Bold values denote statistical significance (p<0.05).
ALT, alanine transaminase; AST, aspartate transaminase; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; Hcy, homocysteine; hs-CRP, high-sensitivity C reactive protein; RNP, ribonucleoprotein; SDI, Damage Index for Systemic Lupus Erythematosus; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; Sm, Smith; WBC, white blood cell.

**Table 4** Prevalence of clinical manifestations in relation to autoantibody phenotype

| | Nucleosome (+) (n=31) | Nucleosome (–) (n=247) | OR (95% CI) | P value | dsDNA (+) (n=204) | dsDNA (–) (n=82) | OR (95% CI) | P value | Sm (+) (n=35) | Sm (–) (n=256) | OR (95% CI) | P value | RNP (+) (n=31) | RNP (–) (n=261) | OR (95% CI) | P value | Ro (+) (n=108) | Ro (–) (n=184) | OR (95% CI) | P value | La (+) (n=27) | La (–) (n=265) | OR (95% CI) | P value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clinical manifestations | | | | | | | | | | | | | | | | | | | | | | | | |
| Arthritis | 19 (65.5) | 129 (54.9) | 1.200 (0.562 to 2.562) | 0.638 | 115 (56.9) | 39 (52.7) | 1.242 (0.715 to 2.158) | 0.442 | 19 (57.6) | 136 (55.5) | 1.113 (0.529 to 2.344) | 0.777 | 18 (62.1) | 137 (55.0) | 1.321 (0.685 to 2.547) | 0.406 | 60 (57.7) | 95 (54.3) | 0.892 (0.539 to 1.477) | 0.658 | 20 (80) | 135 (53.1) | 3.286 (1.184 to 9.124) | **0.022** |
| Facial rash | 11 (37.9) | 127 (54.0 | 0.434 (0.199 to 0.946) | **0.036** | 112 (55.4) | 36 (48.6) | 1.326 (0.759 to 2.314) | 0.321 | 22 (66.7) | 127 (51.8) | 0.536 (0.246 to 1.167) | 0.116 | 22 (75.9) | 127 (51.0) | 1.140 (0.474 to 2.737) | 0.545 | 54 (51.9) | 96 (54.9) | 1.140 (0.688 to 1.889) | 0.611 | 14 (56.0) | 136 (53.5) | 1.018 (0.439 to 2.364) | 0.288 |
| Discoid lupus | 3 (10.3) | 29 (12.3) | 1.313 (0.477 to 3.613) | 0.598 | 22 (10.9) | 15 (20.3) | 1.866 (0.889 to 3.916) | 0.099 | 5 (15.2) | 32 (13.1) | 1.203 (0.430 to 3.372) | 0.725 | 4 (13.8) | 33 (13.3) | 1.473 (0.604 to 3.596) | 0.395 | 12 (11.5) | 25 (14.3) | 0.793 (0.373 to 1.685) | 0.546 | 4 (16.0) | 33 (13.0) | 1.277 (0.405 to 4.027) | 0.718 |
| Mucosal ulceration | 17 (58.6) | 121 (51.5) | 1.478 (0.698 to 3.127) | 0.307 | 104 (51.5) | 40 (54.1) | 1.150 (0.664 to 1.001) | 0.618 | 20 (60.6) | 125 (51.0) | 1.458 (0.692 to 3.071) | 0.321 | 15 (51.7) | 130 (52.2) | 1.151 (0.795 to 1.668) | 0.457 | 55 (52.9) | 90 (51.4) | 1.024 (0.623 to 1.684) | 0.926 | 10 (40.0) | 135 (53.1) | 0.574 (0.246 to 1.337) | 0.198 |
| Photosensitivity | 20 (69.0) | 159 (67.7) | 0.720 (0.331 to 1.567) | 0.408 | 129 (63.9) | 57 (77.0) | 1.829 (0.961 to 3.479) | 0.066 | 24 (72.7) | 165 (8.6) | 1.286/0.557 to 2.972) | 0.556 | 22 (75,9) | 167 (67.1) | 1.473 (0.604 to 3.596) | 0.395 | 69 (66.3) | 120 (68.6) | 0.785 (0.456 to 1.353) | 0.384 | 17 (68.0) | 172 (67.7) | 0.798 (0.326 to 1.954) | 0.115 |
| Hemolytic anemia | 0 | 19 (8.1%) | 0.00 | 0.998 | 15 (7.4) | 4 (5.4) | 0.865 (0.268 to 2.793) | 0.809 | 2 (6.1) | 17 (6.9) | 1.113 (0.242 to 5.118) | 0.891 | 1 (3.4) | 18 (7.2) | 1.047 (0.684 to 1.604) | 0.832 | 7 (6.7) | 12 (6.9) | 0.902 (0.335 to 2.428) | 0.839 | 0 | 19 (7.5) | 0.00 | 0.998 |
| Leukopenia | 24 (82.8) | 136 (57.9) | 3.656 (1.354 to 9.869) | **0.011** | 124 (61.4) | 41 (55.4) | 0.778 (0.447 to 1.354) | 0.375 | 22 (66.7) | 146 (59.6) | 1.393 (0.63 to 3.019) | 0.400 | 19 (65.5) | 149 (59.8) | 1.319 (0.679 to 2.560) | 0.414 | 66 (63.5) | 102 (58.3) | 1.180 (0.708 to 1.966) | 0.525 | 18 (72.0 | 150 (59.1) | 1.734 (0.693 to 4.336) | 0.240 |
| Thrombocytopenia | 5 (17.2) | 34 (14.5) | 1.363 (0.496 to 3.744) | 0.549 | 34 (16.8) | 6 (8.1) | 0.482 (0.188 to 1.235) | 0.128 | 4 (12.1) | 37 (15.1) | 0.757 (0.244 to 2.350) | | 4 (13.8) | 37 (14.9) | 1.115 (0.662 to 1.877) | 0.683 | 12 (11.5) | 29 (16.6) | 0.752 (0.356 to 1.587) | 0.455 | 4 (16) | 37 (14.6) | 1.462 (0.463 to 4.622) | 0.518 |
| Neurological | 3 (10.3) | 32 (13.6) | 0.630 (0.185 to 2.148) | 0.460 | 25 (12.4) | 11 (14.9) | 1.036 (0.467 to 2.300) | 0.930 | 6 (18.2) | 31 (12.7) | 1.589 (0.588 to 4.298) | 0.362 | 4 (13.8) | 33 (13.3) | 1.211 (0.426 to 3.447) | 0.720 | 12 (11.5) | 25 (14.3) | 0.657 (0.307 to 1.408) | 0.280 | 1 (4.0) | 36 (14.2) | 0.231 (0.030 to 1.788) | 0.161 |
| Nephritis | 13 (44.8) | 58 (24.7) | 2.593 (1.169 to 5.750) | **0.019** | 65 (32.2) | 8 (10.8) | 0.226 (0.096 to 0.531) | **0.001** | 9 (27.3) | 64 (26.1) | 1.036 (0.436 to 2.457) | 0.937 | 10 (34.5) | 63 (25.3) | 1.461 (0.626 to 3.407) | 0.381 | 23 (22.1) | 50 (28.6) | 0.910 (0.499 to 1.659) | 0.758 | 5 (20.0) | 68 (26.8) | 0.793 (0.276 to 2.281) | 0.667 |
| Serositis | 4 (13.8) | 27 (208) | 1.168 (0.392 to 3.477) | 0.781 | 31 (15.3) | 5 (6.8) | 0.403 (0.148 to 1.095) | 0.075 | 7 (21.2) | 29 (11.8) | 2.058 (0.815 to 5.197) | 0.127 | 5 (17.2) | 31 (12.4) | 1.447 (0.514 to 4.070) | 0.484 | 9 (8.7) | 27 (15.4) | 0.519 (0.231 to 1.167) | 0.113 | 3 (22) | 33 (13.0) | 0.928 (0.259 to 3.325) | 0.908 |

Data are expressed as mean and frequency and percentage.
Bold values denote statistical significance (p<0.05).
dsDNA, double-stranded DNA; RNP, ribonucleoprotein; Sm, Smith; SSA/Ro and SSA/La, Sjogren syndrome-related antigens.

early-onset SLE. This finding is in agreement with another study conducted among patients with SLE from the Northwestern Spain and from China that showed that patients with late-onset SLE had a lower frequency of anti-DNA than those with early-onset SLE.[21 33]

There is consistent evidence supporting the use of anti-dsDNA antibody tests as a marker of disease activity.[12 35] The current work supports the relationship between anti-dsDNA antibodies and disease activity and highlights the importance of antinucleosome antibodies as a potential biomarker of active lupus. Similarly, previous authors have found a positive correlation between anti-nucleosome antibodies and disease activity in SLE.[4 5 8 12] In fact, a recent study concluded that antinucleosome antibodies show a stronger correlation with SLE disease activity than traditional biomarkers.[4] Nevertheless, we failed to detect any significant associations between SLEDAI scores and anti-RNP, anti-Sm, anti-Ro, and anti-La antibodies, indicating that clinically detectable changes in disease activity do not correlate with the presence of these autoantibodies. In line with our results, Ahn *et al* found no significance differences in SLEDAI scores between 92 patients with and without anti-Sm antibodies at baseline and 6 months.[15] Similarly, a prospective 2-year study of 45 patients with SLE indicated that there was a lack of relationship between SLEDAI score and antiextractable nuclear antigen including Ro, La, Sm, and RNP antibodies.[18] By contrast, Hanly *et al* reported significant associations between SLEDAI scores and anti-Ro and anti-Sm, among others, in a population 192 patients with SLE.[12] Variability in study design, the number of patients evaluated, and differences in ethnic backgrounds could explain these inconsistencies. Based on our research and the majority of publications, unlike anti-dsDNA and anti-nucleosome antibodies, serial measurements of anti-RNP, anti-Sm, anti-Ro, and anti-La antibodies do not appear to provide any additional information regarding disease activity in patients with SLE.

In this study, we also found that antinucleosome antibody-positive patients had higher damage index scores and, therefore, an analysis of this antibody would appear to be useful when assessing damage accrual in clinical practice. To date, few studies have assessed the association between antinucleosome and damage accrual.[36 37] Given that there is still uncertainty regarding the underlying mechanisms between antinucleosome antibodies and damage index, further studies are required to describe the mechanisms leading to nucleosome production and antinucleosome-related autoimmunity.[38] The authors did not detect any significant relationships for anti-dsDNA, anti-RNP, anti-Sm, and anti-La. Likewise, a large study also reported no significant association between anti-Sm antibodies and damage accrual,[17] while another indicated that there was no significant association between autoantibodies and SDI scores.[12] What is more, Taraborelli *et al* did not find any association between damage and autoantibodies, including anti-dsDNA and anti-Sm, in a large cohort of patients with SLE from Italy,[37] whereas Vilá *et al* found that the presence of anti-dsDNA, anti-Sm, and anti-Ro antibodies was associated with higher SDI scores in Puerto Rican patients.[36] As noted previously, variability in genetic, environmental, and sociodemographic factors could explain the inconsistent results among studies. Intriguingly, we observed that anti-Ro antibody-positive patients had a lower damage accrual. Anti-Ro antibodies are seen in up to 90% of cases of Sjögren's syndrome, although they can be also observed in SLE with a prevalence of between 36% and 64%, which could be associated with secondary Sjögren's syndrome.[39] Thus, the sensitivity and specificity of anti-Ro for SLE is lower than that for Sjögren's syndrome.[27] Future investigations involving larger cohorts of Caucasian patients are required to confirm this novel observation.

Consistent with the results of recent studies, we observed that the presence of antinucleosome[5 6 40 41] and anti-dsDNA[8–12 37 38] antibodies was associated with nephritis, supporting that these antibodies may be a biomarker of renal compromise in patients with SLE. In fact, the detection of antinucleosome antibodies has recently been proposed as a useful tool to identify patients at a higher risk of renal relapse.[41] In addition, in our study, antinucleosome positivity correlated with the prevalence of leukopenia and anti-La antibodies were associated with arthritis, which are both relatively rare findings.[36] These observations lend further support to the usefulness of the routine measurement of antinucleosome and anti-La antibodies in patients with SLE. Moreover, it is noteworthy that antinucleosome was unexpectedly associated with a lower prevalence of facial rash. Due to the complex nature of SLE, including robust evidence of the influence of epigenetics, it is not too surprising that some of the antibodies have yielded contrasting results in different studies.[42] Since the longitudinal associations between the aforementioned antibodies and clinical manifestations of SLE are largely unknown at present, future research is needed to determine their potential clinical significance.

In line with the findings mentioned previously, in our study, patients with anti-dsDNA had decreased serum albumin levels, which may reflect the activity and severity of renal damage.[8–12 40 43] Additionally, compared with patients with SLE who are negative for antinucleosome, anti-dsDNA, anti-RNP, and anti-Ro antibodies, those who are positive for these antibodies are more likely to have a higher ESR. This is relevant because ESR has been reported to be a predictor of renal and overall SLE disease activity.[44] We found that higher hs-PCR levels correlated with the presence of anti-dsDNA and anti-La antibodies, and lower C3 levels were also associated with anti-La positivity, which has been reported previously.[45] Furthermore, in line with Vilá *et al*,[36] a lower lymphocyte count was associated with the presence of anti-RNP antibodies. We were surprised to find a negative relationship between decreased serum Hcy levels and anti-RNP. Nevertheless, it should be pointed out that increased serum Hcy levels are only observed in approximately 15% of patients with SLE.[46] Other somewhat unexpected findings were the associations between anti-Ro antibodies and a lower platelet count, and between anti-Ro antibodies and increased albumin levels. As mentioned earlier, anti-Ro and anti-La antibodies have a low sensitivity and specificity for SLE.[27] Ultimately, the study of whether autoantibodies are good indicators of the development of systemic or organ-specific flare-ups is particularly important in an era in which biological therapies have revolutionized the treatment of SLE.[26]

Serum autoantibodies are potentially helpful markers with a prognostic value that can be used to categorize

patients and predict the course of the disease. Therefore, in clinical practice, autoantibodies might help determine the follow-up in autoimmune diseases such as SLE. Nevertheless, regarding the use of autoantibodies in approaches to precision health, autoantibodies only represent a single component (with reasonable costs and within reach for all clinical settings) of a larger scenario with other biomarkers that feature in omics technologies.[47] Health professionals are well-positioned to lead the implementation of precision health through interprofessional collaboration, community outreach efforts, and coordination of care.[48] Precision health, which considers an individual's lifestyle, genetics, behaviors, and environmental context, represents a valuable opportunity to advance practices through innovative transformations in healthcare interventions.[49]

Our study has a number of limitations. First, it was a cross-sectional study and, as such, is subject to the limitations inherent to this type of design. Thus, we did not examine the fluctuation of autoantibodies, as serial measurements were not assessed. A longitudinal prospective study is required to address the impact of the presence of autoantibodies on SLE activity and progression. Second, since our study comprised a well-characterized cohort of Caucasian patients with European lupus, it may limit the generalizability of the results to other ethnic populations since the frequency of autoantibodies is determined by differences in ethnicity and race.[29] Third, we did not make any adjustment for multiple testing in the statistical analysis as it was an exploratory study. The study's strengths include the relatively large cohort and analysis of associations between autoantibodies and several clinical manifestations and serological variables that helped provide new insights into the biological mechanisms underlying the clinical manifestations of SLE. In clinical practice, a major challenge at present is the use of SLE biomarkers to predict disease outcomes. One of the potentially pivotal milestones would be the integration of classic activation markers as complements with target organ antibodies.[38]

This study not only confirms that patients with antinucleosome and anti-dsDNA antibodies have a higher disease activity and are more likely to have nephritis, reinforcing the potential of these antibodies as biomarkers of active lupus, but also demonstrates an association between antinucleosome and damage accrual. Furthermore, we have provided evidence that antinucleosome antibodies are associated with the presence of leukopenia and anti-La antibodies with arthritis in Caucasian patients with SLE. Insight into these autoantibodies may lead to new approaches to the accurate assessment of SLE. Future research involving long-term monitoring of autoantibodies in larger cohorts and incorporating patients with SLE from different ethnic backgrounds might provide more information to help assess the clinical relevance of autoantibodies in SLE.

**Contributors** All authors read and approved the final version of the manuscript. NO-O and BR-M contributed equally to this work. MC-R performed patient's nutritional assessments, analyzed and interpreted the data and wrote the manuscript. GP-G analyzed the data, performed statistical analyses and reviewed/edited manuscript. J-LC-R, RR-F, MM-A, MC-C performed patient recruitment, clinical assessment and reviewed the manuscript. NO-C contributed to the conception and study design, patient recruitment and reviewed/edited manuscript. BR-M contributed to the conception, study design, and data interpretation and reviewed/edited manuscript.

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