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# Comprehensive Description of Clinical Characteristics of a Large Systemic Lupus Erythematosus Cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) With Emphasis on Complete Versus Incomplete Lupus Differences

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**Abstract:** Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiple organ involvement and pronounced racial and ethnic heterogeneity. The aims of the present work were (1) to describe the cumulative clinical characteristics of those patients included in the Spanish Rheumatology Society SLE Registry (RELESSER), focusing on the differences between patients who fulfilled the 1997 ACR-SLE criteria versus those with less than 4 criteria (hereafter designated as incomplete SLE (iSLE)) and (2) to compare SLE patient characteristics with those documented in other multicentric SLE registries.

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RELESSER is a multicenter hospital-based registry, with a collection of data from a large, representative sample of adult patients with SLE (1997 ACR criteria) seen at Spanish rheumatology departments. The registry includes demographic data, comprehensive descriptions of clinical manifestations, as well as information about disease activity and severity, cumulative damage, comorbidities, treatments and mortality, using variables with highly standardized definitions.

A total of 4.024 SLE patients (91% with ≥4 ACR criteria) were included. Ninety percent were women with a mean age at diagnosis of 35.4 years and a median duration of disease of 11.0 years. As expected, most SLE manifestations were more frequent in SLE patients than in iSLE ones and every one of the ACR criteria was also associated with SLE condition; this was particularly true of malar rash, oral ulcers and renal disorder. The analysis—adjusted by gender, age at diagnosis, and disease duration—revealed that higher disease activity, damage and SLE severity index are associated with SLE [OR: 1.14; 95% CI: 1.08–1.20 ($P < 0.001$); 1.29; 95% CI: 1.15–1.44 ($P < 0.001$); and 2.10; 95% CI: 1.83–2.42 ($P < 0.001$), respectively]. These results support the hypothesis that iSLE behaves as a relative stable and mild disease. SLE patients from the RELESSER register do not appear to differ substantially from other Caucasian populations and although activity [median SELENA-SLEDA: 2 (IQ: 0–4)], damage [median SLICC/ACR/DI: 1 (IQ: 0–2)], and severity [median KATZ index: 2 (IQ: 1–3)] scores were low, 1 of every 4 deaths was due to SLE activity.

RELESSER represents the largest European SLE registry established to date, providing comprehensive, reliable and updated information on SLE in the southern European population.

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**Abbreviations**: Ab = antibodies, ACR = American College of Rheumatology, ANA = antinuclear antibodies, BILAG = British Isles Lupus Assessment Group, CI = confidence intervals, CYC = cyclophosphamide, DM = diabetes mellitus, iSLE = incomplete SLE, OR = odds ratio, PHT = pulmonary hypertension, SD = standard deviation, SELENA-SLEDAI = Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-SLEDAI, SER = Spanish Rheumatology Society, SKI = Severity Katz Index, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SLICC/ACR DI = Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease with multiple organ involvement and remains one of the most frequent systemic rheumatic diseases.[1] In Spain, it has a prevalence of 9 per 10,000 persons.[2,3] SLE is a remarkably heterogeneous disease with very different symptoms and outcomes. In recent years, considerable efforts have been made to gain a deeper understanding of the disease and how to best manage it. One such effort involves the setting up of SLE patient registries similar to those that have been active in North and South America, as well as in Europe, since the seventies.[4] These registries contain a large number of subjects and reflect a real-world setting for lupus patients. Data obtained from these lupus registries are essential for planning, designing, and conducting clinical lupus studies.

The severity of SLE may vary considerably from one population to another and the Task Force of the EULAR Standing Committee for International Clinical Studies has included this topic in its suggested research agenda.[5] With the aim of obtaining a more representative, accurate information database about SLE in the southern European population, the Spanish Rheumatology Society (SER) has established a multicenter registry of patients with SLE known as RELESSER (Spanish Rheumatology Society SLE Registry), which is the largest European SLE registry mounted thus far. It offers comprehensive, reliable, and updated information about this complex disease, and is being carried out in two phases. The first part of the registry (RELESSER-T), with cross-sectional data recording has already completed the enrolment process.

There was, however, a subgroup of patients that did not meet the 1997 SLE ACR criteria but that presented symptoms and/or laboratory results which often led to the clinician diagnosing them as SLE patients.[6–8] As there are relatively few studies concerning these types of patients, it was considered worthwhile to include them in the Spanish registry. The availability of a large and well-characterized SLE population via RELESSER provides an excellent opportunity to compare, in detail, both of the patient groups included in the register.

The purposes of the present analysis were to describe the demographic features, cumulative clinical manifestations, severity, treatments, and complications of RELESSER patients at the time of the last medical visit, focusing on the differences between patients who fulfilled 4 or more of the 1997-ACR SLE criteria[9] and those who did not (''incomplete SLE'': iSLE). We also compared these cross-sectional data from RELESSER with those from other large cohorts around the world.

## METHODS

RELESSER-T is a cross-sectional study, recording cumulative clinical data until the last medical visit and the status of the disease and treatments at this time. Its design and the methods have been described in detail elsewhere.[10] In short, 45 Rheumatology Units throughout Spain participated in the study. All of the participating centers belong to the same national public healthcare system and thus have the same resources at their disposal. All clinicians involved in the study were expert rheumatologists in SLE. They were asked to include subjects 16 years of age or older, and who met 4 or more of the 1997 ACR SLE criteria (SLE),[9,11] as well as patients who fulfilled just 3 criteria, but who had been diagnosed with SLE by an experienced rheumatologist (iSLE). The first patient was enrolled in October 2011 and data collection was completed in August 2012. Patients were widely and homogeneously distributed across Spain, thus avoiding selection bias. Bearing in mind that virtually all patients with SLE treated in our country are referred to hospitals, the possibility of center selection bias was minimal.

Patients lacking at least 50% of the defined ''minimal essential data'' were excluded. Data were obtained by reviewing clinical histories and the information was electronically collected using an ad hoc online application.

In order to ensure that the data were homogenous and of high quality, every item in the protocol had a highly standardized definition, all participants had online access to guidelines on how to complete the registration process, and all were trained and evaluated beforehand in the use of the different indices used to assess the disease. Once the electronic enrolment was completed, and the data reviewed and corrected if necessary, the registry was locked down. A review of the database was carried out by a professional monitor with experience in rheumatologic studies. Any and all mistakes were discussed with the principal investigators and final discrepancies were sent to the subinvestigators for resolution.


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## Variables and Definitions

Three hundred fifty-nine variables per patient were collected. Variables were divided into several groups:

1 Demographic data: age, gender, and ethnicity.
2 Chronology: time of first symptom and diagnosis of SLE, follow-up.
3 Cumulative manifestations as defined in (1) the ACR classification criteria for SLE,[9,11] (2) the activity index SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)[12] in the BILAG (British Isles Lupus Assessment Group) Index,[13,14] and (3) the SLICC/ACR DI (Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index).[15]
4 SLE status, using the activity index SELENA-SLEDAI (Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-SLEDAI)[16]; damage, using the SLICC/ACR Damage Index (SLICC/ACR/DI)[15]; and severity, using the Katz Index (SKI), range 0 to 13.[17]
5 Coexistence of antiphospholipid syndrome, as defined by the Sydney classification criteria[18]; mixed connective tissue disease, as defined by Alarcón-Segovia criteria[19]; or Sjögren syndrome if the patient presented sicca syndrome and a positive Schirmer test, as well as typical changes in scintigraphy or a positive labial biopsy.
6 Comorbidities, including severe infections and conditions described in the Charlson Comorbidity Index.[20]
7 Laboratory findings, imaging or pathological studies.
8 Any treatments undergone and the reason for discontinuation, if applicable.
9 Refractory SLE: defined as inefficacy of cyclophosphamide (CYC), use of rituximab, splenectomy, or inefficacy of 2 or more immunosuppressives (methotrexate, leflunomide, abatacept, anti-TNF, azathioprine, mycophenolate mofetil, and/or mycophenolic acid).

A clinical or laboratory finding was considered noteworthy if the patient presented it at any time during the course of the disease.

## Statistical Analysis

Relative and absolute frequencies for qualitative variables were calculated, as were mean and standard deviations or median and interquartile ranges for the quantitative variables, depending on whether the distribution was normal or not. Differences between values due to the number of ACR criteria fulfilled ($<4$ or $\geq 4$) were analyzed using a Student's *t* test for normal quantitative variables and a Mann–Whitney test for abnormal variables. Chi-square was calculated for qualitative independent variables, with corrections made with a Yates or Fisher's exact test for dichotomous variables.

Finally, to investigate the risk factors associated with an iSLE status, we used a case–control design. An analysis based on the estimation of simple and adjusted (by gender, age at onset, and disease duration, for all of the variables studied) odds ratios (ORs) by means of logistic regression with 95% confidence intervals (95% CI) was carried out; *P* values $<0.05$ were considered significant. The analysis was performed using the statistical package SPSS 21.0 for Windows (SPSS, Chicago, IL).

## Ethical Issues

RELESSER adheres to the principles established by the Declaration of Helsinki[21] and the Protocol of Oviedo.[22] Confidentiality was respected in full accordance with Spanish law[23]. In addition, the study was approved by the local ethics committees.

# RESULTS

A total of 4024 patients were included; 3679 (91.4%) patients were SLE and 345 (8.5%) iSLE. Ninety percent were women, the mean age at diagnosis was 35.4 (SD: 15.1) years, and the median duration of disease was 11.0 years with an interquartile range (IQ) of 6.0 to 19.0 years. The rest of the demographic and chronological data contained in the RELESSER registry is described elsewhere.[10]

In the RELESSER registry, SLE patients experienced their first symptom at a younger age and were also typically younger when the diagnosis was first made. However, the delay between the first symptom's appearance and diagnosis was similar in both groups. Disease duration and follow-up were longer in SLE subjects than iSLE ones (Table 1).

The ACR criteria frequencies are shown in Table 2. The most common SLE clinical manifestation in both groups (SLE and iSLE) was arthritis. All ACR criteria had a higher

**TABLE 1.** Demographic and Chronological Characteristics of iSLE and SLE Patients (Bivariate and Multivariate Analyses)

| | N | iSLE | SLE | *P* | OR [95% CI] | OR* [95% CI] | *P* |
|---|---|---|---|---|---|---|---|
| Female, N (%) | 4016 | 292 (84.9) | 3315 (90.3) | 0.002 | 1.65 [1.21–2.27] | — | — |
| Caucasians, N (%) | 3905 | 312 (94.0) | 3326 (93.1) | 0.617 | 1.16 [0.72–1.85] | 1.20 [0.2–1.99] | 0.490 |
| Age at diagnosis mean (SD) | 3990 | 42.9 (16.8) | 34.6 (14.6) | <0.001 | 0.97 [0.96–097] | 0.92 [0.90–0.96] | <0.001 |
| Age at first symptom mean (SD) | 3919 | 41.0 (SD: 17.2) | 32.6 (SD: 14.5) | <0.001 | 0.97 [0.9–0.97] | — | — |
| Diagnostic delay† median (p25–p75) | 3923 | 7.0 (2.0–26.0) | 5.0 (1.0–24.0) | 0.467 | 1.00 [1.00–1.00] | 0.99 [0.99–1.00] | <0.001 |
| Follow-up‡ median (p25–p75) | 3827 | 67.0 (23.3–125.0) | 102.0 (46.0–170.0) | <0.001 | 1.00 [1.00–1.00] | 1.00 [1.00–1.00] | 0.439 |
| Disease duration§ median (p25–p75) | 3846 | 8.0 (3.0–13.0) | 12.0 (6.0–19.0) | <0.001 | 1.07 [1.05–1.08] | — | — |

iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* Adjusted odds ratio by gender, age at first symptom, and disease duration.
† Delay between first symptom and diagnosis, months.
‡ Follow-up at a rheumatology unit, months.
§ Disease duration, years.

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**TABLE 2.** ACR SLE Criteria Fulfilled in iSLE and SLE Patients

| | N | iSLE, N (%) | SLE, N (%) | *P* | OR [95% CI] | OR* [95% CI] | *P* |
|---|---|---|---|---|---|---|---|
| Malar rash | 3963 | 37 (11.0) | 2004 (55.2) | <0.001 | 9.94 [7.02–14.07] | 9.14 [6.20–13.46] | <0.001 |
| Discoid rash | 3928 | 24 (7.1) | 753 (21.0) | <0.001 | 3.45 [2.26–5.26] | 3.09 [1.98–4.82] | <0.001 |
| Photosensitivity | 3901 | 68 (20.5) | 2172 (60.8) | <0.001 | 6.00 [4.56–7.91] | 5.36 [4.00–7.19] | <0.001 |
| Oral ulcers | 3898 | 24 (7.3) | 1645 (46.1) | <0.001 | 10.91 [7.16–16.61] | 9.37 [6.08–14.45] | <0.001 |
| Arthritis | 3963 | 148 (44.2) | 2827 (77.9) | <0.001 | 4.46 [3.54–5.61] | 3.95 [3.09–5.04] | <0.001 |
| Serositis | 3875 | 29 (8.8) | 997 (28.1) | <0.001 | 4.06 [2.76–5.99] | 3.90 [2.60–5.86] | <0.001 |
| Renal disorder | 3783 | 14 (4.3) | 1112 (32.1) | 0.001 | 10.49 [6.11–18.01] | 9.12 [5.18–16.07] | <0.001 |
| Neurological disorder | 3918 | 4 (1.2) | 294 (8.2) | <0.001 | 7.30 [2.70–19.70] | 5.41 [1.99–14.69] | <0.001 |
| Hematological disorder | 3764 | 131 (43.5) | 2762 (79.8) | <0.001 | 5.11 [4.01–6.52] | 4.77 [3.69–6.16] | <0.001 |
| Immunological disorder | 3359 | 145 (55.1) | 2657 (85.8) | <0.001 | 4.93 [3.79–6.41] | 4.56† [3.44–6.04] | <0.001 |
| ANA | 4012 | 323 (94.7) | 3637 (99.1) | <0.001 | 5.96 [3.33–10.67] | 5.70 [2.97–10.91] | <0.001 |

Bivariate and multivariate analyses. iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* OR adjusted by gender, age at first symptom, and disease duration.
† 20.1% of values lost.

prevalence among SLE patients. Moreover, although all of the ACR criteria were associated with SLE, this association was remarkably high in cases of malar rash, oral ulcers, and renal disorder. The presence of antiphospholipid syndrome also correlated with an SLE status (OR: 1.54; 95% CI: 1.03–2.32; $P < 0.04$), as well as pregnancy morbidity (OR: 2.19; 95% CI: 1.11–4.34; $P < 0.03$) and anticardiolipin IgM or IgG antibodies (Ab) (OR: 1.36; 95% CI: 1.02–1.82; $P < 0.04$). However, there were no differences between the two groups in terms of arterial, venous or small vessel thrombosis, anti-beta 2 glycoprotein Ab, and lupus anticoagulant.

Most SLE manifestations were more often found in SLE patients (Table 3). Osteoarticular and mucocutaneous manifestations, excepting cutaneous ulcers, were all associated with SLE.

If considered individually, the frequency of respiratory manifestations such as pleuritis, interstitial alveolitis, alveolar hemorrhage, pulmonary hypertension (PHT), as defined by SLICC/ACR/DI criteria or PTH in echocardiography, lung or pleural fibrosis, and shrinking lung syndrome was no different between the two groups. When general respiratory involvement (any of the above manifestations) was globally considered, however, it was more prevalent in SLE patients. This was similarly true of cardiac and vascular involvement. In general, although such respiratory complications were more frequent in SLE subjects, when these manifestations were analyzed individually, only valvular dysfunction (OR: 3.49; 95% CI: 1.09–11.22; $P < 0.04$) and Raynaud (OR: 1.74; 95% CI: 1.29–2.35; $P < 0.01$) were associated with SLE (adjusted OR).

Lupus nephritis, as defined by clinical or laboratory alterations with or without renal biopsy, was much more prevalent in SLE patients. In fact, 30.3% of SLE subjects present it versus 6.3% iSLE patients. In terms of the relative frequencies of the different patterns of pathological findings, however, there were no differences between the two groups. Class IV (WHO) glomerular disease was the most frequently occurring form of lupus nephritis in renal biopsies (29.4% in iSLE and 48.6% in SLE patients). The association of end-stage renal disease, as defined by SLICC/ACR/DI and SLE status, did not reach statistical significance (adjusted OR: 2.04; 95% CI: 0.63–6.56; $P = 0.23$) (Table 3).

Neuropsychiatric involvement as a whole and seizures in particular were both associated with SLE. Ophthalmological symptoms others than keratoconjunctivitis sicca, such as visual alteration, cataracts, retinopathy or uveitis, were all associated with SLE. They were found in 15% of SLE patients and in nearly 10% of iSLE patients. Most laboratory manifestations, such as hematological alterations, low complement levels, and above all the presence of autoantibodies were also associated with SLE status (Table 3).

Hospitalizations, refractoriness, and mortality were associated with SLE. Furthermore, SLE patients died younger than iSLE ones [55.8 (18.0) vs 71.7(9.0) years], although deaths due to SLE activity did not differ between the two groups (Table 4).

Differences in comorbidity were also explored. Severe infection was associated with SLE. The proportion of patients that smoked or had smoked in the past exceeded 40% in both groups. Although the prevalence of arterial hypertension was higher in SLE patients, there were no differences regarding cardiovascular events or dyslipoproteinemia. Diabetes mellitus (DM) was associated with iSLE (Table 5). Charlson index values were identical in both groups [median: 2 (IQ: 1–3)].

Activity, damage, and severity index scores were higher in the SLE than in iSLE group [median SELENA-SLEDAI 2 (IQ: 0–4) vs 0 (0–2), median SLICC/ACR/DI 1 (0–2) vs 0 (0–1) and SKI 2 (1–3) vs 1 (1–2)] (Figure 1). Additionally, when the analysis was adjusted for gender, age at onset, and disease duration, higher activity, damage and SKI remained more strongly associated with SLE [(OR: 1.14; 95% CI: 1.08–1.20; $P < 0.01$); (OR: 1.29; 95% CI: 1.15–1.44; $P < 0.00$); (OR: 2.10; 95% CI: 1.83–2.42; $P < 0.01$)].

An analysis of the various treatments used showed that although the majority of patients in both groups received or had received corticosteroids (88.9% in SLE vs 69.1% in iSLE) and antimalarials (83.3 vs 69.4%), all such treatments were more commonly associated with SLE (Table 6). One-third of SLE subjects were, or had been on, azathioprine versus just 13.2% of iSLE patients. Statistical differences were also found in terms of treatments involving CYC, mycophenolate mofetil, and rituximab. Approximately 15% of patients received methotrexate, without differences being noted between the two groups.

Treatment with angiotensin-converting enzyme inhibitors, statins, diuretics, and anti-osteoporotic agents were all associated with SLE, while acetylsalicylic acid, oral anticoagulants, and oral hypoglycemic agents were not (Table 5).


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**TABLE 3.** Organ Involvement in iSLE and SLE Patients

| | N | iSLE, N (%) | SLE, N (%) | *P* | OR [95% CI] | OR* [95% CI] | *P* |
|---|---|---|---|---|---|---|---|
| Weight loss | 3952 | 18 (5.4) | 358 (9.9) | 0.009 | 1.93 [1.19–3.15] | 2.03 [1.22–3.39] | 0.006 |
| Adenopathy | 3945 | 11 (3.3) | 374 (10.4) | <0.001 | 3.39 [1.84–6.25] | 2.96 [1.60–5.48] | 0.001 |
| Inflammatory rash | 3962 | 92 (27.2) | 2390 (65.9) | <0.001 | 5.18 [4.04–6.64] | 4.38 [3.36–5.72] | <0.001 |
| Alopecia | 3933 | 54 (16.2) | 1291 (35.9) | <0.001 | 2.90 [2.15–3.91] | 2.23 [1.62–3.06] | <0.001 |
| Cutaneous ulcers | 3966 | 3 (0.9) | 104 (2.9) | 0.047 | 3.32 [1.05–10.51] | 3.83 [0.93–15.80] | 0.064 |
| Any osteoarticular manifestation* | 3917 | 160 (49.1) | 2877 (80.1) | <0.001 | 4.18 [3.32–5.27] | 3.74 [2.92–4.78] | <0.001 |
| Avascular necrosis | 3959 | 3 (0.9) | 151 (4.2) | 0.004 | 4.89 [1.51–15.42] | 4.65 [1.14–19.02] | 0.033 |
| Any respiratory manifestation† | 3648 | 48 (15.8) | 1056 (30.6) | <0.001 | 2.46 [1.79–3.38] | 2.55 [1.82–3.58] | <0.001 |
| Any cardiac manifestation‡ | 3650 | 53 (17.3) | 943 (28.2) | <0.001 | 1.88 [1.38–2.55] | 1.73 [1.25–2.39] | 0.001 |
| Myocardial infarction | 3962 | 12 (3.5) | 71 (2) | 0.081 | 0.55 [0.29–1.02] | 0.68 [0.35–1.33] | 0.257 |
| Peripheral vascular disease§ | 3863 | 75 (22.9) | 1329 (37.6) | <0.001 | 2.02 [1.55–2.64] | 1.65 [1.24–2.19] | 0.001 |
| Raynaud | 3879 | 64 (19.1) | 1200 (33.9) | <0.001 | 2.17 [1.64–2.87] | 1.74 [1.29–2.35] | <0.001 |
| Lupus nephritis | 3930 | 21 (6.3) | 1101 (30.6) | <0.001 | 6.60 [4.22–10.33] | 5.69 [3.53–9.16] | <0.001 |
| End-stage renal disease (SLICC/ACR/DI) | 3872 | 3 (0.9) | 99 (2.8) | 0.059 | 3.17 [1.00–10.04] | 2.04 [0.63–6.56] | 0.232 |
| Neuropsychiatric symptoms¶ | 3743 | 46 (14.9) | 764 (22.2) | 0.004 | 1.63 [1.18–2.25] | 1.46 [1.04–2.04] | 0.030 |
| Seizures (SLICC/ACR/DI) | 3752 | 2 (0.6) | 189 (5.2) | <0.001 | 9.25 [2.29–37.44] | 7.22 [1.77–29.43] | 0.006 |
| Ophthalmological manifestations** | 3832 | 32 (9.9) | 530 (15.1) | 0.015 | 1.61 [1.10–2.35] | 1.82 [1.19–2.77] | 0.006 |
| Retinopathy | 3935 | 7 (2.1) | 162 (4.5) | 0.049 | 2.23 [1.04–4.79] | 1.58 [0.73–3.45] | 0.248 |
| Hematological manifestations†† | 3025 | 151 (48.7) | 2888 (81.0) | <0.001 | 4.48 [3.53–5.68] | 4.35 [3.38–5.60] | <0.001 |
| Low complement | 3934 | 183 (54.1) | 2804 (78.0) | <0.001 | 3.00 [2.39–3.77] | 2.38 [1.86–3.06] | <0.001 |
| Anti Ro Ab | 3888 | 105 (31.9) | 1403 (39.4) | 0.009 | 1.39 [1.09–1.77] | 1.39 [1.07–1.81] | 0.012 |
| Anti La Ab | 3883 | 48 (14.7) | 690 (19.4) | 0.044 | 1.40 [1.02–1.92] | 1.45 [1.03–2.05] | 0.032 |
| Anti RNP Ab | 3866 | 38 (11.7) | 891 (25.2) | <0.001 | 2.55 [1.80–3.61] | 2.25 [1.56–3.25] | <0.001 |
| Sjögren's syndrome | 3937 | 33 (9.7) | 517 (14.4) | 0.023 | 1.56 [1.07–2.26] | 1.60 [1.08–2.37] | 0.019 |

iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* Myositis, amioatrophy, arthritis, or tendon rupture.
† Pleuritis, interstitial alveolitis, alveolar haemorrhage, pulmonary hypertension (PHT) defined by SLICC/ACR/DI/ACR/DI or PHT in echocardiography, lung or pleural fibrosis, or shrinking lung syndrome.
‡ Myocarditis, valvular dysfunction, Libman-Sacks endocarditis, vasculitis, ischemic cardiopathy, or pericarditis.
§ Lower limb claudication, tissue loss, venous thrombosis, or Raynaud.
¶ Organic brain syndrome, cephalea, neuropathy, cognitive damage, psychosis, stroke, or myelitis.
** Visual alteration, cataracts, retinopathy, or uveitis.
†† Anemia, leucopenia, lymphopenia, thrombocytopenia, thrombotic thrombocytopenic purpura, red cell aplasia, or hemophagocytic syndrome.

## DISCUSSION

RELESSER is a large multicenter registry of SLE patients from the European population, created by SER, with high quality and homogeneous data.[10] The narrow confidence intervals in the results presented here underscore the reliability and accuracy of the data drawn from this register. In this study, we have carried out a detailed cross-sectional description of the patients included in the RELESSER registry, focusing on the differences between SLE and iSLE, and providing the largest iSLE cohort assembled now available. We consider this a very pertinent exercise, since iSLE is not a rare condition. In our registry, nearly 10% of the patients diagnosed with SLE by experts should be more properly classified as iSLE. In fact, in the only epidemiologic population-based study published to date, the prevalence of iSLE was about one-quarter that of SLE in the same region.[24]

In our study, there were differences between the two groups with respect to sex and age. It is known that both age at onset and gender modify disease expression.[1,25] In addition,

**TABLE 4.** Bivariate and Multivariate Analyses of Mortality and Other Variables Related to Complications in SLE and iSLE Patients

| | N | iSLE N (%) | dSLE N (%) | *P* | OR [95% CI] | OR* [95% CI] | *P* |
|---|---|---|---|---|---|---|---|
| Hospitalization by SLE activity | 3932 | 94 (28.0) | 1965 (44.6) | <0.001 | 3.10 [2.42–3.97] | 2.79 [2.15–3.63] | <0.001 |
| Deaths | 3695 | 15 (4.7) | 211 (6.3) | 0.314 | 1.36 [0.80–2.33] | 2.25 [1.24–4.08] | 0.008 |
| Death due to SLE activity | — | 5 (33.3) | 55 (26.1) | 0.551 | 0.71 [0.23–2.15] | 0.40 [0.09–1.70] | 0.212 |
| Age at death (mean (SD) | — | 71.7 (9.0) | 55.8 (18.0) | <0.001 | 0.94 [0.90–0.98] | 0.62 [0.43–0.88] | 0.007 |
| Refractory SLE | 4024 | 25 (7.2) | 900 (23.0) | <0.001 | 4.15 [2.74–6.27] | 3.04 [1.98–4.68] | <0.001 |

iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* Adjusted odds ratio by gender, age at first symptom and disease duration.

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**TABLE 5.** Differences in Comorbidities Between iSLE and SLE Patients

| | N | iSLE, N (%) | SLE, N (%) | *P* | OR [95% CI] | OR* [95% CI] | *P* |
|---|---|---|---|---|---|---|---|
| Smoking | 3610 | 139 (46.6) | 1362 (41.1) | 0.073 | 0.80 [0.63–1.01] | 0.80 [0.62–1.04] | 0.092 |
| DM | 3962 | 29 (8.5) | 179 (4.9) | 0.007 | 0.56 [0.37–0.84] | 0.68 [0.44–1.06] | 0.09 |
| DL | 3859 | 99 (30.3) | 1106 (31.3) | 0.745 | 1.05 [0.82–1.34] | 1.16 [0.89–1.52] | 0.269 |
| HTN | 3983 | 70 (20.7) | 1069 (29.3) | 0.001 | 1.59 [1.21–2.09] | 1.88 [1.38–2.56] | <0.001 |
| Cardiovascular events† | 3916 | 30 (9.1) | 368 (10.3) | 0.550 | 1.15 [0.78–1.70] | 1.53 [0.98–2.38] | 0.062 |
| Severe infection | 3795 | 30 (9.6) | 725 (20.8) | <0.001 | 2.49 [1.69–3.66] | 2.16 [1.45–3.23] | <0.001 |
| Malignancy | 3961 | 18 (5.4) | 209 (5.8) | 0.875 | 1.07 [0.65–1.76] | 1.21 [0.71–2.06] | 0.484 |
| Lymphoma | 3961 | 1 (0.3) | 20 (0.6) | 0.99 | 1.85 [0.25–13.80] | 2.08 [0.27–15.95] | 0.482 |

DL = dyslipoproteinemia, DM = diabetes mellitus, HTN = hypertension, iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* OR adjusted by gender, age at onset, and disease duration.
† Stroke or heart attack or peripheral arteriopathy.

disease duration has a significant impact on various parameters such as accrual of clinical manifestations, damage and rate of complications. To avoid these confounding factors, adjusted analyses by gender, age at onset, and disease duration, for all of the variables studied, were carried out. Although disease duration was longer in the SLE population, that of the RELESSER iSLE patients was similarly long; that is, 8 years, which allowed for an adequate characterization of this patient

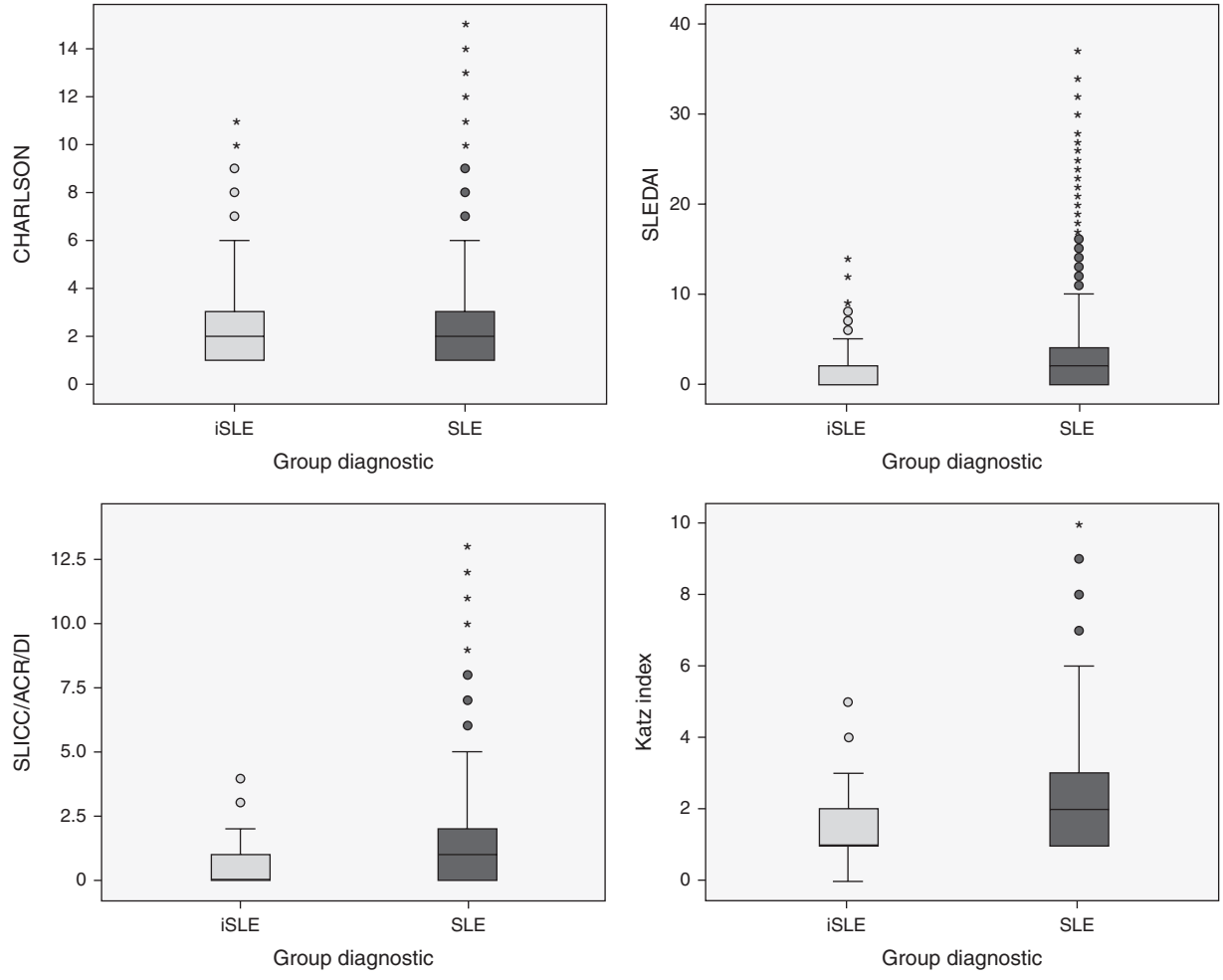


**FIGURE 1.** Charlson comorbidity index, SELENA-SLEDAI index, SLICC/ACR/DI, and Severity Katz Index values in RELESSER patients grouped according to diagnostic category iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.


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**TABLE 6.** Treatments Received by iSLE and SLE Patients

| | N | iSLE, N(%) | SLE, N (%) | *P* | OR [95% CI] | OR* [95% CI] | *P* |
|---|---|---|---|---|---|---|---|
| Corticosteroids | 3823 | 224 (69.1) | 3112 (88.9) | <0.001 | 3.59 [2.77–4.65] | 3.22 [2.43–4.25] | <0.001 |
| Methotrexate | 3798 | 44 (13.8) | 579 (16.6) | 0.207 | 1.25 [0.90–1.74] | 1.22 [0.86–1.74] | 0.268 |
| Leflunomide | 3657 | 8 (2.5) | 128 (3.7) | 0.360 | 1.48 [0.72–3.06] | 1.22 [0.58–2.55] | 0.596 |
| Azathioprine | 3785 | 42 (13.2) | 1143 (33.0) | <0.001 | 3.25 [2.33–4.52] | 2.46 [1.73–3.50] | <0.001 |
| Cyclophosphamide | 3793 | 20 (6.3) | 780 (22.5) | <0.001 | 4.35 [2.74–6.88] | 3.47 [2.12–5.67] | <0.001 |
| Mycophenolate mofetil | 3774 | 13 (4.0) | 525 (15.0) | <0.001 | 4.25 [2.42–7.46] | 3.45 [1.91–6.25] | <0.001 |
| Antimalarials | 3806 | 225 (69.4) | 2899 (83.3) | <0.001 | 2.19 [1.70–2.82] | 1.91 [1.45–2.51] | <0.001 |
| Intravenous immunoglobulin | 3755 | 10 (3.1) | 154 (4.5) | 0.326 | 1.45 [076–2.78] | 1.14 [0.59–2.23] | 0.693 |
| Rituximab | 3791 | 5 (1.6) | 227 (6.5) | <0.001 | 4.38 [1.79–10.70] | 3.34 [1.36–8.23] | 0.009 |
| Acetylsalicylic acid | 3222 | 88 (32.6) | 1097 (37.2) | 0.154 | 1.22 [0.94–1.60] | 1.16 [0.88–1.54] | 0.289 |
| Oral anticoagulants | 3764 | 37 (11.6) | 497 (14.4) | 0.193 | 1.29 [0.90–1.83] | 1.37 [0.93–2.02] | 0.113 |
| Plasmapheresis | 3801 | 1 (0.3) | 56 (1.6) | 0.087 | 5.23 [0.72–37.93] | 4.22 [0.57–31.04] | 0.157 |
| Dialysis | 3774 | 2 (0.6) | 102 (3.1) | <0.021 | 4.98 [1.22–20.26] | 3.33 [0.81–13.70] | 0.095 |
| Statins | 3645 | 58 (18.8) | 847 (25.4) | 0.013 | 1.47 [1.09–1.97] | 1.43 [1.04–1.95] | <0.026 |
| Angiotensin-converting enzyme inhibitors | 3635 | 48 (15.4) | 1045 (31.4) | <0.001 | 2.51 [1.83–3.45] | 2.58 [1.85–3.61] | <0.001 |
| Diuretics | 3604 | 25 (11.5) | 732 (22.2) | <0.001 | 2.20 [1.53–3.16] | 2.41 [1.65–3.53] | <0.001 |
| Anti-osteoporotic agents | 3682 | 55 (17.5) | 831 (24.7) | 0.006 | 1.54 [1.14–2.09] | 1.63 [1.17–2.28] | 0.004 |

iSLE = incomplete Sistemic Lupus Erithematosus, SLE = complete Sistemic Lupus Erithematosus.
* Adjusted odds ratio by gender, age at onset, and disease duration.
† Multivariate analysis was not possible due to the small number of cases.

subgroup. As was perhaps expected, SLE patients presented more manifestations and complications than iSLE subject. The presence of malar rash and oral ulcers was highly prevalent in SLE patients, and both conditions are considered risk factor for SLE progression, as has been documented in previous studies.[6,8] The rate of renal and severe neurological disease was very low in iSLE subjects (4% and 1.2%, respectively). Our adjusted analysis showed higher activity, damage, severity, and global mortality in SLE patients than in those with iSLE. The risk of hospitalization due to SLE activity was lower in iSLE patients, based on their minor index of severity. In addition, a greater number of SLE patients received glucocorticoids, cyclophosphamide, mycophenolate mofetil, and rituximab. Although antimalarials are always recommended in SLE, and while most iSLE patients should probably have been treated with such drugs, up to 30% never received antimalarials, in contrast with 11% of SLE patients who did. Perhaps low awareness or reluctance to prescribe the drug in patients with a less than certain diagnosis could explain this difference. Refractoriness, as defined by consensus in RELESSER, was also associated with SLE.

Although activity and severity scores were low, 1 of every 4 deaths documented in RELESSER was due to SLE activity. This mortality rate is an interesting discussion since it has never been previously analyzed in the context of iSLE. Adjusted mortality was higher in SLE patients, although there were no differences between the two groups in terms of SLE activity-related deaths. This intriguing finding, revealing such a striking difference, may have several explanations. First of all, data regarding cause of death were sometimes incomplete; thus, confounding factor(s) may have played a role. Second, the disease severity in iSLE patients might have been underestimated. This could have resulted in a less closely monitored follow-up, as well as less immunosuppressive therapy, than should have been undertaken. Furthermore, almost one-third of iSLE patients were never prescribed antimalarials, and it is well known that these drugs have beneficial and protective effects on survival.[26] In any case, the relatively low number of deaths precludes the drawing of firm conclusions.

In regards to comorbidity—another topic not previously studied in patients with iSLE—it is worth noting that no differences were noted in the Chalrson Index, which was low in both groups. Perhaps this index is not sufficiently sensitive to identify all of the potential comorbidities in SLE and thus was unable to detect any differences between the two groups. iSLE patients suffer less severe infections, which may reflect the milder disease states they experience, as well as the fact that they receive less immunosuppressive drugs. In terms of cardiovascular complications, the rates of angina or by-pass and heart attack were numerically higher in iSLE subjects, although without reaching statistical significance. iSLE patients were typically older, and presented a higher rate of certain risk factors for coronary disease (eg, smoking and DM), although, again, in the multivariate analysis, such differences lost their statistical significance. Besides, iSLE patients received less statins than those with SLE, even though there were no differences with respect to the prevalence of dyslipoproteinemia between the two groups. This may reflect the lack of tight control over cardiovascular risk factors in a subpopulation assumed to have a milder form of the disease. As described previously,[27] in the RELESSER registry patients with hypertension were more often SLE, which presumably reflects the higher incidence of lupus nephritis found in these individuals.[28]

Consistent with our own results, several authors have suggested that incomplete SLE may be a frequent, mild, and relatively stable or benign form of the disease, apparently with a minority of patients gradually evolving to SLE or other rheumatic disease,[7,8,29] Other groups, however, have obtained results consistent with the hypothesis that iSLE patients encompass a subset that is likely to experience progressive organ damage[30] or to develop complete SLE.[6] Swaak et al[7] studied a multicenter European cohort of patients with incomplete SLE.

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Besides RELESSER, this is the only multicenter study available on iSLE. This study included 122 patients with mean disease duration of 4.5 years. Consistent with our results and with virtually all of the studies completed to date, renal and central nervous system involvement was low (16% and 3%, respectively). Interestingly, even when patients eventually met the ACR-SLE criteria in longitudinal studies, renal and neuropsychiatric manifestations remained low.[6–8] Median basal SLE activity, as measured by SLEDAI, was 2.6 (4.5) in the Swaak study. The figure was higher than in RELESSER iSLE patients;[7] 38% of Swaak patients were on corticosteroids and another 17% were on antimalarials vs RELESSER subjects (69% on corticosteroids and another 69% on antimalarials). This suggests a significant variability in clinical practice, although disease duration at the time of enrollment was higher in RELESSER patients. As with our patients, the low rate of damage accrual in iSLE patients, compared to those with SLE, has been previously reported.[6,30]

We have attempted to compare RELESSER SLE patient characteristics not only with those from the EUROLUPUS cohort, but also with the baseline characteristics of Caucasian patients from the LUMINA and GLADEL cohorts. However, it should be emphasized that differences in patient selection, design, period of time when was conducted, and variable definitions limits the validity of such comparison among these various cohorts. The EUROLUPUS cohort included patients from different European countries; specifically from the internal medicine, rheumatology and nephrology units of only 4 Spanish referral centers. In contrast, RELESSER patients were enrolled at 45 different rheumatology units spread across the country, and thus more comprehensively reflects the current reality of SLE in Spain and likewise a large southern European area. Ninety-three point one percent of RELESSER patients were Caucasian, reflecting the current demographics in Spain, where most of the native population is Caucasian.[31] In contrast, the EUROLUPUS PROYECT, which was carried out in the 1990s, reported 97% of the Spanish population as Caucasian.[32] RELESSER patients were 33.3 (14.9) and 35.4 (15) years old at onset and diagnosis, respectively, which is quite similar to the EUROLUPUS data. In the LUMINA cohort, the mean age at diagnosis varied with ethnicity, Caucasians tending to be older than African-Americans and Hispanics [41.2 (14) vs 33.6 (12) vs 32.4 (13) years, respectively].[33] GLADEL is an inception cohort in which fulfillment of 4 SLE ACR criteria was not mandatory. Here, patients were of similar age at first symptom [29.5 (12) years] and at diagnosis [31.1 (12) years] for the Caucasian subjects group.[34] The median time between first symptom and diagnosis in the RELESSER group was 5.0 (0–618) months, which is similar to the GLADEL registry figure of 6.0 (0.4–301) months. In contrast, in the EUROLUPUS cohort the mean time between first manifestation and final classification as SLE was 2 years.[32] This difference could be explained by differences in the set of criteria used for case definition (ie, ACR-1997 vs ACR-1982).

Musculoskeletal and hematological manifestations are the most frequent symptoms in both RELESSER and GLADEL patients, which means that these types of symptoms are the most common at disease onset, as well as during disease evolution, taking into account that median disease duration in the GLADEL cohort was 34.2 (range: 0.9–333.0) months and in the RELESSER cohort 148.0 (0–640) months. In EUROLUPUS patients, who experienced a mean disease duration of $101 \pm 96$ months, arthritis—followed by malar rash and fever—were the most frequent symptoms.[35]

Thirty percent of RELESSER patients present some kind of renal involvement, which was very similar to the Caucasian population in the LUMINA cohort (32% of patients)[36] and somewhat lower than in the EUROLUPUS and GLADEL registries (39% and 43.6%, respectively). These differences may have stemmed from differences in ethnicity and/or patients sources.

There are striking differences in the prevalence of ocular manifestations. After 5 years of follow-up, only 1.7% of EUROLUPUS patients continued to suffer retinopathy and 2.9% cataracts. One point one percent of GLADEL subjects experienced uveitis, episcleritis, or scleritis. These manifestations were more prevalent in the RELESSER group (15% of SLE subjects), despite the fact that they were not actively recruited; in fact, the incidence rate here is perhaps more in keeping with what is commonly described in ophthalmological consultations.[37] Ocular manifestations of SLE are a reflection of systemic disease[38] and can lead to severe sight impairment, including blindness.[37] This signifies that ophthalmological complaints, frequently overlooked, should be actively investigated.

Global activity has been evaluated using the SELENA-SLEDAI index in RELESSER patients, and baseline S-SLEDAI was low: 2.6 (3.6). The LUMINA cohort was subject to a different index for assessment of disease activity at baseline: the SLAM (Systemic Lupus Activity Measure) index. Using the SLAM index, Caucasians in the LUMINA cohort scored 8.5 (3.7).[36] Although the scoring tools used differed, most likely differences in baseline activity between the two groups was insignificant.

Among the cumulative treatments administered in the GLADEL cohort, corticosteroids were the most frequently used (90.9%). Seventy-five percent of patients were treated with antimalarials, and the immunosuppressive agent most often used was cyclophosphamide (26.8%).[34] As RELESSER and GLADEL patients underwent similar regimens, it appears than the drug treatment did not change with the duration of disease. In other words, drug treatments for SLE patients were generally introduced during the early years of disease. There was a prominent difference in the EUROLUPUS data regarding antimalarial treatments. During the first 5 years of the EUROLUPUS study,[39] only 40.2% of patients received them, in contrast with 75% of RELESSER subjects. This could be due to increased awareness about the benefits of antimalarials benefits or to differences in approach among specialists involved in caring for these patients.

The RELESSER registry has some limitations. The method by which hospitals are chosen to participate in the study, involving rheumatologist specially dedicated to SLE clinical investigation, could introduce some selection bias. Patients seen at these centers may have a more severe form of the disease or may be under stricter care. There may be differences between referral criteria, depending on the level of care or the involvement of certain systems that lead certain patient to particular specialists. In any case, the big sample size and the number and characteristics of the participating units across Spain helped minimize any such selection bias. Another limitation of the present study concerns the incomplete follow-up evident at the rheumatology units. Nonetheless, as the delay between first symptom and rheumatologic evaluation and diagnosis remained relatively short, the loss of information should not have significant ramifications.

However, the most important limitation of the RELESSER registry is its retrospective design, which supposes a higher


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possibility of measurement mistakes and which lacks sufficient information regarding confounding variables.

However, some prospective studies are now being conducted, with a focus on specific patient groups from the RELESSER registry. The ongoing prospective phase of the registry also includes one study involving a cohort of iSLE patients. Such prospective studies will try to confirm any associations between the different variables and activity, damage, severity, mortality, and co-morbidities that become apparent during multivariate analysis of the study's transversal phase.

## CONCLUSIONS

1 RELESSER represents the largest European SLE registry compiled to date, on that provides comprehensive, updated and reliable information on SLE manifestations, disease status, and comorbidity conditions and treatments in daily clinical practice.
2 There are two well-differentiated groups of patients: SLE and iSLE. Although iSLE patients typically present a stable, mild form of the disease with a low rate of major organ involvement and low refractoriness, lupus-caused mortality does not seem to differ between these two groups, with iSLE patients warranting adequate treatment and follow-up.
3 SLE in the southern European population does not seem to differ from other Caucasian populations, being similar in terms of low activity levels and severity grades.

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