# Juvenile- and adult-onset systemic lupus erythematosus: a comparative study in a large cohort from the Spanish Society of Rheumatology Lupus Registry (RELESSER)

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## Abstract

### Objective

*We aimed to describe juvenile-onset systemic lupus erythematosus (jSLE) features and to establish its differences compared to adult-onset SLE (aSLE) from a large national database.*

### Methods

*Data from patients (≥4 ACR criteria) included in Spanish Society of Rheumatology Lupus Registry (RELESSER) were analysed. Sociodemographic, clinical, serological, activity, treatment, cumulative damage, comorbidities and severity data were collected. Patients with disease onset <18 years were described and compared to those with disease onset ≥18 years.*

### Results

*We reviewed 3,428 aSLE patients (89.6% women) and 484 jSLE patients (89.8% girls), 93% Caucasian (both groups). Mean age at diagnosis was 38.1±14 and 16.6±6.3 years (p<0.001) and mean age at the end of follow-up was 48.8±14.3 and 31.5±30 years (p<0.001), respectively. jSLE showed significantly more clinical (including lymphadenopathy, fever, malar rash, mucosal ulcers, pericarditis, pleuritis, Raynaud's phenomenon, lupus nephritis, recurrent nephritis, histologic nephritis changes, thrombocytopenia, haemolytic anaemia, thrombotic thrombocytopenic purpura, seizures, lupus headache and organic brain syndrome) and immunological (a-dsDNA and a-Sm antibodies, hypocomplementaemia) involvement than did aSLE, except for secondary Sjögren's syndrome, a-Ro antibodies, fibromyalgia and osteoporosis. jSLE also showed more SLE family history, longer diagnosis delay, higher SLEDAI and Katz scores, but lower Charlson scores than aSLE. Several specific domains were more frequently involved in SLICC/ACR DI in jSLE. jSLE patients more frequently underwent all SLE-related treatment and procedures, as well as dialysis and kidney transplantations.*

### Conclusion

*jSLE shares many clinical and serological features with aSLE. However, jSLE patients typically manifested more activity, severity, cumulative damage in certain areas, than their aSLE counterparts.*

**Key words**

juvenile-onset systemic lupus erythematosus, adult-onset systemic lupus erythematosus, activity, severity, cumulative damage, comorbidity

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## Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disease. Up to 20% of patients with SLE experience disease onset prior to the age of 18 (1). The annual incidence of juvenile SLE onset (jSLE) is estimated to be 0.36–0.9 per 100,000 children per year, which makes it difficult to collect data and advance our understanding of the disease in the particular patient group (1). Despite the improvement in survival rates during the last decades (10-year survival rate ≈90%) (2), jSLE have a significantly lower life expectancy than the general population, with a 4-fold greater risk of death. Mortality rates are also higher compared to adult-onset SLE (aSLE) (3, 4). Indeed, significant differences between aSLE and jSLE in terms of disease onset and course have been described (5-12). jSLE appears to be more aggressive than aSLE and leads to worse outcomes, which underscores the importance of proper diagnosis, treatment and follow-up (13). However, most of those direct comparisons have been made using small jSLE cohorts (14). In addition, different genetic susceptibility backgrounds related to the age at onset of disease have been described within a large sample of SLE patients (111 jSLE and 1206 aSLE) (15). This specific genetic background probably results in a different SLE phenotype based on the age at onset (16).
Nonetheless, many clinical features and laboratory parameters, as well as activity, comorbidities, treatment, damage measures and other long-term outcomes are yet to be explored in a large series of jSLE patients. Moreover, they remain to be compared to aSLE counterparts.
Therefore, we aimed to 1) describe jSLE clinical and serological profiles and 2) compare all clinical and serological features, activity scores, damage, severity, comorbidities and therapeutic SLE-related features between jSLE and aSLE, within a large cohort from the Spanish Society of Rheumatology Lupus Registry (RELESSER).

## Materials and methods

*Research Study Network*

Data were obtained from the Registry of SLE Patients of the Spanish Society of Rheumatology (RELESSER), which is a hospital-based registry that consists of two stages. The first is a cross-sectional stage, the main objective of which is to describe the characteristics and comorbidities of those patients diagnosed with SLE in Spain. This is followed by a second longitudinal follow-up stage over time involving repeated yearly visits. The RELESSER Registry was conducted by the *Systemic Autoimmune Rheumatic Diseases Study Group* of the Spanish Society of Rheumatology and it included 45 participating rheumatology departments. All investigators signed a written commitment before participation. Informed consent was obtained from all patients who participated in the longitudinal stage. The study was approved by the local ethics committees of the participating centres in accordance with the Declaration of Helsinki's guidelines for research in humans (17).

*Study design*

This is a national, multicentre, descriptive study of a cohort with a cross-sectional analysis made at the time of the last medical visit for every patient (or upon death, if applicable). A detailed description of its methodology has been provided elsewhere (17). Briefly, a specific protocol was created to collect around 400 variables per patient. Information was obtained by reviewing clinical histories and was electronically gathered. In order to minimise missing data, all investigators were encouraged to carry out a census of their SLE patients and fill out any missing data. In order to ensure data homogeneity and quality, every item in the protocol had a highly standardised definition. In addition, all investigators completed a training course beforehand to avoid information bias and all had online access to guidelines on how to complete the protocol. The first patient was enrolled in October 2011 and the electronic data collection was completed by August 2012. Subsequently, a professional monitor with experience in rheumatologic studies reviewed the database to identify any missing or inconsistent. Such occurrences were discussed with the relevant principal investigators and sent to the sub-investigators for additions and/or corrections.

**Table I.** Clinical, serological, activity and chronicity scores, comorbidity and therapeutic features in juvenile-onset-SLE.

| Variable | jSLE (n=484) |
|---|---|
| *Sociodemographics* | |
| Race, Caucasian | 441 (93.0%) |
| Age at the last evaluation, years | 31.5 ± 10.5 30 [24-38] |
| Delay in diagnosis, months | 39.9 ± 5.0 5 [0-37] |
| Age at diagnosis, years | 16.6 ± 6.3 16 [13-18] |
| *Constitutional* | |
| Lymphadenopathy | 60 (12.6%) |
| Weight loss | 52 (10.8%) |
| Splenomegaly | 29 (6.2%) |
| Fever** | 26 (5.4%) |
| *Mucocutaneous* | |
| Malar rash* | 327 (68.3%) |
| Photosensitivity* | 287 (61.4%) |
| Mucosal ulcers* | 245 (52.4%) |
| Discoid rash* | 100 (21.4%) |
| Cutaneous ulcers** | 15 (3.1%) |
| Scarring alopecia** | 9 (1.8%) |
| *Articular* | |
| Arthritis* | 375 (78.2%) |
| Erosive arthritis** | 40 (8.4%) |
| Myositis* | 26 (5.6%) |
| Atrophy, muscle weakness** | 15 (3.1%) |
| Osteoporosis** | 15 (3.2%) |
| Fibromyalgia | 11 (2.4%) |
| Tendon rupture** | 5 (1.0%) |
| Number of avascular osteonecrosis** | 1.6 ± 0.6 2 [1-2] |
| *Respiratory* | |
| Pleuritis* | 134 (28.3%) |
| Interstitial alveolitis | 20 (4.2%) |
| Pulmonary embolism | 11 (2.2%) |
| Lung fibrosis** | 6 (1.2%) |
| Pulmonary hypertension** | 8 (1.6%) |
| Alveolar haemorrhage | 6 (1.2%) |
| Shrinking lung | 4 (0.8%) |
| Pleural fibrosis** | 1.0 (0.2%) |
| Pulmonary infarction** | 1.0 (0.2%) |
| *Heart* | |
| Pericarditis* | 94 (19.9%) |
| Vasculitis* | 60 (12.8%) |
| Vascular disease** | 25 (5.2%) |
| Valvular dysfunction** | 19 (4.0%) |
| Libman-Sachs Endocarditis | 8 (1.7%) |
| Cardiomyopathy** | 7 (1.5%) |
| Angina or by pass** | 6 (1.2%) |
| Myocarditis** | 3 (0.6%) |
| Number of heart attacks** | 1.1 ± 0.0 1.0 [1-1] |
| *Vascular* | |
| Raynaud phenomenon | 172 (37.5%) |
| Small tissue loss** | 22 (4.7%) |
| Major tissue loss** | 3 (0.6%) |
| Venous thrombosis** | 3 (0.6%) |
| Intermittent claudication >6 months** | 1 (0.2%) |
| *Kidney* | |
| Proteinuria >0.5 g* | 220 (46.2%) |
| Lupus nephritis | 216 (45.8%) |

| Variable | jSLE (n=484) |
|---|---|
| Histologic classification | |
| - Class I | 5 (2.7%) |
| - Class II | 25 (13.8%) |
| - Class III | 33 (18.2%) |
| - Class IV | 96 (53.0%) |
| - Class V | 14 (7.7%) |
| - Class VI | 2 (1.1%) |
| - Class II and V | 3 (1.6%) |
| - Class III and V | 1 (0.5%) |
| - Class IV and V | 2 (1.1%) |
| Haematuria* | 191 (42.8%) |
| Cellular casts* | 158 (5.1%) |
| Creatinine units: | |
| - Micromol/L | 6 (3.5%) |
| - Mg/dL | 164 (96.4%) |
| Histological change after re-biopsy | 20 (29%) |
| Recurrent nephritis** | 76 25.1%) |
| New renal biopsy: | |
| - Only 1 | 33 (20.1%) |
| - More than 1 | 4 (2.4%) |
| High blood pressure in 1st nephritis episode | 70 (15.4%) |
| Corticosteroids interruption | 46 (10.3%) |
| Creatinine clearance <50%** | 36 (7.8%) |
| Proteinuria >3.5g/24hs** | 26 (5.5%) |
| Renal terminal failure ** | 27 (5.9%) |
| Proteinuria | |
| - g/24hs | 135 (g/24h) |
| - mg/24hs | 34 (mg/24h) |
| *Neuropsychiatric* | |
| Depression | 71 (15.0%) |
| Seizures* | 65 (13.6%) |
| Seizures** | 46 (9.7%) |
| Lupus headache(s)* | 40 (8.5%) |
| Organic brain syndrome* | 25 (5.3%) |
| Cognitive impairment/ Psychosis** | 21 (4.5%) |
| Psychosis* | 19 (4.0%) |
| Neuropathy** | 13 (2.8%) |
| Transverse myelitis** | 3 (0.6%) |
| Number of strokes** | 1.2±0.6 1[1-1] |
| *Ophtalmological* | |
| Cataract** | 31 (6.5%) |
| Visual disorder* | 24 (5.1%) |
| Retinopathy** | 22 (4.6%) |
| *Gastrointestinal* | |
| Serositis* | 18 (3.9%) |
| Hepatitis | 13 (2.7%) |
| Pancreatic insufficiency | 1 (0.2%) |
| *Haematological* | |
| Leukopenia* | 322 (68.1%) |
| Lymphopenia | 1964 (52.7%) |
| Thrombocytopenia* | 136 (29.4%) |
| Haemolitic anemia* | 70 (14.9%) |
| Severe thrombocytopenia | 44 (9.7%) |
| Haemoglobin< 8 gr/dl* | 40 (9.0%) |
| Haemophagocytic syndrome | 2 (0.4%) |
| Low haematocrit* | 32.3 ± 6.0 33.5 [29-36.8] |

| Variable | jSLE (n=484) |
|---|---|
| *Immunological* | |
| ANA* | 475 (98.5%) |
| Low complement* | 403 (85.2%) |
| Anti-dsDNA* | 391 (83.0%) |
| False Lues serology* | 200 (44.1%) |
| Anti-Ro* | 155 (33.4%) |
| Anti-RNP | 120 (26.0%) |
| Anti-Sm* | 118 (25.9%) |
| Anti-La | 87 (18.8%) |
| *Other* | |
| Amenorrhoea <40 | 22 (51.2%) |
| Rare manifestations | 56 (11.6%) |
| Secondary Sjögren's | 31 (6.5%) |
| Malignant neoplasia** | 18 (3.8%) |
| Other connective | 15 (3.6%) |
| Mixed connective tissue disorder | 7 (1.7%) |
| Number of malignancies** | 1.3 ± 0.6 1 [1-1] |
| *SLE criteria* | |
| Number of SLE criteria | 6.4 ± 1.8 6 [5-8] |
| *Indexes* | |
| SLEDAI | 3.3 ± [4.1] 2 [0-4] |
| SLICC | 1.2 ± 1.6 1 [0-2] |
| KATZ | 3.1 ± 1.9 3 [2-4] |
| CHARLSON | 1.6 ± 1.2 1 [1-2] |
| *Mortality* | |
| Dead | 13 (3%) |
| *Comorbidity* | |
| Smokers | 123 (28.8%) |
| Dyslipidaemia | 104 (22.4%) |
| Family history | 77 (21.3%) |
| High blood pressure | 100 (20.8%) |
| Autoimmune thyroiditis | 31 (6.6%) |
| Alcoholism | 14 (3.1%) |
| Congestive heart failure | 8 (1.7%) |
| Diabetes mellitus**: | |
| - With affectation | 8 (1.7%) |
| - Without affectation | 0 (0%) |
| Chronic obstructive pulmonary disease | 7 (1.5%) |
| Peripheral arterial disease | 3 (0.7%) |
| Malignance**: | |
| - Solid without metastasis | 15 (3.1%) |
| - Solid with metastasis | 0 (0%) |
| - Leukaemia | 1 (0.2%) |
| - Lymphoma | 2 (0.4%) |
| *Pharmacological treatment* | |
| Corticosteroids (ever) | 433 (93%) |
| Corticosteroids dosage: | |
| - <10 mg | 211 (75.3%) |
| - 10-30 mg | 50 (17.8%) |
| - 30-60 mg | 14 (5%) |
| - >60 mg | 5 (1.7%) |
| Antimalarial | 382 (82.2%) |
| Non-steroidal anti-inflammatory drugs | 327 (70.7%) |
| Azathioprine | 212 (46.1%) |
| Aspirin | 167 (41.9%) |
| Cyclophosphamide | 167 (36.1%) |
| Mycophenolate mophetil | 113 (24.7%) |
| Corticosteroids for kidney disease | 119 (24.5%) |
| Corticosteroids for cutaneous disease | 83 (17.1%) |
| Oral anticoagulants | 63 (13.7%) |
| Corticosteroids (for haematological disease) | 64 (13.2%) |
| Methotrexate | 63 (13.1%) |
| Rituximab | 47 (10.3%) |
| Immunoglobulin IV | 41 (9.1%) |
| Mycophenolic acid | 18 (4.6%) |
| Leflunomide | 14 (2.9%) |
| Anti-TNF | 9 (1.9%) |
| Abatacept | 1 (0.2%) |
| *Non pharmacological treatment* | |
| Dialysis | 23 (5%) |
| Kidney transplantation | 15 (3.3%) |
| Splenectomy | 14 (3.1%) |
| Plasmapheresis | 11 (2.3%) |
| *Comorbidities treatment* | |
| Calcium and Vitamin D | 304 (69.3%) |
| Angiotensin converting enzyme inhibitors | 137 (31.1%) |
| Statins | 85 (19.4%) |
| Anti-osteoporotic | 85 (19.1%) |
| Diuretic | 90 (20.7%) |
| Anti-diabetic | 6 (1.4%) |

Mean: standard deviation); Median: [range]; Number: (percentage). *SLEDAI items. **SLICC/ACR items.

*Study population*

Out of 4,024 SLE-diagnosed patients enrolled in the cross-sectional stage of the RELESSER Registry, all those who fulfilled at least four American College Rheumatology (ACR) 1997 SLE criteria (18, 19) were included. We divided patients in two groups, those in whom the disease started prior to 18 years of age (jSLE) and those in whom it started at 18-years-old or later (aSLE).

*Variables*

Socio-demographics: age, ethnicity, sex, age at onset, delay of diagnosis, and disease duration.

Clinical and serological features (by organs and systems) (17): extracted from ACR criteria, SLE Disease Activity Index (SLEDAI), British Island Lupus Assessment Group (BILAG 2004) (20) and Systemic Lupus International Coborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) specific items, infrequent manifestations, mortality and cause of death (17).

Activity score: SLEDAI (21) at the time of the last evaluation.

Immunological factors: complement levels, ANA, anti-Ro/SS-A, anti-La/SS-B, anti-U1RNP, anti-Sm, anti-dsDNA, anti-cardiolipin antibodies and lupus anticoagulant, as measured using standardised techniques.

Damage and severity scores: cumulative

damage was assessed using the SLICC/ACR DI (22), and disease severity with the Katz index (23).

SLE treatment factors: current or previous use (and reason for discontinuation) of non-steroidal anti-inflammatory drugs (NSAIDs), oral and intravenous steroids (including maximum dose and reason for prescribing them), azathioprine, hydroxicloroquine, methotrexate, leflunomide, cyclosporine-A, mycophenolate mophetil, cyclophosphamyde, rituximab, belimumab, immunoglobulins, mycophenolic acid, plasmapheresis, splenectomy, dialysis and kidney transplantation.

Co-morbidities and their treatments: smoking status, dyslipidaemia, diabetes, high blood pressure, hypothyroidism, chronic pneumopathy, chronic obstructive pulmonary disease, peripheral vasculopathy, malignancies, liver disease, severe infections, hospitalisations, oral hypoglycemic drugs, statins, anti-hypertensive medication, oral contraception, calcium-vitamin D andbisphosphonates and Charlson index (17, 24).

Any and all variable-related information was classified as 'present' if it occurred at any time since SLE onset (12). A specific guideline of codes and definitions for all RELESSER investigators was created to standardise and clarify data collection.

*Statistical analyses*

Means and standard deviations or medians and interquartile percentiles for numeric variables based on normal distribution, as well as absolute and relative frequencies for categorical variables, were calculated. Global and segmented population-based analyses on the presence of jSLE *versus* aSLE were carried out. The relation of each independent variable with the dependent variable (age at diagnosis) was assessed by applying statistical tests: the Student's *t*-test for numerical variables and the Chi-squared test for comparing categorical variables among groups.

Statistical significance was assumed as $p<0,05$. All analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

**Table II.** All clinical, serological, activity and chronicity scores, comorbidity and therapeutic features we found significantly different among juvenile-onset-SLE and adult-onset-SLE ($p<0.05$).

| Variable | aSLE (n=3.428) | jSLE (n=484) | *p*-value |
|---|---|---|---|
| *Constitutional* | | | |
| Lymphadenopathy | 321 (9.6%) | 60 (12.6%) | 0.039 |
| Splenomegaly | 96 (2.9%) | 29 (6.2%) | <0.001 |
| Fever** | 117 (3.5%) | 26 (5.4%) | 0.035 |
| *Mucocutaneous* | | | |
| Malar rash* | 1656 (49.0%) | 327 (68.3%) | <0.001 |
| Mucosal ulcers* | 1388 (41.2%) | 245 (52.4%) | <0.001 |
| *Articular* | | | |
| Myositis* | 113 (3.4%) | 26 (5.6%) | 0.033 |
| Osteoporosis** | 252 (7.6%) | 15 (3.2%) | 0.001 |
| Fibromyalgia | 224 (6.7%) | 11 (2.4%) | <0.001 |
| *Heart* | | | |
| Pericarditis* | 486 (15.5%) | 94 (19.9%) | 0.009 |
| Vasculitis* | 267 (8%) | 60 (12.8%) | 0.001 |
| Cardiomyopathy** | 104 (3.1%) | 7 (1.5%) | 0.050 |
| *Respiratory* | | | |
| Pleuritis* | 693 (20.7%) | 134 (28.3%) | 0.001 |
| *Vascular* | | | |
| Raynaud | 1068 (32.2%) | 172 (37.5%) | 0.022 |
| Small tissue loss** | 66 (2%) | 22 (4.7%) | <0.001 |
| *Kidney* | | | |
| Lupus nephritis | 867 (25.9%) | 216 (45.8%) | <0.001 |
| Proteinuria >0.5 g* | 884 (26.7%) | 220 (46.2%) | <0.001 |
| Haematuria* | 853 (26.5%) | 191 (42.8%) | <0.001 |
| Cellular casts* | 568 (17.4%) | 158 (35.1%) | <0.001 |
| Creatinine units | | | |
| - Micromol/L | 522 | 135 | |
| - Mg/dL | 212 | 34 | 0.021 |
| High blood pressure in 1st nephritis flare | 328 (10%) | 70 (15.4%) | <0.001 |
| Recurrent nephritis** | 237 (12.7%) | 76 (25.1%) | <0.001 |
| New renal biopsy: | | | |
| - Only 1 | 96 (11.2%) | 33 (20.1%) | |
| - More than 1 | 15 (1.7%) | 4 (2.4%) | 0.006 |
| Histological change | 49 (14.1%) | 20 (29%) | 0.002 |
| Creatinine clearance <50%** | 160 (4.8%) | 36 (7.8%) | 0.007 |
| Proteinuria >3.5g/24hs** | 106 (3.2%) | 26 (5.5%) | 0.007 |
| Renal failure terminal** | 72 (2.2%) | 27 (5.9%) | <0.001 |
| Corticosteroids interruption | 198 (6.2%) | 46 (10.3%) | 0.001 |
| *Neuropsychiatrics* | | | |
| Seizures* | 178 (5.3%) | 65 (13.6%) | 0.004 |
| Lupus headache* | 180 (5.4%) | 40 (8.5%) | 0.023 |
| Organic brain syndrome* | 83 (2.5%) | 25 (5.3%) | 0.001 |
| Psychosis* | 61 (0.8%) | 19 (4.0%) | <0.001 |
| Cognitive impairment/ Psychosis** | 84 (4.2%) | 21 (4.5%) | 0.015 |
| Seizures** | 141 (4.2%) | 46 (9.7%) | <0.001 |
| *Gastrointestinal* | | | |
| Serositis* | 47 (1.4%) | 18 (3.9%) | <0.001 |
| *Haematological* | | | |
| Thrombocytopenia* | 717 (21.8%) | 136 (29.4%) | 0.001 |
| Haemolytic anaemia* | 257 (7.8%) | 70 (14.9%) | <0.001 |
| Severe thrombocytopenia | 183 (5.6%) | 44 (9.7%) | 0.001 |
| Haemoglobin< 8 gr/dl | 145 (4.4%) | 40 (9.0%) | <0.001 |
| Thrombotic thrombocytopenic purpura | 72 (2.2%) | 17 (3.7%) | 0.046 |
| Haematocrit* | 34±6.0 35 [31-37.8] | 32.3±6.0 33.5 [29-36.8] | <0.001 |

| Variable | aSLE (n=3.428) | jSLE (n=484) | *p*-value |
|---|---|---|---|
| *Serological (immuno-haematological)* | | | |
| Low complement* | 2503 (74.5%) | 403 (85.2%) | <0.001 |
| Anti-dsDNA* | 2300 (68.7%) | 391 (83.0%) | <0.001 |
| False Lues serology* | 1158 (36.7%) | 200 (44.1%) | <0.003 |
| Anti-Ro* | 1315 (39.5%) | 155 (33.4%) | 0.011 |
| Anti-Sm* | 622 (19.0%) | 118 (25.9%) | <0.001 |
| *Other* | | | |
| Amenorrhoea <40 | 74 (6.7%) | 22 (51.2%) | <0.001 |
| Malignant neoplasia** | 206 (6.1%) | 18 (3.8%) | 0.039 |
| Secondary Sjögren's | 508 (15.3%) | 31 (6.5%) | <0.001 |
| Rare manifestations | 257 (7.5%) | 56 (11.6%) | 0.002 |
| Number of malignances** | 1.0 ± 0.2 1 [1-1] | 1.3 ± 0.6 1 [1-1] | <0.001 |
| Number of SLE criteria | 5.4 ± 1.6 5 [4-7] | 6.4 ± 1.8 6 [5-8] | <0.001 |
| *Indexes* | | | |
| SLEDAI | 2.4 ± 3.5 2 [0-4] | 3.3 ± [4.1] 2 [0-4] | <0.001 |
| KATZ | 2.4 ± 1.5 2 [1-3] | 3.1 ± 1.9 3 [2-4] | <0.001 |
| CHARLSON | 2.4 ± 1.9 2 [1-3] | 1.6 ± 1.2 1 [1-2] | <0.001 |
| *Mortality* | | | |
| Death | 207 (6.6%) | 13 (3%) | 0.003 |
| Causes of death | | | |
| - SLE related | 51 (24.6%) | 5 (38.4%) | 0.267 |
| - Infections | 53 (32.3%) | 4 (44.4%) | 0.451 |
| - Malignancy | 32 (19.8%) | 0 (0%) | 0.138 |
| - Cardiovascular | 47 (30.3%) | 5 (55.6%) | 0.114 |
| - Other | 4 (2.7%) | 1 (12.5%) | 0.125 |
| - Unknown | 33 (19.9%) | 2 (16.7%) | 0.787 |
| *Comorbidity* | | | |
| Smokers | 1341 (43.3%) | 123 (28.8%) | <0.001 |
| Dyslipidaemia | 1076 (32.7%) | 104 (22.4%) | <0.001 |
| Family history | 381 (15.2%) | 77 (21.3%) | 0.003 |
| High blood pressure | 1001 (29.5%) | 100 (20.8%) | <0.001 |
| Congestive cardiac insufficiency | 149 (4.4%) | 8 (1.7%) | 0.005 |
| Diabetes mellitus** | | | |
| With organ involvement | 164 (4.8%) | 8 (1.7%) | |
| Without organ involvement | 30 (0.8%) | 0 (0%) | 0.001 |
| Chronic obstructive pulmonary disease | 101 (3 %) | 7 (1.5%) | 0.057 |
| Peripheral arterial disease | 75 (2.4%) | 3 (0.7%) | 0.021 |
| *Pharmacological treatment* | | | |
| Corticosteroids | 2813 (86.3%) | 433 (93%) | <0.001 |
| NSAIDs | 2296 (71.7%) | 327 (70.7%) | 0.008 |
| Azathioprine | 939 (29.1%) | 212 (46.1%) | <0.001 |
| Aspirin | 982 (35.8%) | 167 (41.9%) | 0.017 |
| Cyclophosphamide | 604 (18.7%) | 167 (36.1%) | <0.001 |
| Mycophenolate mophetil | 399 (12.4%) | 113 (24.7%) | 0.034 |
| Corticosteroids for kidney disease | 449 (13.0%) | 119 (24.5%) | <0.001 |
| Corticosteroids for cutaneous involvement | 430 (12.5%) | 83 (17.1%) | 0.017 |
| Corticosteroids for haematological involvement | 326 (9.4%) | 64 (13.2%) | 0.037 |
| Rituximab | 179 (5.6%) | 47 (10.3%) | <0.001 |
| Immunoglobulin IV | 120 (3.6%) | 41 (9.1%) | <0.001 |
| Mycophenolic acid | 66 (2.1%) | 18 (4.6%) | <0.001 |
| *Non pharmacological treatment* | | | |
| Dialysis | 84 (2.7%) | 23 (5%) | 0.002 |
| Kidney transplantation | 42 (1.4%) | 15 (3.3%) | 0.001 |
| Splenectomy | 45 (1.4%) | 14 (3.1%) | 0.008 |
| *Comorbidities treatment* | | | |
| Calcium and Vitamin D | 2028 (64.3%) | 304 (69.3%) | <0.001 |
| Statins | 803 (25.8%) | 85 (19.4%) | 0.013 |
| Anti-osteoporotic | 771 (29.5%) | 85 (19.1%) | <0.001 |
| Anti-diabetic | 154 (4.9%) | 6 (1.4%) | 0.001 |

Mean: (Standard Deviation); Median: [range]; Number: (percentage).
*SLEDAI items. **SLICC/ACR items.

## Results

*Demography*

We included 3.428 aSLE (89.6 % female) and 484 jSLE (89.8 % female); 93.3% of aSLE and 93.0% of jSLE were Caucasians, with mean (±SD) age at diagnosis: 38.1(±14.0) and 16.6 (±6.3) years ($p$<0.001), respectively. Mean (±SD) delay in diagnosis since first disease symptom was 24.7 (±47.4) *vs*. 39.9 (±77.3) months ($p$<0.001), mean disease duration (since diagnosis) 14.9 (±9.7) and 10.7 (±7.2) years ($p$<0.001), respectively; and mean age at end of follow-up: 48.8 (±14.3), 31.5 (±10.5) years ($p$<0.001), respectively.

Prevalence data for all jSLE variables is shown in detail in Table I. Herein we summarise the most frequent (>50%) and clinically relevant findings among each category. Among the more prevalent clinical manifestations (by domains) in jSLE patients were: malar rash, photosensitivity and mucosal ulcers (mucocutaneous); arthritis (musculoskeletal); lupus nephritis, proteinuria and haematuria, with Class IV the most frequent histologic type (renal); pleuritis (pulmonary); pericarditis (cardiovascular); seizures (neuropsychiatric); and leukopenia, lymphopenia (Haematological). Of all the immunological features assessed, hypocomplementaemia and anti-dsDNA were the most prevalent. Among the main treatments used, corticosteroids, antimalarial, NSAIDs, were the drugs most frequently prescribed.

Table II summarises all of the significant differences between the two groups in detail. Herein we recap the most relevant and statistically significant differences that were more frequently observed in jSLE than in aSLE: lymphadenopathy, fever; malar rash, mucosal ulcers; pericarditis, pleuritis, Raynaud's phenomenon; lupus nephritis, proteinuria, haematuria, recurrent nephritis, new renal biopsy; seizures, lupus headache, organic brain syndrome; thrombocytopenia, severe thrombocytopenia, haemolytic anaemia, haemoglobin <8 gr/dl, and thrombotic thrombocytopenic purpura; low complement, anti-dsDNA and false lues serology; higher SLEDAI and KATZ scores; SLE family history; and the use of all SLE-related

treatment types. aSLE patients suffered higher mortality rates, as well as more secondary cases of Sjögren; anti-Ro; fibromyalgia; and osteoporosis.

After adjusting by disease duration, mortality remained higher in the aSLE group compared to jSLE (Table B, Supplementary material).

All other variables that did not reach statistical significance are shown in the Table A of the Supplementary Material section.

## Discussion

In the present paper we show that jSLE presented more severe and greater numbers of SLE features compared to aSLE in a large cohort of patients. Our registry allowed us to explore many SLE-related characteristics in a long-term group of adult- and juvenile- onset SLE patients. Therefore, we are able to confirm previous published data and to add new knowledge to the differing phenotype between these two types of SLE patients.

We found similar data regarding the prevalence of constitutional, haematological, central nervous system and immunological involvement in jSLE than what has been previously described (9, 10, 12, 13). However, we found the incidence of renal disease to be slightly lower than previous authors reported (14), which was mainly due to class-IV nephritis, as other series have shown. Importantly, recurrent renal disease was shown to occur in up to 25% of patients, doubling the recurrence rate observed in aSLE; moreover, changes in histologic class were observed in 28.9% of those who underwent additional biopsies. This latter finding, as well as the greater prevalence of renal disease, probably led to the more frequent use of several immunosuppressant drugs, rituximab, steroids (via any route and at a higher doses), dialysis and renal transplantation observed in our study.

Regarding jSLE CNS involvement, we found lower prevalences of psychosis, seizures, organic brain syndrome, and lupus headaches than other authors have reported (14). A lower prevalence of lymphadenopathy (12.6%) than what has been previously published was also observed. The incidence rate of mucosal ulcers was also higher than previously reported (25). Finally, 8.4% of jSLE patients with arthritis presented deforming Jaccoud's arthropathy.

As previously described, jSLE patients presented more activity and severe disease, and more vital organ involvement than aSLE (1, 3-15). This finding is based on the higher prevalence of severe organ manifestations, such as renal and CNS involvement and the higher need of steroids, immunosuppressant drugs and biological therapies, compared to aSLE. Furthermore, jSLE patients exhibited higher scores in the Katz severity index, a proven index of SLE severity. Although no statistical difference was reached in SLICC/ACR DI index, certain areas of several domains included in this SLE cumulative damage index were more frequent in jSLE patients compared to aSLE. These involved areas were: small tissue loss, creatinine clearance <50%, proteinuria >3.5 g/24hs, terminal renal failure, amenorrhoea <40 years of age, cognitive impairment/psychosis and seizures. Osteoporosis, diabetes mellitus, cardiomyopathy and malignant neoplasia were more frequent in aSLE patients compared to jSLE patients. jSLE scores were higher in several activity, severity and damage indices. To the best of our knowledge, this is the first time that Charlson has been used in a large cohort of jSLE patients. Data on SLICC/ACR DI index scores in jSLE varies among different research groups when comparing to aSLE and late-onset (>50 years old) SLE. Several authors have found higher scores in late-onset SLE than in aSLE and jSLE (26, 27). The latter observation has been attributed to aging, comorbid conditions and the presence of traditional risk factors in late-onset SLE, while being a supposed milder SLE disease. In our study, no differences were observed, although we did not assessed late-onset SLE patients.

With our more robust study, in terms of the number of patients included overall, our results are in agreement with previous studies that recorded more frequent renal, CNS, pericardial, severe haematological and immunological (DNAds, Sm autoantibodies and hypocomplementaemia) manifestations (1, 3-13).

Mortality was higher in the aSLE group, although no differences were observed regarding SLE-related or other specific causes of death. This lower rate of mortality differs from what has been published in the literature, as 90% of jSLE patients achieved a 10-year survival rate in one study (2). We believe one possible explanation for this stems from the likelihood that jSLE patients would be more adherent to follow-up visits, treatments, health behaviour recommendations, and, finally, to tighter control. Indeed, as they are highly encouraged to be more compliant since their juvenile onset by parents, mentors and caregivers, the lower mortality rates observed in these patients is not unexpected. Unfortunately, our study could not assess the latter and we cannot confirm this suggestion. Moreover, since most of our patients were Caucasian we must be cautious in this regard, as jSLE is reportedly more frequent and severe in African-Americans, Native Americans and Hispanic communities compared to Caucasian patients (14). Therefore, our study would not have accounted for the impact on 10-year mortality rates that the inclusion of these ethnicities, if widely represented in our cohort, might have yielded. In addition, aSLE patients presented more comorbidity inherent to aging and adult behaviour (smoking, dyslipidaemia, cardiac failure, obstructive pulmonary disease, malignancy, etc.) that might explain a higher mortality rate in aSLE patients. However, the prevalence of some of these comorbidities remains of real concern in jSLE. Therefore, physicians and healthcare-givers must be aware of them and take them into consideration when treating each individual patient.

However, particular features related to jSLE activity - *e.g.* nephrotic-range proteinuria - have also been posted as risk factors for the presence of long-term comorbidities such as early-onset atherosclerosis (onset prior to 18 years of age), high blood pressure and poorer blood lipid profile; this was the case in a 26 jSLE patient study (16). Our study could not confirm that the greater prevalence of nephrotic-range proteinuria

shown by jSLE *versus* aSLE patients also led to a greater incidence of atherosclerosis-related comorbidities (16). Among other comorbidities, secondary Sjögren's syndrome occurred more often in aSLE, which might be linked to the presence of more frequent anti-Ro positivity in aSLE patients than in jSLE.

Comparing our data with previous studies, we disagree with those who found more frequently lower female:male ratio and more Raynaud's phenomenon in jSLE patients than in the aSLE population (13, 14, 23, 28), except for the study of Martinez-Barrio *et al*. who also found Raynaud's phenomenon as and independent risk factor for damage accrual (26) and the study of Choi *et al*. (29).

One of the limitations of this study is its cross-sectional design; a longitudinal study can more adequately assess clinical and serological features of jSLE over time. Although it is an intrinsic characteristic of real-world settings, another limitation is the lack of unique and homogenous techniques for assessing each laboratory marker. Moreover, the lack of sufficient information concerning non-Caucasian ethnicities would prevent a more complete picture of jSLE. On the other hand, our study has several strengths: the considerable amount of data collected, the large number of patients, the participation of several centres of every region from an entire country and the long follow-up time. Besides, it might be interesting in future studies to compare the impact of the disease on physical and psychosocial development between jSLE and aSLE, to better understand the consequences on the quality of life of an early onset disease

In conclusion, we compared clinical and serological features, treatment, comorbidities, severity, disease activity and damage indexes scores, and mortality between a large group of jSLE and aSLE patients. We found substantial differences among them, not only confirming previously published data, but also adding relevant new information for the management of jSLE patients. We observed that jSLE patients presented more severe disease with frequent organic-specific involvement. Further investigations involving prospective studies are needed to confirm our observations.

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