






## Original Article

# Incidence and prevalence of systemic lupus erythematosus across Italian referral centers and its clinical burden in terms of disease severity, treatment and hospitalization: The ESCULAPIO study



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## ABSTRACT

**Background:** Systemic lupus erythematosus (SLE) is a complex autoimmune disease with multiorgan involvement. Limited data from specialized referral centers are available at national level. This study assessed epidemiologic, clinical, therapeutic features and hospitalization burden of SLE through data from tertiary Italian referral centers. **Methods:** A cross-sectional study was conducted across 16 SLE referral centers in 10 districts of the North, Center and South of Italy. Only patient resident in the districts of interest were included. Demographic, clinical, and therapeutic features were collected. Prevalence and incidence estimates were calculated using data from the National Institute of Statistics.

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**Results:** 2,031 SLE patients were included. In January 2024, the estimated prevalence of SLE was 15.3 cases/100,000 individuals, varying from 11.3 (South and Islands), 13.1 (Center), and 25.3 (North) cases/100,000 individuals. Incidence showed a decreasing trend, from 0.43 cases/100,000 individuals in 2019 to 0.29 in 2022. Most patients were female (89.5 %), with a mean age at diagnosis of 35.4 years. Musculoskeletal (70.7 %) and mucocutaneous (60.2 %) were the most common manifestations. Disease severity was classified as mild (33.2 %), moderate (33.0 %) and severe (33.8 %). 38.6 % patients had a relapsing-remitting course, 13.0 % were chronic-active, and 48.4 % long-quiescent. High reliance on corticosteroids (85 %) and underutilization of biologic DMARDs (26 %) emerged. 55.4 % of patients experienced hospitalizations for any cause and 33.4 % for SLE relapses.

**Conclusion:** This study provides insights into epidemiological, clinical, and therapeutic features of SLE across referral centers highlighting significant regional disparities and emphasizing the need to increasingly align with EULAR recommendations even in highly qualified centers.

## 1. Introduction

Systemic Lupus Erythematosus (SLE) is a multifaceted systemic autoimmune disorder distinguished by a diverse array of clinical manifestations that can potentially impact any organ or system in the body. The disease exhibits a broad spectrum of severity and clinical trajectories, predominantly presenting as persistently active, relapsing-remitting, or frequently flaring phenotypes [1]. Understanding the complexity of SLE is essential, as it not only poses significant challenges for diagnosis and management, but also entails a considerable burden on healthcare systems worldwide.

Epidemiological studies of SLE have been extensively conducted across the globe, revealing how various factors—including genetic predispositions, environmental influences, classification criteria, and the precision of laboratory techniques employed for disease screening—can significantly impact the incidence and prevalence of SLE in different geographical regions [2]. However, a notable gap in data persists, particularly in developing countries, where limited resources and varying levels of healthcare expertise may hinder accurate diagnosis and management. The multivarious clinical presentation of SLE further complicates this challenge, particularly in less experienced healthcare settings. Consequently, the choice of reference population for estimating disease prevalence and incidence emerges as a critical source of bias that must be considered when interpreting SLE epidemiological studies. This complexity underscores the heterogeneity of the disease burden observed in different investigations [3,4]. Focusing on the European context, numerous nationwide analyses concerning SLE epidemiology have been published over the past decade [5–9]. These studies consistently reveal a varied distribution of disease, even within different regions of individual countries. In Italy, however, the available reports are sparse, fragmented, and predominantly based on regional or local estimates [10–14]. As a result, these findings fail to provide a reliable overview of national SLE epidemiology at referral centers.

These studies also offer limited insights into critical parameters such as disease activity and clinical course, as the data sources primarily consist of general practitioners' registries or clinical records, which tend to inadequately capture or overlook these aspects compared to highly specialized centers tasked with systematically evaluating SLE-related activity and damage. Another key indicator of disease severity, as well as a reflection of the effectiveness and quality of care management, is the analysis of hospitalization rates and their causes. To date, only few studies focusing on the Italian SLE population [15,16] have addressed this issue, revealing a decline in hospitalizations for SLE as a primary diagnosis between 2001 and 2012. However, these studies also noted an increase in admissions for cerebrovascular accidents, acute coronary syndrome, and chronic renal failure, indicating potential consequences of improved survival rates and damage accrual resulting from prolonged maintenance therapy.

On these premises, our study aims to estimate the prevalence and incidence of SLE at highly certified centers of expertise for the disease, and to provide a comprehensive evaluation of the clinical characteristics

of SLE patients referred to these care centers across Italy. By doing so, we seek to deliver a more nuanced representation of the disease burden attributable to both disease-related and care-related factors, and their relationship with treatments. This will involve an in-depth analysis of SLE severity and course, disease activity, medical treatment regimens, and the burden of hospitalization, thereby contributing to the understanding and management of SLE.

## 2. Methods

### 2.1. Study design and setting

A cross-sectional study was conducted in 16 Italian referral centers for SLE in 10 districts of the North (Brescia, Ferrara, Padua, Udine), Center (Florence, Pisa, Rome) and South and Islands (Bari, Cagliari, Naples) of Italy. These centers were selected as they act as hub centers for the disease in the districts of interest.

### 2.2. Patients

We retrospectively collected data for patients diagnosed with SLE, actively referring to the 16 centers included in the study. Only patients residing in one of the 10 Italian districts of interest were considered includible in the study, to be more accurate in prevalence and incidence estimates. Data on patients followed at centers different from the district of residence, were reallocated to the district of residence.

### 2.3. Data collection

We collected data regarding demographic, clinical and therapeutic features, overall and at the time of the last available follow-up. Demographic features included sex, age at SLE onset, diagnosis, and features at the last follow-up, as well as the district of residence.

We collected data regarding the following clinical features: fulfillment of 2019 ACR/EULAR classification criteria [17] or the SLICC criteria [18] for SLE; type of disease involvement; overall disease severity; disease activity at last follow-up; overall disease course; number of hospitalizations following SLE diagnosis, categorized as overall or related to SLE relapses, cardiovascular disease (CVD), infections, and bone fractures, separately.

Disease severity was defined according to the EULAR recommendations [19] as major organ threatening disease considering the worst disease manifestations occurred anytime in the whole medical history (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis); thrombocytopenia with platelets  $<20 \times 10^3/\text{mm}^3$ ; TTP-like disease or acute hemophagocytic syndrome; SLEDAI  $>12$ ;  $\geq 1$  BILAG A manifestations.

Disease activity was assessed based on the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K) score, calculated at last available follow-up [20]

Disease course was stratified according to the study by Tselios et al.

(2019) as: prolonged remission, defined as a clinical SLEDAI-2 K achieved within 5 years of enrolment and maintained for  $\geq 10$  years; relapsing-remitting disease, defined for patients with  $\geq 2$  remission periods (clinical SLEDAI-2K = 0 for two consecutive visits); persistently active, defined for patients with no remission [21]

Therapeutic features included pharmacological treatments administered for SLE during the entire follow-up, with a particular focus on glucocorticoids (GC); hydroxychloroquine (HCQ), traditional disease-modifying antirheumatic drugs (tDMARDs), and biologic DMARDs (bDMARDs), with a focus on belimumab and rituximab.

#### 2.4. Statistical analysis

The primary objective of the study was to assess the prevalence and incidence of SLE in patients followed-up by tertiary referral centers across 10 Italian districts.

For prevalence estimates, we considered as numerators all patients with SLE residing in the given districts and actively followed by any of the 16 Centers providing the data, and as denominator the total population resident in those districts on January 1st 2024, according to the Italian National Statistical Institute (ISTAT) [22] Data are reported as percentage per 100.000 residents with 95 % Confidence Intervals (95 % CI), both overall and stratified by region, i.e. North (Brescia, Ferrara Padua, Udine), Center (Florence, Pisa, Rome), and South and Islands (Bari, Cagliari, Naples) of Italy.

For incidence estimates, we considered four calendar years (2019–2022), to provide a pre- and post-pandemic overview. We considered as numerator patients receiving a new diagnosis of SLE in the calendar year of interest, resident in the districts of interest and followed by any of the Centers included in the study, and as denominator the population resident in those districts in the same year according to the ISTAT, excluding resident patients already diagnosed with SLE and included in this study. For each year, data are reported as percentage per 100.000 residents with 95 % Confidence Intervals (95 % CI), overall as well as stratified for the North (Brescia, Ferrara, Padua, Udine), Center (Florence, Pisa, Rome), and South and Islands (Bari, Cagliari, Naples) of Italy.

Patient's features were reported as absolute frequency, percentage relative to the total number of patients with available data, and 95 % CI for categorical variables, and as mean value, standard deviation, and range (min-max) for quantitative variables. Normal distribution was assessed using the Shapiro-Wilk test.

### 3. Results

#### 3.1. Prevalence and incidence of patients followed at referral centers in Italy

A total of 5.414 patients with SLE followed at the 16 reference centers participating in the study, including 1.728 in the North, 2.453 in the Center and 1.233 in the South and Islands were included. Among them, 2.031 patients were resident in the 10 districts included in the study and were therefore included in the final cohort, including 771 (44.6 %) in the North, 738 (30.1 %) in the Center and 522 (42.3 %) in

**Table 1**  
Distribution of patients residing in the study stratified by geographical area.

	North	Center	South and Islands	Overall
Number of SLE patients followed at the referral centers involved in the study	1728	2453	1233	5414
Patients residing in the district of the centers ( % ) involved in the study	771 (44.6 %)	738 (30.1 %)	522 (42.3 %)	2031 (37.5 %)

the South and Islands (Table 1). The distribution of patients across the 10 districts is reported in **Supplementary Table 1**.

On January 1st, 2024, the estimated overall prevalence of SLE in tertiary referral centers was 15.3 cases per 100.000 individuals (Fig. 1a). Following stratification by geographical area (North, Centre, South and Islands) of Italy, the estimated prevalence ranged from 11.3 (South and Islands) to 13.1 (Center), and to 25.3 (North) cases per 100.000 individuals (Fig. 1a).

We also estimated the overall incidence of SLE in tertiary referral centers for the years 2019–2022, reporting 0.431 cases per 100.000 individuals/year in 2019, 0.321 cases in 2020, 0.322 cases in 2021, and 0.293 cases in 2022 (Fig. 1b).

#### 3.2. Clinical features of the cohort included

Clinical and therapeutic data from the cohort of 2.031 patients with SLE referring to 16 Italian referral centers for the disease and resident in 10 districts of the North, Center and South of Italy were retrieved. Demographic data and overall clinical features are reported in Table 2.

1.818/2.031 (89.5 %) were female, with a mean age at onset of 33.7 (14.4; min 1.6 - max 81.0) and mean age at diagnosis of 35.4 (14.5; min 1.8 - max 83.8) years.

Regarding disease involvement, from SLE diagnosis until last available follow-up, 1.436 (70.7 %) patients had articular, 1.223 (60.2 %) mucocutaneous, 907 (44.7 %) hematological, 896 (44.1 %) constitutional, 627 (30.9 %) renal, 352 (17.3 %) cardiovascular, 259 (12.8 %) neurological, and 33 (1.6 %) gastrointestinal involvement (Table 2).

Both SLICC and EULAR/ACR classification criteria were satisfied in around 93 % of patients (Table 2).

#### 3.3. Disease course and severity, treatment and hospitalization rate

The overall disease course (categorized as chronic-active, relapsing-remitting, or long-quiescent) was assessed on 1.682 patients. Overall disease severity (categorized as mild, moderate or severe according to the worst disease manifestations in the whole medical history) was evaluated on 2.030 patients, along with the overall treatment distribution.

Regarding overall disease course, 649 (38.6 %) patients were relapsing-remitting, 219 (13.0 %) chronic-active, and 814 (48.4 %) long-quiescent. Regarding overall disease severity, 674 (33.2 %) patients had mild disease, 670 (33.0 %) moderate disease, and 686 (33.8 %) severe disease. A stratification of the disease course according to overall disease severity and treatment distribution is represented in Fig. 2. Most patients with a long quiescent course had mild disease (97.5 %); as for patients with a chronic-active course, 68.9 % were mild, 22.8 % moderate, and 8.2 % severe. The proportion of severe cases was remarkably higher in the relapsing-remitting course (38.8 % severe, 39.6 % moderate, and 21.8 % mild). When considering overall treatments (i.e. any treatment ever used in the whole medical history), we found that in all disease course groups, GC and HCQ were a cornerstone of therapy (85 % and 89 %, respectively). tDMARDs were co-used in 72.3 % of relapsing-remitting, 81.3 % of chronic-active, and 57.2 % of long-quiescent cases, while bDMARDs were co-used in 33.7 %, 48.4 %, and 11.7 % of cases, respectively. Overall treatment distribution stratified by geographical area is reported in **Supplementary Table 2**, showing that in the North of Italy GC and bDMARDs were used less frequently as compared to the Center and the South and Islands.

The overall disease severity and treatment distribution are shown in Fig. 3. Similar percentages of GC were used in mild and severe patients, while tDMARDs and bDMARDs were mostly used in patients with a severe disease.

Complete data regarding disease course, overall severity, and treatment distribution are reported in **Supplementary Table 3**, whereas clinical features and treatment at last available follow-up, including the proportion of patients receiving ongoing GC and those on  $>5$  mg/day of

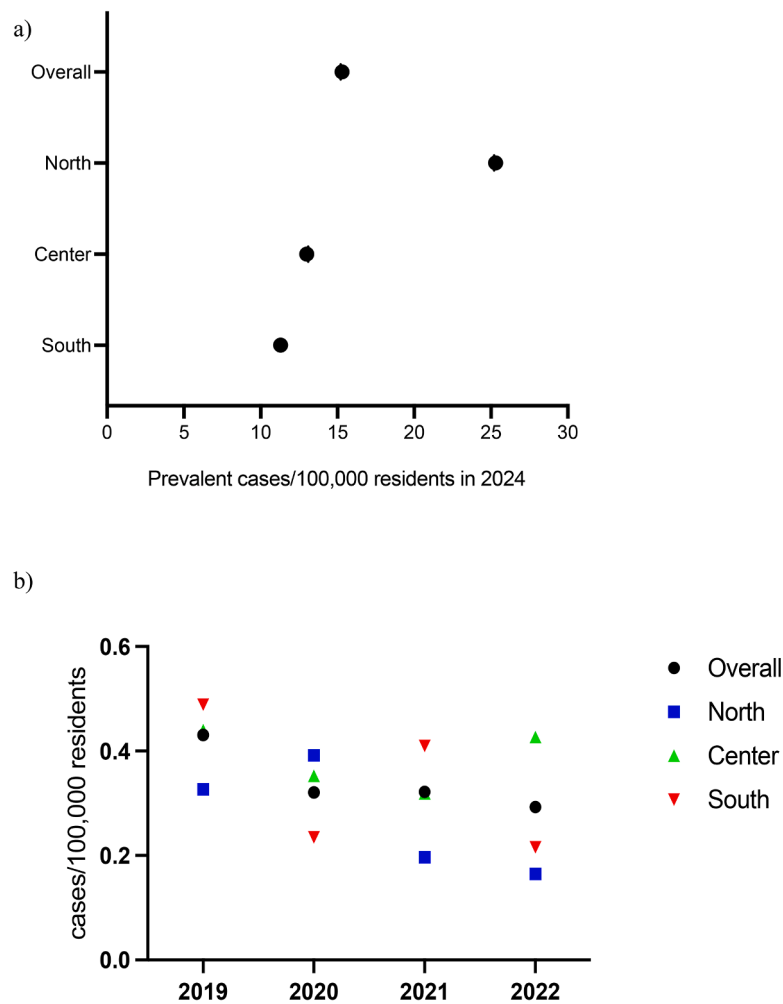


Fig. 1. a) Estimated prevalence (cases/100.000 people) at January 1st 2024, and b) estimated incidence (cases/100.000 people) for the years 2019–2022.

prednisone-equivalent, are reported in **Supplementary Table 4**. Finally, data on the number of hospitalizations were evaluated (**Table 3**). Overall, 941 patients (55.4 %) experienced at least one hospitalization for any cause, the mean number of hospitalizations per patient being of 2.2 (SD 1.8). The proportion of hospitalized patients ranged from 21.5 % for those with mild SLE to 44.9 % for those with severe SLE. Among the investigated causes of hospitalization (i.e., infections, CVD, bone fractures, and SLE relapses), SLE relapses were the major reason (576 cases, 33.4 % of the overall cohort), particularly for severe SLE cases ( $n = 339$ ).

#### 4. Discussion

The findings coming from our study provide insights into the prevalence and incidence and clinical features of patients with SLE, derived from a sizeable cohort of 2,031 patients across 16 referral centers in Italy.

The estimated prevalence of SLE of 15.3 cases per 100,000 individuals at centers of expertise, with regional variations from 11.3 in the South and Islands to 25.3 in the North, underscores the geographical disparities in disease distribution. This difference in disease prevalence is potentially due to healthcare access factors, and the higher prevalence in Northern Italy may reflect a better disease recognition in this area. Notably, the prevalence of SLE in referral centers is far below the estimated prevalence in Italian population, which attests around 60.5 per 100,000 persons (14), suggesting that a large proportion of SLE patients is managed in non-referral centers. Our incidence data, revealing a consistent decline from 2019 to 2022, presents an intriguing narrative

that warrants further exploration. This trend may be influenced by several factors, including the impact of the COVID-19 pandemic on healthcare accessibility and the diagnostic process. Notably, the data suggests that the pandemic might have led to a reduction in new diagnoses, potentially due to reduced healthcare visits, diagnostic delays, or even patient referral to more accessible clinical setting other than tertiary referral centers. This highlights an important aspect of SLE management, where timely diagnosis is crucial for optimizing patient outcomes.

In terms of clinical features, the predominance of female patients (89.5 %) and the average age of onset (33.7 years) reflect the typical demographic profile associated with SLE, consistent with findings from other studies. The high compliance with classification criteria (92.1 % for SLICC and 93.6 % for EULAR/ACR) underscores the adherence to established standards at referral centers, highlighting the importance of specialized care in facilitating appropriate patient assessment. The diversity of clinical manifestations in our cohort—ranging from musculoskeletal (70.7 %) and mucocutaneous (60.2 %) to renal (30.9 %) and neurological (12.8 %) involvement—illustrates the protean nature of SLE. These findings confirm the multi-organ impact of the disease and highlight the necessity for a comprehensive approach to patient management that addresses the myriads of potential complications.

Importantly, when stratifying overall disease severity (categorized as relapsing-remitting, chronic-active, and long-quiescent) and treatment regimens according to disease course, we found that patients with more severe disease tend to experience a relapsing-remitting or chronic-active course and often require more intensive therapies.

**Table 2**  
Demographic, clinical features and treatment of the cohort from SLE diagnosis until last available follow-up.

DEMOGRAPHIC FEATURES	No. PATIENTS
<b>Gender (n = 2031)*</b>	
Female	1818 (89.5 %, 95 % CI 88.1–90.8 %)
Male	213 (10.5 %, 95 % CI 9.2 %–11.9 %)
<b>Age at onset, yrs (n = 1832)**</b>	33.7 (14.4; min 1.6 - max 81.0)
<b>Age at diagnosis, yrs (n = 2007)**</b>	35.4 (14.5; min 1.8 - max 83.8)
<b>Diagnosis in pediatric age (&lt;18 yrs), (n = 2007)*</b>	208 (10.4 %, 95 % CI 9.1–11.8 %)
<b>OVERALL CLINICAL FEATURES</b>	
<b>Classification criteria</b>	
SLICC (n = 1884)*	1736 (92.1 %, 95 % CI 90.8 %–93.3 %)
EULAR/ACR (n = 2030)*	1899 (93.6 %, 95 % CI 92.4 %–94.6 %)
<b>Disease involvement (n = 2031)*</b>	
Articular	1436 (70.7 %, 95 % CI 68.7–72.7 %)
Muco-cutaneous	1223 (60.2 %, 95 % CI 58.1–62.4 %)
Hematological	907 (44.7 %, 95 % CI 42.5–46.9 %)
Constitutional	896 (44.1 %, 95 % CI 41.9–46.3 %)
Renal	627 (30.9 %, 95 % CI 28.9–32.9 %)
Cardiovascular	352 (17.3 %, 95 % CI 15.7–19.1 %)
Neurological	259 (12.8 %, 95 % CI 11.3–14.3 %)
Gastrointestinal	33 (1.6 %, 95 % CI 1.1–2.3 %)
Other	95 (4.7 %, 95 % CI 3.8–5.7 %)

\*n, % out of given total available observations, 95 % CI calculated by binominal “exact” calculation.

\*\* mean (SD; min-max).

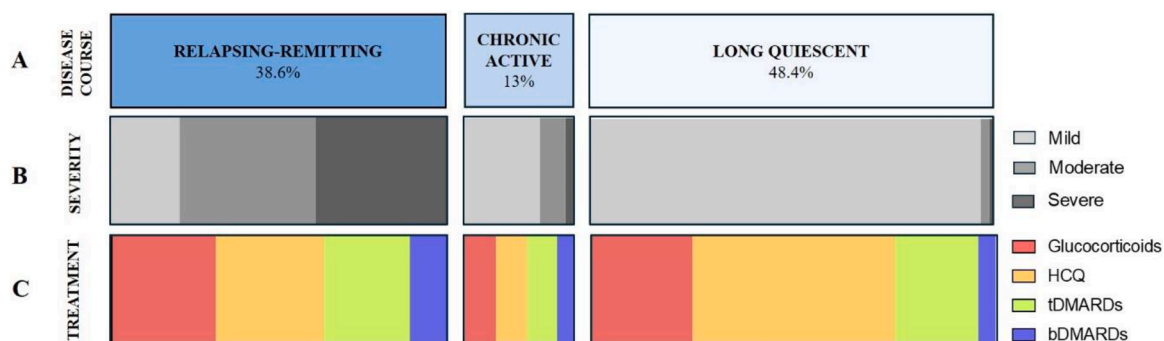
Despite advancement in treatment options over the past few years, a considerable proportion of patients in our study still rely on GC for disease management and >10 % of patients, at last follow-up visit, was still taking >5 mg/day of prednisone equivalent. This reliance highlights ongoing concerns regarding the long-term side effects associated with GC use, as well as the challenges in achieving optimal disease control with newer therapies.

Furthermore, 48.1 % of patients had a SLEDAI-2 K of 0, and among them, 47.2 % were still receiving glucocorticoids at a dose ≤5 mg/day at the last visit. This underscores the relevant role GCs still have in managing disease activity to attain and maintain remission. Furthermore, the utilization of biologic DMARDs remains lower than recommended by

EULAR guidelines, indicating potential barriers to access or awareness regarding these therapies even at referral centers for the disease. Interestingly, our data also reveal notable regional variations in treatment practices: in North Italy, corticosteroids were utilized less frequently than in other regions, which aligns these centers more closely with EULAR recommendations. However, this area also exhibited a lower utilization of biologic DMARDs, raising important questions for further discussion. Moreover, data about the use of HCQ show, in relation to EULAR recommendations, a relatively low percentage of patients taking the antimalarial therapy. This might suggest a problem of scarce compliance or high prevalence of contraindications or adverse effects related to the drug. Further analysis would be warranted for a better assessment of the underlying causes.

Examining hospitalization data, we showed that 941 patients (55.4 %) experienced at least one hospitalization, with a mean of 2.2 admissions per hospitalized patient, with patients with more severe disease experiencing hospitalizations more frequently. SLE relapses accounted for 576 hospitalizations (33.4 %), emphasizing the burden of disease activity on healthcare resources. Infections and CVD were also significant contributors, with 181 (10.7 %) and 178 (10.5 %) admissions, respectively. These data underscore the need for close monitoring of comorbidities and the potential for severe outcomes, particularly given the elevated risk of developing such comorbidities in patients with SLE. Notably, patients with mild disease had fewer hospitalizations related to SLE relapses, infections, and CVD, as compared to patients with moderate-to-severe disease, and this might reflect the need for more aggressive treatment in the latter group. This points to a relationship between disease severity and both CVD and overall relapse rates, while the need for more aggressive treatment may expose SLE patients to a higher risk of infections.

Some limitations coming from this study must be acknowledged: first, the study’s findings are based on patients from tertiary referral centers, which may not represent the broader SLE population in Italy, potentially leading to selection bias; second, the cross-sectional design limits the ability to establish causal relationships between variables and may not account for long-term trends; third, variations in data collection practices across centers may affect the consistency and completeness of the clinical information gathered; fourth, the influence of the COVID-19 pandemic on healthcare access and disease diagnosis may skew the incidence data reported. However, our study also relies on the following strengths: 1) the study includes a substantial number of patients, enhancing the statistical power and generalizability of the findings within the referral context; 2) conducting the study across 16 referral



**Fig. 2.** Overall disease course, stratified according to overall disease severity and treatment distribution\*.

**A)** Disease course stratified according to the study by Tselios et al., 2019. **B)** Disease severity defined according to EULAR recommendations by Fanouriakis. et al., 2019. Considering **relapsing-remitting**: Mild=21 %; Moderate=40 %; Severe=39 %; considering **chronic active**: Mild=69 %; Moderate=23 %; Severe=8 %; considering **long quiescent**: Mild=97 %; Moderate=2 %; Severe=1 %. **C)** Treatment distribution across **relapsing-remitting** is: Glucocorticoids=34 %; HCQ=35 %; tDMARDs=28 %; bDMARDs=13 % (belimumab=9 %; rituximab=4 %); across **chronic active**: Glucocorticoids=12 %; HCQ=11 %; tDMARDs= 11 %; bDMARDs=6 % (belimumab=3 %; rituximab=2 %); across **long quiescent** is: Glucocorticoids= 18 %; HCQ= 34 %; tDMARDs= 14 %; bDMARDs= 3 % (belimumab= 3 %; rituximab= 0 %).

tDMARDs—Traditional disease-modifying antirheumatic drugs; bDMARDs—Biological disease-modifying antirheumatic drugs.

\*Treatments could have been administered individually or in combination.

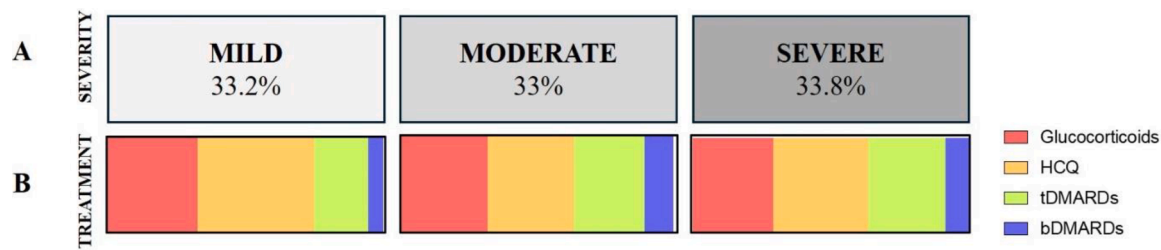


Fig. 3. Overall disease severity distribution according to treatment\*.

A) Disease severity according to EULAR recommendations by Fanouriakis et al., 2019 B) Treatment distribution across mild is: Glucocorticoids=24 %; HCQ=30 %; tDMARDs=14 %; bDMARDs=4 % (belimumab=3 %; rituximab=1 %); across moderate: Glucocorticoids=7 %; HCQ=6 %; tDMARDs=5 %; bDMARDs=2 % (belimumab=2 %; rituximab=0 %); across severe: Glucocorticoids=22 %; HCQ=22 %; tDMARDs=18 %; bDMARDs=6 % (belimumab=5 %; rituximab=1 %). tDMARDs=Traditional disease-modifying antirheumatic drugs; bDMARDs=Biological disease-modifying antirheumatic drugs.

\*Treatments could have been administered individually or in combination.

Table 3 Burden of disease in terms of hospitalizations.

Hospitalizations	N patients	N patients ( %)
<b>For any cause (n = 1698)*</b>	941 (55.4 %, 95 % CI 53.0-57.7 %)	423 severe (44.9 %), 316 moderate (33.6 %), 202 mild (21.5 %)
Mean n for patients with at least 1 hosp. **	2.2 (1.8; min 1- max 14)	
<b>For infections (n = 1699)*</b>	181 (10.7 %, 95 % CI 9.3-12.2 %)	95 severe (52.5 %), 55 moderate (30.4 %), 31 mild (17.1 %)
Mean n for patients with at least 1 hosp. **	1.4 (0.8; min 1- max 6)	
<b>For CVD (n = 1699)*</b>	178 (10.5 %, 95 % CI 9.1-12.0 %)	87 severe (48.9 %), 63 moderate (35.4 %), 28 mild (15.7 %)
Mean n for patients with at least 1 hosp. **	1.4 (0.9; min 1- max 7)	
<b>For bone fractures (n = 1698)*</b>	66 (3.9 %, 95 % CI 3.1-4.9 %)	20 severe (30.3 %), 28 moderate (42.4 %), 18 mild (27.3 %)
Mean n for patients with at least 1 hosp. **	1.2 (0.5; min 1- max 3)	
<b>For SLE relapses (n = 1723)*</b>	576 (33.4 %, 95 % CI 31.2-35.7 %)	339 severe (58.9 %), 172 moderate (29.9 %), 65 mild (11.3 %)
Mean n for patients with at least 1 hosp. **	1.7 (1.3; min 1- max 13)	

\*n, % out of given total available observations, 95 % CI.

\*\* mean (SD; min-max).

centers provides a diverse perspective and reinforces the robustness of the data collected; 3) the comprehensive assessment of clinical manifestations and treatment regimens allows for a nuanced understanding of SLE across different geographic areas.

### 5. Conclusions

Our findings reveal that a strikingly low proportion of SLE patients are being followed up at referral centers, indicating that many individuals may not be receiving the optimal care necessary for effective disease management. Despite the availability of advanced treatment options, there continues to be a significant reliance on corticosteroids, coupled with a relative underutilization of HCQ and biologic DMARDs. The high hospitalization rates resulting from SLE relapses and related comorbidities further highlight the urgent need for improved access to specialized care and strict adherence to treatment guidelines. Overall, this study underscores the critical importance of enhancing disease

management strategies and improving patient outcomes across all regions, ensuring that all SLE patients receive the comprehensive care they require.

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## Supplementary materials

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## References

- [1] Tsokos GC. Systemic lupus erythematosus. *N Engl J Med* 2011;365(22):2110–21.
- [2] Tian J, Zhang D, Yao X, Huang Y, Lu Q. Global epidemiology of systemic lupus erythematosus: a comprehensive systematic analysis and modelling study. *Ann Rheum Dis* 2023;82(3):351–6.
- [3] Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, Ruiz-Irastorza G, Hughes G. Systemic lupus erythematosus. *Nat Rev Dis Primers* 2016 Jun 16;2:16039.
- [4] Barber MRW, Falasinnu T, Ramsey-Goldman R, Clarke AE. The global epidemiology of SLE: narrowing the knowledge gaps. *Rheumatology* 2023;62 (Suppl 1):i4–9.
- [5] Schwarting A, Friedel H, Garal-Pantaler E, Pignot M, Wang X, Nab H, Desta B, Hammond ER. The Burden of Systemic Lupus Erythematosus in Germany: incidence, Prevalence, and Healthcare Resource Utilization. *Rheumatol Ther* 2021; 8(1):375–93. <https://doi.org/10.1007/s40744-021-00277-0>. MarEpub 2021 Feb 5.
- [6] Arnaud L, Fagot JP, Mathian A, Paita M, Fagot-Campagna A, Amoura Z. Prevalence and incidence of systemic lupus erythematosus in France: a 2010 nation-wide population-based study. *Autoimmun Rev* 2014;13(11):1082–9.
- [7] Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J, et al. National registry of patients with systemic lupus erythematosus of the Spanish Society of Rheumatology: objectives and methodology. *Reumatol Clin* 2014;10(1):17–24.
- [8] Simard JF, Sjöwall C, Rönnblom L, Jönsen A, Svenungsson E. Systemic lupus erythematosus prevalence in Sweden in 2010: what do national registers say? *Arthritis Care Res* 2014;66(11):1710–7.
- [9] Ellis J, McHugh N, Pauling JD, et al. Changes in the incidence and prevalence of systemic lupus erythematosus between 1990 and 2020: an observational study using the Clinical Practice Research Datalink (CPRD). *Lupus Sci Med* 2024;11(2): e001213. Published 2024 Jul 27.
- [10] Benucci M, Del Rosso A, Li Gobbi F, Manfredi M, Cerinic MM, Salvarani C. Systemic lupus erythematosus (SLE) in Italy: an Italian prevalence study based on a two-step strategy in an area of Florence (Scandicci-Le Signe). *Med Sci Monit* 2005;11(9): CR420–5.
- [11] Govoni M, Castellino G, Bosi S, Napoli N, Trotta F. Incidence and prevalence of systemic lupus erythematosus in a district of north Italy. *Lupus* 2006;15(2):110–3.
- [12] Tsioni V, Andreoli L, Meini A, et al. The prevalence and incidence of systemic lupus erythematosus in children and adults: a population-based study in a mountain community in northern Italy. *Clin Exp Rheumatol* 2015;33(5):681–7.
- [13] Zen M, Salmaso L, Barbiellini Amidei C, et al. Systemic lupus erythematosus incidence and prevalence in a large population-based study in northeastern Italy. *Rheumatology* 2023;62(8):2773–9.
- [14] Ferrara P, Antonazzo IC, Zamparini M, et al. Epidemiology of SLE in Italy: an observational study using a primary care database. *Lupus Sci Med* 2024;11(1): e001162. May 13.
- [15] Piga M, Casula L, Perra D, et al. Population-based analysis of hospitalizations in a West-European region revealed major changes in hospital utilization for patients with systemic lupus erythematosus over the period 2001–2012. *Lupus* 2016;25(1): 28–37.
- [16] Bortoluzzi A, Padovan M, De Stefani E, et al. AB0502 all-cause hospitalizations in systemic lupus erythematosus from a northern Italian referral centre. *Ann Rheum Dis* 2014;73:973.
- [17] Aringer M, Costenbader K, Daikh D, Brinks R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78(9):1151–9. SepEpub 2019 Aug 5.
- [18] Petri M, Orbai AM. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64(8):2677–86. Aug.
- [19] Fanouriakis A, Kostopoulou M, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78(6): 736–45. Jun.
- [20] Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29(2):288–91. Feb.
- [21] Tselios K, Gladman DD. Disease course patterns in systemic lupus erythematosus. *Lupus* 2019;28(1):114–22. JanEpub 2018 Dec 8.
- [22] [https://dati.istat.it/Index.aspx?DataSetCode=DCIS\\_POPRES](https://dati.istat.it/Index.aspx?DataSetCode=DCIS_POPRES).