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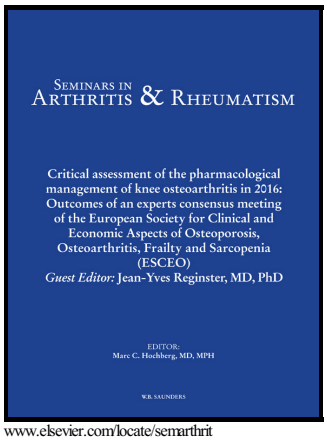

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Incidence, associated factors and clinical impact of severe infections in a large multicentric cohort of patients with Systemic Lupus Erythematosus

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ABSTRACT

Objectives To estimate the incidence of severe infection and investigate the associated factors and clinical impact in a large Systemic Lupus Erythematosus (SLE) retrospective cohort.

Methods All patients in the Spanish Rheumatology Society Lupus Registry (RELESSER) who meet ≥ 4 ACR-97 SLE criteria were retrospectively investigated for severe infections. Patients with and without infections were compared in terms of SLE severity, damage, comorbidities and demographic characteristics. A multivariable Cox regression model was built to calculate hazard ratios (HRs) for the first infection.

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Results A total of 3,658 SLE patients were included: 90% female, median age 32.9 years (DQ 9.7) and mean follow-up (months) 120.2 (±87.6). A total of 705 (19.3%) patients suffered ≥ 1 severe infection. Total severe infections recorded in these patients numbered 1,227. The incidence rate was 29.2 (95% CI:27.6 - 30.9) infections per 1,000 patient years. Time from first infection to second infection was significantly shorter than time from diagnosis to first infection ($p<0.000$). Although respiratory infections were the most common (35.5%), bloodstream infections were the most frequent cause of mortality by infection (42.0%). In the Cox regression analysis, the following were all associated with infection: age at diagnosis (HR 1.016; 95% CI:1.009-1.023), Latin-American (Amerindian-Mestizo) ethnicity (HR 2.151; 95% CI:1.539-3.005), corticosteroids (≥10 mg/day) (HR 1.271; 95% CI: 1.034-1.561), immunosuppressors (HR 1.348; 95% CI:1.079-1.684), hospitalization by SLE (HR 2.567; 95% CI:1.905-3.459) , Katz severity index (HR 1.160; 95% CI:1.105-1.217), SLICC/ACR damage index (HR 1.069; 95% CI:1.031-1.108) and smoking (HR1.332; 95% CI:1.121-1.583). Duration of antimalarial use (months) proved protective (HR 0.998; 95% CI: 0.997-0.999).

Conclusions Severe infection constitutes a predictor of poor prognosis in SLE patients, is more common in Latin Americans and is associated with age, previous infection and smoking. Antimalarials exerted a protective effect.

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Keywords

Systemic Lupus Erythematosus, Infection, Antimalarials

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1. Introduction

Infection remains an important cause of mortality and morbidity in patients with Systemic Lupus Erythematosus (SLE). Severe infection occurred in 11-45% of SLE patients depending on case definition, study population, observation period, etc (1-7). Although several centres reported their incidence of infection, specific studies on severe infection from large multicenter SLE cohorts are lacking. Roughly 30% of deaths in SLE patients are related to infections and recent data from a multicenter French registry suggests that overall mortality for infectious diseases in SLE is higher than thought (8). Additionally, severe infections account for 11-23% of all hospitalization in SLE patients (3, 9,10), with hospitalization rates for serious infections 12 times higher than that in patients without SLE (11), thus forming a significant part of the direct health-related costs associated with SLE (12).

Several factors are associated with a predisposition to infection in SLE patients, including disease-related factors, immunosuppressant and corticosteroid use and intrinsic immune deregulations (13-15). However, the relative contribution of each is not well known and comprehensive infection risk factor analysis is lacking. To determine the density of incidence of severe infection, delineate any associated factors and explore its clinical impact, we analyzed cumulative infection data from the RELESSER-T registry (Spanish Society of Rheumatology Lupus Registry - retrospective phase), a very large, non-selected multicenter, well-characterized SLE patient cohort containing abundant data on comorbidities (16).

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2. Methods

Patients from the RELESSER-T registry who met at least 4 ACR-97 SLE criteria were included. The variables, definitions, processes and methodological characteristics of the registry have been previously described in detail (17, 18). In short, RELESSER- T is a multicenter, hospital-based registry, with retrospective cross-sectional collection of data from a large representative sample of adult non-selected patients with SLE attending Spanish rheumatology services from the public national health system. The patients were consecutively included until deadline of the study. Forty-five centers were involved and all of the participating research carried a specific training on the study procedures and on the use of SLE assessment tools (i.e., activity, severity and damage indexes). A total of 359 variables per patient were collected, with highly standardized definitions, encompassing sociodemographic data, cumulative clinical and laboratory characteristics as well as comorbidities and Charlson index, all of which were retrospectively recorded until the last available visit per RELESSER, including deceased. SLICC/ACR/Damage index (SDI), Severity Katz index (SKI) (19) and activity (SELENA-SLEDAI) (S-SLEDAI) at the last visit (when enrollment occurred) were calculated. Regarding treatments, the use of glucocorticoids (GC) and immunosuppresants (IS) was recorded in three ways: "use at last visit", "any use" and "use at the time of the infection". Only in the case of antimalarials was time of exposure (months) also recorded.

The first patient was enrolled in October 2011 and data collection was completed in August 2012.

Severe infection was defined as either the need for hospitalization with parenteral anti-biotherapy for a potentially fatal infection or death caused by the infection. Isolation of the causative agent was not required in every case, with final classification as an

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infection being made using standard clinical criteria. Nevertheless, just in case of no-isolation, a strict clinical diagnosis of infection, with a response to antibiotics, was also classified as an infectious event. Only infections recorded during the follow-up period were included. We considered death due to infection only when it had a decisive influence on the death, based on RELESSER investigator criteria.

2.1 Statistical analysis

Numerical variables are expressed as mean and standard deviation for those having a normal distribution, and as median and interquartile range for non-normal distributions (Kolmogorov test). The categorical variables are described by absolute frequency and percentage.

The rate (density) of incidence of infection during periods of patient monitoring was calculated, comparing incidence densities based on exposure (assessed retrospectively) to various factors including comorbidities etc., and calculating the relative risks for each.

Survival analysis (Kaplan-Meier) was conducted to assess when and how frequently the infections occurred as a function of the length of the follow-up period. Subsequent comparisons between survival curves were made using a log-rank test.

Comparisons of numerical variables were performed using a Student t test or a Mann-Whitney U test, according to normality adjustments, and categorical variables using a Chi square (or Fisher's exact test as necessary).

To assess the temporal evolution, annual rates were smoothed using moving averages (five-year periods) to depict time trends, thereby avoiding short-term variations.

Variables reaching statistical significance in the bivariate analysis and those considered clinically meaningful (e.g., alcohol abuse etc.) were entered into a multivariate model (Cox proportional hazards regression) using the forward LR entering method. Given

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that the dependent variable (severe infection) corresponded to a model of "repeated events", a variation of the Cox model (Andersen-Gill), which takes into account the given circumstances, was also carried out (20).

Variables ultimately included in the multivariable models were sex, ethnicity, age at diagnosis, previous severe infection, tobacco use, Charlson index, corticoid (any time), immunosuppressants (any time), time on antimalarials (months), hospitalization by active SLE (excluding by infection), lupus nephritis, last S-SLEDAI, SDI and SKI index, chronic hepatopathy, HCV infection, AISD, COPD, diabetes, malignancy, splenectomy and alcohol abuse.

The IBM-SPSS for Windows statistical software package (v. 19.0) was used for all statistical analyses. Significance was defined as $p < 0.05$.

2.2 Ethical issues

Study procedures complied with the Helsinki Declaration (2008 Seoul update). Authorizations were obtained from the corresponding research ethics committee at each facility

3. Results

A total of 3,658 SLE patients were included, 90% female, median age 32.9 years, interquartile range (IQR):19.4. Regarding ethnic distribution, 93% were Caucasian, 5% Hispanic (Latin-American: Amerindian or Mestizo) (N=185) and less than 1% other ethnic groups. Mean follow-up (months) was 120.2 (SD: ±87.6; range: 508).

The main clinical characteristic of the cohort has been extensively described elsewhere (15). The ACR97 SLE criteria distribution is showed in table 1. The median S-SLEDAI score at time of last evaluation was 2.00 (IQR: 4), median SDI was 1 (IQR: 2) and median SKI score was 2 (IQR: 2). SLE-related treatments at the time of the

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RELESSER-T assessment (corresponding to the last visit before enrolment), at the time of the infection, and cumulative figures are shown in Table 2. GC doses at the infection time were: <10 mg/day 53.1%, between 10-30 mg/day, 30.2% and >30mg/day, 16.7%. Mean time (months) on antimalarial treatment during the disease course was 78.4 (±78.4).

A total of 705 (19.3%) patients suffered ≥ 1 severe infection. The total number of severe infections recorded was 1,227. The mean infection rate per patient was: 1.7 (SD±1.25) and the median was 1; 426 patients (60.4%) had only one infection, 266 (37.7%) 2 to 5 infections and 13 (1.9%) ≥ 6. The incidence rate was 29.2 (95% CI: 27.6 - 30.9) infections / 1000 patient years. The incidence rate for a second infection was 71.1 (95% CI: 63.1 -79.8) infections/1000 patient years. The time elapsed from first infection to second infection was lower than the time from baseline to first infection (median time 1.86 vs. 5.61 years, log rank p<0.000). (Figure 1),

The SKI was higher in patients with ≥ 1 severe infection compared to the whole cohort, even when excluding patients with GC (>10mg) or IS (whichever) at the time of the severe infection (N=244; SKI: 3.41±1.65 vs. 2.65±1.67, p <0.0001). When comparing patients with only one infection versus those with ≥ 2, those with > 1 infection had a higher SKI score (4.35 ±2.05 vs. 3.42 ±1.86, p=0.000) and a higher SDI score (3.33 ±2.75 vs. 1.84 ±1.98, p=0.000] at the last assessment.

Regarding etiologic agents, there was a clear predominance of bacterial causes (51.9%), with 30.4% corresponding to unknown cause (Table 3). The rate of incidence of mycobacterial infections was 1/1000 patient-years. Analysing the soft rates (mobile-means every 5 years), a steady incidence rate was observed throughout the follow-up period. However, when mycobacterial infection rates were analysed, the incidence rate showed an annual decrement (p=0.02).

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Concerning localization, the respiratory tract was the most frequently involved (35.5%), followed by the urinary tract (15.0%) (Table 3). A total of 208 (5.7%) patients died during follow-up, 24.5% by infection. The predominant localization for the fatal infection was the circulatory stream (bacteraemia, regardless of their source) (42.0%), followed by respiratory-related ones (34.0%).

3.1 Bivariate analysis

Several variables were associated with severe infection in the bivariate analysis, with density of incidence serving as a dependent variable (table 4), highlighting the hospitalization by SLE (Relative Risk: 5.67) and immunosuppressant use (RR: 10.20). Several co-morbidities/situations were also associated with severe infection, such as occurred with tobacco smoking (any history) (RR: 1.35) (Table 4). Furthermore, in the bivariate analysis any history of smoking was also associated with respiratory infections (RR: 1.36).

Regarding antimalarials, current and past use of antimalarials were protective factors [RR 0.49 (95% CI: 0.43-0.57) and 0.76 (95% CI: 0.65-0.88), respectively p=0.0000]. Furthermore, when quintiles of time on antimalarials (months) were analyzed, we observed an inverse relationship with the incidence of severe infection; namely, a proportional decrease in the incidence ratio with each quintile, from RR: 1 for Q1 (9.4 months on antimalarials) to RR: 0,66 (95% CI: 0,53-0,84) for Q5 (68.3 months). Specifically, antimalarial users suffered viral infections less frequently than non-users (2.8% in users vs. 5.8% in non-users, p<0.001).

GC use at the time of the infectious event was associated with increased viral (14.6% vs. 11.1%) and fungal infections (3.8% vs. 0.8%), with a higher percentage of agent isolations (75.8% vs. 62.8% in non-GC users) (p<0.0001).

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We also observed an association between GC at time of infection and mycobacterium as an etiologic agent: 3.7% in GC users vs. 0.2% in non-GC users (any dose), p <0.00001. As shown in Table 4, there were differences in cumulative IS use between patients with and without severe infection. Interestingly, 45.1% of patients that died by infection were on IS at that time vs. 9.6% of the surviving patients with severe infection (p<0.001). Furthermore, 45.1% of the patients that died by infection were on GC (> 10 mg/day) vs. 9.5% of survivors (p<0.001).

In a bivariate sub-analysis of mycobacterial infections, the following factors were all associated with this group of microorganism: Hospitalization by SLE (RR = 2.88; 95%CI:1.33-6.23; p= 0.007), renal disease (RR = 1.98; 95%CI:1.08-3.66; p = 0.04), severity [SKI>4: RR = 2.10 (1.10-4.03), p=0.04] and comorbidity [Charlson>4: RR=2.47 (95%CI:1.29-4.76), p=0.009].

3.2 Multivariable analysis

In the Cox proportional-hazards regression model, which used time until first infection as the dependent variable, the following were associated with severe infection: age at diagnosis, Latin-American ethnicity, any history of glucocorticoid (≥10 mg/day), immunosuppressor or tobacco use, time on antimalarials (months), hospitalization due to SLE, renal involvement, SKI, and SDI (Table 5). When the IS were considered separately, Rituximab (HR=1.61, p<0.001), Abatacept (HR=1.58, p=0.01) and Mycophenolate mofetil or Mycophenolic acid (HR=1.41, p=0.01) showed all of them statistical significative association with severe infection.

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When using a time repeated-events Cox regression (Andersen-Gill variant) model, with time of follow-up to infection being the dependent variable, results proved similar (Table 5), although immunosuppressant use, time on antimalarials and SDI lost statistical significance. Worth noting, however, is that previous severe infection reached significance only in the last model.

4. Discussion

The incidence of severe infection in SLE patients in the RELESSER registry (19.3%) was not very different than previous reports involving other large cohorts (4, 9, 21, 22), although certainly lower than in previous studies from monocentric cohorts in Spain, ranging from 29 to 38% (23, 24), or than was recently reported by Feldman et al in a study involving an extensive administrative SLE database from the USA (25) . Differences in patient selection and/or time of follow-up could explain these discrepancies or, as in the case of the North American cohort, the explanation might lie rather in ethnic or heath system differences. In fact, these patients were treated under Medicaid, a public health insurance program for low-income individuals, a socioeconomic status that could influence the infection risk (25).

Consistent with most other studies, the RELESSER data confirm that respiratory infections are the most common severe infection in SLE (3, 21-28).

Regarding aetiology, bacteria were the most common agent involved followed by virus and fungus, which is also consistent with previous reports (25, 29). The percentage of infections of unknown origin was relatively high (a third of the total), but that was not unexpected, given the high percentage of respiratory infections in this cohort. In fact, in SLE, as in the general population the aetiology of pneumonias remains unknown in ~50% of all cases (15, 30-32).

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There are scarce, reliable data concerning mycobacterium infections in the largest cohorts of SLE. The reported prevalence of M. tuberculosis infection in SLE patients ranges widely, from 5% to 30% (33, 34). A total of 42 mycobacterium infections (3.5%) were registered in RELESSER, equivalent to a prevalence of 1.14% in the global RELESSER cohort. This prevalence is higher than the mycobacterium tuberculosis infection rate expected in the general Spanish population (34). Furthermore, consistent with other studies (33, 35, 36), we found a higher proportion of extrapulmonary mycobacterium infections than expected, with an even higher percentage of extrapulmonary (vs. pulmonary) in our patients (57.1%). Additionally, we observed that this infection tended to appear during the first years of the SLE course and was associated with GC use at the time of infection, suggesting a relationship exists between higher disease activity and higher levels of immunosuppressive therapy.

We found an association, previously unreported, between tobacco use and recurrent severe infection in the RELESSER database. This is not surprising, since active smoking increases the risk of developing community-acquired pneumonia in the general population (37, 38). Intriguingly, despite the fact that pneumonia is the most common severe infection in SLE, studies specifically addressing pneumonia in SLE have failed to demonstrate tobacco use as a specific risk factor (15, 31). This apparent absence of association could be explained by its limited statistical power or, alternately, tobacco use could be a risk factor for any type of infection, not just respiratory ones. In fact, tobacco use increases an individual's susceptibility to bacterial infections in general, compromising the anti-bacterial function of leukocytes, including neutrophils, monocytes, T and B cells (39). In any case, we have demonstrated an association between tobacco use and respiratory infections in the RELESSER data.

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According to our findings, a previous infectious event appears to increase the risk of a new infection in SLE patients, a fact only sporadically explored (40). While this risk factor could be a mere consequence of persistent predisposing factors that increase the susceptibility to recurrent infections, our data provides information about the global risk of infection, shedding light on unknown predisposing factors.

The association of severe infection with IS or GC use is well known (1-5,13). Any use of GC ≥ 10mg increases the risk of infection in our study, and 84% of the patients were been treated with GC at the infection time. These findings reinforce the role of GC as severe infection risk factor in SLE. Perhaps more interesting from our analysis is that the use of these treatments at the time of infection increases the risk of mortality from severe infection. On the other hand, a negative association between antimalarials exposure time and severe infection was observed in our study, reinforcing the possible role these drugs play in protecting against infection, a finding previously reported (25, 27, 41, 42). Our results, however, do not agree with the other available multicenter study, which analyzed the exposure time to antimalarials in the GLADEL cohort. In that multi-nation inception cohort, no association was found between infection prevalence or death by infection and antimalarial exposure time. However, the follow-up period in this study was relatively short, with low numbers of infection and lesser mean durations of antimalarial drug exposure (48.5 months vs. 78.4 in RELESSER) (43). An alternative, and somewhat provocative, explanation could lie in ethnic factors, given the Latin-American origins of the entire GLADEL cohort. While those differences may reflect the low severity of lupus in the European Caucasian population, one could also speculate that antimalarials might be less effective in Hispanics. This would also explain why we found a higher incidence of severe infection in this ethnic minority in our own study. Interestingly, in our analysis, the association of exposure

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duration with antimalarials was independent of severity, as measured by a validated quantitative severity index. This suggests the absence of a cofounding variable since it points to a less severe cases bias. The alkalinization of phagolysosomes and the inhibition of DNA replication has been posited as one mechanism explaining the protective ability of antimalarials, particularly against intracellular microorganisms such a salmonella, viral agents, etc. (44-48). Consistent with this, protection against viral infections was observed in our analysis.

Finally, the protective effect of the antimalarials on infection risk could be reduced by the tobacco use, even though both factors showed an independent effect on infection risk in our statistical models.

We identified age at diagnosis as an independent factor associated with infection in this study, even when adjusted for co-morbidity as measured by the Charlson comorbidity index. This finding suggests that lupus exerts perhaps more impact over the immune system with increasing age than previously realized, an explanation that makes biological sense. In fact, in the general population the incidence of pneumonia increases with aging (49).

A higher risk of infection was identified in the Latin-American (Amerindian-Mestizo) minority. This ethnic difference has been previously noted in Afro-American SLE patients (25, 50) but not, to the best of our knowledge, in Latin Americans. Indeed, Feldman et al observed a slightly reduced risk of serious infection among Hispanics (HR 0.90 [95% CI 0.82–0.99]) in their previously named analysis. If confirmed, our results are particularly interesting, given that the difference was adjusted by severity and that the Latin American patients from the RELESSER cohort lived in Spain during the observation period and had complete access to the same public and universal health system as native Caucasian patients. This suggests that ethnicity, and not simply

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severity or socioeconomic factors, influences the incidence of infection.

The primary objective of our study was to explore the differences between SLE patients with or without previous severe infection. According to our data, SLE patients with serious infection suffer more severe disease. Not only are they more frequently hospitalized for SLE activity, but they also seem to have lower survival rates than patients without such infections. An independent relationship between SLE severity and pneumonia has been previously reported (15). This is not an unexpected finding given the fact that SLE itself entails several immunologic disorders predisposing individuals to infection (1, 14). However, weighing the impact of severity and immunosuppressive treatment on severe infection incidence remains problematic due to the presence of collinearity, as the most severely affected patients tends to receive more immunosuppressive therapy.

Some limitations of this study must be acknowledged. Several variables, such as measures of activity and damage, were not documented at the time of infection due to the multi-purpose nature of the RELESSER-T registry, which was never specifically designed to study infection in SLE. Although its retrospective design has an inherent bias, we believe that a bias towards unreported infections was unlikely given the definition of severe infection used in our study, which encompassed hospitalization. This definition of severe infection could exclude some patients suffering from pneumonia or others severe infections not subject to hospitalization. However, given the characteristics of our Sanitary Health System, where the vast majority of patients with severe infections are managed inpatient, we believe our cohort sufficiently comprehensive and representative of severe infection in SLE.

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Concerning SLE characteristics and covariates, the large number of patients and the special standardization effort carried out (17) minimize the impact of the retrospective design in missing data and quality.

The relative rates of mortality by infection in SLE patients are consistent in most cohorts, accounting for at least a quarter of all deaths (2, 3, 51-53). Interestingly, blood stream infections were the first cause of fatal infection in our cohort, supplanting respiratory-related causes at the top of the list. These results reinforce previous findings that lupus patients with bacteraemia episodes have poor outcomes (54-56). Strategies to reduce bacteraemia-related mortality - such as immediate instauration of antibiotic therapy if sepsis is suspected and others (e.g., the so-called "surviving sepsis campaign" strategy) should be implemented with particular care in SLE febrile patients, particularly patients on IS (57). In fact, delayed or inadequate antibiotic therapy was the most significant independent factor for mortality in SLE-infected patients from one intensive care unit (58).

5. Conclusions

Our results need to be confirmed in prospective studies; specifically, with a more exhaustive inclusion of variables related to infection. Nonetheless, several remarkable conclusions can be drawn from our data:

1. Severe infection is associated with severity and damage in SLE patients. There are ethnic differences in the prevalence of infection in SLE, with rates appearing to be higher in Latin Americans.
2. Respiratory bacterial infections are the most commonly found severe infection in SLE, although bacteraemia are more often fatal. Indeed, there is an urgent need to implement improvements in both the early detection and aggressive management of this dangerous complication of SLE.

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3. A previous infectious event increases the risk of a subsequent infection in SLE patients. Tobacco use seems to be a risk factor for severe infection in SLE patients. In addition, antimalarials exert a time-dependent protective effect.

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Tables

Table 1: ACR-97 SLE criteria distribution

SLE criteria	% (N)
Malar rash	55.2% (1990)
Discoid rash	20.9% (747)
Photosensitivity	60.2% (2160)
Oral ulcers	44.8% (1639)
Arthritis	78.0% (2814)
Serositis	23.0% (821)
Renal disease	33.7% (1187)
Central nervous system	8.5% (305)
Hematologic disorders	80.9% (2947),
Immunologic disorders	91.3% (3135)
Antinuclear antibodies	99.1% (3617)
Median SLE criteria	5.86 (IQR: 2)

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Table 2: SLE-related treatments

	At time of RELESSER-T assessment	At time of severe infection	Cumulative Treatments (any use)			
	N	%	N	%	N	%
Corticosteroids	1918	52.4%	1009	87.2%	3095	84.6%
Methotrexate	215	5.9%	39	6.6%	577	15.8%
Leflunomide	47	1.3%	1	0.2%	127	3.5%
Azathioprine	431	11.8%	196	33.3%	1140	31.2%
Cyclophosphamide	53	1.4%	130	22.1%	776	21.2%
Mycophenolate mofetil	322	1.4%	117	19.9%	522	14.3%
Mycophenolic acid	64	1.7%	16	2.7%	85	2.3%
Antimalarials	2021	55.2%	NR	NR	2882	78.7%
Rituximab	71	1.9%	25	4.2%	226	6.1%

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Table 3: Localization and cause of severe infection

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Localization	N	%
Respiratory	425	35.5%
Urinary tract	180	15.0%
Soft tissues	159	13.3%
Bacteraemia /sepsis	141	11.8%
Gastrointestinal	108	9.0%
Septic arthritis	39	3.3%
CNS	33	2.8%
Endocarditis	11	0.9%
Others	102	8.5%
Total	1198	100%
Agent	N	%
Bacteria	622	51.9%
Mycobacterium	42	3.5%
Fungus	27	2.3%
Virus	143	11.9%
Unknown	364	30.4%

CNS: central nervous system

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Table 4 Rate of infection in presence or absence of factor and relative risks. Bivariate analysis (dependent variable: Density of incidence = number of infections/1000 patients-year)

Independent variables	N (%)	Present (infections/1000 patients-year)	Absent (infections/1000 patients-year)	RR (95%CI)	P value
Age at diagnosis (years) (≤30)	1523 (42)	30.6	27.6	1.12 (1.03-1.22)	0.01
Male sex	353 (9.7)	36.6	28.5	1.69 (1.31-2.16)	<0.0001
Latin-American ethnicity	185 (5.1)	48.5	28.5	1.69 (1.31-2.16)	< 0.0001
SLEDAI > 2	1239 (34.1)	38.6	25.0	1.54(1.38-1.73)	<0.0001
Last SKI > 4	515 (14.2)	68.3	20.9	2.78(2.55-3.04)	<0.0001
Renal involvement	1296 (35.7)	45.4	18.3	2.48 (2.21-2.79)	0.0001
Charlson index > 3	727 (20.0)	47.7	23.1	1.98(1.82-2.16)	0.001
Chronic liver disease	38 (1.0)	129.5	28.4	4.56 (3.47-5.99)	< 0.0001
HIV/AIDS	9 (0.2)	102.6	29.0	3.54 (1.82-6.20)	0.007
Hepatitis C virus infection	48 (1.3)	79.0	28.3	2.79 (2.16-3.61)	< 0.0001
Malignancy	207 (5.7)	40.5	28.3	1.40 (1.17-1.68)	0.0004
COPD	98 (2.7)	65.6	28.0	2.34 (1.89-2.89)	<0.0001
Splenectomy	52 (1.4)	53.7	28.8	1.86 (1.33-2.61)	0.0004
Dialysis	106 (2.9)	88.3	27.3	3.31 (2.80-3.92)	< 0.0001
Diabetes	179 (4.9)	58.2	27.5	2.12 (1.78-2.53)	< 0.0001
Tobacco smoking (any history)	1353 (37.3)	32.8	27.2	1.35 (1.06-1.73)	0.018
Hospitalization by SLE	1954 (53.8)	43.8	7.7	5.67 (4.73-6.80)	< 0.0001
Antimalarials use ≤5 years	951 (26.2)	34.4	24.0	1.39(1.11-1.74)	0.004
IS (any use)	394 (10.8)	132.3	13.0	10.20 (9.10-11.44)	< 0.0001

RR = relative risk; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SKI= Severity Katz index; HIV: Human Immunodeficiency Virus; COPD = Chronic obstructive pulmonary disease; SLE = Systemic Lupus Erythematosus; IS = immunosuppressant; HCV=hepatitis C virus.

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Table 5 Cox proportional-hazards regression model. Dependent variable: time to first infection

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	β	*p* value	HR*	95%CI
Age at diagnosis	0.01566111	0.0000	**1.016**	1.009–1.023
Hispanic ethnicity	0.76575765	0.0000	**2.151**	1.539–3.005
Corticoids (≥10 mg/day), any use	0.23954448	0.0224	**1.271**	1.034–1.561
Time on antimalarials (months)	0.00175786	0.0022	**0.998**	0.997–0.999
Immunosuppressors, any use	0.29879736	0.0085	**1.348**	1.079–1.684
Hospitalization by SLE	0.94264204	0.0000	**2.567**	1.905–3.459
Renal involvement	0.31466771	0.0013	**1.370**	1.130–1.660
SKI	0.14835582	0.0000	**1.160**	1.105–1.217
SDI	0.06663931	0.0003	**1.069**	1.031–1.108
Tobacco any use	0.28698037	0.0011	**1.332**	1.121–1.583

Table 6 Time repeated-events Cox regression. Dependent variable: Time to severe infection

	β		HR*	95%CI	*p* value
Age at diagnosis (quintiles)	0,1163		**1.12**	1.07–1.18	0.001
Male sex	0.3962		**1.49**	1.22–1.81	0.0001
Hispanic ethnicity	0.427		**2.40**	2.29–2.50	0.001
Corticoids (≥10mg/day), any use	0.2878		**1.33**	1.15–1.55	0.001
Hospitalization by SLE	1.0049		**2.73**	2.22–3.35	0.0000
SKI	0.062		**1.06**	1.03–1.10	0.002
Previous infection (order)	0.8739		**2.40**	2.29–2.50	0.0000

*HR: hazard ratio. SLE= Systemic Lupus Erythematosus; SKI= Severity Katz Index. Enter method: Forward likelihood-ratio. Variables not included in the model: Charlson (p =0.134), SLEDAI (p =0.103), SLE Damage Index (p= 197), diabetes (p =0.151), malignancy (p =0.145), hepatitis C virus infection (p =0.184), antimalarials (p =0.096).

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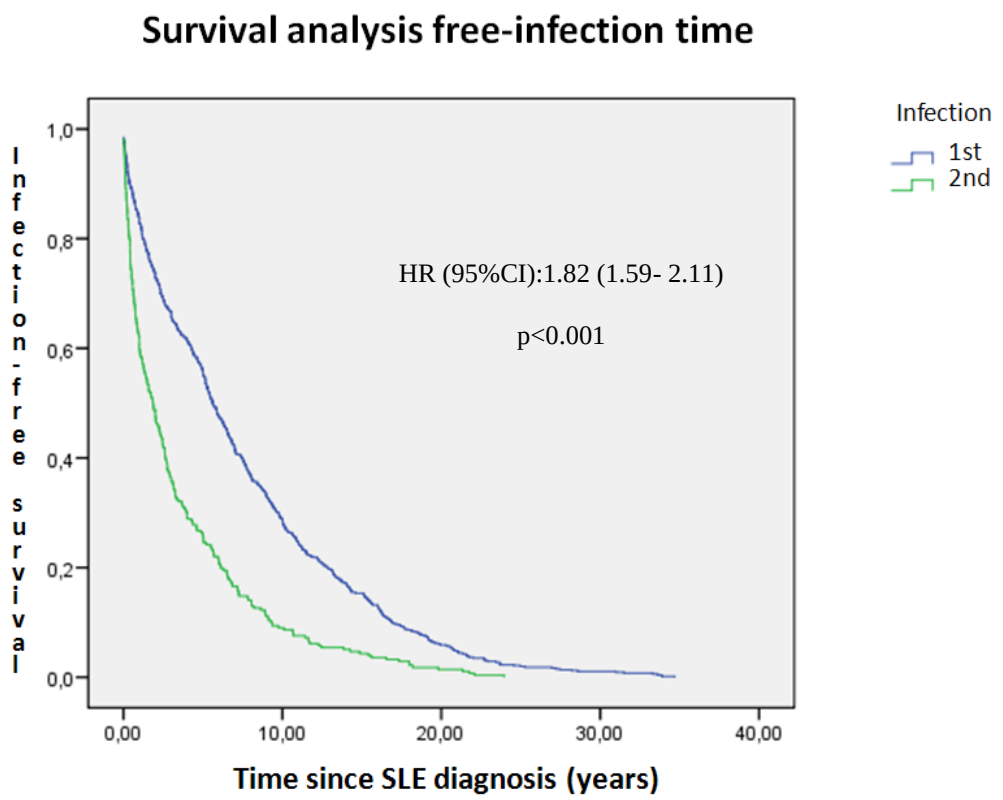

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Captions

Figure 1: Comparative survival analysis / infection-free time graphic.

The time until second infection was lower than time until first infection