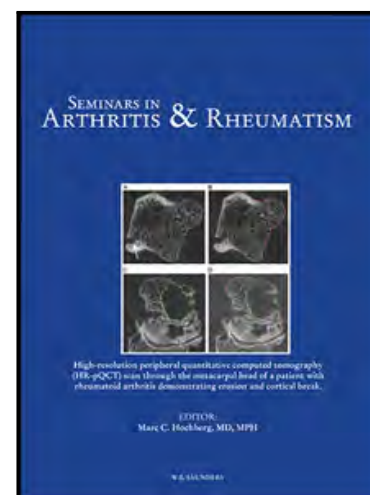


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Associated factors to serious infections in a large cohort of juvenile-onset systemic lupus erythematosus from Lupus Registry (RELESSER).

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ABSTRACT

OBJECTIVE: To assess the incidence of serious infection (SI) and associated factors in a large juvenile-onset systemic lupus erythematosus (jSLE) retrospective cohort.

METHODS: All patients in the Spanish Rheumatology Society Lupus Registry (*RELESSER*) who meet ≥ 4 ACR-97 SLE criteria and disease onset < 18 years old (jSLE), were retrospectively investigated for SI (defined as either the need for hospitalization with antibacterial therapy for a potentially fatal infection or death caused by the infection). Standardized SI rate was calculated per 100 patient years. Patients with and without SI were compared. Bivariate and multivariate logistic and Cox regression models were built to calculate associated factors to SI and relative risks.

RESULTS: A total of 353 jSLE patients were included: 88.7% female, 14.3 years (± 2.9) of age at diagnosis, 16.0 years (± 9.3) of disease duration and 31.5 years (± 10.5) at end of follow-up. A total of 104 (29.5%) patients suffered 205 SI (1, 55.8%; 2-5, 38.4%; and ≥ 6 , 5.8%). Incidence rate was 3.7 (95%CI: 3.2–4.2) SI per 100 patient years. Respiratory location and bacterial infections were the most frequent. Higher number of SLE classification criteria, SLICC/ACR DI score and immunosuppressants use were associated to the presence of SI. Associated factors to shorter time to first infection were higher number of SLE criteria, splenectomy and immunosuppressants use.

CONCLUSIONS: The risk of SI in jSLE patients is significant and higher than aSLE. It is associated to higher number of SLE criteria, damage accrual, some immunosuppressants and splenectomy.

INTRODUCTION

Juvenile-onset systemic lupus erythematosus (jSLE) represents ≈20% of all diagnosed systemic lupus erythematosus (SLE). While treatments and knowledge have been improved within the last decades, there are questions not answered yet. Infections are still one of the most important complications that jSLE patients suffer and one of the leading causes of mortality in jSLE (1). If serious or recurrent, infections reduce survival rate and increase damage accrual, respectively (2, 3). Recently, serious infections (SI) rates have been widely investigated in adult-onset SLE (aSLE) (4). Determinants for the presence of infections in SLE patients have been previously posted: end-organ involvement, disease activity and immunosuppressive treatment (5, 6, 7). The presence of recurrent major infections worsens jSLE patients' prognosis *per se* (3). Specific ethnicity has been described as a potential predisposing factor of suffering SI (8). On the other hand, a Chinese study showed that jSLE patients are at lower risk of developing comorbidities and death caused by infection than late-onset SLE patients (2). Nevertheless, jSLE population has not been deeply assessed in this issue.

We aim to assess the rate of SI in jSLE patients in a large cohort and to assess associated factors to its presence.

MATERIALS AND METHODS

Research Study Network

Data were obtained from the Registry of SLE Patients of the Spanish Society of Rheumatology (RELESSER), whose main objective is to provide “real world” comprehensive and reliable information on clinical manifestations, disease status, comorbid conditions and treatments of patients diagnosed with SLE in Spain (8). The RELESSER Registry was conducted by the *Systemic Autoimmune Rheumatic Diseases Study Group* (GT EASSER) of the Spanish Society of Rheumatology and it included 45 participating rheumatology departments. The retrospective study was approved by the Ethics Committee at Doctor Negrín Hospital in accordance with the Declaration of Helsinki’s guidelines for research in humans. A detailed description of its methodology has been provided elsewhere (9), with a data collection of around 360 variables per patient. The first patient was enrolled in October 2011 and the electronic data collection was completed by August 2012. Subsequently, a professional monitor reviewed the database to identify any missing or inconsistent information. Such occurrences were discussed with the relevant principal investigators and sent to the sub-investigators for additions and/or corrections.

Study Population

Out of 4,024 SLE-diagnosed patients enrolled in the cross-sectional stage of the RELESSER Registry, we selected all those who fulfilled at least four American College Rheumatology (ACR) 1997 SLE criteria (10, 11) in whom the disease started prior to 18 years of age (jSLE), as inclusion criteria. They were retrospectively investigated for SI, defined as either the need for hospitalization with antibiotherapy for a potentially fatal infection or death caused by the infection. Isolation of the causative agent was not required in every case, with final diagnosis as an infection being made using standard clinical criteria. Nevertheless, just in case of non- isolation, a strict clinical diagnosis of infection, including a response to antibiotics as necessary, was also classified as an infectious event.

Variables

At the last follow-up visit, the following variables were collected: Socio-demographics: age, ethnicity, sex, age at onset and disease duration.

Clinical and serological features (by organs and systems): using definitions of ACR criteria, SLE Disease Activity Index (SLEDAI) (12), British Island Lupus Assessment Group (BILAG 2004) (13) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR

DI) (14) specific items, mortality and cause of death. Activity score: SELENA-SLEDAI 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 standardized techniques. Damage and severity scores: cumulative damage was assessed using the SLICC/ACR DI, and disease severity with the Katz index (15).

jSLE treatment factors: current or previous use (and reason for discontinuation) of oral and intravenous steroids (including maximum dose and reason for prescribing them), azathioprine, hydroxyclozoquine, methotrexate, leflunomide, cyclosporine-A, mycophenolate mophetil, cyclophosphamide, rituximab, belimumab, immunoglobulins, mycophenolic acid, plasmapheresis, splenectomy, dialysis and kidney transplantation.

Co-morbidities and its treatments: smoking status, dyslipidaemia, diabetes, high blood pressure, hypothyroidism, chronic pneumopathy, chronic obstructive pulmonary disease, peripheral vasculopathy, malignancies, liver disease, severe infections, hospitalizations, oral hypoglycemic drugs, statins, anti-hypertensive medication, oral contraception, calcium-vitamin D and antiresorptive therapy and Charlson index (16).

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

Statistical Analyses

Patients with and without SI were compared in terms of jSLE severity, damage, comorbidities, and demographic characteristics.

Mean and standard deviation or median and interquartile range for numeric variables based on normal distribution, as well as absolute and relative frequencies for categorical variables, were calculated.

Comparisons of numerical variables were performed using a Student's 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).

The rate (density) of incidence of infection during periods of patient monitoring was calculated, comparing incidence densities based on exposure to several factors 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.

Variables reaching statistical significance in the bivariate analysis and those considered clinically meaningful were entered into a multivariate model (Logistica Regression and Cox proportional hazards regression) using the forward likelihood ratio entering method. Those variables identified in the literature as potentially associated to infection (e.g.: ethnicity, tobacco smoking, alcohol abuse, etc.) were considered clinically meaningful. Given that the dependent variable (SI) 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 (17). A multivariate Cox regression model was built to calculate hazard ratios (HR) for the first infection.

As differences among the administration of immunosuppressants might be associated to the non-randomized selection of the patients, a propensity score was conducted to minimize the hypothetical confusion variable of receiving a specific drug.

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

Ethical issues

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

RESULTS

A total of 353 jSLE were included (88.7% female), mean age at diagnosis 14.3 (\pm 2.9) years, mean disease duration 16 (\pm 9.3) years (main socio-demographics are shown in Table 1). A total of 104 (29.5%) patients suffered \geq 1 SI (1, 55.8%; 2-5, 38.4%; and \geq 6, 5.8%). The total number of severe infections recorded was 205, with a total amount of 5,543 patient-years of follow-up, which represents an Incidence Rate (IR) of 3.7 SI per 100 person year (CI 95% of 3.2-4.2). SI localization and available causal agents are summarized in Table 2. Free-Infection time was longer from SLE diagnosis to 1st infection than from 1st infection to 2nd infection (Figure 1). Figures 2 and 3 reflect free-infection time based on immunosuppressants use and splenectomy, respectively. Overall mean time to 1st infection from diagnosis was 113.6 (SD 9.49) months. Four patients (1.13%) died due to SI, two after bacteriemia and one each after gastrointestinal and respiratory infection. An infection rate comparison between jSLE and aSEL was also performed (Supplementary material Table S2).

Bivariate analysis

Variables such as smoking habit, lupus nephritis, kidney transplantation, corticosteroids use, higher corticosteroids dosage, immunosuppressants use (azathioprine, mycophenolate, cyclophosphamide and rituximab), hospitalization due to jSLE flare, higher scores on SLEDAI, KATZ and CHARLSON indexes were associated with SI. The complete bivariate analysis results are shown in the supplementary material section Table S1. Several variables were associated with SI in the bivariate analysis and are summarized in Table 3.

Logistic Regression analysis

In the regression model that used the time until first infection as the dependent variable, the following were associated with SI: higher number of SLE classification criteria, higher SLICC/ACR DI score and treatment with cyclophosphamide, mycophenolate mofetil or mycophenolic acid or rituximab (Table 4).

Cox Regression analysis

When using a Cox regression model, with time to first infection being the dependent variable, the variables associated with SI were higher number of SLE classification criteria, treatment with cyclophosphamide, mycophenolate mofetil/ or mycophenolic acid or rituximab and splenectomy (Table 5).

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DISCUSSION

We present data on SI in a large cohort of jSLE, showing a 3.7 SI rate per 100 patient-years. The most frequent SI location was at the respiratory tract and bacteria was the most frequent causal agent.

Regarding the incidence rate, Costa-Reis et al. found higher rate than ours (169/1000 patient-years vs. 3.7/100 patient-years, in 37% vs. 29% of patients, respectively) (18). However, there are some differences between both studies: ethnicity of patients included (Hispanic-African-American vs. Caucasian), disease duration (5.3 vs. 16 years), number of patients included (120 vs. 353), SI definition (causative agent/accurate diagnosis vs. non mandatory causative agent) and registry's study purpose (major infections assessment vs. large cohort of SLE multipurpose study). Lee et al. found up to 57% of infections in 47 patients with high rates of recurrence (25%) as well as Hiraki et al (33% in 3500 jSLE) (3, 8), which were lower than ours (45% in 353 jSLE). Aggarwal et al found a 26.4% infections in 273 jSLE patients (no clear definition of 'Infection' is provided) that represented a mortality leading factor in the multivariate analysis (1). The definition of serious and major infections in the above-mentioned studies basically differed in the duration of the antimicrobial treatment and the presence of death associated to SI. A study assessing the presence of SI in SLE in our population reported lower rate of SI in the global cohort than in our jSLE cohort. Moreover, we found jSLE in a 33% higher risk of developing SI than adult SLE RELESSER patients (Supplementary Material Table S2). However, Feng et al found late-onset SLE patients as at higher risk of death caused by SI in comparison to early-onset and juvenile-onset SLE (2). The latter has been suggested to probably appear in close relation to the higher frequency of comorbidities that late-onset SLE patients suffer throughout life.

Substantial differences were found in terms of most frequent location: skin and soft tissues location was more prevalent in the study by Costa-Reis et al., while respiratory tract more prevalent in ours (18). The respiratory tract was also the main SI location found by Hiraki et al among jSLE patients (18). The latter has not been found as common in other observations involving jSLE (3). More controversial data must be taken into account regarding causal agent. Hiraki et al. found bacteria as the most frequent microbial agent, in contrast to both Costa-Reis et al. and Lee et al.'s, where viral infection was the most frequently microbial agent (3, 8, 18). Lee et al suggested *Varicella zoster* infection and skin and oral mucosal location the most frequent causal agent and involved area (3), in Hong Kong. High rates of mycobacterial infection (20.9%) were found by Aggarwal et al., in India (1).

African Americans and American Indians are at higher risk than other ethnicities as suggested by previous research (8, 18), which would be related to higher disease activity and other related factors

that usually they present. Similar findings have been shown for Asian jSLE patients (2). As the main ethnicity included in our study was Caucasian, we are not able to perform any direct or indirect comparison and interpretation from previous published data, as the latter mostly included Hispanic and African-American patients. It seems reasonable to consider that higher SI rates are expected in communities including more severe jSLE phenotypes.

Regarding the presence of SI in jSLE, several characteristics have been mentioned as potential risk factors in the literature: jSLE-related treatment exposure, jSLE activity and jSLE damage. Immunosuppressants have been posted as underlying factors to the presence of SI in SLE. We could confirm Costa-Reis et al. previous observations, as cyclophosphamide and mycophenolate were independent predictors of SI, although we also found rituximab as a strong predictor (18). However, azathioprine was not as strongly associated to SI compared to the previously mentioned immunosuppressants. We consider our data in the multivariate analysis reliable due to the propensity score used in order to avoid confounders (as those who showed highest activity were also those more likely to receive more immunosuppressants and corticosteroids). Unfortunately, no protective effect on SI appearance was detected for antimalarials, what actually was demonstrated in Rúa-Figueroa et al's observation in a large SLE population (9).

Cumulative doses of corticosteroids have been demonstrated as independent factor for the presence of SI, and the combination of corticosteroids and cyclophosphamide an even stronger association (8, 18). The association between cumulative dosages of corticosteroids and SI is well-known in the literature (9), which must be considered as bullet-point when treating jSLE in order to reduce the risk of SI. Physicians must aware the fact that many of jSLE patients do not reach inactive disease and clinical remission within 5 years of follow-up and need intensive treatment (19). Noteworthy, there are some other features that have been associated to infection in patients admitted to an intensive care unit (ICU): higher C-reactive protein levels to infection at ICU admission, cyclophosphamide use associated to ICU nosocomial infection (20).

Costa-Reis et al. also demonstrated that higher SLEDAI score at diagnosis, low C3 complement (univariate) and neurological involvement (univariate) were associated to SI. On the other hand, Hiraki et al. found lupus nephritis as main organ involved in those who developed SI (8, 18). Based on our results, renal domain was the main jSLE-related organ involvement associated to the presence of SI. However, multivariate analyses showed no specific risk associated to a specific clinical involvement, while higher number of SLE criteria at diagnosis actually did. Besides, SLE-related treatments such as splenectomy would remind us the need to identify patients in risk of SI, as we found it as a strong risk

factor in the multivariate analysis. However, to date, no association to any particular haematological domain has been associated to SI in jSLE.

Lee et al. observed that patients in higher risk of presenting more long-term damage are more likely to developed infections. Moreover, the more infections showed, the higher the damage accrual(4). Costa-Reis et al. also demonstrated that patients who developed major infection showed more damage, especially those who presented sepsis (18). We could confirm the above-mentioned observations, as we observed that a strong predictor of SI was the presence of higher SLICC/ACR DI score. No specific damage domain has been particularly associated to SI based in our study and previous research. The latter might be explained because of the low amount of cases when reducing for each particular domain.

As limitation of our study we remark the retrospective study and the design not specifically addressed to assess SI and their particular features and outcomes. Moreover, definition of SI varies in the literature, although we consider we reasonably covered most SI definitions. Besides, activity and damage measures were not documented at the time of the SI onset. Another limitation is the main presence of Caucasian population within the registered sample. However, based on SLE features and covariates recorded, the high number of patients assessed and the specific data collection minimize the impact of the cross-sectional design in missing data.

In conclusion, our data confirm the high impact that SI have on patients with SLE. Some factors related both with the disease itself, its treatment and damage are associated with SI. Better identification of jSLE patients at higher risk of infection will contribute to optimize the strategies of prevention. On the other hand, a more cautious use of the therapeutic armamentarium and damage prevention are mandatory to minimize the burden of SI in jSLE patients.

Table 1. Socio-demographics and main juvenile-onset systemic lupus erythematosus related variables.

VARIABLE	jSLE N=353
Gender, <i>female</i>	313 (88.7)
Race, <i>Caucasian</i>	320 (90.6)
Age at diagnosis, <i>years</i>	14.3 ± 2.9
Age at last evaluation, <i>years</i>	31.5 ± 10.5
Malar rash	240 (67.9)
Photosensitivity	215 (60.9)
Mucosal ulcers	184 (52.1)
Discoid rash	72 (20.3)
Arthritis	275 (77.9)
Pleuritis	99 (28.1)
Pericarditis	70 (19.8)
Vasculitis	44 (12.4)
Proteinuria >0.5 g	166 (47.1)
Lupus Nephritis	206 (58.4)
Seizures	47 (13.3)
Lupus Headache(s)	30 (8.5)
Organic brain syndrome	19 (5.3)
Psychosis	14 (3.9)
Leukopenia	241 (68.2)
Thrombocytopenia	102 (28.8)
Haemolytic anemia	52 (14.7)
Antinuclear Antibodies	348 (98.5)
Low complement	301 (85.2)
Anti-dsDNA	293 (83.0)
Anti-Ro	118 (33.4)
Anti-La	17 (4.8)
Number of SLE criteria	6.4 ± 1.8
Index SLEDAI	3.3 ± 4.1
Index SLICC	1.2 ± 1.6
Index KATZ	3.1 ± 1.9
Index CHARLSON	1.6 ± 1.2

Abbreviations: *juvenile-onset Systemic Lupus Erythematosus (jSLE).*

**All variables expressed as Number (Percentage), Mean (±Standard Deviation).*

Table 2. Serious Infection Location and Causal Agent in juvenile-onset Systemic Lupus Erythematosus (RELESSER).

	Number of cases*	Percentage
<i>Location</i>		
- Respiratory	48	24.6
- Urinary	30	15.4
- Soft Tissues	30	15.4
- Gastrointestinal	29	14.9
- Bacteraemia	25	12.8
- Other	18	9.2
- Central Nervous System	8	4.1
- Osteoarticular	5	2.6
- Endocarditis	2	1
Total	195	100
<i>Causal Agent</i>		
- Bacteria	103	52.8
- Unknown	55	28.2
- Virus	29	14.9
- Mycobacteria	4	2.1
- Fungus	4	2.1
Total	195	100

*These data refer to the 195 patients with complete information about location and causal agent.

Table 3. Rate of Serious infection in presence or absence of factor and relative risks. Bivariate analysis (dependent variable: density of incidence = number of infections/100 patients-year)

Independent Variables	Present (infections/100 patients-year)	Relative Risk (95% Confidence Interval)	p Value
Female sex	3.92	2.4 (95% CI 2.2 – 4.7)	<0.05
Renal involvement	4.9	2.8 (95% CI 2.0 – 4.1)	<0.001
CHARSLON index score >5	11.2	3.2 (95% CI 1.7 – 5.5)	0.002
SELENA-SLEDAI Index score >4	6.1	3.0 (95% CI 2.0 – 4.5)	<0.001
KATZ Index score >4	6.8	3.7 (95% CI 2.3 – 6.4)	<0.001

Table 4. Logistic regression analysis (Dependent variable: Severe Infection).

	β	p value	Odds Ratio	Confidence Interval 95%
Number of Criteria	0.179	0.04	1.2	1.00-1.43
SLICC/ACR DI	0.333	0.001	1.4	1.17-1.66
Cyclophosphamide/mycophenolate/rituximab Treatment	0.936	0.001	2.55	1.44-4.52

Table 5. Cox Regression analysis (Dependent variable: Time to Infection).

	β	p value	Odds Ratio	95% Confidence Interval
Number of Criteria	0.232	0.001	1.26	1.11-1.43
Splenectomy	1.251	0.009	3.5	1.37-8.93
Cyclophosphamide/mycophenolate/rituximab Treatment	0.865	0.001	2.38	1.48-3.80

FIGURES

Figure 1. Comparative survival analysis/infection-free time graphic. The time until second infection was lower than time until first infection.

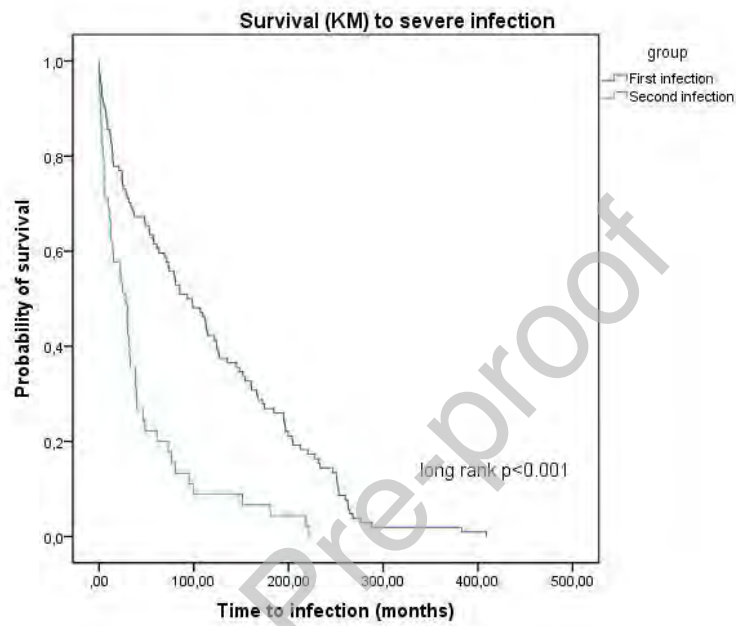


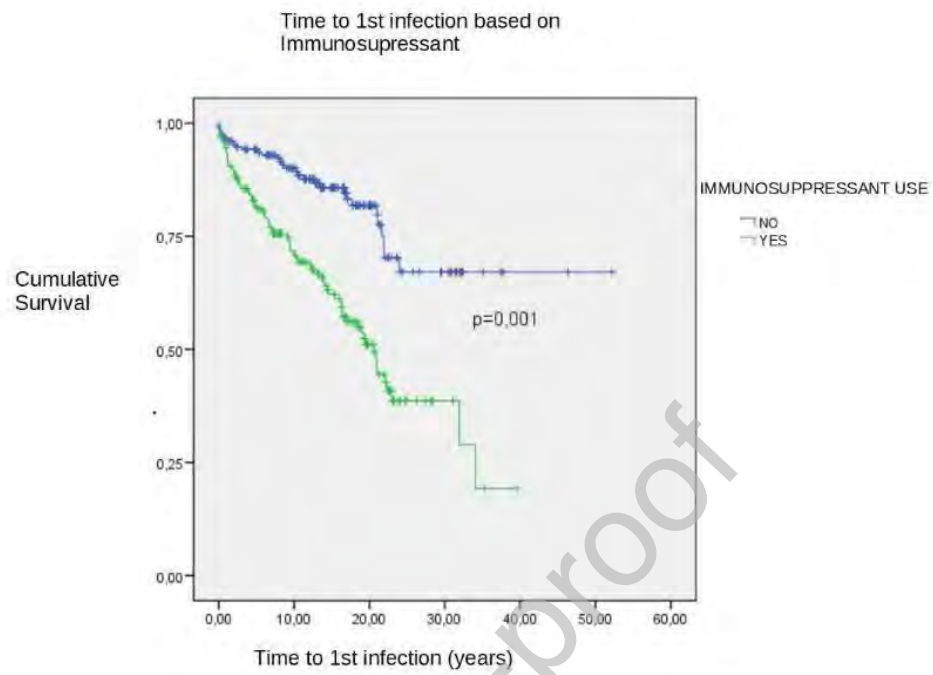
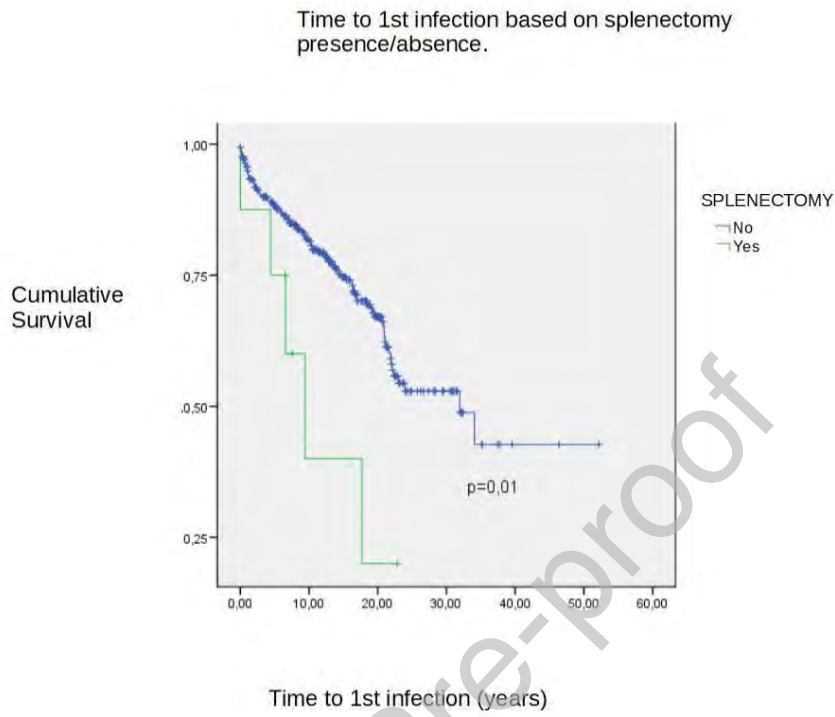
Figure 2. Time to first-Serious Infection based on immunosuppressant use.

Figure 3. Time to first-Serious Infection based on splenectomy.



REFERENCES

- (1) Aggarwal A, Phatak S, Srivastava P, Lawrence A, Agarwal V, Misra R. Outcomes in juvenile onset lupus: single center cohort from a developing country. *Lupus* 2018;27:1867-75.
- (2) Feng X, Zou Y, Pan W, Wang X, Wu M, Zhang M, et al. Associations of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus. *Lupus*. 2014;23:327-34.
- (3) Lee PP, Lee TL, Ho MH, Wong WH, Lau YL. Recurrent major infections in juvenile-onset systemic lupus erythematosus-a close link with long-term disease damage. *Rheumatology (Oxford)*. 2007;46:1290-6.
- (4) Rúa-Figueroa Í, López-Longo J, Galindo-Izquierdo M, Calvo-Alén J, Del Campo V, Olivé-Marqués A, et al. Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus. *Semin Arthritis Rheum*. 2017;47:38-45.
- (5) Ravelli A, Duarte-Salazar C, Buratti S, Reiff A, Bernstein B, Maldonado-Velazquez MR, et al. Assessment of damage in juvenile-onset systemic lupus erythematosus: a multicenter cohort study. *Arthritis Rheum*. 2003;49:501-7.
- (6) Brunner HI, Silverman ED, To T, Bombardier C, Feldman BM. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. *Arthritis Rheum*. 2002;46:436-44.
- (7) Lilleby V, Flatø B, Førre O. Disease duration, hypertension and medication requirements are associated with organ damage in childhood-onset systemic lupus erythematosus. *Clin Exp Rheumatol*. 2005;23:261-9.
- (8) Hiraki LT, Feldman CH, Marty FM, Winkelmayer WC, Guan H, Costenbader KH. Serious Infection Rates Among Children With Systemic Lupus Erythematosus Enrolled in Medicaid. *Arthritis Care Res (Hoboken)*. 2017;69:1620-6.
- (9) Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J, Galindo-Izquierdo M, Loza E, García de Yébenes MJ, et al. National registry of patients with systemic lupus erythematosus of the Spanish Society of Rheumatology: objectives and methodology. *Reumatol Clin* 2014;10:17-24.

- (10) Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
- (11) Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271-7.
- (12) Hawker G, Gabriel S, Bombardier C, Goldsmith C, Caron D, Gladman D. A reliability study of SLEDAI: A disease activity index for systemic lupus erythematosus. *J Rheumatol* 1993;20:657-60.
- (13) Yee CS, Farewell V, Isenberg DA, Prabu A, Sokoll K, Teh LS, et al. Revised British Isles Lupus Assessment Group 2004 Index. A reliable tool for assessment of systemic lupus erythematosus activity. *Arthritis Rheum* 2006;54: 3300-5.
- (14) Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363-9.
- (15) Katz JD, Senecal JL, Rivest C, Goulet JR, Rothfield N. A simple severity of disease index for systemic lupus erythematosus. *Lupus* 1993;2:119-23.
- (16) Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613-9.
- (17) Gill R. Understanding Cox's regression model. *Experientia* 1982;41(Suppl.): S187-99.
- (18) Costa-Reis P, Nativ S, Isgro J, Rodrigues T, Yildirim-Toruner C, Starr A, et al. Major infections in a cohort of 120 patients with juvenile-onset systemic lupus erythematosus. *Clin Immunol* 2013;149:442-9.
- (19) Abdelrahman N, Beresford MW, Leone V; UK Juvenile-onset Systemic Lupus Erythematosus Study Group. Challenges of achieving clinical remission in a national cohort of juvenile-onset systemic lupus erythematosus patients. *Lupus*. 2019;28:667-74.

(20) Restrepo-Escobar M, A Ríos N, Hernández-Zapata LJ, Velásquez M, Eraso R. Factors associated with infection amongst paediatric patients with systemic lupus erythematosus treated in the intensive care unit. *Lupus*. 2019;28:1141-7.

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