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Original Investigation

Infection detection in patients with systemic lupus erythematosus using a hospital administrative database

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ABSTRACT

Objective: To estimate the frequency of infections and to describe the pattern of these infections among patients diagnosed with Systemic Lupus Erythematous (SLE) treated at the Central Military Hospital (HOMIL).
Methods: A descriptive study was carried out using an administrative database of the military hospital, we used a validated algorithm that classifies patients as having SLE in administrative databases. Infection was defined as an event with main diagnosis using the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding algorithm or by searching the antibiotics prescription database, additionally, we abstracted some variables related to SLE status in the group of patients in whom infections were documented during the infection event.
Results: 237 SLE patients were identified. The mean age was 41.9 years (CI 29.0–54.3), 80% were female, 97.7% used conventional disease-modifying anti-rheumatic drugs (DMARDs). Of these 237 patients, 22 (9.4%) met the operative definition of infection, in this group the mean age was 44.3 years (SD 16.4). All the 22 patients received conventional DMARDs and none of them had concomitant biologic therapy. In this group of patients, the most common type of infection was bacterial (72.7%), followed by viral (9.1%) including a patient with SARS-CoV-2 infection.

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Conclusion: Hospital administrative databases can be a useful source of information for monitoring outcomes that generate significant morbidity and mortality in patients with SLE, in the group of patients in whom infections were documented, bacterial infections were the most frequent. The most documented clinical findings were leukopenia, systemic steroid therapy, and concomitant disease activity.

Detección de infecciones en pacientes con lupus eritematoso sistémico utilizando una base de datos administrativa hospitalaria

Palabras clave:
Lupus eritematoso
Sistémico
Infección
Base de datos
Actividad lúpica

RESUMEN

Objetivo: Estimar la frecuencia de las infecciones y describir su patrón de presentación en pacientes con diagnóstico de lupus eritematoso sistémico (LES) atendidos en el Hospital Militar Central (Homil) en Bogotá, Colombia.

Métodos: Se realizó un estudio descriptivo en el que se utilizó una base de datos administrativa del Hospital Militar y se empleó un algoritmo validado que clasificó a los pacientes con LES en las bases de datos administrativas. La infección se definió a partir de los códigos CIE-10 o por la búsqueda en la base de datos de la prescripción de antibióticos; adicionalmente, en las historias clínicas del grupo de pacientes en los que se documentaron infecciones, se revisaron algunas variables relacionadas con el estado de LES durante el evento de la infección.

Resultados: Se identificaron 237 pacientes con LES, cuya edad media fue de 41,9 años (IC 29,0-54,3), el 80% eran mujeres y el 97,7% usaba medicamentos antirreumáticos modificadores de la enfermedad (DMARD) convencionales. De estos 237 pacientes, 22 (9,4%) cumplieron con la definición operativa de infección; en este grupo la edad media fue de 44,3 años (DE = 16,4). Los 22 pacientes recibieron DMARD convencionales y ninguno recibió terapia biológica concomitante. En este grupo, el tipo de infección más común fue la bacteriana (72,7%), seguida de la viral (9,1%), incluido un paciente con infección por SARS-CoV-2.

Conclusiones: Las bases de datos administrativas hospitalarias pueden ser una fuente útil de información para el seguimiento de los eventos que generan una morbimortalidad significativa en los pacientes con LES. En el grupo de pacientes en los que se documentaron infecciones, las infecciones bacterianas fueron las más frecuentes y los hallazgos clínicos más comúnmente documentados fueron la leucopenia, la terapia con esteroides sistémicos y la actividad de la enfermedad concomitante.

Introduction

Infections are an important cause of morbidity and mortality in patients with Systemic Lupus Erythematosus (SLE). Patients with SLE have a higher infection rate than the general population. This may occur as a consequence of impaired immune function or as a consequence of immunosuppression used to treat the disease.[1] Likewise, severe forms of exacerbation of lupus can have catastrophic results in patients with infections. It is estimated that at least 50% of them will suffer a severe infectious episode during the course of the disease.[1] Further meticulous exclusion of infection is mandatory in patients with SLE, because infections may masquerade as exacerbation of underlying disease.[2]

In the last few years, administrative databases[3,4] are gaining relevance due to the possibility of retrieving demographic variables among other descriptive variables from patients in parallel with the provision of health care. They serve as an information source that can answer questions related to epidemiological surveillance and public health.[4]

The term "administrative health data"[4–6] refers to those data usually collected by decision makers for some administrative purpose (tracking the population eligible for certain benefits or for billing and payment to different providers). It is also information generated upon provision of health services; in all cases, research is not the main purpose.

The data usually contains demographic information, primary and secondary diagnoses, information related to the procedures performed, service provider and payer, billing data, and, in some cases, the drugs prescribed. Unlike prospective records, they do not contain diagnostic test results or clinical findings.[4]

Some studies have used these databases[7] to estimate the risk of severe infection in patients with diverse immune

diseases, finding them a very useful source. Also, they allow to document factors associated with a higher infection risk such as advanced age and comorbidities,[7] findings similar to those found in prospective registries.[8]

The growing popularity of the use of these databases lies in the coverage of the target population, which is difficult to obtain from prospective records. Additionally, the relatively low cost of acquisition makes them an interesting source to be used for research purpose.

In Colombia, national administrative databases have been used to estimate lupus prevalence[9] and other autoimmune conditions in our country. Nonetheless, their use in the hospitals is restricted to administrative purposes. Now, taking into account the importance of infection in the outcome of patients with SLE and in consequence, the importance of a continuous surveillance of the behavior of these infections in the daily practice, we designed this study to estimate the frequency of infections and to describe the pattern of these infections, among patients diagnosed with SLE treated at the HOMIL using an institutional administrative database.

Materials and methods

Sources of information

This study was carried out using two sources of information, the first one was the administrative database of the HOMIL, this database contain details of individual health services provided to the affiliates of the health system of military forces in Colombia and their families, claims recorded in the databases contains demographic variables, data regarding health care provider, service type, detailed utilization, expenditure in terms of procedures, and prescription drug claims and primary and secondary diagnostic codes. Three databases of patients attended between 2016 and 2020 were linked, the first was that of outpatients and consist of 1′559.267 records, the second one corresponds to patients who required a hospitalization and consist of 83.021 records, and the third contain prescription drug claims and consist of 2′020.461 records. Additionally, hospital care Information on the patient's age at the start of follow-up, traditional or biologic DMARDs prescriptions were abstracted, as well as all secondary diagnoses which were used to calculate Charlson's Comorbidity Index using the International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding algorithm[10] for each patient.

The second source of information we used was the review of medical records (contains all the clinical characteristics of the patient registered by the treating physician, including diagnostic test results), to confirm the diagnoses, and to extract the laboratory results as well as the data related to lupus activity.

Patients

To improve the accuracy of SLE diagnosis in our data source we used an algorithm described by Moore et al.[11] that classifies patients as having SLE if they satisfy the following condition: the case when a patient has records with those codes at least in two outpatient claims, such that the difference length of time between them could not be neither less than 30 days nor greater than 2 years. The associated codes to SLE were M320, M321, M328 and M329 and if he receives at least one immunosuppressive medicine, for the process of validation of this algorithm the author used Bayesian estimation techniques resulting in an estimated specificity of 99.9% (95% CI 99.8% to 100%) and an estimated sensitivity of 45% for physician billing data and sensitivity of 42–6% for hospital data.[12]

Definition of infection

The outcome of interest was infection defined as an event with main diagnosis CIE-10 code or by the search in the database of the antibiotics prescription.

To measure the accuracy of our operative definitions we use as a reference standard the clinical records of the patients to confirm the lupus diagnosis, and the infection diagnosis, additionally, we abstracted in the group of patients in whom infections was documented some variables related to the SLE status at the event of infection.

The institutional ethics committee approved this research study.

Statistical analysis

For continuous variables, means, standard deviations, and medians and interquartile ranges were calculated according to the type of distribution, while for qualitative variables absolute and relative frequencies were calculated. The statistical package used was Stata 16MP.

Results

The database was analyzed for hospitalized and ambulatory patients at HOMIL between 2016 and 2020. Using SLE operative definition 307 patients were found, after revising their medical record, 70 patients were excluded as they didn't have a confirmed diagnosis according to the SLICC 2012 criteria. 237 patients were included. The mean age was 41.9 years old (CI 29.0–54.3), 80% were female, 56% had a Charlson's index of 1; 97.7% used conventional DMARDs (Table 1). From these 237 patients, 22 (9.4%) met the operative definition of infection, in this group the mean age was 44.3 years old (SD 16.41). All of the 22 patients received conventional DMARDs and none of them had concomitant biologic therapy (Table 1). In this group of patients, the most common type of infection was bacterial (72.7%), followed by viral (9.10%) including a patient with SARS-CoV-2 infection, and 4 patients had fungal infection. 10 patients were taking systemic steroids; after reviewing their medical record, we found that 8 patients had active disease according to the systemic lupus erythematosus disease activity index (SLEDAI) scale at the time of the infection. 5 patients had positive anti-DNA antibodies, 4 has decreased complement, 5 has nephritis, 7 has leukopenia, and none of them were documented to have concomitant antiphospholipid syndrome. With respect to comorbidities, the mean Charlson's index for infected patients was 3; 1 patient has diabetes, none of them has Chronic obstructive pulmonary disease (COPD) or

Table 1 – Demographic characteristics and medical treatment in patients (*n* = 237).

Characteristic	Non infected patients (*n* = 215)	Infected patients (*n* = 22)
Age (SD)	41.34 (16.4)	44.6 (16.4)
Age group (%)		
0–10	1 (0.4)	0 (0.0)
11–20	23 (10.7)	1 (4.5)
21–30	32 (14.8)	4 (18.2)
31–40	44 (20.4)	4 (18.1)
41–50	39 (18.1)	2 (9.0)
51–60	41 (19.0)	8 (36.3)
61–70	26 (12.0)	2 (9.0)
71–80	8 (3.7)	1 (4.5)
>80	1 (0.4)	0 (0.0)
Gender		
Female	174 (80.9)	20 (90.9)
Type of medication used		
Conventional	210 (97.6)	22 (100)
Biologic agent	5 (2.3)	0 (0.0)
Charlson's index	1 (1–3)	3 (1–4)

chronic renal insufficiency, none of the patients die due to the infection (Table 2).

Discussion

Infections are an important cause of morbidity and mortality in patients with SLE, Cervera et al.[8] found that 25% of the patients died as a consequence of an infection, in turn, infections represent up to a third of hospitalizations in these patients.[13–15]

For this reason, for the services in charge of caring for patients with SLE, the monitoring of infections is essential, as well as the identification of the factors that predispose them to a higher risk of infections[16] and the adoption of measures in order to mitigate the risk of this complication, it is for this reason that administrative databases in health can be a very useful source of information for the continuous monitoring of complications such as this in populations of patients with SLE.[17,18]

In our study we used the hospital administrative database in order to track infections in patients with SLE from descriptive analytical techniques, we used validated algorithms to identify patients with SLE diagnosis[12] and in turn to identify infections in these patients, similarly to the methodology used in other studies.[19]

Of the 307 patients initially identified using the algorithm, when reviewing the medical history, 70 patients who did not have a confirmed diagnosis of SLE were excluded, in turn, of the 30 initially identified infections, 8 were excluded because they were prescribed antibiotics with a prophylactic purpose prior to procedures or for the treatment of acne.

237 patients with a confirmed diagnosis of SLE were included, of which 22 (9.4%) had infections, this frequency is lower than that documented in the Euro lupus cohort in which it was documented that 36% of the patients presented infections during follow-up,[8] this difference is probably due to limitations inherent to the source of information due to underreporting of the codes corresponding to infections in the databases.

Table 2 – Infection characteristics, clinical condition and medication of infected patients (*n* = 22).

Type and site of infection	Infected patients (%)
Bacterial	16 (72.7)
Genitourinary tract	7 (38.8)
Upper respiratory tract	4 (22.2)
Skin	2 (11.1)
Hematogenous	2 (11.1)
Ear	1 (5.5)
Viral	2 (9.1)
Skin	1 (50.0)
Respiratory tract (COVID-19)	1 (50.0)
Fungal	4 (18.1)
Skin/nails	4 (100)
Clinical condition related SLE	
Active disease	8 (36.3)
Leukopenia	7 (31.8)
High anti-DNA titres	5 (22.7)
Low complement levels	4 (18.2)
Nephritis	5 (22.7)
Prednisone equivalent doses over 7.5–10 mg/day	2 (9.1)
Cyclophosphamide high-dose regimens	1 (4.5)
Medication used	
Systemic steroids	
Deflazacort	6 (27.2)
Pprednisolone	3 (13.6)
Methylprednisolone	1 (4.5)
Antimalarial drugs	
Chloroquine	1 (4.5)
Hydroxychloroquine	8 (36.3)
Immunosuppressants	
Cyclophosphamide	1 (4.5)
Cyclosporine	1 (4.5)
Azathioprine	1 (4.5)

The most frequent infections in patients with SLE are bacterial infections, followed by viral and fungal infections.[16] In our study, infections by type of microorganism retained the same distribution reported in the literature, with bacterial infections being the most frequent in the in 72.7% of patients.

The most frequent infections by site of infection are for bacterial, upper respiratory tract, urinary tract and skin,[13,20] for viral the most frequent site is skin and respiratory tract[21,22] in our patients we found similar results (Table 2), the difference in our results can be seen in the case of fungal infections, given that literature shows the gastrointestinal and genitourinary tract[23] as the main site of these infections and our results show skin and nails as shown in Table 2. However, this distribution may vary depending on whether the area of infection is ambulatory or in-hospital, in our study we document a higher frequency of bacterial urinary tract infections, in the case of viral infections, a patient presented pneumonia due to COVID-19 which required in-hospital care without the requirement of mechanical ventilation, and this patient recovered from the infection.

Immune system dysfunction has been widely described in patients with SLE,[24] the number of T lymphocytes is decreased and the activity of T-helper cells against viral

agents, toxoids and alloantigens is compromised, as well as the system macrophage monocyte, and complement function in SLE patients, particularly during disease exacerbations.[25] Disease activity could increase susceptibility to infections, however, in the hospital setting it's hard to distinguish between disease activity and infections, in fact they can coexist,[2,13] 8 of the 22 patients who presented infections in our study had concomitant disease activity.

Several clinical factors have been associated with the development of infections in patients with SLE,[26,27] such as the chronic use of systemic steroids, particularly doses greater than 7.5–10 mg per day[23] and cyclophosphamide,[23] of the 22 infected patients, almost half were receiving treatment with systemic steroids, and 1 patient of the 22 was on treatment with cyclophosphamide, of the other factors described in the literature[20] (high titers of anti-DNA, consumed complement, antiphospholipid syndrome antibodies, nephritis and leukopenia) the most frequent in our study was leukopenia in 7 patients, with regard to multimorbidity, diabetes mellitus, COPD and kidney failure[21] have been associated with an increased risk of infections in patients with autoimmune diseases,[27] in our study, although the average Charlson's index was 3, only one patient out of 22 had a diagnosis of diabetes mellitus.

The main limitation of our study is related to the source of information since it is an administrative database whose purpose is not research, an imprecise coding of diagnoses could be presented, particularly of infection diagnoses as it is a secondary diagnosis. This could generate selection bias or poor qualification which impacts on comparability with other studies, however, this limitation was managed using operational definitions described in the literature, as well as a review of medical records in order to evaluate the precision in the diagnoses of both the disease and the infection, even so, we found a sub-record of the diagnosis of infection in the database.

Additionally, given the characteristics of the study design, it is not possible to know the temporal sequence of clinical variables, such as leukopenia, and since there is no control group, it is not possible to attribute certain conditions such as the use of steroids to the development of infections in these patients.

However, despite the limitations, the value of our study lies in the use of hospital administrative databases for monitoring relevant outcomes in patients with SLE, which may be a useful strategy for decision-making by services in charge of the care of these patients.

Conclusions

Hospital administrative databases can be a useful source of information for monitoring outcomes that generate significant morbidity and mortality in patients with SLE, in the group of patients in whom infections were documented, bacterial infections were the most frequent and the most frequently documented findings were leukopenia, and systemic steroid therapy.

The coexistence between lupus activity and infection is a frequent finding and continues to be a common diagnostic challenge for rheumatologists.

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Conflict of interests

The authors declare that they have no competing interests.

REFERENCES

1. Ospina FE, Echeverri A, Zambrano D, Suso JP, Martínez-Blanco J, Cañas CA, et al. Distinguishing infections vs flares in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2017;56:i46–54, http://dx.doi.org/10.1093/rheumatology/kew340.
2. Beltrán A, Mora C, Bastidas AR, Aragón Guzmán DM. Caracterización de pacientes con lupus y fiebre: actividad, infección o ambas. Rev Colomb Reumatol. 2020;27:95–102, http://dx.doi.org/10.1016/j.rcreu.2020.01.004.
3. Cohen JE, Spasoff RA. Epidemiologic methods for health policy. J Public Health Policy. 2000;21:240, http://dx.doi.org/10.2307/3343346.
4. Virnig BA, McBean M. Administrative data for public health surveillance and planning. Annu Rev Public Health. 2001;22:213–30, http://dx.doi.org/10.1146/annurev.publhealth.22.1.213.
5. Spasoff RA. Epidemiologic methods for health policy. New York: Oxford University Press; 1999.
6. U.S. Food and Drug Administration. FDA's sentinel initiative. Silver Spring; 2010. Available from: https://www.fda.gov/Safety/%20FDAsSentinelInitiative/default.htm
7. Quartuccio L, Zabotti A, Del Zotto S, Zanier L, De Vita S, Valent F. Risk of serious infection among patients receiving biologics for chronic inflammatory diseases: usefulness of administrative data. J Adv Res. 2019;15:87–93, http://dx.doi.org/10.1016/j.jare.2018.09.003.
8. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period. Medicine (Baltimore). 2003;82:299–308, http://dx.doi.org/10.1097/01.md.0000091181.93122.55.
9. Fernández-Ávila DG, Bernal-Macías S, Rincón-Riaño DN, Gutiérrez Dávila JM, Rosselli D. Prevalence of systemic lupus erythematosus in Colombia: data from the national health registry 2012–2016. Lupus. 2019;28:1273–8, http://dx.doi.org/10.1177/0961203319864168.
10. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol. 2004;57:1288–94, http://dx.doi.org/10.1016/j.jclinepi.2004.03.012.
11. Moores KG, Sathe NA. A systematic review of validated methods for identifying systemic lupus erythematosus (SLE) using administrative or claims data. Vaccine. 2013;31:K62–73, http://dx.doi.org/10.1016/j.vaccine.2013.06.104.
12. Bernatsky S, Joseph L, Pineau CA, Tamblyn R, Feldman DE, Clarke AE. A population-based assessment of systemic lupus erythematosus incidence and prevalence – results and implications of using administrative data for epidemiological studies. Rheumatology. 2007;46:1814–8, http://dx.doi.org/10.1093/rheumatology/kem233.
13. Goldblatt F, Chambers S, Rahman A, Isenberg D. Serious infections in British patients with systemic lupus

erythematosus: hospitalisations and mortality. Lupus. 2009;18:682–9, http://dx.doi.org/10.1177/0961203308101019.
14. Lee J, Dhillon N, Pope J. All-cause hospitalizations in systemic lupus erythematosus from a large Canadian referral centre. Rheumatology. 2013;52:905–9, http://dx.doi.org/10.1093/rheumatology/kes391.
15. Petri M, Genovese M. Incidence of and risk factors for hospitalizations in systemic lupus erythematosus: a prospective study of the Hopkins Lupus Cohort. J Rheumatol. 1992;19:1559–65.
16. Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. Lupus. 2013;22:1286–94, http://dx.doi.org/10.1177/0961203313493032.
17. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2011;70:414–22, http://dx.doi.org/10.1136/ard.2010.137216.
18. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis. 2010;69:1269–74, http://dx.doi.org/10.1136/ard.2009.117200.
19. Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, et al. Serious infections among adult medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol. 2015;67:1577–85, http://dx.doi.org/10.1002/art.39070.
20. Duffy KN, Duffy CM, Gladman DD. Infection and disease activity in systemic lupus erythematosus: a review of hospitalized patients. J Rheumatol. 1991;18:1180–4.
21. Gladman DD, Hussain F, Iban D, Urowitz MB. The nature and outcome of infection in systemic lupus erythematosus. Lupus. 2002;11:234–9, http://dx.doi.org/10.1191/0961203302lu170oa.
22. Noël V, Lortholary O, Casassus P, Cohen P, Généreau T, André MH, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis. 2001;60:1141–4, http://dx.doi.org/10.1136/ard.60.12.1141.
23. Pryor BD, Bologna SG, Kahl LE. Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum. 1996;39:1475–82, http://dx.doi.org/10.1002/art.1780390906.
24. Cuchacovich R, Gedalia A. Pathophysiology and clinical spectrum of infections in Systemic Lupus Erythematosus. Rheum Dis Clin North Am. 2009;35:75–93, http://dx.doi.org/10.1016/j.rdc.2009.03.003.
25. Bermas BL, Petri M, Goldman D, Mittleman B, Miller MW, Stocks NI, et al. T helper cell dysfunction in systemic lupus erythematosus (SLE): relation to disease activity. J Clin Immunol. 1994;14:169–77, http://dx.doi.org/10.1007/BF01533366.
26. Enberg GM, Kahn CM, Goity FC, Villalón SMV, Zamorano RJ, Figueroa EF. Infecciones en pacientes con lupus eritematoso sistémico. Rev Med Chil. 2009;137:1367–74.
27. Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. Clin Rheumatol. 2018;37:2081–6, http://dx.doi.org/10.1007/s10067-018-4102-6.