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In-hospital mortality and associated factors in patients with systemic lupus erythematosus: analysis over more than 11 years in a reference hospital center

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Abstract

Systemic lupus erythematosus (SLE) is a disease that affects the immune system, and it can lead to increased morbidity and mortality. The primary causes of mortality for individuals with SLE are disease activity, infections, drug toxicity, and other health conditions. The aim of this study is to estimate the mortality rate of patients with SLE who are hospitalized, describe the causes of death, and identify factors associated with mortality. The study was conducted at a referral hospital from 2009 to 2021, utilizing a nested case–control design. The records of patients with SLE who were hospitalized in the Department of Rheumatology were reviewed. Cases were identified as individuals who died during their hospitalization, while controls were those who were discharged alive during the same period. Elective hospitalizations were not included in the study. The primary causes of death were recorded, and demographic, clinical, laboratory, and immunological variables were analyzed as potential risk factors associated with in-hospital mortality. The study included 105 patients who died while hospitalized and 336 who were discharged alive. The estimated mortality rate was 10.93 deaths per 1000 hospital admissions per year. The leading causes of death were SLE activity (20%), infections (34.2%), or a combination of both (24.8%). Risk factors associated with in-hospital mortality were any infection (OR 2.5, CI 95% 1.2–5.2), nosocomial infections (OR 5.0, CI 95% 1.8–13.7), SLEDAI-2K > 2 (OR 2.0, CI 95% 1.02–3.8), lymphopenia (OR 2.1, CI 95% 1.01–4.6), anemia (OR 2.9, CI 95% 1.4–5.7), and thrombocytopenia (OR 3.3, CI 95% 1.7–6.4). Disease activity and infections, particularly nosocomial infections, are significant causes of mortality in hospitalized patients with SLE. Furthermore, hematological manifestations play a significant role in in-hospital mortality for these patients.

Keywords Systemic lupus erythematosus · Mortality · Infections · Risk factors

Introduction

Systemic lupus erythematosus (SLE) is a systemic, immune-mediated disease characterized by an extensive production of autoantibodies with multiorgan involvement that results in significant morbidity and mortality [1]. Despite notable advances in the knowledge of the pathogenesis of the disease and its therapeutic approach, patients with SLE still have a higher mortality compared to the general population, adjusted for age and sex [2]. Several studies have reported standardized mortality rates (SMR) between 1.8 and 4.5 [3–7]. The information from Latin American countries is scarce and comes mainly from the cohort of the Grupo Latino Americano de Estudio de Lupus (GLADEL for its acronym in Spanish). In this cohort of 1480 patients with SLE, the survival rate at 4 years was found to be 94% [8] More recently, in a report on global mortality trends in systemic autoimmune diseases from 2001 to 2014, the SMR in patients with SLE was higher in Latin America (5.53) compared to North America (2.69) [9]. In Mexico, SLE is one

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of the main causes of death in young women (15–44 years) [10].

For several decades, it has been noted that SLE patients experience two mortality peaks. Infections and SLE activity usually cause the first peak in the short term, while the second peak is attributed to cardiovascular complications and neoplasms in the long term [11]. In developing countries, the leading causes of in-hospital death in patients with SLE are disease activity, infections, or a combination of both [12–14]. Neoplasms are another recognized cause of death, although less frequently reported [9]. In addition, various risk factors have been associated with mortality, such as older age at onset, male gender, high activity scores, fever, myositis, neurological, cardiovascular, premature atherosclerosis, lupus nephritis (class IV and VI), associated antiphospholipid syndrome (APS), gastrointestinal involvement, vasculitis, serum creatinine, thrombocytopenia, persistent C3 hypocomplementemia, high levels of C-reactive protein (CRP), presence of antiphospholipid antibodies (aPL) as well as high dose pulses of methylprednisolone and IV cyclophosphamide [13]. Thus, the mortality rate in patients with SLE can vary and may be influenced by various factors such as epidemiological, sociodemographic, genetic, clinical, and economic factors [2, 15–18]. Therefore, it is essential to collect local data to improve patient care and facilitate effective diagnosis and treatment for hospitalized SLE patients. Here, our aim was to determine the in-hospital mortality rate and the causes and risk factors associated with mortality in patients with SLE who were admitted to a referral hospital.

Patients and methods

We conducted a nested case–control study at the Hospital de Especialidades Dr. Antonio Fraga Mouret, Centro Médico Nacional La Raza, a national tertiary center in Mexico City, Mexico. We included patients aged > 18 years at the time of admission with the diagnosis of SLE according to the 2012 ACR/SLICC criteria admitted to the Department of Rheumatology between January 2009 and December 2020 [19]. We did not include patients admitted electively to perform a procedure (e.g., renal biopsy), for the scheduled administration of a drug (such as cyclophosphamide or rituximab) or pregnant women. Subsequently, we identified those patients who died during the hospitalization, and the primary cause of death was categorized into disease activity, infection, a combination of both, and other causes (e.g., drug toxicity, gastrointestinal bleeding, thrombosis). Patients who died (cases) were compared with those who were discharged alive (controls) in the same study period in a 1:3 ratio matched for age and sex.

For each patient, we collected demographic, clinical, biochemical, and immunological data from the medical records. Clinical variables included organ involvement in SLE, type and degree of SLE activity, and index of chronic damage. Disease activity was calculated using the SLE Disease Activity Index 2K (SLEDAI-2K) and a score equal to or greater than 4 was considered active disease. The chronic damage to the patients was calculated using the SLICC/ACR Damage Index and its presence was considered with a score equal to or greater than 1. Antiphospholipid syndrome (APS) was diagnosed using the updated 2006 Sydney criteria [20]. Patients whose symptoms began before 18 years old were classified as childhood-onset SLE. Biochemical variables included complete blood count, urea, urea nitrogen, serum creatinine, transaminases, serum lipids, general urinalysis, glomerular filtration rate (GFR), and 24-h proteinuria. Anemia was defined as Hb < 10 g/dL, lymphopenia as lymphocytes < 1000/μL, and thrombocytopenia as platelets < 100,000/μL. The immunological variables obtained were C3 and C4 serum complement (determined by nephelometry), antinuclear antibodies (ANA) by indirect immunofluorescence, anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Sm antibodies, anti-SSA/Ro antibodies, anti-SSB/La antibodies (determined by ELISA), lupus anticoagulant (LA), anti-cardiolipin antibodies, and anti-β2-glycoprotein-1 antibodies. Comorbidities such as obesity, diabetes, and arterial hypertension were also recorded. Diagnosis of infection was established based on a combination of clinical characteristics, systemic inflammatory response, imaging studies, and/or isolation of the causative microorganism by the culture of the affected site. Furthermore, infections were classified as community-acquired or nosocomial. Nosocomial infections were defined according to the WHO, as those infections acquired during the hospital stay and that were not present either in the incubation period or at the time of patient admission. The duration of hospital stays, as well as the medications taken both before and during hospitalization, were documented.

Statistical analysis and ethical considerations

Categorical variables are presented in simple frequencies and percentages. Continuous variables are presented as means with standard deviations (SD) or medians with interquartile ranges, as appropriate. We compared the characteristics of SLE patients who died during hospitalization (cases) vs. those who were discharged alive (controls) using Student's *t* test or Wilcoxon test for continuous measures and Pearson's Chi-square or Fisher's exact test for categorical measures. A comparison of variables among the death categories was made using the Chi-square test, ANOVA test, or Kruskal–Wallis test, as appropriate. We conducted a receiver operating characteristic (ROC) curve analysis to identify the

SLEDAI-2K score threshold that provides the most accurate prediction of in-hospital mortality. Additionally, we calculated both the positive predictive value (PPV) and negative predictive value (NPV). A multivariable logistic regression analysis was conducted to determine the potentially predictive variables with a p value less than 0.1 in the bivariate analysis. The dependent variables included in-hospital mortality, active disease mortality, infection mortality, and early mortality. The results from multivariable analysis and ROC curve analysis were expressed as odds ratio (OR) and its 95% confidence interval (CI). A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (v. 25.0, IBM 2010). The Local Health Research Committee number 3501 of our hospital approved the study protocol on December 15, 2021 (registry number R-2021-3501-134), and it was conducted in accordance with the declaration of Helsinki. Informed consent was not required as patient information was anonymized before analysis. The data of the patients were treated in accordance with the General Law of Protection of Personal Data in force in our country.

Results

We identified 1109 hospital admissions of SLE patients over 11 years. Of the total number of patients admitted to the hospital, we excluded 235 of them because they had been hospitalized electively (Fig. 1). From the remaining 834 patients, we identified 105 hospitalized patients who died. The estimated mortality rate was 10.93 deaths/1000 hospital admissions/year. To compare the variables, we selected 336 hospitalized patients who were discharged alive (controls) in the same study period, with a 1:3 strategy. Of the total number of hospitalized patients included in the analysis, 17% of them had > 1 admission to the hospital.

Comparison of dead patients with those alive at hospital discharge

Of the total included patients, 82% were female with a mean age of 34 ± 12 years (Table 1). Patients who died had a shorter duration of SLE (36 vs 60 months, $p = 0.03$), higher SLEDAI-2K scores (4 vs. 2 points, $p < 0.001$), a higher percentage of active patients (61% vs. 39.6%, $p < 0.001$), a lower percentage of APS (13.3% vs. 24.4%, $p = 0.01$), and a higher proportion of chronic kidney disease (35.2% vs. 14.9%, $p < 0.001$) compared to those who were discharged alive (Table 1). Constitutional symptoms (39.9% vs. 20%,

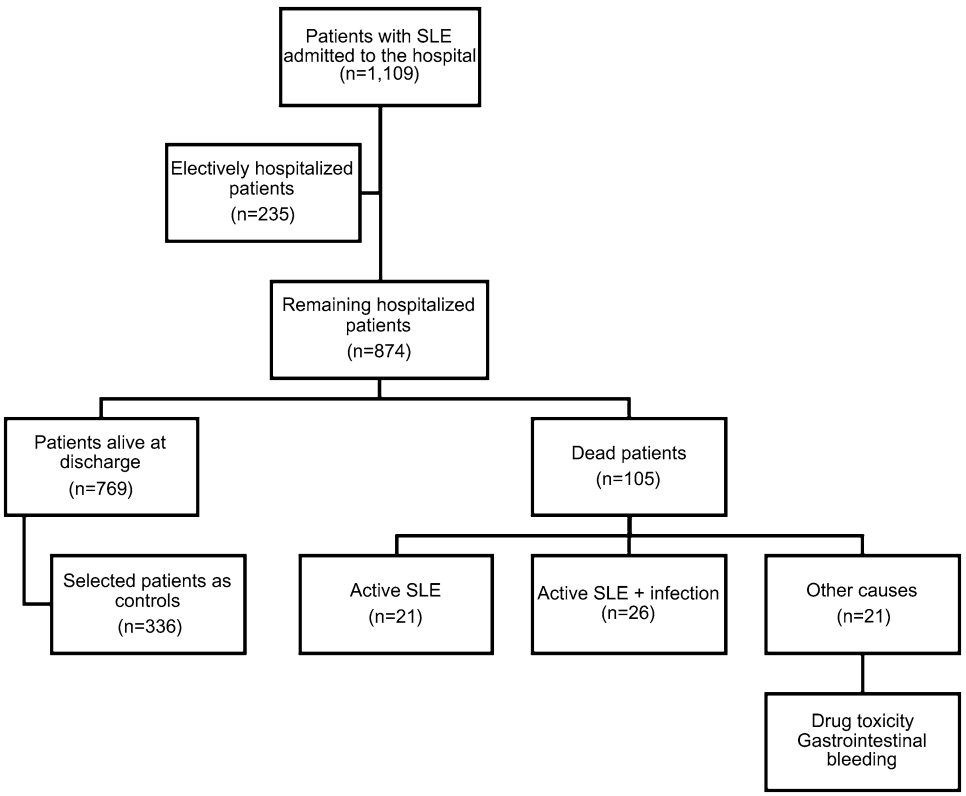

Fig. 1 Flowchart of the patients included in the study

Table 1 Baseline demographic and clinical characteristics of patients with SLE

Variable	Dead ($n=105$)	Survivors ($n=336$)	p value
Female, *n* (%)	88 (83.8)	272 (81.0)	0.509[a]
Age, years, mean (SD)	34.8 ± 13.2	32.9 ± 11.9	0.174[b]
SLE duration, months, median (IQR_{25-75})	36.0 (0.0–96.0)	60.0 (12.0–120.0)	0.033[c]
Length of stay, days, median (IQR_{25-75})	8.0 (2.0–14.0)	6.0 (4.0–10.0)	0.168[c]
Childhood-onset SLE, *n* (%)	21 (20.0)	74 (22.0)	0.660[a]
Active SLE (SLEDAI-2K ≥ 4), *n* (%)	64 (61.0)	133 (39.6)	<0.001[a]
SLEDAI-2K score, median (IQR_{25-75})	4.0 (2.0–10.0)	2.0 (0.0–8.0)	<0.001[c]
SLICC score, median (IQR_{25-75})	0 (0.0–3.0)	0 (0.0–1.0)	0.753[c]
Accrual damage, *n* (%)	40 (38.1)	159 (47.3)	0.097[a]
APS, *n* (%)	14 (13.3)	82 (24.4)	0.016[a]
Thrombotic events, *n* (%)	17 (16.2)	80 (23.8)	0.100[a]
Stroke, *n* (%)	5 (4.8)	12 (3.6)	
Ischemic heart disease, *n* (%)	1 (1.0)	2 (0.6)	
Deep venous thrombosis, *n* (%)	1 (1)	22 (6.5)	
Pulmonary embolism, *n* (%)	2 (1.9)	8 (2.4)	
Acute mesenteric ischemia	2 (1.9%)	2 (0.6)	
Comorbidity, *n* (%)	72 (68.6)	224 (66.7)	0.717[a]
Organ involvement, *n* (%)			
Constitutional symptoms	21 (20.0)	134 (39.9)	<0.001[a]
Skin	65 (61.9)	305 (90.8)	<0.001[a]
Arthritis	60 (57.1)	219 (65.2)	0.136[a]
Neuropsychiatric	18 (17.1)	65 (19.3)	0.614[a]
Serositis	9 (8.6)	58 (17.3)	0.030[a]
Lung	25 (23.8)	42 (12.5)	0.005[a]
Heart	8 (7.6)	9 (2.7)	0.022[a]
Lupus nephritis	67 (63.8)	193 (57.4)	0.247[a]
Hematologic	65 (61.9)	167 (49.7)	0.005[a]
Infection, *n* (%)	60 (57.1)	94 (28.0)	<0.001[a]
Site of infection, *n* (%)			
Pneumonia	36 (60.0)	17 (18.1)	<0.001[a]
Soft-tissue infection	5 (8.3)	20 (21.2)	<0.001[a]
Urinary tract infection	7 (11.7)	23 (24.5)	0.003[a]
Type of infection, *n* (%)			
Nosocomial	35 (58.3)	10 (14.7)	<0.001[a]
Community-acquired	25 (41.7)	58 (85.8)	0.950
Drugs, *n* (%)			
Glucocorticoids	87 (82.9)	328 (97.6)	<0.001[a]
Pulse methylprednisolone	37 (35.2)	82 (24.6)	0.002[a]
Chloroquine	53 (50.5)	210 (62.5)	0.007[a]
MMF	23 (21.9)	87 (27.4)	0.258[a]
CYC	17 (16.2)	66 (19.6)	0.430
Azathioprine	29 (27.6)	106 (31.5)	0.446[a]
Rituximab	4 (3.8)	22 (6.5)	0.399

[a]Chi-square; [b]Student's *t* test; [c]U Mann–Whitney

SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC, Systemic Lupus International Collaborating Clinics Damage Index; APS, antiphospholipid syndrome; CYC, cyclophosphamide; MMF, mycophenolate mofetil

$p < 0.001$), mucocutaneous manifestations (90.8% vs. 61.9%, $p < 0.001$), and serositis (17.3% vs 8.6%, $p = 0.03$) were more frequent in patients alive at hospital discharge, while cardiovascular involvement (7.6% vs. 2.7%, $p = 0.02$), pulmonary manifestations (23.8% vs. 12.5%, $p = 0.005$), and hematological manifestations (61.9% vs. 49.7%, $p = 0.005$) were more common in dead patients. About 60% of patients had lupus nephritis with a similar distribution in both groups. Mesangial glomerulonephritis (class II) was more frequently observed in those patients who survived and diffuse glomerulonephritis (class IV) in those who died. According to the class of lupus nephritis confirmed by biopsy, patients with class II lupus nephritis most frequently received mycophenolate mofetil (53.8%) followed by IV cyclophosphamide (26.9%) and azathioprine (15.3%); in those with class III, mycophenolate mofetil (36.8%) followed by azathioprine (31.5%) and tacrolimus (15.7%); in those with class IV, mycophenolate mofetil (44.7%) followed by IV cyclophosphamide (32.8%) and azathioprine (30.2%); and finally in those with class V, mycophenolate mofetil (37.5%) followed by azathioprine (31.2%) and IV cyclophosphamide (25%). Considering laboratory parameters, the patients who died presented more frequently with anemia (75.7% vs. 37.5%, $p < 0.001$), lymphopenia (83.5% vs. 65.4%), $p < 0.001$, thrombocytopenia (47.6% vs. 17%, $p < 0.001$), elevated serum creatinine (1.5 mg/dL vs. 0.8 mg/dL, $p < 0.001$), decreased GFR (75% vs 43.1%, $p < 0.001$), and C3 hypocomplementemia (74% vs. 51.7%, $p < 0.001$) on hospital admission compared to those who were alive (Table 2). Interestingly, a smaller proportion of deceased patients were taking chloroquine (50.5% vs. 62.5%, $p = 0.007$) but received methylprednisolone pulses more frequently than those living patients (35.2% vs. 24.6%, $p = 0.002$). Infections (57.1% vs. 28%, $p < 0.001$), especially nosocomial infections (58.3% vs. 14.7%, $p < 0.001$), more frequently complicated patients who died compared to those who did not die, with pneumonia being the most observed infection (60% vs. 18.1%, $p < 0.001$) (Table 3). On the other hand, soft-tissue infections (21.3% vs. 8.3%, $p < 0.001$) and urosepsis (24.5% vs. 11.7%, $p = 0.003$) were more frequent in patients who survived compared to those who died. Of 40 patients in which the results of their cultures were obtained, a microorganism was isolated in 38, with *E. coli*, *S. aureus*, *C. albicans*, *P. aeruginosa*, *K. pneumoniae*, and *A. faecium* being the most frequently recovered microorganisms. Patients who developed a nosocomial infection had a greater number of days of hospital stay (11 vs. 8, $p < 0.001$), lower SLEDAI scores (4 vs. 5, $p = 0.008$), a higher frequency of chronic kidney disease (41.7% vs. 17.1%, $p < 0.001$), anemia (70.8% vs. 40.3%, $p < 0.001$), and thrombocytopenia (43.8% vs. 22%, $p < 0.001$) as well as higher CRP levels (28.7 mg/dL vs. 7.83 g/dL, $p = 0.01$) compared to those without it.

Analysis of mortality subgroups

According to the attributed cause of death, 36 patients (34.2%) died from infections, 21 (20%) from SLE activity, 26 (24.8%) from a combination of both, and 21 (20%) from other causes, mostly gastrointestinal hemorrhage, malignancies, drug toxicity, liver disease, and SARS-CoV2 infection. The comparison of the variables studied by the different mortality subgroups of patients is shown in Table 3. Of the total number of dead patients, 68 (64.5%) had less than 5 years of evolution (early death).

Table 2 Comparison of biochemical and immunological characteristics between dead patients and those discharged alive from the hospital

Variable	Dead ($n = 105$)	Survivors ($n = 336$)	p value
Anemia (Hb < 10 g/dL), *n* (%)	78 (75.7)	126 (37.5)	< 0.001[a]
Thrombocytopenia (platelets < 100,000/µl), *n* (%)	50 (47.6)	57 (17.0)	< 0.001[a]
Lymphopenia (lymphocytes < 1000/µl), *n* (%)	86 (83.5)	219 (65.4)	< 0.001[a]
Serum creatinine, mg/dL, median (IQR_{25-75})	1.5 (0.82–3.31)	0.8 (0.68–1.34)	< 0.001[b]
eGFR 24 h decrease (< 70 ml/min), *n* (%)	66 (75.0)	113 (43.1)	< 0.001[a]
Active urinary sediment, *n* (%)	33 (32.0)	127 (38.4)	0.245[a]
C3, mg/dL, median (IQR_{25-75})	53 (35.0–76.0)	77 (55.0–102.0)	0.701[b]
C4, mg/dL, median (IQR_{25-75})	12 (7.0–17.0)	11.0 (7.0–18.0)	0.182[b]
Low C3, *n* (%)	77 (74.0)	172 (51.7)	< 0.001[a]
Low C4, *n* (%)	71 (67.6)	213 (64.5)	0.494[a]
Positive anti-dsDNA antibodies, *n* (%)	40 (38.1)	158 (47.0)	0.088[a]
Positive anti-Ro antibodies, *n* (%)	15 (14.3)	49 (14.6)	0.931[a]
Positive anti-La antibodies, *n* (%)	4 (3.8)	18 (5.3)	0.521[a]
Positive anti-Sm antibodies, *n* (%)	12 (11.4)	52 (15.5)	0.493[a]
High CRP (> 8 mg/L), *n* (%)	49 (34.3)	113 (26.7)	< 0.001[a]

[a]Chi-square; [b]U Mann–Whitney

eGFR, glomerular filtration rate; CRP, C-reactive protein

Table 3 Comparison of patient subgroups by attributed cause of death

Variable	Infection ($n=36$)	Disease activity ($n=21$)	Infection and disease activity ($n=26$)	Others ($n=22$)	p value
Age, years, mean (SD)	34 ± 14	33 ± 9	34 ± 13	38 ± 16	0.364[b]
SLE duration, months, median (IQR_{25-75})	42 (12–96)	0 (0–48)	24 (2–192)	48 (36–84)	0.197[c]
SLEDAI-2 K score, median (IQR_{25-75})	2 (1–4)	9 (6–14)	10 (4–14)	2 (0–4)	< 0.001[c]
Length of stay, days, median (IQR_{25-75})	5 (2–14)	10 (5–18)	11 (2–17)	8 (4–11)	0.199[c]
Early death, *n* (%)	22 (61.1)	17 (81.0)	16 (61.5)	13 (59.1)	< 0.001[a]
Comorbidity, *n* (%)	25 (69.4)	12 (57.1)	17 (65.4)	18 (81.8)	0.516[a]
Anemia (Hb < 10 g/dL), *n* (%)	27 (75.0)	14 (73.7)	21 (80.8)	16 (72.7)	< 0.001[a]
Thrombocytopenia (platelets < 100,000/µl), *n* (%)	17 (47.2)	11 (57.9)	13 (50.0)	9 (40.9)	< 0.001[a]
Lymphopenia (lymphocytes < 1000/µl), *n* (%)	27 (75.0)	18 (94.7)	22 (84.6)	19 (86.4)	0.005[a]
Active urinary sediment, *n* (%)	10 (27.8)	6 (31.6)	10 (38.5)	7 (31.8)	0.718[a]
Low C3, *n* (%)	27 (75.0)	18 (85.7)	18 (72.0)	14 (63.6)	< 0.001[a]
Low C4, *n* (%)	22 (61.1)	19 (90.5)	17 (65.4)	13 (59.1)	0.152[a]
Positive anti- dsDNA antibodies, *n* (%)	10 (27.8)	10 (47.6)	13 (52.0)	7 (31.8)	0.111[a]
High CRP (> 8 mg/L), *n* (%)	15 (68.2)	9 (69.2)	14 (87.5)	11 (68.8)	< 0.001[a]
Autoantibody, *n* (%)					
Anti-Ro antibodies	3 (8.3)	7 (33.3)	5 (19.2)	0 (0.0)	
Anti-La antibodies	1 (2.8)	2 (9.5)	1 (3.8)	0 (0.0)	
Anti-Sm antibodies	4 (11.1)	5 (23.8)	2 (7.7)	1 (4.5)	0.742[a]
Organ involvement, *n* (%)					
Constitutional symptoms	9 (25.0)	3 (14.3)	5 (19.2)	4 (18.2)	0.006
Skin	26 (72.2)	11 (52.4)	12 (46.2)	16 (72.2)	< 0.001[a]
Arthritis	16 (44.4)	11 (52.4)	18 (69.2)	15 (68.2)	0.103[a]
Neuropsychiatric	3 (8.3)	4 (19.0)	8 (30.8)	3 (13.6)	0.229 [a]
Serositis	1 (2.8)	2 (9.5)	2 (7.7)	4 (18.2)	0.124[a]
Lung	3 (8.3)	12 (57.1)	6 (23.1)	4 (18.2)	< 0.001[a]
Heart	1 (2.8)	3 (14.3)	2 (7.7)	2 (9.1)	0.037[a]
Lupus nephritis	24 (66.7)	13 (61.9)	16 (61.5)	14 (63.3)	0.818[a]
Hematologic	17 (47.2)	17 (81.0)	19 (73.1)	12 (54.5)	0.013
Drugs, *n* (%)					
Oral glucocorticoids	31 (86.1)	14 (66.7)	20 (76.9)	21 (100.0)	< 0.001[a]
Pulse methylprednisolone	8 (22.2)	13 (61.9)	10 (38.5)	6 (28.6)	0.003[a]
Chloroquine	17 (47.2)	5 (23.8)	15 (57.7)	16 (72.7)	0.003[a]
MMF	7 (19.4)	3 (14.3)	6 (23.1)	7 (31.8)	0.531[a]
CYC	6 (16.7)	2 (9.5)	5 (19.2)	4 (18.2)	0.835[a]
Azathioprine	11 (30.6)	5 (23.8)	3 (11.5)	10 (45.5)	0.119[a]

[a]Chi-square; [b]ANOVA; [c]Kruskal–Wallis

CRP, C-reactive protein; CYC, cyclophosphamide; MMF, mycophenolate mofetil

In the group of patients with early death, a lower proportion of childhood SLE (8.8% vs. 40.5%, $p < 0.001$), higher SLEDAI scores (4 vs. 2, $p = 0.01$), lower proportion of accrual chronic damage (27.9% vs. 56.8%, $p = 0.004$), a lower frequency of arterial hypertension (19.1% vs. 32.4%, $p = 0.001$), and chronic kidney disease (31.3% vs. 43.2%, $p = 0.01$) were observed compared with the group with late death. As expected, the median SLEDAI-2K scores were higher in those patients who died due to SLE activity with and without associated infection (median of 10 and 9 points, respectively; $p < 0.001$). Anemia and thrombocytopenia were more frequently found in patients who died due to SLE activity with and without associated infection (80.8% and 76.2%, $p < 0.001$; 50% and 56.1%, $p < 0.001$; respectively). C3 hypocomplementemia was more frequent in patients who died due to disease activity (85.7%, $p < 0.001$). A lower proportion of patients who died due to SLE activity were taking chloroquine ($p < 0.003$) but more frequently received methylprednisolone pulses ($p < 0.003$) at hospital admission compared to the other subgroups.

Mortality predictors

In the multivariate analysis, we found that hematological manifestations such as anemia (OR 2.9, CI 95% 1.4–5.7), lymphopenia (OR 2.1, CI 95% 1.01–4.6), and thrombocytopenia (OR 3.3, CI 95% 1.7–6.4) as well as any kind of infection (OR 2.5, CI 95% 1.2–5.2), particularly nosocomial infections (OR 5.0, CI 95% 1.8–13.7) were independent risk factors associated with in-hospital mortality (Fig. 2). ROC curve analysis showed that a SLEDAI score > 2 had a PPV of 83% and an NPV of 35% to predict in-hospital mortality (OR 2.0, CI 95% 1.02–3.8). In contrast, the presence of constitutional symptoms (OR 0.3, CI 95% 0.1–0.7), skin and joint involvement (OR 0.2, CI 95% 0.1–0.5), serositis (OR 0.1, CI 95% 0.06–0.4), and use of prednisone (OR 0.2, CI 95% 0.05–0.8) were factors associated with less in-hospital mortality. Finally, it was not possible to analyze risk factors by cause of death subgroup due to an insufficient number of subjects in the outcome group.

Discussion

We conducted a study to examine the mortality rate of SLE patients during their hospital stay and to identify the contributing factors and causes of death over an 11-year period at a reference hospital. Our findings revealed a significant mortality rate, with disease activity and infections, particularly those acquired in the hospital or a combination of both, as the primary causes of death in SLE patients. We also found that anemia, thrombocytopenia, and hospital-acquired infections were independent risk factors for mortality in SLE patients during their hospitalization.

Over the past 50 years, the survival rate of patients with SLE has significantly improved. In the 1950s, the survival rate was less than 50%, but at the beginning of the twenty-first century, it had increased to almost 95% thanks to a better understanding of the disease and advancements in diagnosis and treatment [21]. However, mortality rates still vary across different ethnicities, races, and regions. In the United States, the risk of death for hospitalized patients with SLE decreased from 2.2 to 1.5% between 2006 and 2016, but Black and Hispanic individuals were more likely to die than other ethnic groups [18, 22]. Developed countries like Canada, the UK, Denmark, and Finland have an SMR ranking of 1.48 to 4.53 [5, 23–25], while a Brazilian study showed a mortality rate of 4.76 deaths per 100,000 inhabitants [26]. Developing countries like Pakistan and South Africa report lower survival rates, ranging from 57 to 80% [27, 28]. Our study reported a high mortality rate of 10.93 deaths per 1000 hospital admissions annually. It should be noted that our research was conducted at a high-complexity medical center, which provides care to severe patients that probably had worse disease outcomes. Additionally, our patients are of Hispanic ethnicity and are of low socioeconomic status, factors known to impact disease outcomes, as previously reported [15–18].

Our research has found that infections, especially nosocomial infections, and SLE flare-ups (either alone or combined with infection) are the primary causes of death. This finding is consistent with similar studies conducted in other countries [29–32]. For instance, a review of 174,105 SLE hospitalizations in the United States using the National Inpatient Sample (NIS) in 2016 revealed that infections were the leading cause of death [29]. In China, a nationwide SLE cohort of 29,510 hospitalized patients between 2005 and 2014 found that infections and complications related to SLE activity were the most common causes of death [30]. In Colombia, a retrospective case series of SLE patients who died between January 2011 and June 2017 also identified

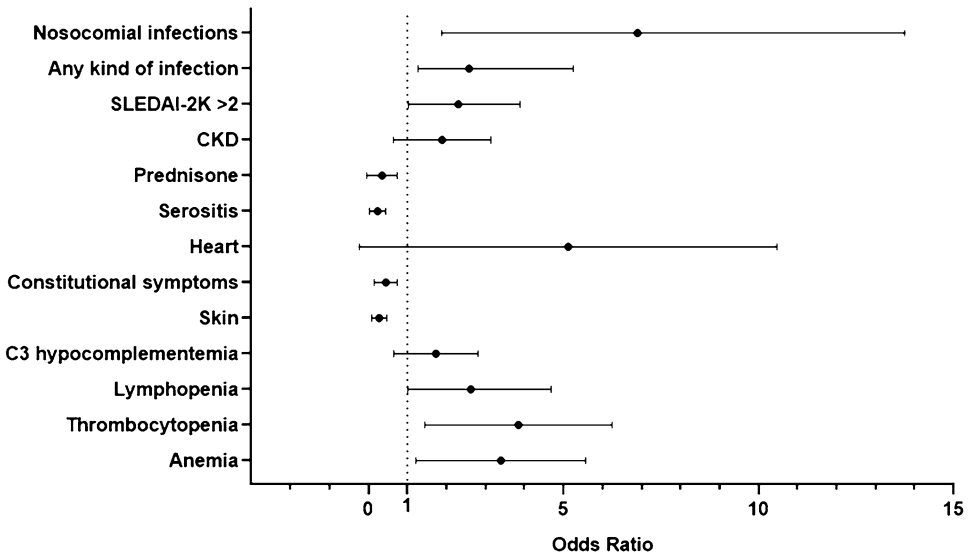

Fig. 2 Predictive factors of in-hospital mortality in our patients with SLE

disease activity and infections as the primary causes of death [31]. However, our findings differ from other researches that report cardiovascular disease and malignancy as the significant causes of death in SLE patients, especially in developed countries [33–41]. Generally, during the early stages of illness, infections, or complications of active disease (such as lupus nephritis) are the leading causes of death, while cardiovascular disease and cancer are the primary causes of late death in SLE patients [2]. However, in a recent British study, unexpectedly no cardiovascular causes of death were found, suggesting a change in the trend of causes of mortality in patients with SLE, similar to our results [42]. It is worth mentioning that the median evolution time in our patients was 48 months, which partly explains why we observed few cardiovascular complications, such as ischemic heart disease. Therefore, factors such as ethnicity, socioeconomic status, regional cultural background, and the availability of medical resources can influence the course and outcomes of patients with SLE.

The importance of infections as a potentially serious complication in patients with SLE should not be overlooked. Bacterial infections are the most frequent, followed by viral, fungal, and protozoan infections, with the respiratory and urinary tracts being the most affected sites [2]. SLE patients are more prone to bacteremia, which has a higher mortality rate compared to other infections [43, 44]. Mortality is also higher in those with nosocomial infections and active lupus [27, 45–47] which agrees with our results. SLE patients with high disease activity and intense immunosuppressive therapy are more susceptible to infections [27, 48]. Additionally, different therapeutic responses have been described with the use of immunosuppressants in different ethnicities, which may influence disease control and potential adverse effects [49]. Our study revealed that a significant number of patients had active SLE and were treated with pulse methylprednisolone and other immunosuppressants, resulting in a high incidence of infections. On the other hand, antimalarial medication has been shown to lower the risk of infections in SLE patients [49]. Antimalarials can provide protection against infections by regulating pH and post-translational protein modifications [31]. In our study, those who died had lower chloroquine use. Therefore, it is crucial to provide outpatient care, ensure adherence to treatment, identify the optimal immunosuppression treatment, and educate patients to reduce the risk of death.

Based on our analysis using both bivariate and multivariable models, we can confirm that organ involvement related to SLE significantly impacts the outlook of these patients. Hematological manifestations of the three cell lines were found to be an independent risk factor for mortality by the multivariable logistic regression analysis. Our results are consistent with previous research such as Moghazy et al.'s report, which identified lymphopenia as a risk factor for mortality in the multivariate Cox regression analysis [50]. Wo et al.'s study also found hematological abnormalities to be associated with mortality in both univariate and multivariate analyses [30]. In a case series by Aguirre-Valencia et al., patients who passed away often had lymphopenia, anemia, leukopenia, or thrombocytopenia with a frequency between 73.4 and 89.8% [31]. In a previous case–control study by Miranda-Hernandez et al. of hospitalized SLE patients, those were admitted for hematological manifestations had a higher risk of death (OR 3.8, 95% CI 1.1–8.8, $p < 0.001$), particularly those with thrombocytopenia, compared to those admitted for other SLE symptoms or complications [51]. Minor manifestations of SLE (serositis, skin and joint involvement) were associated with lower mortality, which may simply show less severity of the disease. In fact, higher SLEDAI scores at SLE diagnosis are associated with higher mortality. Unfortunately, we did not have this complete information to perform our analysis. Therefore, it is crucial to quickly identify any hemocytopenia in a hospital setting as it can affect the mortality risk of SLE patients.

Our study has some limitations that need to be acknowledged. First, we only included patients from a single hospital center, so our findings may not apply to other healthcare settings. Nonetheless, the insights gained from this study can help improve the care provided to these patients. Second, due to the retrospective design of our study, some relevant data may have been missed. For example, it was not possible to obtain the SLEDAI score at diagnosis or calculate the cumulative glucocorticoid dose. However, we made sure to exclude patients with incomplete information, which may have introduced some level of selection bias. Third, it was not possible to recover the isolated causative agent in all patients with infection. Lastly, our research only focused on patients admitted to the Department of Rheumatology, and therefore we may have underestimated the incidence of cardiovascular or malignant mortality in the wider hospital population.

In conclusion, infections and disease activity remain the primary causes of death among individuals with SLE. It is crucial to undertake comprehensive measures that account for varying disease severity, evaluate the effectiveness of immunosuppressants, comply with management guidelines, ensure adequate access to healthcare, and address social determinants of health to reduce the disparity in in-hospital mortality rates for SLE patients.

Authors' contributions All authors meet the ICMJE criteria for authorship. MAS, NZZ, and MAC were involved in drafting or revising this article critically for important intellectual content. DMH, RBG, and AEGR made substantial contributions to the conception or design of the work. AEGR and MÁS drafted the work or revised it critically for important intellectual content. MAC, GMD, DTR, and BLZ contributed to the data collection and analysis. MPCD and MÁS revised the

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Declarations

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