Clinical correlates and outcomes in a group of Puerto Ricans with systemic lupus erythematosus hospitalized due to severe infections

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Abstract

Objective: Infections are a major cause of morbidity and mortality in systemic lupus erythematosus. Clinical outcomes of systemic lupus erythematosus patients hospitalized due to infections vary among different ethnic populations. Thus, we determined the outcomes and associated factors in a group of Hispanics from Puerto Rico with systemic lupus erythematosus admitted due to severe infections.

Methods: Records of systemic lupus erythematosus patients admitted to the Adult University Hospital, San Juan, Puerto Rico, from January 2006 to December 2014 were examined. Demographic parameters, lupus manifestations, comorbidities, pharmacologic treatments, inpatient complications, length of stay, readmissions, and mortality were determined. Patients with and without infections were compared using bivariate and multivariate analyses.

Results: A total of 204 admissions corresponding to 129 systemic lupus erythematosus patients were studied. The mean (standard deviation) age was 34.7 (11.6) years; 90% were women. The main causes for admission were lupus flare (45.1%), infection (44.0%), and initial presentation of systemic lupus erythematosus (6.4%). The most common infections were complicated urinary tract infections (47.0%) and soft tissue infections (42.0%). In the multivariate analysis, patients admitted with infections were more likely to have diabetes mellitus (odds ratio: 4.20, 95% confidence interval: 1.23–14.41), exposure to aspirin prior to hospitalization (odds ratio: 4.04, 95% confidence interval: 1.03–15.80), and higher mortality (odds ratio: 6.00, 95% confidence interval: 1.01–35.68) than those without infection.

Conclusion: In this population of systemic lupus erythematosus patients, 44% of hospitalizations were due to severe infections. Patients with infections were more likely to have diabetes mellitus and higher mortality. Preventive and control measures of infection could be crucial to improve survival in these patients.

Keywords

Systemic lupus erythematosus, severe infections, clinical manifestations, comorbidities, outcomes

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease that is characterized by a wide spectrum of immunologic abnormalities and clinical manifestations.[1] Because of the immunosuppression caused by SLE itself or its treatment, infectious disorders are a common complication and a major culprit of morbidity and mortality in this population.[2] Infections have been reported as a cause of death in 12%–60% of patients.[3] In addition, infections are accountable for as much as 50% of hospitalizations of lupus patients.[3] Severe infections are those that are disseminated, require intravenous (IV) antibiotic therapy or hospitalization, and

that could lead to death.[4] Mortality secondary to these infections are usually seen early during the course of disease.[5]

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Generally, the infectious pathogens affecting lupus patients do not differ from the general population, although opportunistic infections have also been reported.[5,6] The frequency, severity, and types of infections vary among different ethnic groups, but few studies examining the outcomes of SLE requiring hospitalization due to major infection have been reported in Hispanic populations. Therefore, we examined the outcomes and factors associated with infections in a group of Hispanics from Puerto Rico with SLE hospitalized due to severe infections.

Methods

Patient population

A retrospective analysis was performed in consecutive SLE patients admitted to the Rheumatology Service at the Adult University Hospital, San Juan, Puerto Rico, from January 2006 to December 2014. Lupus patients ≥21 years of age who fulfilled the 1992 revised American College of Rheumatology (ACR) classification criteria for SLE were included in the study.[7] Patients <21 years of age and those with drug-induced lupus were excluded. The Adult University Hospital is a 350-bed tertiary hospital which serves as teaching facility for the University of Puerto Rico School of Medicine and its training programs. It is a government hospital administered by the Department of Health of Puerto Rico that delivers health services mainly to the medically indigent population of Puerto Rico. Major services offered include Internal Medicine, Obstetrics and Gynecology, Surgery, Physical Medicine, and several medical and surgical subspecialties. The appointed attending physicians are faculty members of the University of Puerto Rico School of Medicine. This study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (protocol number 7510115). Written informed consent was waived by the Institutional Review Board.

Variables

Demographic factors, disease duration (time interval between SLE diagnosis and hospitalization), SLE manifestations, comorbidities, pharmacologic profile prior to hospitalization, treatment and complications during hospitalization, and outcome measures were examined. The demographic factors studied included age, sex, and type of medical insurance (either public, private, Medicare, or none). Disease duration was defined as the time period between SLE diagnosis and first hospitalization, or last hospitalization for those patients with more than one admission. Clinical variables included the main reason for admission, lupus manifestations, and comorbidities. Infection was ascertained by clinical grounds using history, physical examination, laboratory tests, cultures, and/or imaging studies, as appropriate. Disease flare was defined as the existence of an increase in disease activity or new organ system involvement associated with different clinical manifestations

and/or laboratory findings warranting further immunosuppressive therapy. Lupus manifestations were defined per the ACR classification criteria[7] and included malar rash, photosensitivity, oral ulcers, arthritis, serositis, central nervous system (CNS) involvement, renal involvement, and hematologic disorders (hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia). The following comorbidities were studied: hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, cerebrovascular accident, acute kidney disease, chronic kidney disease, hypothyroidism, and malignancy antiphospholipid syndrome, Sjögren's syndrome, and fibromyalgia. For patients who were admitted due to infection, the type of infection was determined.

Pharmacologic treatment prior to hospitalization (within 1 month) was ascertained, including corticosteroids, hydroxychloroquine, mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, rituximab, tacrolimus, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aspirin, other antiplatelet drugs, full anticoagulation (warfarin, heparin, or factor Xa inhibitors), and statins. Prednisone dose (or equivalent) prior to hospitalization was categorized as low (≤10 mg daily) or high (>10 mg daily) dose. Also, the following therapies during hospitalization were determined: IV corticosteroid pulse, IV high-dose corticosteroids, oral corticosteroids, hydroxychloroquine, mycophenolate mofetil, azathioprine, IV cyclophosphamide, IV rituximab, IV immunoglobulins, IV antibiotics, and plasmapheresis. Finally, inpatient complications (respiratory failure requiring mechanical ventilation, failure requiring hemodialysis, and nosocomial infection) and outcome measures (length of hospital stay, readmissions (within 1 month), and mortality) were examined.

Statistical analysis

Demographic and clinical and characteristics of SLE patients were summarized using descriptive statistics. SLE patients admitted with infections were compared to those not presenting with infection (disease flare and initial presentation of SLE). All patients' admissions were analyzed in the mixed effects logistic regression models in order to estimate the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for infection and various complications according to patients' characteristics. In addition, the association between infections (as predictor) and length of stay in the hospital (in days) was determined through a linear mixed effects regression model estimating the beta coefficients and 95% CIs. Statistical significance was set at <0.05. Statistical analysis was performed using STATA v.14 (College Station, TX, USA).

Results

In total, 204 admissions were reviewed corresponding to 129 SLE patients. The main cause for admission was lupus flare (45.1%), followed by infection (44.0%) and initial presentation of SLE (6.4%). More than one infection was observed in

Table 1. Demographic features of SLE patients at first hospital admission (n = 129 patients).

Age	
Mean ± SD	34.7 ± 11.6
Median (P25–P75)	31 (26–43)
Sex, n (%)	
Male	13 (10.1)
Female	116 (89.9)
Health insurance, n (%)	
Public	87 (68.0)
Private	29 (22.7)
Medicare	10 (7.8)
None	2 (1.6)

SLE: systemic lupus erythematosus; SD: standard deviation; P: percentile.

Table 2. Lupus manifestations and comorbidities at hospital admission anytime during the study period (n = 129 patients).

Duration of SLE disease[a] (in years)	
Mean ± SD	8.7 ± 8.2
Median (P25, P75)	7 (1, 13)
SLE manifestation,[b] n (%)	
Malar rash	63 (56.8)
Photosensitivity	49 (44.1)
Oral ulcers	37 (33.3)
Arthritis	67 (60.4)
Serositis	21 (18.9)
CNS involvement	21 (19.1)
Renal involvement	62 (48.1)
Hematologic involvement	81 (74.3)
Hemolytic anemia	12 (11.0)
Leukopenia	33 (30.3)
Lymphopenia	51 (46.8)
Thrombocytopenia	40 (36.7)
Times admitted to the hospital, n (%)	
One	88 (68.2)
Two	26 (20.2)
Three	7 (5.4)
More than three	8 (6.2)
Hospital admission due to infection, n (%)	
Yes	67 (51.9)
No	62 (48.1)
Comorbidities, n (%)	
Hypertension	71 (55.0)
Diabetes mellitus	17 (13.2)
Dyslipidemia	16 (12.4)
Coronary artery disease	1 (0.8)
Cerebrovascular accident	2 (1.6)
Acute kidney injury	4 (3.1)
Chronic kidney injury	12 (9.3)
Hypothyroidism	22 (17.1)
Malignancy	2 (1.6)
Antiphospholipid syndrome	19 (14.7)
Sjögren's syndrome	8 (6.2)
Fibromyalgia	6 (4.7)

SLE: systemic lupus erythematosus; SD: standard deviation; P: percentile; CNS: central nervous system.
[a]In total, 109 patients had information on SLE duration.
[b]Per ACR classification criteria, 111 patients had information on SLE manifestations.

24.3% of hospitalizations due to serious infections. The most common infections were complicated urinary tract infections (47.0%), soft tissue infections (42.0%), pneumonia (14.4%), fungal infections (12.2%), and Herpes Zoster (7.8%).

Tables 1 and 2 depict the demographic parameters, lupus manifestations, and comorbidities of the 129 SLE patients; 90% were women, and the mean ((standard deviation (SD)) age was 34.7 (11.6) years. The mean (SD) duration of SLE disease in years was 8.7 (8.2) years. The most common SLE manifestations were hematologic involvement (74%), arthritis (60%), and malar rash (57%). Renal and CNS involvement were observed in 48% and 19% of patients, respectively. The most frequent comorbidities were hypertension (55%), hypothyroidism (17%), antiphospholipid syndrome (15%), diabetes mellitus (13%), and dyslipidemia (12%).

Table 3 shows pharmacological treatment prior and during hospitalization at anytime during the study period. Prior to hospitalization, 78% of SLE patients were taking corticosteroids, 63% hydroxychloroquine, 31% mycophenolate mofetil, and 19% azathioprine. During hospitalization, 47% of lupus patients received IV high-dose corticosteroids, 34% oral corticosteroids, 28% cyclophosphamide, and 25% IV corticosteroid pulse.

Multilevel mixed effects models for demographic features, lupus manifestations, comorbidities, and pharmacologic treatment are shown in Table 4. In the unadjusted model, serious infections were associated with diabetes mellitus and exposure to IV corticosteroid pulse, oral corticosteroids, and cyclophosphamide during hospitalization. In the multivariate analysis, diabetes mellitus, IV cyclophosphamide, and IV antibiotics retained significance. Also, in the multivariate analysis, serious infection was associated with aspirin treatment prior to hospitalization. No association was found for exposure to corticosteroids prior to hospitalization.

Finally, multilevel mixed effects models for complications and outcomes are shown in Table 5. Patients admitted with serious infection were more likely to have higher mortality in the multivariate analysis adjusted for age and sex. However, this observation was not significant in the multivariate

analysis adjusted for age, sex, disease duration, and diabetes mellitus. No significant differences were observed for respiratory failure, renal failure requiring hemodialysis, nosocomial infections, readmissions, and length of stay.

Discussion

Serious infections are one of the most common life-threatening complications in SLE and represent a significant cause for hospital admission. In a national population-based study, lupus patients had 12–24 times higher risk of hospitalization

Table 3. Treatments prior and during hospitalization of SLE patients at anytime during the study period (n = 129 patients).

Treatment prior hospitalization	n (%)	Treatment during hospitalization	n (%)
Corticosteroids	100 (77.5)	IV corticosteroid pulse	32 (24.8)
Hydroxychloroquine	81 (62.8)	IV high-dose corticosteroids	61 (47.3)
Mycophenolate mofetil	40 (31.0)	Oral corticosteroids	44 (34.1)
Azathioprine	24 (18.6)	Hydroxychloroquine	49 (38.0)
Methotrexate	1 (0.8)	Mycophenolate mofetil	8 (6.2)
Cyclophosphamide	4 (3.1)	Azathioprine	3 (2.3)
ACE inhibitors	47 (36.4)	Cyclophosphamide	36 (27.9)
ARBs	22 (17.1)	IV rituximab	3 (2.3)
Aspirin	15 (11.6)	IV immunoglobulins	2 (1.6)
Other antiplatelet drugs	3 (2.3)	IV antibiotics	79 (61.2)
Full anticoagulation	18 (14.0)	Plasmapheresis	6 (4.7)
Statins	18 (14.0)		

SLE: systemic lupus erythematosus; IV: intravenous; ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers.

due to serious infections than the general population.[8] Nearly half of the lupus patients have an increased risk of developing major infections throughout the course of disease.[9] Previous studies have shown that immunologic abnormalities, disease activity, and immunosuppressive therapy are linked with serious infections in lupus patients.[10] Other studies have reported that Black race, socioeconomic factors, and renal insufficiency are associated with infections.[11,12] Even though infections complicate the course and outcome of SLE and that risk factors for serious infections may vary among different ethnic populations, few studies have been conducted in Hispanic populations. Thus, we examined the frequency and clinical correlates of serious infections in SLE patients who required hospitalization.

The main causes for admission in our study were lupus flare-ups (45.1%), followed by infection (44.0%) and initial presentation of SLE (6.4%). In agreement with our study, the major reasons for admission in the Hopkins Lupus Cohort were active SLE (35%), infection and/or active SLE (14%), infection alone (11%), and medical complications of SLE (13%). In that study, 90% of infections were bacterial.[13] Likewise, Edwards et al.[14] described pulmonary and skin bacterial infections the most common causes of serious infections. Different types of infection have been reported, but there is a consensus that bacterial infections are the most frequent. In our work, we found that complicated urinary tract infections and soft tissue infections were the most common.

Lupus patients admitted with serious infections were more likely to have type 2 diabetes mellitus. It is well documented that impaired glycemic control affects the phagocytic activity of polymorphonuclear cells, chemotaxis, oxidative burst, and intracellular killing, thus increasing the risk for infections.[15–18] In addition, microvascular and macrovascular damage and peripheral neuropathy associated with diabetes indirectly play a role in promoting infections.[19] Therefore, the higher prevalence of diabetes in our patients having serious infections is not unexpected. However, there are only few studies that have reported this association in these patients. In a mortality study, Ward et al.[11] acknowledged that SLE patients

with diabetes mellitus had an increased susceptibility of having infectious disorders. On the other hand, these results contrast data from Pryor et al.[20] in which diabetes mellitus did not seem to be a risk factor for infection in lupus patients treated with cyclophosphamide and high-dose corticosteroids.

In the multivariate analysis, we found that the use of aspirin prior to hospitalization was associated with infections. Some studies suggest that aspirin may modulate the immune system which could be troublesome for patients who are already immunosuppressed. In a double-blind, placebo-controlled study performed in 60 healthy volunteers, the use of aspirin was associated with suppression of the serum neutralizing response to the challenge of intranasal rhinovirus type 2.[21] Exposure to oral corticosteroids during hospitalization was higher in the group of patients with infection. This finding could be explained by the fact that in the setting of active infection, patients are treated less aggressively with immunosuppressive drugs to avoid further complications. Consistent with this notion, our patients admitted with serious infections were less likely to receive IV methylprednisolone pulse and IV cyclophosphamide. In other studies, the use of corticosteroids has been associated with an increased risk of infections. However, in our study, we did not find that corticosteroid therapy prior to hospitalization was related to infectious processes.

Immunosuppressive therapy with mycophenolate mofetil, azathioprine, cyclophosphamide, tacrolimus, rituximab, and methotrexate prior to hospitalization was not associated with an increased risk of serious infection. Similarly, in a prospective observational cohort about predictors of major infections in SLE, treatment with immunosuppressive agents (azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, or cyclosporine) did not confer an increased risk of developing major infections.[4] On the contrary, a retrospective study about the prevalence of community-acquired and nosocomial infections in hospitalized SLE patients reported an increased frequency of infections in patients who received cyclophosphamide, methylprednisolone, and prednisone.[3]

In the multivariate analysis of our study adjusted for age and sex, we found that patients admitted with infection had a

Table 4. Multilevel mixed effects models for demographic features, lupus manifestations, comorbidities, and pharmacologic treatment among SLE patients with infections (n = 204 hospitalizations).

Demographic features

Predictors	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
Age	1.01 (0.98–1.04)	0.98 (0.95–1.01)
Sex—males[b]	0.68 (0.21–2.24)	1.35 (0.43–4.20)
SLE manifestations[c]		
Malar rash	1.07 (0.53–2.14)	0.68 (0.31–1.51)
Photosensitivity	0.93 (0.47–1.86)	0.61 (0.28–1.37)
Oral ulcers	0.86 (0.40–1.87)	0.94 (0.39–2.26)
Arthritis	1.83 (0.95–3.53)	1.92 (0.89–4.18)
Serositis	0.90 (0.35–2.32)	0.65 (0.24–1.80)
CNS involvement	0.62 (0.24–1.57)	0.53 (0.20–1.39)
Renal involvement	0.62 (0.15–2.64)	0.50 (0.08–3.33)
Hematologic involvement	0.65 (0.33–1.30)	0.52 (0.22–1.24)
Hemolytic anemia	1.26 (0.40–3.93)	1.03 (0.30–3.53)
Leukopenia	0.51 (0.23–1.16)	0.66 (0.24–1.77)
Lymphopenia	0.69 (0.35–1.38)	0.45 (0.19–1.05)
Thrombocytopenia	0.60 (0.29–1.24)	0.63 (0.26–1.50)
Comorbidities[c]		
Hypertension	1.55 (0.71–3.35)	1.33 (0.60–2.97)
Diabetes mellitus	3.83 (1.10–13.37)*	4.20 (1.23–14.41)*
Dyslipidemia	0.67 (0.22–2.07)	1.18 (0.35–3.99)
Hypothyroidism	1.72 (0.64–4.57)	1.07 (0.39–2.95)
Antiphospholipid syndrome	1.09 (0.37–3.25)	1.06 (0.35–3.21)
Treatment prior hospitalization[c]		
Corticosteroids	1.97 (0.85–4.60)	1.58 (0.66–3.74)
Prednisone ⩽10 mg daily	0.99 (0.50–1.96)	1.03 (0.48–2.22)
Hydroxychloroquine	2.11 (0.95–4.71)	1.92 (0.82–4.48)
Mycophenolate mofetil	1.17 (0.53–2.58)	1.25 (0.54–2.85)
Azathioprine	1.07 (0.38–3.00)	0.50 (0.17–1.51)
ACE inhibitors	0.95 (0.45–2.01)	0.68 (0.32–1.47)
ARBs	1.32 (0.46–3.81)	1.50 (0.53–4.31)
Aspirin	2.32 (0.66–8.14)	4.04 (1.03–15.80)*
Full anticoagulation	1.66 (0.58–4.73)	1.39 (0.47–4.11)
Statins	1.41 (0.47–4.29)	2.59 (0.71–9.48)
Treatment during hospitalization[c]		
IV corticosteroid pulse	0.31 (0.12–0.79)*	1.07 (0.33–3.49)
IV high-dose corticosteroids	0.82 (0.41–1.63)	0.71 (0.28–1.78)
Oral corticosteroids	2.26 (1.05–4.84)*	1.54 (0.68–3.50)
Hydroxychloroquine	0.93 (0.45–1.95)	0.56 (0.26–1.21)
Cyclophosphamide	0.22 (0.09–0.56)*	0.24 (0.07–0.77)*
IV antibiotics	12.68 (4.86–33.11)*	12.86 (5.14–32.18)*

SLE: systemic lupus erythematosus; OR: odds ratio; CI: confidence interval; CNS: central nervous system; ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; IV: intravenous.
[a]Models were adjusted for age, sex, disease duration, diabetes mellitus, IV corticosteroid pulse, oral corticosteroids, cyclophosphamide, and IV antibiotics.
[b]Females were used as reference.
[c]Absence of comorbidities or treatment was used as reference, as appropriate.
*p < 0.05.

higher mortality than those without infection. This finding is consistent with an SLE mortality study in Puerto Rico assessed by multiple cause-of-death analysis which showed that the most common cause of death was infection.[22] The time period of that study was from January 2006 to December 2014, which is similar to our work. Serious infections in other countries are also accountable for a significant proportion of deaths in lupus patients. In a large British SLE cohort, infections were responsible for 25% of deaths.[23] In addition, Han et al.[10] described that mortality was as high as 40% in SLE

Table 5. Multilevel mixed effects models[a] for complications and outcomes among SLE patients admitted with infections (n = 204 hospitalizations)[b].

Complications and outcomes	Unadjusted	Model 1 adjusted[c]	Model 2 adjusted[d]
Dichotomous variables	OR (95% CI)	OR (95% CI)	OR (95% CI)
Respiratory failure requiring mechanical ventilation	1.26 (0.17 to 9.24)	1.54 (0.42 to 5.65)	2.15 (0.23 to 7.55)
Renal failure requiring hemodialysis	0.19 (0.03 to 1.19)	0.20 (0.03 to 1.41)	0.13 (0.001 to 8.31)
Nosocomial infections	0.56 (0.17 to 1.79)	0.55 (0.17 to 1.83)	0.64 (0.12 to 3.43)
Readmission	0.94 (0.38 to 2.35)	1.00 (0.39 to 2.55)	1.02 (0.35 to 3.02)
Mortality	2.92 (0.18 to 46.71)	6.00 (1.01 to 35.68)*	6.00 (1.01 to 35.68)*
Continuous variable	$\hat{\beta}$ (95% CI)	$\hat{\beta}$ (95% CI)	$\hat{\beta}$ (95% CI)
Length of stay (in days)	2.53 (−1.25 to 6.31)	2.58 (−1.21 to 6.38)	1.68 (−2.08 to 5.44)

SLE: systemic lupus erythematosus; OR: odds ratio; CI: confidence interval.
[a]Logistic or linear mixed effects regression models were used as appropriate.
[b]Non-infection was used as reference.
[c]Model was adjusted for age and sex.
[d]Model was adjusted for age, sex, disease duration and diabetes mellitus.
*$p < 0.05$.

patients with infection who were admitted to the intensive care unit. On the other hand, in the multivariate analysis of our study adjusted for age, sex, disease duration, and diabetes mellitus, the association between infection and mortality was not retained. This finding could be explained by the effect of diabetes mellitus, which is a known risk factor for overall mortality.

Discrepancies between our work and others could be related to differences in the genetic background, socioeconomic status, major organ involvement, and type of immunosuppressive treatment. Therefore, this work highlights the importance of conducting studies in distinct ethnic groups or countries based on their own characteristics rather than generalizing results from other research works.

Our study has some limitations that must be addressed. First, it is a retrospective study for which it has the limitations and disadvantages inherent to its design. Second, this study may not be representative of the entire SLE population of Puerto Rico as patients were admitted to the Adult University Hospital, which is the major referral center for complicated and severe cases. Third, we were unable to assess disease activity or disease damage using validated instruments such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the Systemic Lupus International Collaborating Clinics Damage Index (SLICC DI).

In conclusion, this is the first study in Hispanics from Puerto Rico that explores serious infections and associated factors in hospitalized lupus patients. Our results showed that serious infections are responsible for nearly 45% of admissions and that those admitted with infections are more likely to have diabetes mellitus, exposure to aspirin prior to hospitalization, and higher mortality than those without infection. This study provides a better understanding of major infections in Puerto Ricans with SLE. Awareness of

these factors may lead to design better preventive strategies to decrease the morbidity and mortality of these patients.

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