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Serious Infections among Adult Medicaid Beneficiaries with Systemic Lupus Erythematosus and Lupus Nephritis

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Abstract

Objective—While serious infections are significant causes of morbidity and mortality in systemic lupus erythematosus (SLE), the epidemiology in a nationwide cohort of SLE and lupus nephritis (LN) patients has not been examined.

Methods—Using the Medicaid Analytic eXtract (MAX) database, 2000-2006, we identified patients 18-64 years with SLE and a subset with LN. We ascertained hospitalized serious infections using validated algorithms, and 30-day mortality rates. We used Poisson regression to calculate infection incidence rates (IR), and multivariable Cox proportional hazards models to calculate hazard ratios (HR) for first infection, adjusted for sociodemographics, medication use, and a SLE-specific risk adjustment index.

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Results—We identified 33,565 patients with SLE and 7,113 with LN. There were 9,078 serious infections in 5,078 SLE patients and 3,494 infections in 1,825 LN patients. The infection IR per 100 person-years was 10.8 in SLE and 23.9 in LN. In adjusted models, in SLE, we observed increased risks of infection among males compared to females (HR 1.33, 95% CI 1.20-1.47), in Blacks compared to Whites (HR 1.14, 95% CI 1.06-1.21), and glucocorticoid users (HR 1.51, 95% CI 1.43-1.61) and immunosuppressive users (HR 1.11, 95% CI 1.03-1.20) compared with non-users. Hydroxychloroquine users had a reduced risk of infection compared to non-users (HR 0.73, 95% CI 0.68-0.77). The 30-day mortality rate per 1,000 person-years among those hospitalized with infections was 21.4 in SLE and 38.7 in LN.

Conclusion—In this diverse, nationwide cohort of SLE patients, we observed a substantial burden of serious infections with many subsequent deaths.

Keywords

Systemic lupus erythematosus; lupus nephritis; epidemiology; infections; mortality

Serious infections are thought to be an important cause of morbidity and mortality for patients with systemic lupus erythematosus (SLE). (1-6) Prior studies suggest that up to 50 percent of SLE patients are hospitalized for a serious infection during their disease course. (1, 4) Adults with SLE who develop lupus nephritis (LN) may have even higher overall rates of infections.(2, 5, 7, 8) Case series and academic cohort studies of SLE patients have found that the majority of infections are bacterial, affecting the skin, respiratory system or urinary tract. (3, 6, 9-11) Increased cases of tuberculosis, non-tuberculous mycobacterial infections and fungal infections are noted, but we lack population-based studies to fully understand the incidence rates of these infection subtypes. (11-13) SLE patients may also be at higher risk for viral infections, including herpes zoster and cytomegalovirus, but similarly, prospective cohort studies that examine the population distribution of these infections are limited. (14-17) In addition, from research to date, it is not clear whether the increased burden of serious infections seen in patients with SLE relates to the nature of the autoimmune disease itself, the medications used for treatment, or the interplay between these factors. (3, 8, 18)

Currently, the population-based incidence rates of serious infections overall and by infection subtype in SLE and LN patients are unknown. An understanding of the distribution of serious hospitalized infections and the subsequent mortality in a large, nationwide SLE population would inform clinical care and likely heighten prevention efforts. We therefore aimed to delineate the burden of disease and associated mortality in a racially and ethnically diverse population of patients enrolled in Medicaid, the largest public health insurance program in the U.S., covering >60 million low-income individuals nationwide.(19) We hypothesized that we would observe racial/ethnic variation in infection rates in SLE and LN, and that immunosuppressive drugs and glucocorticoid use would be related to infection risk.

Patients and Methods

Patient Population

We utilized the Medicaid Analytic eXtract (MAX), an administrative database that includes billing claims and demographic information for all Medicaid enrollees from 47 states and

the District of Columbia. Arizona, Tennessee and Maine do not contribute to MAX. We included all adults, aged 18-64 years, enrolled in Medicaid for ≥6 months between January 1, 2000 and December 31, 2006. More than 90 percent of U.S. adults 65 years and older are enrolled in Medicare and therefore we excluded this age group from our analyses given the potential for incomplete Medicaid claims among the dual-eligible. (20)

SLE and Lupus Nephritis Cohorts

We identified all adults in MAX with prevalent SLE, defined as ≥3 International Classification of Diseases, ninth revision (ICD-9) codes for SLE (710.0), separated by at least 30 days, from hospital discharge diagnoses or physician visit claims. (21, 22) Among patients identified with SLE, we defined LN as ≥2 ICD-9 hospital discharge diagnoses or physician billing claims for nephritis, proteinuria and/or renal failure, ≥30 days apart, on or after the SLE claims. This algorithm for identifying LN patients has a positive predictive value of 80 percent in the Medicaid population.(23) All patients meeting these criteria were followed from the date when SLE or LN criteria were met (index date), until disenrollment from Medicaid or death. We required continuous enrollment for at least six months prior to the index date in order to collect baseline covariates.

Outcome: Serious Infections

In our prevalent SLE and LN cohorts, we identified serious infections using ICD-9 hospital discharge diagnosis codes for bacterial infections (bacteremia, cellulitis, pneumonia, pyelonephritis, osteomyelitis, septic arthritis, endocarditis), fungal infections (aspergillosis, cryptococcosis, histoplasmosis, pneumocystosis), viral infections (herpes zoster, cytomegalovirus, varicella zoster, influenza) and mycobacterial infections (tuberculosis, non-tuberculous mycobacteria) (Supplementary Table).(24) A cross-sectional validation study in a large health care database demonstrated a positive predictive value of 80 percent for ICD-9 discharge diagnosis codes for all bacterial conditions combined, and 76 percent for opportunistic infections excluding systemic candidiasis. (24). We similarly excluded systemic candidiasis from our outcome definition based on results from this validation study. (24) We excluded meningitis and encephalitis given the inability to distinguish infectious versus SLE-related etiologies. We chose to limit our analysis to hospitalized infections to reduce the potential surveillance bias that would be more likely to occur if we included outpatient infections. We excluded common nosocomial infections including urinary tract and surgical site infections, both to restrict our analyses to the most serious infections, and also to focus on infections that were most likely to warrant hospitalization rather than to occur as a result of hospitalization. We did not limit our analyses to only infections listed as the primary discharge diagnosis, but rather included any discharge diagnosis for one of the aforementioned serious infections. We did this in order to understand the overall burden of serious infections in a population in which SLE may be listed as the primary discharge diagnosis.

We assessed serious infections beginning the day following the index date. We required that infection discharge diagnosis codes be separated by ≥30 days to reduce the possibility of counting readmissions for the same infection. We therefore excluded any infection within the same subtype as the previous infection (bacterial, viral, fungal, mycobacterial) if it

occurred within 30 days of discharge. The choice of 30 days was based on studies that use this time frame to classify readmissions for the same indication as the prior hospitalization. (25)

Patient Characteristics

Patient characteristics were ascertained during the baseline period, defined as the six months of continuous enrollment prior to and including the index date. We obtained demographic information at the index date for all Medicaid enrollees identified with SLE and LN, including age sex, U.S. geographic region (Northeast, Midwest, South, West) and race/ethnicity. Race/ethnicity was obtained using Medicaid's categorizations based on self-report and due to small numbers that would prevent reporting in accordance with Centers for Medicare and Medicaid Services policies, we described combined categories: White, Black or African American, Hispanic or Latino (including Hispanic or Latino and one or more races), Asian (including Native Hawaiian or other Pacific Islander), Native American (including American Indian or Alaskan Native) and Other (including unknown). (26)

We determined area-level socioeconomic status (SES) using a previously validated composite score of seven U.S. Census variables: median household income, proportion with income below 200 percent of federal poverty level, median home value, median monthly rent, mean education level, proportion of people age ≥25 who were college graduates, and proportion of employed persons with a professional occupation.(27) We obtained U.S. Census data by ZIP code for each patient and aggregated this to the county level and then divided it into binary categories of higher versus lower area-level SES.

We also assessed medications, characterized as ever versus never use, during the six-month baseline period prior to and including the index date. Medications included hydroxychloroquine (HCQ), glucocorticoids, including prednisone, methylprednisolone, dexamethasone, hydrocortisone, prednisolone and cortisone, and immunosuppressive drugs (mycophenolate mofetil, mycophenolic acid, oral or intravenous cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, or tacrolimus). We used a previously developed SLE-specific risk adjustment index to characterize comorbidities in our SLE and LN cohorts occurring during the baseline period. We used the median score in our population to divide patients into higher or lower risk categories. This index utilizes ICD-9 codes for comorbidities particularly relevant to SLE patients and was shown to account for more variation in the risk of mortality among SLE patients than the traditionally used Charlson comorbidity index. (28)

We used the uniform period of six months prior to and including the index date to assess medications and comorbidities for all patients to ensure that increased medication use or greater comorbidities did not occur because of longer periods of enrollment. Since this is a prevalent SLE cohort, the index date represents the date at which follow-up for the outcome of interest begins among patients meeting our criteria for SLE, not the date of incident SLE. We defined separate periods for covariate assessment and for outcome measurement in order to minimize over adjustment by factors that may lie on the causal pathway.

Statistical Analysis

We calculated the incidence rates (IR, cases per 100 person-years) of serious infections overall and by bacterial, viral, fungal and mycobacterial subtype, in the SLE cohort and LN subcohort. We stratified overall IRs of infections by age, sex, race/ethnicity, geographic region, SES (higher versus lower), SLE-specific risk adjustment index (higher versus lower) and baseline use of glucocorticoids, HCQ and immunosuppressive medications. We used Poisson regression to determine incidence rate ratios (IRR) and 95% confidence intervals for all serious infections by socioedemographic group. To assess whether the burden of infection was clustered among certain patients, we also determined the number of infections per patient in categories of 1, 2 and ≥3 infections. We examined mortality rates (deaths per 1,000 person-years) during or within 30 days of the hospitalization when a serious infection occurred and until the end of their enrollment or follow-up in our database (December 31, 2006). Deaths are reported directly to Medicaid and also obtained from the National Death Index. Specific cause of death was not available.

We utilized multivariable Cox proportional hazard models to determine the hazard of first serious infection among patients with SLE and LN by age, sex, race/ethnicity, geographic region and medication use. We adjusted by age, sex, race/ethnicity, region, area-level SES, calendar year, baseline SLE-specific risk adjustment index, and baseline HCQ, glucocorticoid and immunosuppressive use. We tested the proportional hazards assumption using time-dependent covariates for the variables of interest and observed no significant deviations. (29)

All analyses were conducted using SAS, Version 9.3 (Cary, NC). Data were obtained from the Centers for Medicare and Medicaid Services through an approved data use agreement. Results are presented in accordance with their policies; cell sizes <11 are suppressed. The Partners Healthcare Institutional Review Board approved this study.

Results

SLE Cohort

From 2000 to 2006, we identified 33,565 patients with prevalent SLE and ≥6 months of continuous enrollment prior to the index date (Table 1). The mean age was 38.8 years (SD 12.5) and the mean follow-up was 2.5 years (SD 1.9) In this cohort, 93% were female, 37.9% were Black, 37.5% were White and 14.7% were Hispanic. During the baseline period, 49.2% SLE patients received glucocorticoids, 38.6% received HCQ, and 16.7% received an immunsuppressive drug.

We identified 9,078 serious infections in 5,068 SLE patients. Among these patients, 3,174 (62.6%) experienced one serious infection, 989 (19.5%) had two, and 905 (17.9%) had three or more. 96% of infections were bacterial (8,715 cases). Most bacterial infections were pneumonia (3,337 cases), cellulitis (2,322 cases) or bacteremia (2,200 cases). We observed 33 cases of tuberculosis and 18 cases of non-tuberculous mycobacterial infections. Viral infections were predominately herpes zoster (160 cases) and influenza (55 cases). The fungal infections were primarily aspergillosis (27 cases), pneumocystosis (18 cases), and cryptococcosis (14 cases).

The IR of all infections among patients with SLE was 10.8 per 100 person-years and the IR of bacterial infections was 10.4 per 100 person-years (Table 2). We stratified our unadjusted IRs for all infections by sociodemographic factors and the SLE-specific risk adjustment index (Table 3). We observed a higher IR of infections in the oldest age group (51-64 years) compared to the youngest (18-34 years) (IRR 1.16, 95% CI 1.10-1.23), among Blacks (IRR 1.23, 95% CI 1.19-1.31) and Native Americans (IRR 1.40, 95% CI 1.20-1.64) compared to Whites, among patients from lower SES areas compared to higher (IRR 1.14, 95% CI 1.09-1.19) and among those with higher SLE-specific risk adjustment index scores (IRR 2.68, 95% CI 2.57-2.79).

In our adjusted multivariable Cox proportional hazards model, the risk of first infection among patients with SLE was higher in the oldest age group compared to the youngest (HR 1.14, 95% CI 1.05-1.22) and higher in males compared to females (HR 1.33, 95% CI 1.20-1.47) (Table 4). We observed an increased risk of infection in Blacks (HR 1.14, 95% CI 1.06-1.21) and Native Americans (HR 1.37, 95% CI 1.12-1.67), and a slightly reduced risk among Hispanics (HR 0.90, 95% CI 0.82-0.99) compared to Whites. With respect to medication use, baseline users of HCQ had a reduced risk of infection (HR 0.73, 95% CI 0.68-0.77) compared to non-users. Immunosuppressive medication users had significantly increased risks of infection compared to non-users (HR 1.11, 95% CI 1.03-1.20) and this was the case for glucocorticoid users as well (HR 1.51, 95% CI 1.43-1.61).

Additionally, we examined mortality among SLE patients with serious infections (Table 5). Of the 5,078 SLE patients with hospitalized infections, 778 (15.3%) died during their enrollment in Medicaid prior to the end of the study period. Of those patients, 354 (45.5%) died within 30 days of their hospitalized infection. The overall mortality rate for SLE patients after infection was 46.95 per 1,000 person-years (95% CI 46.90-47.00). The mortality rate during hospitalization or within 30 days of discharge was 21.36 per 1,000 person-years (95% CI 21.33-21.39).

LN Subcohort

Among the patients in our cohort with SLE, we identified a subcohort of 7,113 with prevalent LN (Table 1). The mean age for LN patients was 35 years (SD 12.9) and the mean follow-up was 2.1 years (SD 1.7). LN patients were 90% were female, 48.2% Black, 23.3% White, and 16.4% Hispanic. The median SLE comorbidity index score was higher for patients with LN. During the baseline period, 67% LN patients received glucocorticoids, 39% received HCQ and 32.5% received an immunosuppressive drug.

We identified 3,494 hospitalized infections occurring among 1,825 LN patients. Of these, 1,055 (57.8%) had one infection, 385 (21.1%) had two infections and 385 (21.2%) had three or more infections. The majority of serious infections (3,318, 95%) were bacterial. Most bacterial infections were bacteremia (1,277 cases), pneumonia (1,073 cases), or cellulitis (656 cases). Of the fungal cases, there were 11 cases of cryptococcosis. Of the 33 tuberculosis cases in the SLE cohort, 21 occurred in patients with LN. Similar to the overall SLE cohort, the majority of viral infections in LN patients were herpes zoster (77 cases) and influenza (23 cases).

The IR of overall infections in LN patients was 23.9 per 100 person-years (Table 2). Similar to the SLE cohort, in our unadjusted analyses, we observed a higher incidence of serious infection in the oldest age group compared to the youngest (IRR 1.37, 95% CI 1.22-1.54), among males compared to females (IRR 1.14, 95% CI 1.00-1.30) and among Blacks compared to Whites (IRR 1.13, 95% CI 1.02-1.24) (Table 3). The incidence of infection in LN patients did not differ significantly by area SES (IRR 1.04, 95% CI 0.96-1.13). As with the SLE cohort, those with higher SLE-specific risk adjustment indices had higher rates of infection (IRR 2.12, 95% CI 1.96-2.30).

In our adjusted analyses, we observed an increased risk of infection in the oldest age group compared to the youngest (HR 1.28, 95% CI 1.12-1.46), and among Blacks compared to Whites (HR 1.13, 95% CI 1.00-1.28) (Table 4). Similar to the SLE cohort, among LN patients, baseline HCQ users had a reduced risk of infection (HR 0.78, 95% CI 0.71-0.87) compared to non-users, and glucocorticoid users had an increased risk (HR 1.23, 95% CI 1.10-1.36) compared to non-users. However, while we observed an increased risk of infection among immunosuppressive medication users compared to non-users in the overall SLE cohort, this was not the case among those with LN (HR 0.92, 95% CI 0.83-1.03).

We observed 372 (20.3%) deaths among 1,825 LN patients with serious infections during the follow-up period (Table 5). Of these patients, 181 (48.7%) died during the hospitalization or within 30 days of discharge. The mortality rate during follow-up was 79.25 per 1,000 person-years (95% CI 79.06-79.44) and the mortality rate within 30 days of discharge was 38.56 per 1,000 person-years (95% CI 38.43-38.69).

Discussion

In this nationwide study of a large cohort of racially, ethnically and geographically diverse patients with SLE, we observed an extremely high burden of serious hospitalized infections. This was particularly pronounced among patients with LN who had an incidence rate more than twice that of all SLE patients. When placed in the context of other rheumatic diseases, a similar size cohort of patients with rheumatoid arthritis receiving glucocorticoids was found to have an incidence rate of bacterial infections of 2.2 per 100 person-years. (30) Our SLE cohort experienced an incidence rate of bacterial infections nearly 5 times greater; 10 times greater among those with LN.

Our results are in line with prior studies that demonstrate that SLE patients have high rates of bacterial, fungal and viral infections and a diminished ability to fight these infections likely in the setting of chronic inflammation. (31, 32) Proposed biological explanations for this include intrinsic defects in the innate and adaptive immune responses notably impaired chemotaxis and phagocytosis of macrophages and polymorphonuclear cells, possible mannose-binding lectin deficiency, hypocomplementemia, decreased clearing of immune complexes, and abnormal T-cell production. (33-35)

Medications used for SLE, especially glucocorticoids, particularly at high dosages and when administered intravenously, have been associated with increased infection rates (3, 5, 9, 36-38). Immunosuppressive drugs including mycophenolate mofetil, azathioprine and

cyclophosphamide have been shown in small cohort and case-control studies to be independent risk factors for infection, particularly when combined with glucocorticoids (3, 5, 9, 36-38). In our adjusted analyses, we did note, as expected, significantly increased risks of infection in SLE and LN patients who received glucocortiocoids during the baseline period, compared to those who did not. Among SLE patients, we observed a higher risk of infection among baseline immunosuppressive users compared to non-users, but this was not true among those with LN. Interestingly, we noted a decreased risk of infection in SLE and LN patients prescribed HCQ, suggesting the possibility of a protective effect. In addition to the known use of HCQ as an antimalarial, studies also suggest a potential role for HCQ and chloroquine as therapies for certain infections. (39, 40) It is also possible that HCQ users may be healthier than non-users, possibly with better controlled or less severe SLE, which may in part explain their decreased risk of serious infections.

We observed a significantly increased risk of first infection among males with SLE compared to females. This is in line with prior studies that suggest that males with SLE may have more complications and more severe disease than females. (41) However, we did not observe the same increased risk among males with LN compared to females, suggesting that once a patient develops LN, sex may no longer confer excess risk. We also found increased rates of infection among Blacks and Native Americans compared to Whites. Prior studies from our group and others have demonstrated both increased burden of SLE and LN in these racial/ethnic minorities, and also increased complications and higher mortality in these populations. (42-44)

In addition to the substantial burden of serious infections in this population of patients with SLE and LN, we observed high mortality among those with infections. While the specific cause of death was not available in our data, among patients with SLE or LN who died during their enrollment in Medicaid, more than 45% died during a hospitalization with a diagnosis of serious infection or within 30 days of discharge. To our knowledge, no prior studies examined mortality rates following discharge among SLE patients hospitalized with infections. However, prior studies have shown that 20-30% of all SLE deaths result from serious infections. (45-47) We also observed more than 1.5 times greater mortality rates among LN patients compared to SLE patients overall. While these patients may have severe SLE and other comorbidities as well, their higher mortality is likely attributable in part to serious infections. A prior study among Medicaid beneficiaries with SLE demonstrated that all-cause mortality was more than two times higher among LN patients compared to SLE patients overall. (48)

There are limitations to this study. We were unable to validate our SLE definition in Medicaid claims data due to federal privacy restrictions. However, we chose to use a conservative definition of ≥3 ICD-9 codes to increase specificity and to exclude individuals who may have been seen once for “rule-out” SLE and once in follow-up. We used this definition previously to examine the prevalence and incidence of SLE in the Medicaid population and obtained results in line with prior studies.(21, 22) In addition, information on disease activity and severity are not available in claims data. While certain complications such as LN are associated with increased infection rates, the role of disease activity as an independent risk factor for infection is less clear, particularly among those with more severe

disease at baseline. (3, 8, 9, 36) However, it is plausible that other related aspects such as hospitalizations and immunosuppressive medications may result in increased concomitant infections. While we adjusted for use of HCQ, glucocorticoids and immunosuppressives at baseline, we did not address dose or duration of therapy in these analyses. Of note, we chose to adjust only for baseline medication use to prevent overadjustment for fluctuations in disease activity. Additional studies are needed to further address the role that specific immunosuppressive medications play in serious infection incidence.

In addition, we did not account for vaccinations for influenza or pneumonia, or prophylactic medications such as trimethoprim-sulfamethoxazole for pneumocystosis, which may play a role in reducing infection incidence. We also chose to look at serious infections using inpatient discharge diagnoses to improve the specificity of our outcome definition and to reduce surveillance bias. Therefore, we are likely underestimating the burden of all infections, including infections that are treated in the outpatient setting, that affect patients with SLE. However by not limiting our analyses to only infections listed as the primary discharge diagnosis, we feel that we were able to sufficiently capture the majority of infections that result in hospitalization. While we were unable to distinguish between infections requiring hospitalization and hospital-acquired infections, we attempted to minimize the latter by excluding urinary tract and surgical site infections. In addition, this study identifies infections in SLE patients enrolled in Medicaid. The burden of chronic and infectious diseases in this low-income population may be higher than the overall U.S. population and therefore not generalizable to all patients with SLE. However, Medicaid is the largest source of funding for health-related services for this at-risk population and therefore these findings demonstrating the high burden of infection have significant public health implications.

Strengths of this study include the use of a diverse, nationwide population-based cohort, which allowed us to demonstrate the significant burden of serious infections in patients with SLE by different sociodemographic factors. This also enabled us to delineate the risk of infections overall and by subtype in a large subset of patients with LN. We were able to follow individual SLE and LN patients over the course of multiple years of Medicaid enrollment and observe the incidence rates of all serious hospitalized infections. In addition, we accounted for baseline medication use and SLE-specific comorbidities in our assessment of infection risk. We were also able to assess mortality rates within 30 days of hospital discharge, which are likely attributable to infectious complications.

In this nationwide, racially and ethnically diverse cohort of Medicaid beneficiaries, we demonstrated the significant burden of serious infections and associated mortality among patients with SLE and LN. Males, older adults, Black and Native Americans, and patients from lower SES areas may be at especially high risk. The results of this study suggest that resources should be allocated to ensure that the most vulnerable patients have access to vaccinations, prophylactic medications, and early treatment for infectious complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline characteristics of Medicaid beneficiaries with prevalent SLE and LN, 2000-2006

	SLE Cohort (N=33,565)	LN Subcohort (N=7,113)
Mean follow-up in years (SD)	2.5 (1.86)	2.06 (1.69)
Age at index date -mean (SD)	38.8 (12.48)	35 (12.86)
Age (years) -N (%)		
18-34	12,735 (37.94)	3,728 (52.41)
35-50	14,046 (41.85)	2,333 (32.80)
51-64	6,784 (20.21)	1,052 (14.79)
Sex – N (%)		
Female	31,380 (93.49)	6,403 (90.02)
Male	2,185 (6.51)	710 (9.98)
Race/Ethnicity – N (%)		
White	12,578 (37.47)	1,658 (23.31)
Black	12,735 (37.94)	3,429 (48.21)
Hispanic	4,927 (14.68)	1,165 (16.38)
Asian	1,308 (3.9)	443 (6.23)
Native American	529 (1.58)	116 (1.63)
Other	1,488 (4.43)	302 (4.25)
Region		
Northeast	6,979 (20.79)	1,421 (19.98)
South	12,657 (37.71)	2,761 (38.82)
Midwest	6,275 (18.7)	1,428 (20.08)
West	7,654 (22.8)	1,503 (21.13)
Socioeconomic status		
Mean (SD)	1.12 (1.76)	1.21 (1.76)
Median	0.98	1.09
SLE-specific Risk Index		
Mean (SD)	1.12 (2.06)	3.11 (2.82)
Hydroxychloroquine Use – N (%)		
Never	20,610 (61.4)	4,342 (61.04)
Ever	12,955 (38.6)	2,771 (38.96)
Immunosuppressive Use* – N (%)		
Never	27,978 (83.35)	4,801 (67.5)
Ever	5,587 (16.65)	2,312 (32.5)
Glucocorticoid Use – N (%)		
Never	17,048 (50.79)	2,345 (32.97)
Ever	16,517 (49.21)	4,768 (67.03)

* Immunosuppressives include mycophenolate mofetil, mycophenolic acid, oral or intravenous cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, or tacrolimus

Table 2

Incidence rates (IR) of serious infections overall and by subtype among SLE and LN patients

Infection Subtype	SLE Cohort		LN Subcohort	
	Cases (N)	IR*	Cases (N)	IR*
Overall	9,078	10.81	3,494	23.87
Bacterial	8,715	10.38	3,318	22.67
Viral	244	0.29	120	0.82
Fungal	68	0.08	29	0.20
Mycobacterial	51	0.06	27	0.18

* Incidence Rate (IR) per 100 person-years; IR for SLE cohort is cases per 83,959.33 total person-years, IR for LN subcohort is cases per 14,637.14 total person-years

Table 3

Unadjusted incidence rates (IR) and incidence rate ratios (IRR) of serious infections in SLE and LN patients, stratified by sociodemographic factors and the SLE-specific risk index

	SLE Cohort		LN Subcohort	
	IR*	IRR+ (95% CI)	IR*	IRR+ (95% CI)
Age				
18-34	10.34	(ref)	22.13	(ref)
35-50	10.64	1.03 (0.98-1.08)	24.00	1.08 (0.99-1.19)
51-64	12.03	1.16 (1.10-1.23)	30.34	1.37 (1.22-1.54)
Sex				
Female	10.58	(ref)	23.57	(ref)
Male	14.72	1.39 (1.28-1.51)	26.88	1.14 (1.00-1.30)
Race				
White	10.22	(ref)	24.10	(ref)
Black	12.75	1.25 (1.19-1.31)	27.12	1.13 (1.02-1.24)
Hispanic	8.24	0.81 (0.75-0.87)	16.94	0.70 (0.61-0.81)
Asian	6.63	0.65 (0.57-0.74)	13.33	0.55 (0.44-0.69)
Native American	14.33	1.40 (1.20-1.64)	26.63	1.10 (0.82-1.50)
Other	10.68	1.05 (0.95-1.17)	29.01	1.21 (1.00-1.50)
Region				
Northeast	9.29	(ref)	21.23	(ref)
South	12.10	1.30 (1.23-1.38)	24.13	1.14 (1.01-1.27)
Midwest	13.90	1.50 (1.40-1.60)	33.55	1.58 (1.40-1.78)
West	7.90	0.85 (0.79-0.91)	17.19	0.81 (0.71-0.93)
Socioeconomic Status (SES)				
Lower	11.53	1.14 (1.09-1.19)	24.35	1.04 (0.96-1.13)
Higher	10.10	(ref)	23.44	(ref)
SLE-specific risk index				
Lower	7.10	(ref)	17.36	(ref)
Higher	19.02	2.68 (2.57-2.79)	36.87	2.12 (1.96-2.30)

*Incidence rate (IR) is cases per 100 person-years

+IRR is the incidence rate ratio with 95% confidence interval (95% CI)

Table 4

Adjusted hazard ratios (HR)* of first serious hospitalized infection among adults with SLE and LN

	SLE cohort HR (95% CI)	LN Subcohort HR (95% CI)
Age (18-34=ref)		
35-50	1.03 (0.96-1.09)	1.03 (0.93-1.15)
51-64	**1.14 (1.05-1.22)**	**1.28 (1.12-1.46)**
Sex (Female= ref)		
Male	**1.33 (1.20-1.47)**	1.09 (0.93-1.27)
Race (White=ref)		
Black	**1.14 (1.06-1.21)**	**1.13 (1.00-1.28)**
Hispanic	**0.90 (0.82-0.99)**	0.92 (0.78-1.08)
Asian	0.85 (0.72-1.01)	0.84 (0.66-1.07)
Native American	**1.37 (1.12-1.67)**	1.24 (0.88-1.75)
Other	1.09 (0.95-1.25)	**1.27 (1.00-1.61)**
Region (Northeast=ref)		
Midwest	**1.42 (1.30-1.56)**	**1.60 (1.38-1.87)**
South	**1.28 (1.17-1.39)**	**1.30 (1.12-1.50)**
West	0.93 (0.85-1.03)	1.03 (0.88-1.21)
Medication Use (Never=ref)		
Hydroxychloroquine	**0.73 (0.68-0.77)**	**0.78 (0.71-0.87)**
Immunosuppressives+	**1.11 (1.03-1.20)**	0.92 (0.83-1.03)
Glucocorticoids	**1.51 (1.43-1.61)**	**1.23 (1.10-1.36)**

*Cox proportional hazard models adjusted for age, sex, race/ethnicity, region, area-level SES, SLE-specific risk index, calendar year, and hydroxychloroquine, immunosuppressive and glucocorticoid use during the baseline period

+Immunosuppressives include mycophenolate mofetil, mycophenolic acid, oral or intravenous cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, or tacrolimus

Bolded HRs indicate statistically significant ($p<0.05$) values

Table 5

Mortality among SLE and LN patients with one or more serious hospitalized infection

	≥1 serious infection	Mortality after infection during follow-up period		Mortality during hospitalization or within 30 days of discharge	
	N (%)	Deaths-N (%)*	Mortality rate+	Deaths-N (%)**	Mortality rate+
SLE (n=33,565)	5,068 (15.10)	778 (15.35)	46.95 (46.90-47.00)	354 (45.50)	21.36 (21.33-21.39)
LN (n=7,113)	1,825 (25.66)	372 (20.38)	79.25 (79.06-79.44)	181 (48.66)	38.56 (38.43-38.69)

* Percent of those with ≥1 serious infection

+ Mortality rate with 95% confidence interval is per 1,000 person-years

** Percent of total deaths