

Health Care Utilization and Costs of Systemic Lupus Erythematosus by Disease Severity in the United States

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ABSTRACT (250-word limit, currently (248))

Objective: To quantify health care utilization and costs by disease severity for patients with systemic lupus erythematosus (SLE) in the United States

Methods: We conducted descriptive analyses of Humedica electronic health record (EHR) data from 2011 to 2015 (utilization analysis) and integrated Optum administrative claims/Humedica EHR data from 2012 to 2015 (cost analysis) for patients with SLE. All-cause utilization outcomes examined were hospitalizations, outpatient visits, emergency department (ED) visits, and prescription drug use. Analyses of costs stratified by disease severity were limited to patients enrolled in an Optum-participating health insurance plan for ≥ 1 year after the earliest observed SLE diagnosis date. Costs were converted to 2016 US dollars.

Results: Health care utilization was evaluated in 17,257 patients with SLE. Averaged over the study period from 2011 to 2015, 13.7% of patients had ≥ 1 hospitalization per year, 25.7% had ≥ 1 ED visit, and 94.4% had ≥ 1 outpatient visit. Utilization patterns were generally similar across each year studied. Annually, 88.0% of patients had ≥ 1 prescription, including 1.3% who used biologics. Biologic treatment doubled between 2011 (0.7%) and 2015 (1.4%). Cost analyses included 397 patients. During 2012 to 2015, patients with severe SLE had mean annual costs of \$52,951, compared with \$28,936 and \$21,052 for patients with moderate and mild SLE, respectively. Patients with severe SLE had increased costs in all service categories: inpatient, ED, clinic/office visits, and pharmacy.

Conclusion: US patients with SLE, especially individuals with moderate or severe disease, utilize significant health care resources and incur high medical costs.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multiorgan autoimmune disease with prevalence in the United States ranging from 42 to 300 cases per 100,000 persons across studies(1). SLE symptoms vary in manifestation and severity and include skin rash, fatigue, fever, hair loss, neuropsychological dysfunction, and joint pain(2,3). Multiorgan involvement and long-term corticosteroid use result in progressive organ damage, a key feature of SLE, and may increase disease burden(2,3).

SLE disease progression is associated with organ damage that affects several systems, including musculoskeletal, neuropsychiatric, renal, cardiovascular, and integumentary(1–4). As a consequence, disease progression leads to more hospitalizations and increased health care costs(5,6). Long-term treatments for SLE, including corticosteroids and immunosuppressive therapies, are also associated with increased risk of adverse events, such as infections and cardiovascular events. Additionally, corticosteroids may increase the risk of osteoporosis and cataracts. These adverse outcomes further impact health care utilization and costs for patients with SLE(7).

Previous studies evaluating health care utilization and costs for patients with SLE were primarily performed using claims data prior to 2010(6,8–10). In these studies, patients with SLE were identified as having greater health care utilization and higher costs than control patients who were matched on demographics and clinical characteristics(6,8–10).

We provide an updated profile of health care utilization and costs among patients with SLE in the United States. Focusing on a time period after the introduction of biologics for SLE, such as belimumab and rituximab (used off-label), we performed a retrospective analysis of administrative claims integrated with electronic health record (EHR) data. We assessed health care utilization from 2011 to 2015 and evaluated health care costs from 2012 to 2015. To gain a deeper understanding of the burden of SLE, we also examined how SLE disease severity may contribute to health care costs.

MATERIALS AND METHODS

Study Design

Overview

In this study, we conducted a retrospective analysis of EHR data (utilization analysis) and integrated claims and EHR data (cost analysis) for 2 cohorts of patients with SLE in the United States. We quantified the following: 1) incidence and prevalence of SLE; 2) health care resource use patterns of patients with SLE, including hospitalizations/inpatient visits, outpatient visits including emergency department (ED) and office or clinic visits, and prescription drug use; and 3) annual direct medical and pharmacy costs incurred, stratified by SLE disease severity. Institutional review board approval was not required because this study utilized anonymized administrative claims and EHR data.

Data source

We used Optum administrative claims and EHR data from Humedica Inc. The EHR data contain information for 70 million patients, of whom 50 million are associated with integrated delivery networks (IDNs), groups that provides a spectrum of health care services. These data include laboratory results; vital signs; body measurements; lifestyle observations; biomarkers; inpatient and outpatient treatments, including written prescriptions; inpatient-administered medications; and provider notes. The Optum claims database includes medical and pharmacy claims from approximately 40 million commercially insured patients and 6.1 million Medicare Advantage enrollees. For the purposes of this study, a project-specific data extract was generated. It included all EHR and integrated claims data for patients who had ≥ 1 SLE-related health care encounter, defined by the presence of International Classification of Diseases, Ninth and Tenth

Revisions, Clinical Modification (ICD-9-CM, ICD-10-CM) codes 710.0 or M32.X, respectively, in their EHRs. Both the EHR and claims data sets use billing nomenclature to code health care services provided. Diagnosis status and procedures performed are coded using ICD-9-CM and ICD-10-CM. Medication use was identified by the National Drug Codes and Healthcare Common Procedure Coding System, J codes.

Patient Identification

Patients with SLE were identified in EHR data using algorithms that required patients to be associated with an IDN, to mitigate for the effects of unobserved services, and have ≥ 2 SLE-related encounters ≥ 60 days apart and ≥ 1 pharmacy claim for an SLE-related medication OR ≥ 2 SLE-related encounters ≥ 60 days apart, of which ≥ 1 was a visit to a rheumatologist(11). An SLE-related health care encounter was defined by the assignment of an ICD-9-CM code 710.0 or ICD-10-CM code M32.X to the patient's EHR for hospitalization, office or clinic visit, ED visit, or other outpatient service visit. SLE-related medications included 4 drug classes used to manage SLE: antimalarial medications, immunosuppressive agents, systemic corticosteroids, and biologics.

Disease severity (mild, moderate, or severe) was determined for each patient by a health care utilization-based algorithm derived from the severity of diagnoses listed on claims, prescription drug claims, and conditions associated with SLE severity available in nonlaboratory claims (e.g., renal impairment was considered moderate and end-stage renal disease was considered severe)(9). Disease severity was determined for each patient during each year of the study, and

the severity assigned to a particular year was the highest severity category attained by the patient during that year (see Supplementary Table 1 for full description of the SLE severity algorithm).

Study Measures and Outcomes

Incidence and prevalence of SLE

We identified 2 retrospective cohorts, incident and prevalent, from the EHR data to determine annual incidence and prevalence of SLE from 2011 to 2015. An incident case of SLE referred to both newly diagnosed patients and patients whose SLE condition was dormant during the pre-estimation year. To be considered an incident or a newly diagnosed SLE case in a given year, patients had to meet the SLE case definition between January 1 and December 31 of the year of estimation. Incident patients also had to be included in EHR data for ≥ 365 days (with no SLE-related codes) before their first SLE-related encounter. To be considered a prevalent SLE case, newly diagnosed or patients with existing SLE had to meet the case definition for SLE and have information in the database during the year of estimation. Patients who did not have information in the database for a given year were not counted during that year. The denominator used for determining yearly incidence and prevalence was the number of patients who had ≥ 1 encounter during the year.

Patterns of health care utilization for patients with SLE

Health care utilization was determined for the years 2011–2015. Patients were followed from their index dates (earliest SLE diagnosis date observed in the database) until the month of their last observed activities in the EHR database or date of death, whichever was first. All study participants were required to be part of the EHR database during the calendar year of estimation

to assess annual health care utilization patterns and to have ≥ 1 calendar year of data after the index date.

All-cause health care utilization was measured in the following categories: hospitalizations, outpatient visits (ED and office or clinic visits), total drug prescriptions, and SLE-related drug prescriptions (antimalarial medications, immunosuppressive agents [azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, leflunomide, cyclophosphamide, chlorambucil, nitrogen mustard], systemic corticosteroids, and biologics [rituximab, belimumab]). Disease severity was not measured in this cohort because corticosteroid dose could not be determined for all patients.

Direct medical and pharmacy costs associated with SLE

Health care cost analyses were limited to data from 2012 to 2015 in a separate cohort. To be included in the cost analysis, patients had to: 1) be identified in the EHR database, 2) be enrolled in an Optum-participating health insurance plan with both medical and pharmacy benefits on the index date, and 3) have ≥ 1 calendar year of data after the index date.

SLE-related outcomes evaluated were annual direct medical costs for patients with ≥ 1 service-type encounter, stratified by service type (e.g., hospitalizations, ED visits, office/clinic visits, and other patient services); annual prescription drug costs, including both outpatient- and inpatient-administered drugs; and annual direct medical costs associated with SLE. Study outcomes were also stratified by service type and SLE disease severity (mild, moderate, or severe)(9). All costs

were converted to 2016 US dollars using the Consumer Price Index annual averages for medical care(12).

Statistical Analyses

Patient demographics were characterized using descriptive statistics. Health care utilization for 2011–2015 was stratified by year and evaluated using descriptive statistics. Health care costs for 2012–2015 were categorized and reported annually for hospitalizations, outpatient visits, ED visits, clinic or office visits, outpatient services, and medications. Annual costs were also reported by SLE disease severity.

All analyses were performed using SAS version 9.4.

RESULTS

Health Care Utilization Analysis

Patient characteristics

A total of 17,257 patients met the SLE case definition within the EHR database and were included in the analysis of health care utilization (Figure 1). The majority were female (89.7%, n=15,482) and white (69.3%, n=11,962). Mean (standard deviation [SD]) age was 48.4 (15.6) years. The distribution of medical insurance coverage among the population was as follows: commercial insurance 32.6% (n=5628), Medicare 16.6% (n=2864), Medicaid 5.5% (n=945), unknown insurance coverage 12.8% (n=2215), and uninsured 30.4% (n=5249) (Table 1).

From 2011 to 2015, the yearly incidence of SLE (incident or newly-treated SLE cases) ranged from 10.7 to 14.0 per 100,000 patients (Table 2). The estimated prevalence of patients with SLE was 44.1 per 100,000 patients in 2011, increasing to 85.3 per 100,000 patients in 2015 (Table 2).

All-cause health care utilization

Health care utilization generally remained the same for each year of the study (2011–2015), except for trends noted below (Table 2). For patients with ≥ 1 outpatient visit, including ED visits, the median (interquartile range) number of annual visits increased from 15 (7–28) in 2011 to 19 (9–37) in 2015. The proportion of patients with ≥ 1 ED visit increased from 22.8% in 2011 to 29.3% in 2015. Of patients with ≥ 1 prescription from 2011 to 2015, the proportion of those who were prescribed biologics increased from 0.7% to 1.4% (Table 2). The proportion of patients prescribed antimalarial medications generally decreased from 2011 to 2015 (21.2%, 19.9%, 16.4%, 16.8%, and 17.1%). The proportion of patients prescribed systemic

corticosteroids decreased each year from 2011 to 2014, with an increase in 2015 (21.8%, 19.0%, 17.7%, 17.2%, 18.3%).

When averaged over the period from 2011 to 2015, 13.7% of patients had ≥ 1 hospitalization per year, with a mean (SD) of 1.7 (1.4) hospital visits per year and an average hospital stay of 5.4 (13.4) days (Table 2). Almost all patients had ≥ 1 outpatient visit (ie, all noninpatient services, which include ED and clinic or office visits) per year (94.4%), with a mean (SD) of 24.1 (23.8) visits per year. ED services (≥ 1 visit) were sought by 25.7% of patients, with a mean (SD) of 2.5 (3.4) visits annually, and 86.3% of patients had ≥ 1 clinic or office visit per year, with a mean (SD) of 10.0 (10.2) visits per year. Over the study period from 2011 to 2015, a mean of 88.0% of patients had ≥ 1 prescription claim for any type of medication each year. Systemic corticosteroids (18.8%), antimalarial medications (18.3%), immunosuppressants (10.3%), and biologics (1.3%) were among the prescribed medications.

Health Care Cost Analysis Stratified by SLE Disease Severity

Patient characteristics

Data from the 397 patients identified in the EHR database who were also enrolled in an Optum-participating health insurance plan from 2012 to 2015 were utilized in the SLE cost analysis (Figure 1). Baseline characteristics of patients in the cost analysis were similar to those of patients in the health care utilization analysis (Table 1). Using the SLE severity algorithm(9), 256 patients were categorized as having mild SLE, 106 had moderate SLE, and 149 had severe SLE. SLE severity categorization was performed each year throughout the study period. Because SLE severity varies over time, an individual patient may meet >1 SLE severity category during

the study period. Therefore, the number of patients per severity category represents the time-varying nature of SLE severity and indicates the number of patients who spent time in mild, moderate, and severe SLE states rather than the total number of patients included in the analysis (see Supplementary Table 2A and 2B for patient population sizes per disease category by year and across entire study period).

All-cause health care utilization in cost cohort

The annual proportion of patients with ≥ 1 hospitalization or ED visit increased with disease severity (Table 3). The proportion of patients hospitalized annually was greater for those with severe SLE (36.9%) compared with moderate (17.9%) or mild SLE (16.8%). ED visits also increased with disease severity; 38.3% of patients with severe SLE, 31.1% with moderate SLE, and 28.5% with mild SLE had ≥ 1 ED visit each year. Patients prescribed biologics increased with SLE severity over the study period. Patients with mild, moderate, and severe SLE prescribed biologics were 2.0%, 3.8%, and 4.7%, respectively.

Direct Medical and Pharmacy Costs Associated with SLE

Over the study period from 2012 to 2015, total mean annual costs for patients with SLE who had ≥ 1 health care encounter were \$32,374 (Table 3, Figure 2). Patients with severe SLE had mean annual costs of \$52,951, compared with \$28,936 and \$21,052 for patients with moderate and mild SLE, respectively. The increased costs associated with greater SLE severity were observed for each category of health care service: inpatient, ED and clinic/office visits, and pharmacy costs. Total mean annual health care costs were 2.5-fold greater for patients with severe SLE compared with patients with mild SLE. Mean hospitalization, ED visit, clinic/office visit, and pharmacy costs were also greater for patients with severe compared with mild SLE with ≥ 1

admission/visit/prescription (differences 1.8-, 1.7-, 1.7-, and 2.0-fold, respectively). Total median annual costs analyzed on a yearly basis also increased with SLE severity each year from 2012 to 2015 (Table 4).

DISCUSSION

In this study, we describe patterns of health care utilization and costs among patients with SLE in the United States in separate cohorts for utilization and cost analyses. We identified that, overall, patients with SLE utilized significant health care resources; between one-fifth and one-third of patients required an ED visit annually, and an average of 13.7% of patients required inpatient services each year. For patients with SLE, health care utilization and costs remained important elements of disease burden during 2011–2015, as was reported prior to 2010(6,8–10). Patients with SLE had means of 1.7 hospitalizations, 2.5 ED visits, and 10 clinic/provider visits annually. By comparison, for the general adult population in the US Healthcare Cost and Utilization Project, hospitalizations ranged from 78.9 to 502.2 per 1000 persons for those 18–44 and ≥ 85 years of age in 2012(13). In the US National Hospital Ambulatory Medical Care Survey, ED visits for the general adult population ranged from 47 to 61 per 100 persons for those 25–44 and ≥ 75 years of age in 2015(14).

To the best of our knowledge, this is the first study to combine integrated claims and EHR data to evaluate costs by disease severity for a population with SLE. This approach is advantageous because the data sources complement each other; the EHR database provides a more complete set of patient diagnoses compared with claims records, and claims records provide more complete documentation of services and medications used compared with EHR data. Together, both data sources provide more comprehensive insight into health care utilization and costs for patients with SLE than either could provide alone.

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Patients with severe disease had markedly greater health care utilization and costs compared with those with mild and moderate disease. This could potentially be because patients with severe disease have previously been shown to have greater organ involvement, faster disease progression, and increased flare frequency and intensity than patients with mild or moderate disease(1–4). For patients with severe SLE, the annual rate of hospitalization was 2-fold greater than that of patients with milder forms of SLE. Patients with severe SLE also required 10% more ED visits than patients with mild disease. The greatest impact of SLE severity on cost was for outpatient visits. Mean annual SLE-related costs for hospitalizations were \$27,937 for mild SLE compared with \$49,474 for severe SLE in patients with ≥ 1 admission; mean annual outpatient visit costs were \$10,396 for mild SLE compared with \$23,468 for severe SLE in patients with ≥ 1 visit.

The relationship between SLE severity and cost was observed during every year in the study and reflects increased burden for patients with SLE as their disease progresses. Disease progression is associated with multiorgan involvement, including the central nervous, cardiovascular, urinary, and coagulation systems(1–4). As disease severity increases, additional treatment is required, as reflected in the mean annual prescription costs for patients with SLE who had ≥ 1 prescription, which were much greater for severe SLE (\$10,628) than mild SLE (\$5320). A similar pattern of increasing medical costs with progression to greater disease severity has been reported in a study of 2-year costs of SLE, in which medical costs increased from \$15,117 to \$61,455 for patients with moderate vs. severe SLE(9). Greater disease severity in related disorders, such as rheumatoid arthritis, has also been associated with greater medical costs(15),

and spending $\geq 50\%$ of the time in a low disease activity state has been associated with a 25.9% reduction in annual direct medical costs for patients with SLE(16).

Over the study period from 2012 to 2015, annual total health care costs generally remained the same. For the individual cost components, such as inpatient costs, there was some variability that may have been associated with the low number of patients in each group. Median annual pharmacy costs, however, were generally greater every year compared with 2012, with a 38% (\$773) increase in 2015. Increases in pharmacy costs over the years may reflect the increased use of biologics.

Corticosteroids were among the most widely used SLE-related medications in our utilization analysis (18.8%), reflecting a common treatment strategy for management of SLE, flares in particular, in hospital and ED settings(17). Because corticosteroid use is associated with increased risk of adverse effects(7), it may increase health care utilization and costs in the longer term for patients with SLE. The proportion of patients prescribed antimalarials was between 21.2% and 17.1% during the study period, which was somewhat surprising. Use of antimalarials in the treatment of SLE has been shown to be safe and efficacious(18) and is recommended per treatment guidelines(17). Biologic (rituximab and belimumab) use was low (1.3%) and ranged from 0.7% in 2011 to 1.4% in 2015. This finding is similar to that of another US cohort of patients with SLE identified in 2013–2015, in which biologic use at 1 year after diagnosis was 1% for belimumab and 0.9% for rituximab(19).

Prevalence rates in the EHR study population increased between 2011 and 2015: 44.1 per 100,000 patients in 2011, increasing to 85.3 per 100,000 patients in 2015. This estimated prevalence falls within range of reported SLE prevalence estimates in the United States (20 to 150 cases per 100,000)(20-22).

There were some limitations with this study. Health care utilization patterns were estimated using an open-cohort population. Services received outside the EHR-reporting network were not available for analyses. To mitigate for the effects of unobserved services, the study was restricted to patients who were associated with Integrated Delivery Networks, a group that provides a spectrum of services (eg, hospital, dispensing pharmacy, outpatient, community care sites) under an umbrella organizational structure. In addition, patients who paid cash for medicines were not captured in the health care utilization analysis.

In this study, cost estimates were based on modeled charges rather than actual expenditures, which may result in inaccurately reflected costs for some claims that were not reimbursed. SLE disease severity was determined by a proxy method that has been used previously and validated to identify severe, moderate, and mild SLE(9). However, SLE severity may have been misclassified in some patients using this claims-based method. Strengths of this study include the large cohort of patients evaluated and the extension of the time frames that were evaluated in previous studies. In addition, the use of administrative claims integrated with EHRs is a unique aspect of this study that allows comprehensive evaluation of health care utilization and costs, including analysis of the association between disease severity and costs.

This study provides an updated estimate of the economic burden of SLE and demonstrates that moderate and severe SLE remain a significant driver of health care utilization and costs in the United States. These findings underscore the importance of developing innovative treatments for SLE that may be both disease modifying and steroid sparing to reduce health care utilization and costs.

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REFERENCES

1. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol* 2016;12:605-20.
2. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Manifestations of systemic lupus erythematosus. *Maedica (Buchar)* 2011;6:330-6.
3. Taraborelli M, Cavazzana I, Martinazzi N, Lazzaroni MG, Fredi M, Andreoli L, et al. Organ damage accrual and distribution in systemic lupus erythematosus patients followed-up for more than 10 years. *Lupus* 2017;26:1197-204.
4. Lam NC, Ghetu MV, Bieniek ML. Systemic lupus erythematosus: primary care approach to diagnosis and management. *Am Fam Physician* 2016;94:284-94.
5. Bertsias GK, Salmon JE, Boumpas DT. Therapeutic opportunities in systemic lupus erythematosus: state of the art and prospects for the new decade. *Ann Rheum Dis* 2010;69:1603-11.
6. Kan HJ, Song X, Johnson BH, Bechtel B, O'Sullivan D, Molta CT. Healthcare utilization and costs of systemic lupus erythematosus in Medicaid. *Biomed Res Int* 2013;2013:808391.
7. Bakshi J, Segura BT, Wincup C, Rahman A. Unmet needs in the pathogenesis and treatment of systemic lupus erythematosus. *Clin Rev Allergy Immunol* 2018;55:352-67.
8. Garris C, Shah M, Farrelly E. The prevalence and burden of systemic lupus erythematosus in a Medicare population: retrospective analysis of Medicare claims. *Cost Eff Resour Alloc* 2015;13:9.

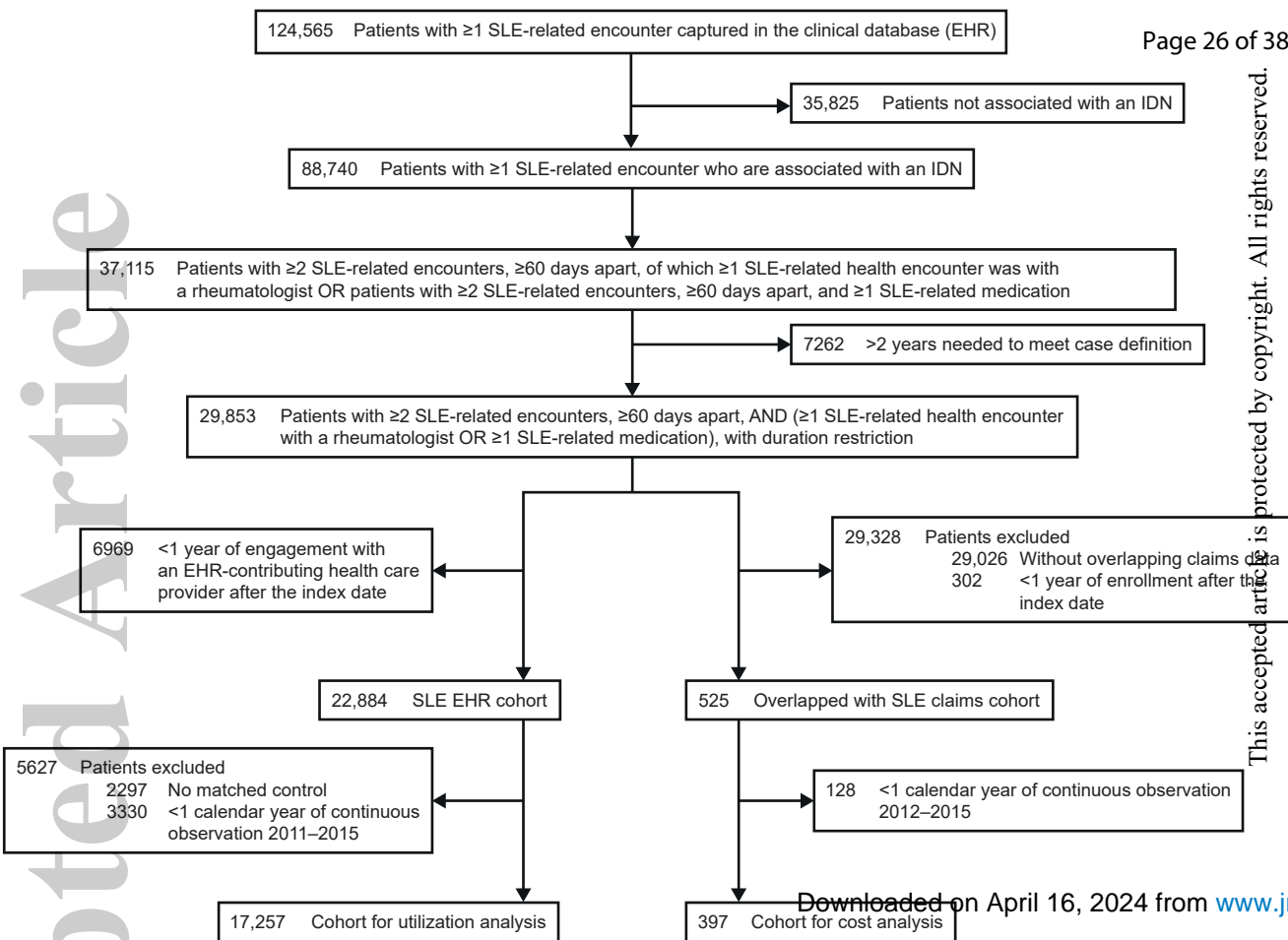
9. Garris C, Jhingran P, Bass D, Engel-Nitz NM, Riedel A, Dennis G. Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan. *J Med Econ* 2013;16:667-77.
10. Furst DE, Clarke A, Fernandes AW, Bancroft T, Gajria K, Greth W, et al. Resource utilization and direct medical costs in adult systemic lupus erythematosus patients from a commercially insured population. *Lupus* 2013;22:268-78.
11. Hammond E, Trenz H, Wang X, Tummala R, Desta B, Halpern R. Validation of systemic lupus erythematosus (SLE) diagnosis in claims data using electronic health records (EHR) [abstract]. *Pharmacoepidemiol Drug Saf* 2017;26:445-6.
12. US Department of Labor, Bureau of Labor Statistics. Consumer Price Index detailed report tables. 2004–2016. [Internet. Accessed September 10, 2019.] Available from: <https://www.bls.gov/bls/news-release/cpi.htm>.
13. Weiss AJ, Elixhauser A. Overview of hospital stays in the United States, 2012. Agency for Healthcare Research and Quality. [Internet. Accessed September 10, 2019.] Available from: <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb180-Hospitalizations-United-States-2012.pdf>.
14. Centers for Disease Control and Prevention. National hospital ambulatory medical care survey: 2015 emergency department summary tables [Internet. Accessed September 10, 2019.] Available from: https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf.
15. Shafrin J, Tebeka MG, Price K, Patel C, Michaud K. The economic burden of ACPA-positive status among patients with rheumatoid arthritis. *J Manag Care Spec Pharm* 2018;24:4-11.

16. Yeo AL, Koelmeyer R, Kandane-Rathnayake R, Golder V, Hoi A, Huq M, et al. Lupus low disease activity state is associated with reduced direct healthcare costs in patients with systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2019 Jul 8 (E-pub ahead of print).
17. Gordon C, Amissah-Arthur M-B, Gayed M, Brown, S, Bruce IN, D'Cruz D, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. *Rheumatology (Oxford)* 2018;57:e1-45.
18. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010;69:20-8.
19. Kariburyo F, Xie L, Sah J, Li N, Lofland JH. Real-world medication use and economic outcomes in incident systemic lupus erythematosus patients in the United States. *J Med Econ* 2019;23:1-9.
20. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum* 2010;39:257-68.
21. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778-99.
22. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum* 2007;56:2092-4.

FIGURE LEGENDS

Figure 1. Derivation of the study cohort. EHR, electronic health record; IDN, Integrated Delivery Network; SLE, systemic lupus erythematosus.

Figure 2. Disease severity and mean annual health care costs associated with SLE, 2012–2015 (Optum/Humedica integrated claims/EHR data). EHR, electronic health record; SLE, systemic lupus erythematosus; USD, US dollars.



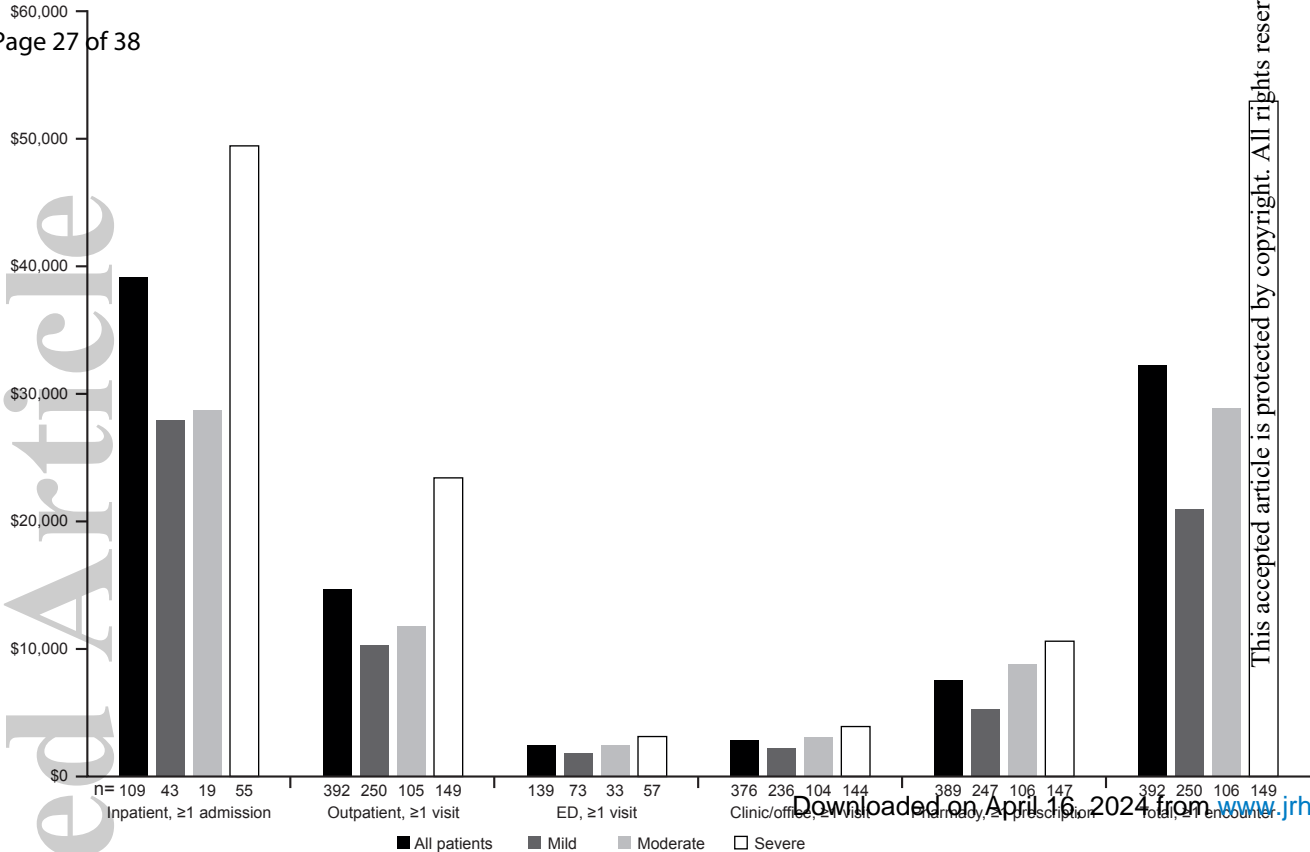


Table 1. Characteristics of Patients with SLE Evaluated in the Health Care Utilization Cohort, 2011–2015 (Humedica EHR Data), and the Health Care Costs Cohort, 2012–2015 (Optum/Humedica Integrated Claims/EHR Data)

	Health Care Utilization	Health Care Costs*
Patient Characteristic	N=17,257	N=397
Age at index date, years		
Mean (SD)	48.4 (15.6)	51.1 (14.9)
Median (IQR)	49 (37, 59)	52 (40, 62)
Female, n (%)	15,482 (89.7)	350 (88.2)
Race, n (%)		
African-American	3209 (18.6)	64 (16.1)
White	11,962 (69.3)	276 (69.5)
Other/unknown	2086 (12.1)	57 (14.4)
Ethnicity, n (%)		
Hispanic	1218 (7.1)	20 (5.0)
Non-Hispanic	14,655 (84.9)	344 (86.6)
Unknown	1384 (8.0)	33 (8.3)
Geographic region, n (%)		
Midwest	7149 (41.4)	148 (37.3)
Northeast	2282 (13.2)	118 (29.7)
South	6056 (35.1)	91 (22.9)
West	1310 (7.6)	32 (8.1)
Other/unknown	460 (2.7)	8 (2.0)
Primary insurance, n (%) [†]		
Commercial	5628 (32.6)	272 (68.5)
Medicaid	945 (5.5)	0
Medicare	2864 (16.6)	115 (29.0)

Uninsured	5249 (30.4)	0
Unknown	2215 (12.8)	0
Several	356 (2.1)	10 (2.5)
Household income, \$ [‡]		
Mean (SD)	41,748 (10,206)	43,873 (10,948)
College educated, n (%) [§]		
≤10%	27 (0.2)	1 (0.3)
11%–20%	5310 (30.8)	77 (19.4)
21%–30%	8577 (49.7)	211 (53.1)
>30%	2882 (16.7)	100 (25.2)
Unknown	461 (2.7)	8 (2.0)

[†]Insurance that was most commonly used in the health care utilization cohort for a health care encounter. [‡]Average household income at the individual’s 3-digit zip code. [§]Percentage college educated at the individual’s 3-digit zip code level. EHR, electronic health record; IQR, interquartile range; SD, standard deviation; SLE, systemic lupus erythematosus.

Table 2. Annual Health Care Utilization Patterns, 2011–2015 (Optum/Humedica Integrated Claims/EHR Data)

	2011	2012	2013	2014	2015	
SLE prevalence (per 100,000 patients in EHR)	44.1	56.6	69.6	76.3	85.3	
SLE incidence (per 100,000 patients in EHR)	12.1	12.7	14.0	13.7	10.7	Average
Number of patients	4551	7208	9469	11,275	9063	Annual*
Inpatient services						
Patients with ≥ 1 inpatient admission, n (%)	615 (13.5)	1024 (14.2)	1260 (13.3)	1476 (13.1)	1296 (14.3)	13.7
Number of admissions for those with ≥ 1 inpatient stay, median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	1 (1, 2)	
mean (SD)	1.7 (1.4)	1.7 (1.5)	1.7 (1.4)	1.7 (1.5)	1.7 (1.4)	1.7 (1.4)
Duration of stay (days) for those with ≥ 1 inpatient stay, median (IQR)	4 (2, 6)	3.5 (2, 6)	3.3 (2, 5.9)	4 (2, 6)	3.5 (2, 5.7)	
mean (SD)	5.5 (15.6)	5.4 (12.5)	5.5 (17.2)	5.4 (12.6)	5.1 (6.2)	5.4 (13.0)
Number of admissions for all patients, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
mean (SD)	0.2 (0.8)	0.2 (0.8)	0.2 (0.8)	0.2 (0.8)	0.2 (0.8)	0.2 (0.8)
Outpatient services						
Patients with ≥ 1 visit, n (%)	4304 (94.6)	6769 (93.9)	8695 (91.8)	10,577 (93.8)	8869 (97.9)	94.4
Number of visits for those with ≥ 1 visit, median (IQR)	15 (7, 28)	16 (7, 31)	16 (7, 32)	17 (7, 33)	19 (9, 37)	
mean (SD)	21.0 (20.4)	22.7 (22.1)	23.5 (23.5)	24.5 (24.6)	27.1 (25.7)	24.1 (23.8)
Number of visits for all patients, median (IQR)	14 (6, 27)	15 (6, 29)	14 (5, 30)	15 (6, 32)	19 (8, 36)	
mean (SD)	19.8 (20.4)	21.3 (22.1)	21.6 (23.4)	23.0 (24.6)	26.5 (25.7)	22.8 (23.7)
Emergency department (ED) visits						
Patients with ≥ 1 ED visit, n (%)	1036 (22.8)	1811 (25.1)	2349 (24.8)	2965 (26.3)	2654 (29.3)	25.7
Number of visits for those with ≥ 1 ED visit, median (IQR)	1 (1, 2)	1 (1, 3)	1 (1, 3)	1 (1, 3)	1 (1, 3)	
mean (SD)	2.4 (3.1)	2.4 (3.1)	2.6 (4.0)	2.4 (3.3)	2.6 (3.2)	2.5 (3.4)
Number of ED visits for all patients, median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 1)	
mean (SD)	0.5 (1.8)	0.6 (1.9)	0.6 (2.3)	0.6 (2.0)	0.8 (2.1)	0.6 (2.1)
Clinic/provider office visits						
Patients with ≥ 1 clinic/provider office visit, n (%)	4046 (88.9)	6320 (87.7)	7949 (83.9)	9389 (83.3)	7943 (87.6)	86.3
Number of visits for those with ≥ 1 visit, median (IQR)	7 (3, 13)	7 (3, 13)	7 (3, 13)	7 (3, 13)	7 (3, 13)	
mean (SD)	10.0 (10.3)	10.3 (10.3)	9.9 (9.9)	9.8 (10.1)	10.2 (10.3)	10.0 (10.2)
Number of visits for all patients, median (IQR)	6 (2, 12)	6 (2, 12)	5 (2, 12)	5 (2, 11)	6 (2, 12)	

mean (SD)	8.9 (10.2)	9.0 (10.2)	8.3 (9.7)	8.1 (9.9)	9.0 (10.2)	8.6 (10.0)
Prescription drug use, n (%)						
Patients with ≥1 prescription for any medication	4047 (88.9)	6355 (88.2)	7965 (84.1)	9714 (86.2)	8399 (92.7)	88.0
Antimalarial medications	966 (21.2)	1432 (19.9)	1557 (16.4)	1897 (16.8)	1553 (17.1)	18.3
Biologics	30 (0.7)	90 (1.2)	150 (1.6)	161 (1.4)	128 (1.4)	1.3
Immunosuppressants	531 (11.7)	775 (10.8)	911 (9.6)	1065 (9.4)	926 (10.2)	10.3
Systemic corticosteroids	992 (21.8)	1371 (19.0)	1678 (17.7)	1935 (17.2)	1657 (18.3)	18.8

*Percentage or mean (SD). As percentages were an annual average of each year of the study, which had different numbers of patients each year, n values were not given. Total number of patients for the entire study was 17,257. ED, emergency department; EHR, electronic health record; IQR, interquartile range; SD, standard deviation; SLE, systemic lupus erythematosus.

Table 3. Annual Health Care Costs Associated with SLE, Stratified by Disease Severity and Service Use, 2012–2015 (Optum/Humedica Integrated Claims/EHR Data)*

Cost Categories	All Patients with	Patients by SLE Disease Severity		
	SLE	Mild	Moderate	Severe
2016 U.S. Dollars				
Total costs				
All patients, n	397	256	106‡	149‡
Median (IQR)	12,944 (5965, 32,230)	9039 (4054, 20,106)	16,178 (7395, 36,341)	22,103 (11,380, 53,408)
Mean (SD)	31,800 (58,216)	20,337 (43,504)	28,936 (33,359)	52,951 (80,971)
Inpatient costs				
All patients, n	397	256	106	149
Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	(0, 5276)
Mean (SD)	6727 (28,200)	2971 (13,751)	4593 (14,657)	14,326 (45,547)
Patients with ≥1 admission, n (%)	109 (27.5)	43 (16.8)	19 (17.9)	55 (36.9)
Median (IQR)	17,735 (7951, 41,864)	17,735 (7776, 35,470)	17,735 (11,618, 38,656)	21,597 (7452, 53,224)
Mean (SD)	39,207 (58,128)	27,937 (33,167)	28,756 (25,887)	49,474 (73,964)

Combined outpatient costs				
All patients, n	397	256	106	149
Median (IQR)	5696	4010	7000	8500
	(2450, 13,083)	(1488, 8983)	(3168, 13,850)	(4609, 21,868)
Mean (SD)	14,430 (35,709)	9996 (32,801)	11,790 (14,555)	23,468 (45,775)
Patients with ≥1 visit, n (%)	392 (98.7)	250 (97.7)	105 (99.1)	149 (100.0)
Median (IQR)	5865	4307	7031	8500
	(2590, 13,317)	(1784, 9639)	(3172, 13,912)	(4609, 21,868)
Mean (SD)	14,745 (36,032)	10,396 (33,390)	11,873 (14,572)	23,468 (45,775)
Emergency department costs				
All patients, n	397	256	106	149
Median (IQR)	0 (0,0)	0 (0, 0)	0 (0, 71)	0 (0, 200)
Mean (SD)	578 (2072)	344 (1420)	712 (2148)	902 (2798)
Patients with ≥1 visit, n (%)	139 (35.0)	73 (28.5)	33 (31.1)	57 (38.3)
Median (IQR)	1069	813	1005	1471
	(311, 2813)	(215, 2178)	(378, 3704)	(403, 3328)
Mean (SD)	2481 (3707)	1815 (2832)	2629 (3490)	3159 (4521)
Clinic/office service costs				
All patients, n	397	256	106	149

Median (IQR)	1691 (882, 3401)	1283 (584, 2522)	1970 (1268, 3838)	2384 (1229, 4512)
Mean (SD)	2700 (3494)	1996 (2389)	2972 (3837)	3749 (4475)
Patients with ≥ 1 visit, n (%)	376 (94.7)	236 (92.2)	104 (98.1)	144 (96.6)
Median (IQR)	1865 (1059, 3660)	1521 (893, 2871)	2006 (1310, 3856)	2582 (1403, 4818)
Mean (SD)	2940 (3548)	2279 (2423)	3035 (3853)	3916 (4501)
Pharmacy costs				
All patients, n	397	256	106	149
Median (IQR)	2289 (711, 6377)	1649 (343, 3838)	3158 (930, 8097)	3966 (1418, 10,603)
Mean (SD)	7363 (16,988)	5031 (17,177)	8869 (17,298)	10,505 (15,921)
Patients with ≥ 1 prescription, n (%) [†]	389 (98.0)	247 (96.5)	106 (100.0)	147 (98.7)
Median (IQR)	2434 (804, 6732)	1809 (483, 3968)	3158 (930, 8097)	3982 (1516, 10,639)
Mean (SD)	7606 (17,214)	5320 (17,621)	8869 (17,298)	10,628 (15,974)

[†]N values based on the entire 4-year period; an individual patient may meet ≥ 1 SLE severity category during the entire study period. Therefore, the number of patients per severity category differs from the total number of patients included in the analysis.

[†]Antimalarial medications, n (%): mild 132 (51.6), moderate 67 (63.2), severe 99 (66.4); biologics, n (%): mild 5 (2.0), moderate 4 (3.8), severe 7 (4.7); immunosuppressants, n (%): mild 37 (14.5), moderate 29 (27.4), severe 69 (46.3); systemic corticosteroids, n (%): mild 64 (25.0), moderate 92 (86.8), severe 105 (70.5). [‡]By definition, patients with moderate or severe SLE used ≥ 1 health care service during the year. EHR, electronic health record; IQR, interquartile range; SD, standard deviation; SLE, systemic lupus erythematosus.

Table 4. Annual Health Care Costs Associated with SLE, Stratified by Disease Severity, Service Use, and Year (Patients with ≥ 1 SLE-Related Encounter), 2012–2015 (Optum/Humedica Integrated Claims/EHR Data)*

Cost Categories	All Patients with SLE	Patients by SLE Disease Severity		
		Mild	Moderate	Severe
	Median (Interquartile Range) in 2016 U.S. Dollars, n			
Total costs				
2012	13,116 (4649, 28,824), 139	8887 (3711, 15,465), 70	15,584 (7354, 41,438), 27 [†]	23,551 (9928, 50,868), 42 [†]
2013	14,346 (6557, 33,034), 206	10,870 (4562, 21,897), 108	14,813 (9239, 38,175), 34 [†]	19,254 (10,892, 63,222), 64 [†]
2014	12,338 (5153, 32,735), 225	8426 (4135, 19,137), 122	18,222 (8284, 38,310), 39 [†]	23,082 (8348, 64,752), 64 [†]
2015	14,643 (6676, 34,009), 275	9216 (5044, 23,710), 142	16,411 (6475, 27,232), 44 [†]	22,104 (12,429, 48,660), 89 [†]
Inpatient costs				
2012	16,424 (10,080, 32,331), 21	17,619 (10,667, 26,020), 6	37,262 (16,424, 71,253), 3	13,394 (9094, 26,964), 12
2013	20,326 (7776, 46,050), 39	15,147 (6847, 17,735), 13	17,735 (9893, 41,999), 9	37,350 (20,326, 90,972), 17
2014	28,869 (16,213, 45,869), 35	17,735 (6066, 34,783), 11	21,292 (17,735, 38,656), 5	33,028 (24,720, 74,366), 19
2015	16,790 (7190, 36,722), 50	25,278 (14,653, 56,863), 17	14,857 (11,749, 17,735), 6	12,082 (6148, 36,722), 27
Combined outpatient costs				
2012	5594 (2082, 12,382), 135	4153 (1768, 8983), 67	8280 (2822, 16,593), 26	8892 (4003, 17,069), 42

2013	6661 (3080, 14,008), 200	5389 (2068, 12,244), 102	6461 (3162, 13,912), 34	8475 (4680, 20,996), 64
2014	4901 (2516, 12,471), 222	3720 (1664, 7791), 119	7032 (3834, 16,337), 39	10,941 (3890, 28,772), 64
2015	6042 (2514, 14,026), 270	4110 (1925, 10,066), 137	6717 (3014, 12,678), 44	8488 (5135, 21,868), 89
ED visit costs				
2012	693 (298, 2155), 26	508 (202, 874), 9	1005 (570, 10,894), 7	591 (310, 1987), 10
2013	1092 (345, 3272), 50	557 (238, 2012), 19	1974 (427, 4082), 9	1316 (363, 3879), 22
2014	1350 (478, 2228), 55	1722 (544, 3227), 28	978 (165, 2228), 10	1272 (597, 1798), 17
2015	1023 (256, 2898), 66	473 (178, 1892), 28	669 (391, 2417), 13	2513 (617, 4372), 25
Clinic/office visit costs				
2012	1695 (946, 3078), 126	1465 (843, 2699), 61	1826 (1085, 2739), 26	2163 (1190, 4272), 39
2013	2242 (1248, 3922), 184	2054 (977, 3049), 92	2296 (1785, 3906), 33	2722 (1554, 5565), 59
2014	1718 (985, 3712), 208	1383 (857, 2841), 108	2378 (1373, 5070), 38	2159 (1009, 4467), 62
2015	1745 (1109, 3577), 258	1460 (913, 2639), 126	1712 (1109, 2765), 44	2913 (1601, 4761), 88
Pharmacy costs				
2012	2043 (712, 6197), 134	1577 (651, 3560), 66	3305 (472, 9629), 27	2901 (844, 11,495), 41
2013	2358 (865, 6583), 199	1626 (577, 3899), 101	3122 (710, 7253), 34	3910 (1404, 10,075), 64
2014	2279 (711, 6186), 218	1806 (326, 4029), 115	3560 (808, 7506), 39	3580 (1312, 9585), 64
2015	2816 (976, 7849), 267	2159 (569, 4139), 136	2696 (1078, 9005), 44	4568 (2182, 12,295), 87

*An individual patient may meet ≥ 1 SLE severity category during the entire study period. Therefore, the number of patients per severity category differs from the total number of patients included in the analysis. [†]By definition, patients with moderate or severe SLE had ≥ 1 health care encounter during the year. ED, emergency department; EHR, electronic health record; SLE, systemic lupus erythematosus.