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Disease and economic burden increase with systemic lupus erythematosus severity 1 year before and after diagnosis: a real-world cohort study, United States, 2004–2015

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ABSTRACT

Objective To assess the economic burden of patients with SLE by disease severity in the USA 1 year before and after diagnosis.

Methods Patients aged ≥18 years with a first SLE diagnosis (index date) between January 2005 and December 2014 were identified from administrative commercial claims data linked to electronic medical records (EMRs). Disease severity during the year after diagnosis was classified as mild, moderate, or severe using claims-based algorithms and EMR data. Healthcare resource utilisation (HCRU) and all-cause healthcare costs (2017 US$) were reported for 1 year pre-diagnosis and post-diagnosis. Generalised linear modelling examined all-cause costs over 1 year post-index, adjusting for baseline demographics, clinical characteristics, Charlson Comorbidity Index and 1 year pre-diagnosis costs.

Results Among 2227 patients, 26.3% had mild, 51.0% moderate and 22.7% severe SLE. Mean per-patient costs were higher for patients with moderate and severe SLE compared with mild SLE during the year before diagnosis: mild US$12 373, moderate $22 559 and severe US$39 261 (p<0.0001); and 1-year post-diagnosis period: mild US$13 415, moderate US$29 512 and severe US$68 260 (p<0.0001). Leading mean cost drivers were outpatient visits (US$13 566) and hospitalisations (US$10 252). Post-diagnosis inpatient utilisation (≥1 stay) was higher for patients with severe (51.2%) and moderate (22.4%) SLE, compared with mild SLE (12.8%), with longer mean hospital stays: mild 0.47 days, moderate 1.31 days and severe 5.52 days (p<0.0001).

Conclusion HCRU and costs increase with disease severity in the year before and after diagnosis; leading cost drivers post-diagnosis were outpatient visits and hospitalisations. Earlier diagnosis and treatment may improve health outcomes and reduce HCRU and costs.

Key messages

What is already known about this subject?

- SLE is associated with significant healthcare resource utilisation (HCRU) and costs, especially during periods of heightened disease activity.
- Patients who receive earlier diagnoses have lower flare rates, less HCRU and lower costs, compared with those who have later diagnoses.

What does this study add?

- This study used administrative commercial claims data linked to electronic medical records to evaluate the economic burden of US patients with newly diagnosed SLE in the 1-year period before and after diagnosis.
- In the year before diagnosis, unadjusted all-cause healthcare costs were 1.8-fold higher for patients with severe SLE and 3.2-fold higher for patients with moderate SLE than for mild SLE, predominantly owing to outpatient visits and hospitalisations.
- In the year post-diagnosis, healthcare costs were 2.2-fold and 5.1-fold for patients with moderate and severe SLE, respectively, compared with mild SLE. Multiple factors, including the presence of ≥2 Charlson Comorbidity Index comorbidities at baseline, the use of ≥3 medications at baseline and higher healthcare costs during the baseline period, are associated with increased healthcare costs during the year after diagnosis.

How might this impact on clinical practice or future developments?

- These findings highlight the importance of early diagnosis and rapid treatment. Early diagnosis and treatment may improve disease control and health outcomes to reduce the economic burden of SLE.

INTRODUCTION

SLE is a chronic autoimmune disease associated with significant morbidity and mortality, affecting multiple organ systems.[1 2] SLE is associated with high annual costs of care that are greater than for some other chronic conditions, such as fibromyalgia and rheumatoid arthritis.[3–5] In a systematic review of SLE healthcare costs and utilisation, mean annual direct costs per patient ranged $15 171–$88 445 (2016 US$), with the broad

range underscoring the effect that disease severity can have on overall healthcare costs.[3]

SLE is characterised by episodes of increased disease activity; flares are separated by periods of remission.[2] Studies have shown that 65%–70% of patients with SLE may experience at least one flare per year.[6 7] SLE flares are associated with increased annual medical costs, which increase with flare severity.[8–11] As there is currently no curative therapy for SLE, one of the main treatment goals is to prevent flares and disease progression.[2]

Current medications approved by the US Food and Drug Administration to treat SLE include corticosteroids, antimalarials such as hydroxychloroquine, and belimumab, a biologic.[12–17] Other therapies for SLE management include nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressive and/or immunomodulatory agents, and rituximab, a biologic.[18] Although corticosteroids provide clinical benefits, long-term use has been associated with organ damage and toxicity, along with increased healthcare resource utilisation (HCRU) and costs.[16 19–21]

Previous studies demonstrated that SLE disease severity is associated with substantial HCRU and costs.[9 11 13–15 17 22] The time from symptom onset to SLE diagnosis can be long, with one study reporting a mean duration of 21.8 months.[23] Patients who receive earlier diagnoses have lower flare rates, less HCRU and lower costs, compared with those who have later diagnoses.[24] Given the complexity of SLE disease progression, few studies have quantified the economic burden along the patient journey from the period leading up to diagnosis through post-diagnosis treatment in the USA. Only one study, in a population-based Canadian cohort, has evaluated the economic burden of SLE pre-diagnosis. This study showed an increase in incremental direct medical costs of SLE over the 5 years before diagnosis; however, the results were not stratified by disease severity.[25]

The objective of this study was to assess the economic burden of SLE and its association with disease severity in the year before and after initial diagnosis. We conducted a retrospective study using administrative commercial claims data linked to electronic medical records (EMRs) among a cohort of US patients with newly diagnosed SLE.

PATIENTS AND METHODS

Data sources

This retrospective study leveraged the IBM MarketScan commercial database linked to the General Electric Centricity EMR database (GE EMR) with data from January 2004 to December 2015. The IBM MarketScan commercial database contains fully integrated, longitudinal, de-identified, patient-level healthcare claims data on clinical utilisation, expenditures and enrolment across inpatient, outpatient, prescription drug and carve-out services. The data are from large employers, health plans, and government and public organisations and include private sector health data from approximately 350 payers; historically, >20 billion service records have been included.

The GE EMR database includes patient-level information on the following: demographics; lifestyle characteristics; insurance coverage; vital signs; International Classification of Diseases, Ninth Revision (ICD-9) and ICD-10 medical diagnoses; patient complaints; diagnostic and laboratory tests with results; procedures; prescriptions; and information from specialty healthcare providers. Clinical data are captured from >725 member institutions and 33 000 providers and include >38 million patients from 49 US states and the District of Columbia.

The study dataset was constructed by linking patient data from IBM MarketScan and GE EMR using a patented and proprietary encryption algorithm developed by IQVIA.[26–28] Patient data were de-identified across data suppliers using the encryption algorithm, followed by deterministic matching based on patient-level information. Each patient was then assigned a unique and persistent IQVIA patient ID with linkage across various databases.

The study data consist of fully de-identified datasets, in compliance with the US Health Insurance Portability and Accountability Act; therefore, the study did not require Institutional Review Board approval.

Study design and patient selection

Patients with SLE from the linked dataset were eligible for inclusion if they had at least one SLE diagnosis (ICD-9-CM: 710.0x, ICD-10-CM: M32.9) in EMR records or claims in any position, either as ≥1 inpatient SLE diagnosis or ≥2 separate outpatient diagnoses (including the index diagnosis) that were ≥60 days apart between 1 January 2005 and 31 December 2014. Two medical claims for outpatient settings were required to limit potential misclassification of SLE cases, which tends to be more likely in outpatient settings than inpatient and emergency department (ED) settings. The date of first observed SLE diagnosis was defined as the index date. To further minimise potential misclassification, and confirm patients with SLE, patients were also required to have used SLE-related medications, identified by national drug codes or healthcare common procedure coding system codes in the pharmacy claim, within 6 months before and after the index date (online supplemental table 1). Patients were ≥18 years of age on the index date, with continuous health plan enrolment for at least 12 months pre-index (baseline period) and 12 months post-index (follow-up period). The continuous enrolment requirement ensured that HCRU and costs were comprehensively captured within the data sources. To ensure newly diagnosed, not prevalent SLE cases, patients were excluded if they had a prior diagnosis of SLE or lupus nephritis during the baseline period. Patients were also excluded if their data were incomplete or had other quality issues, such as missing age or sex. Figure 1 presents details of the inclusion and exclusion criteria with attrition of the study population.

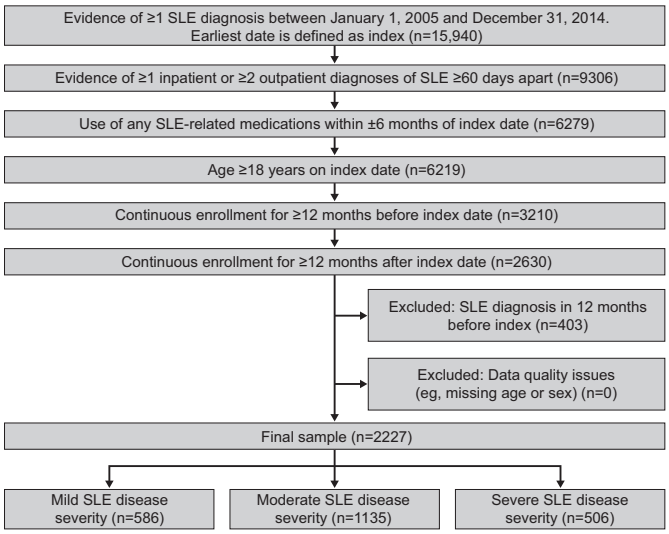

Figure 1 Attrition of the identified study population of US patients with newly diagnosed SLE.

Study measures

SLE disease severity

Disease severity was classified as mild, moderate or severe based on the highest disease severity experienced over 1 year post-diagnosis using claims-based algorithms,[9] which combined SLE diagnosis, disease activities and SLE-related conditions, medications and health services use, supplemented with EMR. The algorithms are described in online supplemental table 2. We chose the 1-year post-diagnosis window because it reflects an accurate and comprehensive view of disease severity, accounting for the variation in the disease process over time while allowing sufficient time for clinical evaluation and diagnosis.

Baseline characteristics

Baseline demographic characteristics included age, sex, race/ethnicity, geographical region, health plan type and payer type, assessed at the index date. Baseline clinical characteristics included Charlson Comorbidity Index (CCI) score and medication use, assessed over the baseline period. In addition, the proportions of patients with 0, 1, 2 and ≥3 CCI comorbidities, individual CCI conditions and SLE-related non-CCI conditions were reported. All-cause healthcare costs as the total payments received by providers, including the amounts paid by payers and patient out-of-pocket cost (eg, copay, co-insurance), converted to 2017 US dollars using the medical component of the Consumer Price Index, were also measured during the baseline period.

Outcome measures

The study outcomes included all-cause healthcare costs, HCRU and treatment patterns during the 1-year post-diagnosis period, overall and by care setting (inpatient, ED, outpatient, office, laboratory and pharmacy). Healthcare costs were estimated for the 1-year post-diagnosis period; a similar estimate was made for baseline costs. Components of inpatient HCRU assessed included the proportion of patients with ≥1 inpatient hospitalisation, mean number of hospitalisations and mean hospital length of stay. Outpatient, ED, office, laboratory and pharmacy HCRU were assessed as the proportion of patients with ≥1 visit, service or prescription, and the mean number of utilisations for each category. Outpatient services include all nonpharmacy claims not categorised as inpatient, ED, office or laboratory services. Prescribed SLE treatments during the 1-year post-diagnosis period were also assessed. Outcomes were evaluated for all patients and stratified by SLE disease severity.

Statistical analyses

Baseline patient characteristics and clinical outcomes during the follow-up period were reported as counts or proportions for categorical variables and means and SD for continuous variables. Descriptive comparisons between SLE severity groups were examined with Pearson's χ^2 test or F-test for categorical variables and analysis of variance or t-test for continuous variables. A generalised linear model with gamma distribution and log link was fit to evaluate the incremental cost by SLE severity as well as factors associated with total all-cause healthcare cost during the 1-year post-diagnosis period, adjusting for baseline demographic and clinical characteristics, and all-cause healthcare costs during the baseline period. Statistical tests were two-sided with an α-level of 0.05 for statistical significance. All analyses were performed with SAS V.9.4 (SAS Institute, Cary, NC, USA).

Patient and public involvement

Patients and the public were not involved in the research process, research questions, study design, or result dissemination plans.

RESULTS

Patient demographics and clinical characteristics

The study population included 2227 patients newly diagnosed with SLE: 586 (26.3%) with mild SLE, 1135 (51.0%) with moderate SLE and 506 (22.7%) with severe SLE. Baseline demographics and clinical characteristics are reported in table 1. The mean (SD) age of patients was 50.2 (13.0) years, 54.4% were non-Hispanic white and 90.6% were female. Overall, 58.5% of patients were from the South, 18.6% from the Northeast and 13.0% from North central US regions. Patients were largely covered by commercial insurance (87.7%) and the remaining by employer-provided Medicare supplemental insurance (12.3%). Across SLE severity groups, demographics were similar except that patients with severe SLE were more likely to be >65 years old, male and covered by Medicare (table 1).

The mean (SD) CCI score at baseline was 1.2 (1.5) for all patients and increased with SLE disease severity: 0.8 (1.1) for mild SLE, 1.1 (1.4) for moderate SLE and 1.8 (1.8) for severe SLE (p<0.0001). The presence of ≥1 CCI comorbidity at baseline was more frequent among patients with severe SLE (73.7%) and moderate SLE (59.4%)

Table 1 Baseline demographics and clinical characteristics* for patients with newly diagnosed SLE by disease severity

Variable	All patients (N=2227)	SLE disease severity†			P value
		Mild (n=586)	Moderate (n=1135)	Severe (n=506)	
Demographics					
Age, mean years (SD)	50.2 (13.0)	50.0 (12.2)	49.7 (13.1)	51.8 (13.3)	0.0088
Age category, n (%)					
18–44 years	709 (31.8)	187 (31.9)	373 (32.9)	149 (29.4)	0.0298
45–64 years	1252 (56.2)	336 (57.3)	640 (56.4)	276 (54.5)	
≥65 years	266 (11.9)	63 (10.8)	122 (10.7)	81 (16.0)	
Female, n (%)	2017 (90.6)	544 (92.8)	1030 (90.7)	443 (87.5)	0.0113
Race/ethnicity, n (%)					
Non-Hispanic white	1212 (54.4)	318 (54.3)	621 (54.7)	273 (54.0)	0.2913
Non-Hispanic black	298 (13.4)	87 (14.8)	136 (12.0)	75 (14.8)	
Hispanic	105 (4.7)	25 (4.3)	61 (5.4)	19 (3.8)	
Other	124 (5.6)	40 (6.8)	58 (5.1)	26 (5.1)	
Unknown	488 (21.9)	116 (19.8)	259 (22.8)	113 (22.3)	
Region, n (%)					
Northeast	415 (18.6)	92 (15.7)	211 (18.6)	112 (22.1)	0.0517
North central	289 (13.0)	75 (12.8)	139 (12.2)	75 (14.8)	
South	1303 (58.5)	354 (60.4)	681 (60.0)	268 (53.0)	
West	210 (9.4)	64 (10.9)	97 (8.5)	49 (9.7)	
Unknown	10 (0.4)	1 (0.2)	7 (0.6)	2 (0.4)	
Health plan type, n (%)					
HMO	219 (9.8)	60 (10.2)	114 (10.0)	45 (8.9)	0.0873
Indemnity	169 (7.6)	43 (7.3)	74 (6.5)	52 (10.3)	
POS	244 (11.0)	73 (12.5)	119 (10.5)	52 (10.3)	
PPO	1367 (61.4)	355 (60.6)	719 (63.3)	293 (57.9)	
Other	164 (7.4)	40 (6.8)	82 (7.2)	42 (8.3)	
Unknown	64 (2.9)	15 (2.6)	27 (2.4)	22 (4.3)	
Payer type, n (%)					
Commercial	1953 (87.7)	521 (88.9)	1008 (88.8)	424 (83.8)	0.0098
Medicare supplemental	274 (12.3)	65 (11.1)	127 (11.2)	82 (16.2)	
Clinical characteristics					
Medication use, n (%)					
Opioids	1199 (53.8)	248 (42.3)	649 (57.2)	302 (59.7)	<0.0001
Antidepressants	784 (35.2)	173 (29.5)	420 (37.0)	191 (37.7)	0.0034
Muscle relaxants	523 (23.5)	111 (18.9)	294 (25.9)	118 (23.3)	0.0054
Sedatives	508 (22.8)	106 (18.1)	254 (22.4)	148 (29.2)	<0.0001
Gabapentin	189 (8.5)	23 (3.9)	116 (10.2)	50 (9.9)	<0.0001
Antimigraine	133 (6.0)	23 (3.9)	86 (7.6)	24 (4.7)	0.0042
CCI, mean (SD)	1.2 (1.5)	0.8 (1.1)	1.1 (1.4)	1.8 (1.8)	<0.0001
CCI category, n (%)					
0	895 (40.2)	301 (51.4)	461 (40.6)	133 (26.3)	<0.0001
1	664 (29.8)	177 (30.2)	345 (30.4)	142 (28.1)	
2	341 (15.3)	72 (12.3)	172 (15.2)	97 (19.2)	
≥3	327 (14.7)	36 (6.1)	157 (13.8)	134 (26.5)	

Continued

Table 1 Continued

Variable	All patients (N=2227)	SLE disease severity†			P value
		Mild (n=586)	Moderate (n=1135)	Severe (n=506)	
Individual comorbidities from the CCI, n (%)					
Diabetes mellitus	298 (13.4)	50 (8.5)	147 (13.0)	101 (20.0)	<0.0001
Cerebrovascular accident	140 (6.3)	15 (2.6)	44 (3.9)	81 (16.0)	<0.0001
Liver disease	142 (6.4)	23 (3.9)	69 (6.1)	50 (9.9)	0.0003
Any malignancy	135 (6.1)	28 (4.8)	68 (6.0)	39 (7.7)	0.1280
Peripheral vascular disease	106 (4.8)	13 (2.2)	53 (4.7)	40 (7.9)	<0.0001
Congestive heart failure	85 (3.8)	12 (2.0)	38 (3.3)	35 (6.9)	<0.0001
Myocardial infarction	22 (1.0)	0 (0.0)	11 (1.0)	11 (2.2)	0.0014
Metastatic disease	13 (0.6)	4 (0.7)	5 (0.4)	4 (0.8)	0.5793
Severe liver disease	2 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0.7317
AIDS	3 (0.1)	1 (0.2)	1 (0.1)	1 (0.2)	0.7949
Other SLE-related comorbidities not included in the CCI,‡ n (%)					
Hypertension	897 (40.3)	195 (33.3)	450 (39.6)	252 (49.8)	<0.0001
Infections	759 (34.1)	176 (30.0)	385 (33.9)	198 (39.1)	0.0066
Rheumatoid arthritis	522 (23.4)	126 (21.5)	285 (25.1)	111 (21.9)	0.1630
Myositis	506 (22.7)	112 (19.1)	281 (24.8)	113 (22.3)	0.0292
Anaemia	451 (20.3)	73 (12.5)	230 (20.3)	148 (29.2)	<0.0001
Depression	347 (15.6)	78 (13.3)	173 (15.2)	96 (19.0)	0.0330
Anxiety	273 (12.3)	50 (8.5)	140 (12.3)	83 (16.4)	0.0004
Rash	262 (11.8)	64 (10.9)	125 (11.0)	73 (14.4)	0.1068
Sjögren's syndrome	194 (8.7)	56 (9.6)	86 (7.6)	52 (10.3)	0.1408
Pleuritis	165 (7.4)	26 (4.4)	81 (7.1)	58 (11.5)	<0.0001
Osteoporosis	140 (6.3)	27 (4.6)	81 (7.1)	32 (6.3)	0.1226
Chronic renal failure	122 (5.5)	4 (0.7)	62 (5.5)	56 (11.1)	<0.0001
Raynaud's syndrome	118 (5.3)	30 (5.1)	65 (5.7)	23 (4.5)	0.5992
Alopecia	80 (3.6)	25 (4.3)	38 (3.3)	17 (3.4)	0.5936
Nephritis	78 (3.5)	9 (1.5)	35 (3.1)	34 (6.7)	<0.0001
Thrombocytopenia	56 (2.5)	11 (1.9)	25 (2.2)	20 (4.0)	0.0581
Pulmonary fibrosis	56 (2.5)	11 (1.9)	25 (2.2)	20 (4.0)	0.0581
Pulmonary hypertension	45 (2.0)	8 (1.4)	19 (1.7)	18 (3.6)	0.0184

*During the 1-year period before diagnosis.
†Disease severity was assessed during the 1-year period after diagnosis, and patients were classified to the most severe level during that period.
‡SLE-related non-CCI comorbidity reported if ≥2% among all patients.
CCI, Charlson Comorbidity Index; HMO, health maintenance organisation; POS, point of service; PPO, preferred provider organisation.

compared with mild SLE (48.6%). Patients with severe or moderate SLE had significantly higher frequencies of diabetes mellitus, cerebrovascular accident, liver disease, peripheral vascular disease, congestive heart failure and myocardial infarction, compared with patients with mild SLE (all p<0.01). For the top 10 most observed comorbidities not included in the CCI, patients with severe or moderate SLE had significantly higher frequencies of hypertension, infections, myositis, anaemia, depression, anxiety and pleuritis, compared with mild SLE (table 1).

SLE medications prescribed during the 1-year post-diagnosis (follow-up) period

The most commonly prescribed medications during the post-diagnosis period were corticosteroids (76.1%), hydroxychloroquine (59.7%), NSAIDs (36.7%) and methotrexate (14.7%) (online supplemental table 3). Biologic drugs, belimumab and rituximab, were prescribed to 1.4% and 1.3% of patients, respectively.

Medication use differed with SLE disease severity. Hydroxychloroquine was the most frequently prescribed

Table 2 Healthcare resource utilisation during the 1-year post-diagnosis (follow-up) period for patients with newly diagnosed SLE by disease severity

Resource	All patients (N=2227)	SLE disease severity at index*			P value
		Mild (n=586)	Moderate (n=1135)	Severe (n=506)	
Inpatient					
≥1 stay, n (%)	588 (26.4)	75 (12.8)	254 (22.4)	259 (51.2)	NA
No of hospitalisations, mean (SD)	0.44 (1.00)	0.16 (0.45)	0.32 (0.73)	1.04 (1.58)	<0.0001
Hospital stay days, mean (SD)	2.05 (6.77)	0.47 (1.69)	1.31 (3.69)	5.52 (12.33)	<0.0001
Emergency department					
≥1 visit, n (%)	919 (41.3)	157 (26.8)	469 (41.3)	293 (57.9)	NA
No of visits, mean (SD)	1.00 (2.34)	0.43 (0.88)	0.92 (2.11)	1.86 (3.48)	<0.0001
Outpatient†					
≥1 visit, n (%)	2219 (99.6)	582 (99.3)	1131 (99.6)	506 (100.0)	NA
No of visits, mean (SD)	21.61 (20.01)	14.78 (14.50)	20.35 (16.31)	32.36 (27.39)	<0.0001
Office					
≥1 visit, n (%)	2225 (99.9)	585 (99.8)	1135 (100.0)	505 (99.8)	NA
No of visits, mean (SD)	16.19 (10.08)	11.61 (6.81)	16.07 (8.86)	21.77 (12.75)	<0.0001
Laboratory					
≥1 service, n (%)	1979 (88.9)	515 (87.9)	1003 (88.4)	461 (91.1)	NA
No of services, mean (SD)	29.43 (32.76)	19.53 (18.44)	28.71 (29.85)	42.53 (45.27)	<0.0001
Pharmacy					
≥1 prescription, n (%)	2053 (92.2)	509 (86.9)	1062 (93.6)	482 (95.3)	NA
No of prescriptions, mean (SD)	45.84 (37.78)	29.82 (27.02)	48.28 (38.39)	58.94 (40.64)	<0.0001

*Disease severity was assessed during the 1-year period after diagnosis, and patients were classified to the most severe level during that period.
†Outpatient services included all nonpharmacy claims not categorised as inpatient, emergency department, office or laboratory services.
NA, not assessed.

medication for patients with mild SLE (63.7%), compared with 61.3% and 51.6% for patients with moderate and severe SLE, respectively (p<0.0001 for difference between groups). Corticosteroids were the most frequently prescribed medication for patients with moderate and severe SLE (87.5% and 86.2%, respectively), compared with 45.4% of patients with mild SLE (p<0.0001). Patients with moderate and severe SLE received more prescriptions for immunosuppressants and biologics compared with patients with mild SLE. Methotrexate, mycophenolate mofetil, azathioprine and cyclophosphamide were prescribed to proportionally more patients with moderate and severe disease compared with mild disease (online supplemental table 3). Prescriptions for belimumab were more frequent among patients with severe (1.8%) and moderate SLE (1.9%) compared with mild SLE (0.3%, p<0.03). A total of 5.7% of patients with severe SLE received prescriptions for rituximab, compared with no patients with moderate SLE or mild SLE (p<0.0001) (online supplemental table 3).

All-cause HCRU during the 1-year post-diagnosis (follow-up) period

Overall, 26.4% of patients with SLE had ≥1 inpatient hospitalisation during the 1-year post-diagnosis period, with a mean (SD) length of stay of 2.05 (6.77) days (table 2). The proportion of patients with ≥1 inpatient hospitalisation increased with disease severity: 12.8%, 22.4% and 51.2% for mild, moderate and severe SLE, respectively; as did mean (SD) length of stay, with 0.47 (1.69) days, 1.31 (3.69) days and 5.52 (12.33) days, respectively (p<0.0001) (table 2). Patients with severe and moderate SLE had a higher mean (SD) number of hospitalisations, with 1.04 (1.58) visits and 0.32 (0.73) visits, respectively, compared with 0.16 (0.45) visits for patients with mild SLE (p<0.0001). Overall, 41.3% of patients had ≥1 ED visit; 26.8% of patients with mild, 41.3% with moderate and 57.9% with severe SLE had ≥1 ED visit.

Outpatient services (≥1 visit) were used by >99% of patients, regardless of disease severity. Patients with severe and moderate SLE had a higher mean (SD) number of outpatient visits, 32.36 (27.39) and 20.35 (16.31), respectively, compared with patients with mild SLE, who had 14.78 (14.50) visits (p<0.0001). Office services were used by >99% of patients and laboratory and pharmacy services by >85%, regardless of disease severity.

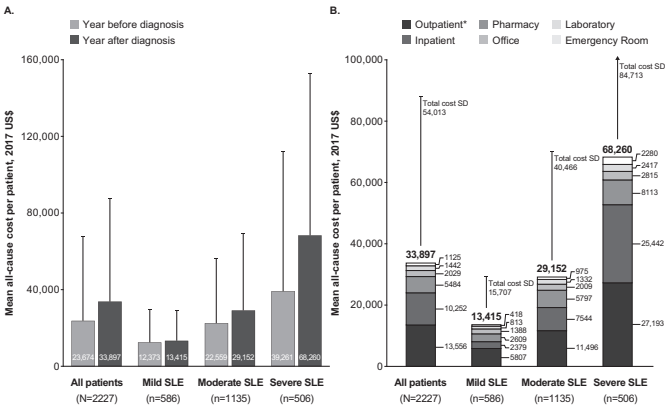

Figure 2 All-cause healthcare costs per patient (A) during the baseline and 1-year post-diagnosis (follow-up) periods for all patients with newly diagnosed SLE and by SLE disease severity and (B) during the 1-year post-diagnosis (follow-up) period for all patients with newly diagnosed SLE, by SLE disease severity and setting. Error bars show SD. A detailed breakdown of costs per care setting is available in online supplementary table 4. *Outpatient services included all nonpharmacy claims not categorised as inpatient, emergency department, office or laboratory services.

All-cause healthcare costs during the 1-year baseline and post-diagnosis (follow-up) periods

The mean (SD) unadjusted all-cause healthcare costs during the baseline period for patients with newly diagnosed SLE were US$23 674 (US$44 113). The mean (SD) all-cause costs increased with increasing disease severity: mild SLE US$12 373 (US$17 171), moderate SLE US$22 559 (US$33 674) and severe SLE $39 261 (US$72 768), p<0.0001 (figure 2A). All-cause healthcare costs were 1.8-fold and 3.2-fold higher for patients with moderate and severe SLE, respectively, compared with mild SLE.

The mean (SD) unadjusted all-cause healthcare costs during the 1-year post-diagnosis period were US$33 897 (US$54 013) for all patients. Healthcare costs increased with increasing SLE severity: US$13 415 ($15 707) for patients with mild SLE, US$29 152 (US$40 466) for moderate SLE and US$68 260 (US$84 712) for severe SLE (p<0.0001) (figure 2A). This represents a 2.2-fold and 5.1-fold higher healthcare cost for patients with moderate and severe SLE, respectively, compared with mild SLE.

When adjusted for baseline demographics, clinical characteristics and all-cause healthcare costs during the baseline period, increasing SLE disease severity remained associated with increasing healthcare costs (table 3). Moderate and severe SLE was associated with significantly higher total costs, compared with mild SLE (moderate SLE cost ratio (95% CI): 1.81 (1.65 to 1.98), p<0.0001; severe SLE cost ratio (95% CI): 4.24 (3.80 to 4.73), p<0.0001). Other factors associated with higher healthcare costs during the post-diagnosis period include the presence of ≥2 CCI comorbidities at baseline, use of ≥3 medications at baseline and higher healthcare costs during the baseline period (table 3).

During the post-diagnosis period, the leading cost driver for all patients was outpatient visits at a mean (SD) cost of US$13 566 (US$32 747), followed by hospitalisations at US$10 252 (US$30 550) (figure 2B online supplementary table 4). Pharmacy services were US$5484 (US$10 446) for all patients. Similar trends were observed in each severity group, with outpatient visits and hospitalisations remaining the leading cost drivers (figure 2B, online supplementary table 4).

DISCUSSION

This study characterised a cohort of US patients with newly diagnosed SLE across the spectrum of disease severity, describing patient demographics and clinical characteristics, medication use and the economic burden of SLE. Our findings show that healthcare costs increase in the year before SLE diagnosis and are associated with SLE severity. A similar trend was apparent in the year after diagnosis, when HCRU and costs were shown to increase with increasing disease severity. To our knowledge, previous studies have not evaluated costs in adult US patients during 1-year periods both before and after diagnosis and analysed costs by disease severity.

SLE diagnosis may require an extended period between first symptom onset and official diagnosis, estimated across two studies as a mean of 21.8 months or median of 26.4 months.[23 29] Multiple physician and specialist visits may be involved,[30] which may be associated with high healthcare costs. Our present findings demonstrate that significant costs are incurred during the year preceding SLE diagnosis, with higher costs among patients who were subsequently diagnosed with more severe disease. Our results follow a similar trend to that reported in a Canadian study that found direct healthcare costs per patient with SLE increased by 97% in the year preceding diagnosis, after rising by 35% annually in the 5 years before diagnosis.[25] The results in McCormick *et al* [25] were not stratified by disease severity; therefore, we do not know whether these costs were driven by patients subsequently diagnosed with severe disease, as was the case in our study, or whether patients with mild disease take longer to be diagnosed and therefore incur the largest costs more than 1 year before diagnosis.

In these analyses, we classified SLE disease severity using a claims-based algorithm,[9] categorising 26.3% of patients as having mild, 51.0% moderate and 22.7% severe SLE over the year after their initial diagnosis. This distribution of SLE severity is consistent with a previous study that developed this algorithm using a different commercial claims dataset[9] and similar to observations in clinical practice.[17 22] Other studies have used a different algorithm or different time period. For example, Clarke *et al* classified SLE severity during the 6-month period after index in a commercially and Medicaid-insured cohort using claims-based data and identified a similar proportion of patients with moderate/severe SLE (commercial: 67.4%; Medicaid: 74.8%) or mild SLE (commercial:

Table 3 Factors associated with total all-cause healthcare costs during the 1-year post-diagnosis (follow-up) period for patients with newly diagnosed SLE: multivariable regression model analysis

Variable*	Cost ratio	Lower 95% CI	Upper 95% CI	P value
SLE disease severity for each patient (ref. mild)				
Moderate SLE	1.81	1.65	1.98	<0.0001
Severe SLE	4.24	3.80	4.73	<0.0001
Age (ref. ≥65 years)				
18–44 years	1.33	0.94	1.89	0.1103
45–64 years	1.36	0.97	1.92	0.0766
Female (ref. male)	0.99	0.87	1.13	0.9266
Race/ethnicity (ref. non-Hispanic white)				
Non-Hispanic black	0.95	0.85	1.07	0.4375
Hispanic	1.10	0.92	1.31	0.3195
Other/unknown	0.99	0.91	1.08	0.8213
Region (ref. Northeast)				
North central	0.92	0.80	1.05	0.2223
South	1.01	0.92	1.12	0.7948
West	1.01	0.87	1.17	0.9129
Unknown	0.64	0.36	1.12	0.1206
Payer type (ref. commercial)				
Medicare	1.18	0.84	1.65	0.3470
CCI (ref. 0)				
1	1.06	0.96	1.16	0.2488
2	1.21	1.08	1.36	0.0010
≥3	1.29	1.14	1.46	<0.0001
No of medications at baseline (ref. 0)				
1	0.96	0.86	1.07	0.4411
2	0.99	0.89	1.11	0.9095
≥3	1.18	1.05	1.33	0.0051
Total all-cause healthcare cost per patient during 1-year baseline period (logged)	1.23	1.21	1.26	<0.0001
Intercept	1160.49	757.71	1777.39	<0.0001

*Generalised linear models with gamma distribution and log transformation.
CCI, Charlson Comorbidity Index; ref., reference.

32.6%; Medicaid: 25.2%) to our study.[13] The consistency of our findings with other independent cohorts and with results seen in clinical practice provide further support for the use of claims-based algorithms in assessing disease severity by proxy in SLE observational studies where clinical measures of disease severity are not available.

Unadjusted all-cause healthcare costs during the year after diagnosis were 2.2-fold higher for patients with severe SLE and 5.1-fold higher for patients with moderate SLE than for mild SLE. After adjusting for baseline demographics and clinical characteristics, CCI and costs during the baseline period, healthcare costs during the first year post-diagnosis were 81% higher for moderate SLE and 324% higher for severe SLE compared with mild SLE. Although there is an increasing body of evidence that severe SLE is associated with higher costs up to 3 years post-diagnosis compared with milder disease,[3 9 11 13–15] the present analysis showed that this association is evident as early as the first year after diagnosis.[25]

The largest cost drivers for all patients were outpatient visits and inpatient hospitalisations, consistent with previous studies.[9 11 13–15 25 31] These cost drivers were the top 2 HCRU categories across all disease severity groups; however, their contribution was greatest for patients with severe SLE. In our study, outpatient visits included injections of SLE-related medications and dialysis, which are costly and may be more frequently associated with severe SLE. Combined outpatient visits and inpatient hospitalisations made up 77% of the total average costs for patients with severe SLE, compared with 65% and 61% for those with moderate and mild SLE, respectively. This result is consistent with the overall study findings and shows that

while the largest cost drivers were observed across disease severity categories, the contribution of the various cost drivers increased with increasing SLE severity in the year after diagnosis.

The present study identified multiple factors, including the presence of ≥2 CCI comorbidities at baseline, the use of ≥3 medications at baseline and higher healthcare costs during the baseline period, that are associated with increased healthcare costs during the year after diagnosis. Previous findings identified association of several of these factors with organ damage progression in patients with SLE.[32–34] CCI comorbidities and hypertension (a non-CCI comorbidity) are associated with increased organ damage risk.[32 33] Long-term and high-dose corticosteroid use is also a risk factor for organ damage.[32–34] Organ damage may increase healthcare costs and, perhaps most importantly, mortality.[32 35–37] When taken together, these factors, which are associated with both SLE cost and organ damage, may serve as proxies for long-term outcomes and mortality.

Strengths of this study include that it was conducted within the IBM MarketScan commercial claims database, a large and comprehensive data source providing a complete and long-term view of the patient journey in real-world settings that was linked to EMR data. This enabled us to explore additional measures, such as race/ethnicity, for a more comprehensive picture of the patient population. Previous studies were limited in this regard by only having access to a single data source.[9 10 16] The present study also analysed healthcare costs in the year before and after diagnosis, which was previously only reported in one Canadian cohort study. Another study strength is the adjusted costs analysis during the year after diagnosis, which accounts for variables in the year before diagnosis, including healthcare costs and comorbidities. This approach allowed us to adequately assess the drivers of SLE healthcare costs.

A limitation is that our study population was largely commercially insured (87.7%). Patients with Medicare supplemental insurance were only 12.3% of the population, and no Medicaid patients were included. However, linking claims and EMR data ensured that we comprehensively captured SLE-related HCRU and costs and that our study cohort was similar to studies that used commercially and Medicare insured study populations.[13 15] Another limitation involves potential misclassification using a claims-based algorithm, both in identifying newly diagnosed patients with SLE and classifying them into appropriate disease severity groups, because HCRU was used to classify SLE severity and to calculate costs. However, the distribution of severity was similar to that observed in clinical practice and we supplemented the claims-based algorithm with EMR data to further reduce any potential misclassification or bias. Finally, indirect costs such as diminished work and non-work productivity, and caregiver burden are not captured in the linked database. Indirect costs may be substantial for patients with SLE. Studies estimate that indirect costs exceed direct costs by up to 2- to 4-fold.[38] Thus, the full economic burden of SLE is likely to be much higher than the direct costs reported in our study.

In conclusion, this retrospective real-world study of US patients with newly diagnosed SLE demonstrates that moderate and severe SLE was associated with higher HCRU and all-cause healthcare costs in the 1-year period after diagnosis compared with mild SLE. Baseline comorbidities and all-cause healthcare costs were also higher among patients with moderate and severe SLE during the year before diagnosis. These findings highlight that early diagnosis, and treatments to achieve disease control, may improve health outcomes and reduce the economic burden of SLE.

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Contributors ERH, BD, XW and MJ conceived and designed the study. AMN acquired the data and designed the study. All authors analysed and interpreted the data. All authors were involved in development, review and final approval of the manuscript.

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Competing interests MJ, BD, XW and ERH are employees of AstraZeneca. AMN is an employee of IQVIA and was paid by AstraZeneca to conduct this research study.

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Data availability statement Data are available upon reasonable request. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. This study is based on de-identified data obtained and analysed by IQVIA under license from IBM MarketScan and GE Healthcare, and so are not publicly available. The interpretation and conclusions contained in this study are those of the authors alone. The authors do not own these data and hence are not permitted to share the data in the original form.

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Supplementary Material:

Disease and Economic Burden Increase With Systemic Lupus Erythematosus Severity 1 Year Before and After Diagnosis: A Real-World Cohort Study, United States, 2004–2015

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Table S1. SLE-Related Medications Required Within 6 Months Before and After the Index Date

Medication class	Code	Medication description
Azathioprine	C9436	Azathioprine, parenteral, brand name, per 100 mg
	J7500	Azathioprine, oral, 50 mg
	J7501	Azathioprine, parenteral, 100 mg
	K0119	Azathioprine - oral, tab, 50 mg
	K0120	Azathioprine - parenteral, 100 mg
Belimumab	J0490	Injection, belimumab, 10 mg
	Q2044	Injection, belimumab, 10 mg
Chloroquine	J0390	Injection, chloroquine hydrochloride, up to 250 mg
Corticosteroids	J0702	Injection, betamethasone acetate 3 mg and betamethasone sodium phosphate 3 mg
	J0704	Injection, betamethasone sodium phosphate, per 4 mg
	J0810	Injection, cortisone, up to 50 mg
	J1020	Injection, methylprednisolone acetate, 20 mg
	J1030	Injection, methylprednisolone acetate, 40 mg
	J1040	Injection, methylprednisolone acetate, 80 mg
	J1094	Injection, dexamethasone acetate, 1 mg
	J1095	Injection, dexamethasone acetate, per 8 mg
	J1100	Injection, dexamethasone sodium phosphate, 1 mg
	J1690	Injection, prednisolone tebutate, up to 20 mg
	J1700	Injection, hydrocortisone acetate, up to 25 mg

	J1710	Injection, hydrocortisone sodium phosphate, up to 50 mg
	J1720	Injection, hydrocortisone sodium succinate, up to 100 mg
	J2640	Injection, prednisolone sodium phosphate, to 20 mg
	J2650	Injection, prednisolone acetate, up to 1 ml
	J2920	Injection, methylprednisolone sodium succinate, up to 40 mg
	J2930	Injection, methylprednisolone sodium succinate, up to 125 mg
	J3300	Injection, triamcinolone acetonide, preservative free, 1 mg
	J3301	Injection, triamcinolone acetonide, not otherwise specified, 10 mg
	J3302	Injection, triamcinolone diacetate, per 5 mg
	J3303	Injection, triamcinolone hexacetonide, per 5 mg
	J7506	Prednisone, oral, per 5mg
	J7509	Methylprednisolone oral, per 4 mg
	J7510	Prednisolone oral, per 5 mg
	J7512	Prednisone, immediate release or delayed release, oral, 1 mg
	J8540	Dexamethasone, oral, 0.25 mg
	S0173	Dexamethasone, oral, 4mg
Cyclophosphamide	C9420	Cyclophosphamide, brand name, 100 mg
	C9421	Cyclophosphamide, lyophilized, brand name, 100 mg

	J8530	Cyclophosphamide; oral, 25 mg
	J9070	Cyclophosphamide, 100 mg
	J9080	Cyclophosphamide, 200 mg
	J9090	Cyclophosphamide, 500 mg
	J9091	Cyclophosphamide, 1.0 gram
	J9092	Cyclophosphamide, 2.0 gram
	J9093	Cyclophosphamide, lyophilized, 100 mg
	J9094	Cyclophosphamide, lyophilized, 200 mg
	J9095	Cyclophosphamide, lyophilized, 500 mg
	J9096	Cyclophosphamide, lyophilized, 1.0 gram
	J9097	Cyclophosphamide, lyophilized, 2.0 gram
Methotrexate	J8610	Methotrexate; oral, 2.5 mg
	J9250	Methotrexate sodium, 5 mg
	J9260	Methotrexate sodium, 50 mg
Mycophenolate mofetil	J7517	Mycophenolate mofetil, oral, 250 mg
	K0412	Mycophenolate mofetil, oral, 250 mg
Rituximab	J9310	Injection, rituximab, 100 mg

Table S2. Claims-Based Algorithm for Defining SLE Disease Severity*

Claims-based algorithm*	EMR adaptation
Mild Disease	
• Did not meet criteria for moderate or severe disease • Patients who died and had less than 1 month (30 days) of enrollment in the time period (follow-up, year 1, or year 2) were classified as having died with short enrollment rather than being assigned an SLE disease severity level	• Did not meet criteria for moderate or severe disease
Moderate Disease	
• Had no filled prescriptions for cyclophosphamide or rituximab or oral corticosteroid with ≥60 mg/day of prednisone equivalent dose and no claims with a diagnosis of a 'severe' condition; AND	
• Met one or both of the following criteria at any time during the follow-up period: o Had ≥1 nonlaboratory claim with a diagnosis of a condition listed as 'moderate', where the	• Had ≥1 EMR record with a diagnosis listed as 'moderate'

diagnosis occurs in any position on the claim; OR ○ Had ≥1 filled prescription for an oral corticosteroid with a prednisone equivalent dose of ≥7.5 mg/day and <60 mg/day or for an immunosuppressive agent (other than cyclophosphamide) • Moderate conditions: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, hepatitis (nonviral), ischemic necrosis of bone, nephritis, renal impairment other than nephritis or end-stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis vasculitis (excluding aortitis)	• Moderate conditions: acute pancreatitis, chorioretinitis, demyelinating syndrome/acute inflammatory demyelinating polyradiculoneuropathy, episcleritis/scleritis, hemolytic anemia, hepatitis (nonviral), ischemic necrosis of bone, nephritis, renal impairment other than nephritis or end-stage renal disease, lupus enteritis/colitis, mononeuropathy/polyneuropathy, myelopathy, myocarditis, pericarditis, pleurisy/pleural effusion, pseudotumor cerebri, seizure, uveitis vasculitis (excluding aortitis)

Severe Disease		
• Had ≥1 filled prescription for cyclophosphamide or rituximab or oral corticosteroid with a prednisone equivalent dose of ≥60 mg/day; OR		
• Had ≥1 nonlaboratory claim with a diagnosis listed as 'severe', where the diagnosis occurs in any position on the claim		• Had ≥1 EMR record with a diagnosis listed as 'severe'
• Severe conditions: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end-stage renal disease, optic neuritis, pulmonary hemorrhage, stroke/transient ischemia attack		• Severe conditions: acute confusional state/psychosis, aortitis, arterial/venous thrombosis, aseptic meningitis, cardiac tamponade, cranial neuropathy, intestinal pseudo-obstruction, end-stage renal disease, optic neuritis, pulmonary hemorrhage, stroke/transient ischemia attack

EMR = electronic medical records, SLE = systemic lupus erythematosus.

*Claim-based algorithm previously published, from Garris C, Jhingran P, Bass D, et al. Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan. *J Med Econ* 2013;16:667-77.

Table S3. Medications Prescribed in the 1-Year Post-Diagnosis (Follow-up) Period for All Patients With Newly Diagnosed SLE and by SLE Disease Severity

		SLE disease severity at index*			
Medication	**All patients (N=2227)**	**Mild (n=586)**	**Moderate (n=1135)**	**Severe (n=506)**	***P*-value**
Corticosteroids, n (%)	1695 (76.1)	266 (45.4)	993 (87.5)	436 (86.2)	<0.0001
Antimalarial drugs, n (%)					
Hydroxychloroquine	1330 (59.7)	373 (63.7)	696 (61.3)	261 (51.6)	<0.0001
Chloroquine	9 (0.4)	4 (0.7)	4 (0.4)	1 (0.2)	0.4545
Immunosuppressants, n (%)					
Methotrexate	327 (14.7)	55 (9.4)	197 (17.4)	75 (14.8)	<0.0001
Mycophenolate mofetil	145 (6.5)	0 (0.0)	84 (7.4)	61 (12.1)	<0.0001
Azathioprine	116 (5.2)	0 (0.0)	81 (7.1)	35 (6.9)	<0.0001
Cyclophosphamide	23 (1.0)	1 (0.2)	2 (0.2)	20 (4.0)	<0.0001
NSAIDs, n (%)	818 (36.7)	190 (32.4)	454 (40.0)	174 (34.4)	0.0039
Biologics, n (%)					
Belimumab	32 (1.4)	2 (0.3)	21 (1.9)	9 (1.8)	0.0342
Rituximab	29 (1.3)	0 (0.0)	0 (0.0)	29 (5.7)	<0.0001

NSAIDs = nonsteroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus.

*Disease severity was assessed during the 1-year period after diagnosis, and patients were classified to the most severe level during that period.

Table S4. All-Cause Health Care Costs per Patient During the 1-Year Post-Diagnosis (Follow-up) Period by Setting of Care for All Patients With Newly Diagnosed SLE and by SLE Disease Severity

		SLE disease severity*			
All-cause cost†	**All patients (N=2227)**	**Mild (n=586)**	**Moderate (n=1135)**	**Severe (n=506)**	***P*-value**
Total cost, mean (SD)	$33,897 ($54,013)	$13,415 ($15,707)	$29,152 ($40,466)	$68,260 ($84,713)	<0.0001
By setting, mean (SD)					
Inpatient	$10,252 ($30,550)	$2379 ($8278)	$7544 ($25,719)	$25,442 ($47,217)	<0.0001
Emergency department	$1125 ($4237)	$418 ($1320)	$975 ($4236)	$2280 ($5903)	<0.0001
Outpatient‡	$13,566 ($32,747)	$5807 ($9382)	$11,496 ($21,757)	$27,193 ($57,414)	<0.0001
Office	$2029 ($1483)	$1388 ($876)	$2009 ($1378)	$2815 ($1854)	<0.0001
Laboratory	$1442 ($2636)	$813 ($1287)	$1332 ($2151)	$2417 ($4108)	<0.0001
Pharmacy	$5484 ($10,446)	$2609 ($4371)	$5797 ($9590)	$8113 ($15,351)	<0.0001

SD, standard deviation; SLE, systemic lupus erythematosus.

*Disease severity was assessed during the 1-year period after diagnosis, and patients were classified to the most severe level during that period.

†2017 US dollars.

‡Outpatient services included all nonpharmacy claims not categorized as inpatient, emergency department, office, or laboratory services.