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Lupus Low Disease Activity State is Associated with Reduced Direct Healthcare Costs in Patients with Systemic Lupus Erythematosus

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COMPETING INTERESTS

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ABSTRACT (250 words)

Objective:

Treat to target endpoints for Systemic Lupus Erythematosus (SLE) have been assessed for impact on damage accrual and flare, but whether they impact on the high healthcare utilization and costs

in SLE has not been studied. We hypothesized that the recently described lupus low disease activity state (LLDAS) would be associated with reduced healthcare cost.

Methods:

Data from a single tertiary hospital longitudinal SLE cohort were assessed. Baseline demographics, disease activity (SLE Disease Activity Index (SLEDAI)-2K; physician global assessment, PGA; and, flare index) and medication use were evaluated, and direct healthcare utilization and cost data were obtained from hospital information systems. LLDAS was defined as previously published: briefly, SLEDAI-2K ≤ 4 with no new activity, PGA ≤ 1, prednisolone ≤7.5mg/day, and optimal standard immunosuppressive agents. Analysis was performed using multivariable linear regression.

Results:

Two hundred SLE patients, contributing 357.8 person-years observation, were included. A history of lupus nephritis was present in 42%, and damage (SLICC-ACR damage index >0) was present at study commencement in 57.3%. The mean (±standard deviation) annual direct medical cost per patient was US$7,413 (±US$13,133)/year. In multivariable analysis, increased cost was associated with the presence of baseline organ damage (41.7% increase, *P*=0.009), and corticosteroid use (>7.5-15 mg/day, 55.7% increase, *P*=0.02; > 15 mg/day, 202% increase, *P*<0.001). In contrast, spending ≥50% of the observation period in LLDAS was associated with a 25.9% reduction in annual direct medical cost (p=0.04).

Conclusion:

Greater time spent in LLDAS was associated with significantly reduced direct hospital healthcare costs among patients with SLE.

KEYWORDS

Systemic Lupus Erythematosus, Lupus Low Disease Activity State, Direct Medical Cost

Significance and Innovations

- Achieving Lupus Low Disease Activity State (LLDAS) ≥50% of the time is associated with reduced healthcare costs
- These insights demonstrate that targeting a low disease activity state provides benefits to patient care as well as outcomes and better healthcare utilization

The need for treat to target (T2T) approaches to systemic lupus erythematosus (SLE), based on validated T2T endpoints, has recently been highlighted (1). In response to this need, a Lupus Low Disease Activity State (LLDAS) definition has been proposed (2), and its attainment has been shown to be associated with protection from damage accrual and improved health-related quality of life (HRQoL) (2-4). Adoption of T2T endpoints requires evidence of cost benefit as well as improved health outcomes, but no data on the impact of T2T endpoint attainment on healthcare utilization and cost have been reported. Direct healthcare costs reported for SLE vary depending on clinical characteristics (5), leading to a hypothesis that a low disease activity state could be associated with lower costs. For example, renal disease, recent disease flare and severe disease activity are associated with up to six-fold increase in costs compared to patients with mild disease and no recent flares (6, 7). The primary objective of this study was to evaluate the association of LLDAS attainment with healthcare utilization and direct cost.

PATIENTS AND METHODS

Study design, setting and participants

This study was conducted using data collected at Monash Health, a public, tertiary hospital in Melbourne, Australia, on patients enrolled in the Asia Pacific Lupus Collaboration , a multi-national prospective cohort (8). Adult patients who fulfilled the American College of Rheumatology (ACR) (9) or the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE (10), and had at least two visits to the Monash Lupus Clinic during the period October 2013 to June 2016, were included. Ethics approval for this study was obtained from the Monash Health Human Research Ethics Committee.

Data collected

At the baseline visit, patient age, gender, and ethnicity were recorded. Disease-related information was obtained at baseline and each subsequent visit. Data collected included disease activity measured using the SLE Disease Activity Index (SLEDAI)-2K, Physician Global Assessment (PGA; on a 3 cm visual analogue scale where 0=no disease activity, 3=maximum disease activity), and the Safety of Estrogens in Lupus Erythematosus National Assessment

(SELENA)-SLEDAI Flare Index (SFI), as described (8), as well as immunomodulatory and other medication use, and routine clinical laboratory data. Irreversible organ damage was evaluated annually using the SLICC/ACR Damage Index (SDI) as described (8). Time adjusted mean SLEDAI (AMS) was calculated as a measure of overall disease activity across time (11). LLDAS was defined as described previously (2). In brief, if a patient met all five criteria, s/he was categorized as being in LLDAS at the time of the study visit: 1. SLEDAI-2K ≤4, with no disease activity in major organ systems (renal; central nervous system, CNS; cardiopulmonary; vasculitis; and fever) and no hemolytic anemia or gastrointestinal activity; 2. No new features of lupus disease activity compared to the previous assessment; 3. PGA ≤1 (0-3); 4. Current prednisolone (or equivalent) dose ≤ 7.5 mg daily; and 5. Well-tolerated standard maintenance doses of immunosuppressive drugs and/or approved biologic agents. For the first visit, new disease activity was assessed using SFI; where the patient did not have a prior visit before study commencement, the new disease activity criterion was omitted. Patients were deemed to be in LLDAS from the date of their clinic visit until the day prior to their next review. The differentiating point for outcome measurement chosen was ≥50% observed time in LLDAS (2).
Data on healthcare utilization were obtained from hospital clinical information systems. Healthcare utilization assessed included hospitalizations, emergency department presentations, specialist visits and investigations. Prescription medication use was obtained from the medical record. Costing data was captured for all inpatient and outpatient resources the patient consumed at Monash Health, and for all prescription medications, regardless of where the prescription was filled. Total direct medical costs were calculated for each patient using actual costs assigned for hospitalizations, emergency department presentations, specialist visits and medical investigations by Monash Health clinical costing. Prescription medication costs were based on the cost under the Australian Pharmaceutical Benefits Scheme (12). For hospitalizations and emergency department presentations, all in-scope healthcare utilization activities and services delivered as part of each presentation were assigned to that presentation. Otherwise, costs were assigned in respect of healthcare utilization in the ambulatory care setting. Geographic distance of patients' home address from the hospital was determined using Google Maps and the patient's residential postcode, and was categorized into a binary variable based on the 75th centile (35 km). Socioeconomic status was based on the Australian Bureau of Statistics' Index of Relative Socio-economic Disadvantage (IRSD) (13) and assigned using the patient's residential postcode.
All costs were calculated in 2016 Australian Dollars (AU$) and converted to 2016 United States Dollars (US$) using the Organization for Economic Co-operation and Development (OECD) 2016 purchasing power parity conversion rate used in Gross Domestic Product calculations (a

conversion rate of 1 AU$ = 0.690826242 US$). To calculate the annual direct medical cost for each patient, the total healthcare utilization cost for each patient was divided by that patient's observation period in years. The observation period was calculated from the date of the patient's first study visit until their last contact with Monash Health.

Statistical methods

All statistical analyses were performed using Stata version 14 (StataCorp, College Station, Texas, USA). Descriptive statistics were used to summarize patient characteristics, healthcare utilization, and the estimated annual direct medical cost. Bivariate testing was carried out using techniques appropriate for variable type and distribution (e.g., χ^2 test, Fishers exact test, Wilcoxon rank sum test, univariable linear regression models). Multivariable analysis of the association of LLDAS with annual direct medical cost was carried out using multivariable linear regression. Summary measures were calculated so that the analysis could be conducted at a per patient level, with each patient contributing a single observation over the follow-up period. Annual direct healthcare costs were found to be skewed, and were therefore $\log_{10}$-transformed for regression analyses. A smearing factor, as discussed by Glick *et al*., (14) was used to estimate the arithmetic mean following back-transformation. For multivariable models, the likelihood ratio test was used to determine the appropriate transformation of continuous exposure variables, and correlation coefficients were calculated to assess potential collinearity between variables included in the models. Since there was a low level of missing data (<5%), missing data were excluded from the analysis, with the exception of missing pathology data required for SLEDAI-2K scoring (missing for 12.9% of assessments), in which case the last observation was carried forward to replace missing data, resulting in data completeness of 95.7% for SLEDAI-2K scoring. A p value ≤ 0.05 was set as the threshold for statistical significance.

RESULTS

Cohort characteristics

Two hundred patients with SLE met the eligibility criteria and were included in the study. Patients were followed for a median observation time of 2.1 years, resulting in total observation of 357.8 person-years. Most patients (81.5%) were followed for at least one year. At study enrolment, patients' median age was 42 years, 88.0% were female and 39.5% were of Asian ethnicity (Table 1). The median time since diagnosis was 7.0 years. Positive anti-nuclear antibody tests were documented in 99.5%, and 70.0% of patients were positive for anti-dsDNA

autoantibodies. Organ damage (SDI > 0) was present at study commencement in 55.0% of patients. Just over 75% of included patients resided within 35 kilometers of the hospital.

In this cohort overall, 51.0% of patients spent ≥50% of the observation period in LLDAS (Supplementary Table 1). However, 47.5% of patients had active disease over the observation period (AMS > 4), 64.5% experienced at least one mild/moderate flare, two-thirds (67.5%) had at least one SLEDAI-2k ≥6, one third (29.5%) at least one SLEDAI-2k ≥10, and 16.0% of patients accrued organ damage over the observation period (Supplementary Table 1). Achieving LLDAS for ≥50% of the observation period was less common amongst participants with higher disease activity (AMS >4: 21.1%, AMS ≥6: 2.6%, SLEDAI-2K ever ≥6: 34.1%, SLEDAI-2K ever ≥10: 15.3%).

Healthcare utilization

Over the study period, patients attended a median of 6.1 (IQR 4.3 – 10.0) specialist visits per year, 5.0 (3.6 – 6.3) of which were visits to the Lupus Clinic (Supplementary Table 1). Other specialists seen most commonly included obstetrician/gynecologists, ophthalmologists and dermatologists (19.0%, 11.8% and 11.0%, respectively). Patients had a median of 5.2 episodes per year of medical investigations. Most patients (88.5%) were prescribed hydroxychloroquine and just over two-thirds (68.5%) were prescribed prednisolone during the observation period. A lower proportion of patients were prescribed other immunomodulatory medications (Supplementary Table 1). In addition to immunomodulatory medications, patients were prescribed a median of 3.0 (IQR 2.0 – 4.0) other medications. Close to a third of patients (31.5%) presented to the emergency department at least once during the observation period. Over one third of patients were hospitalized for a day procedure (35.5%). 28.5% of patients had at least one multi-day hospital admission, with a median length of stay of 4 days (IQR 2 – 55 days) (Supplementary Table 1).

Healthcare costs

Direct hospital healthcare utilization over the observation period resulted in a median (IQR) annual direct medical cost per patient of US$3,453 (US$1,978 – 7,264) and mean (SD) annual direct medical cost of US$7,413 (US$13,133). Annual direct medical costs were positively skewed, with the maximum annual direct medical cost observed being US$109,623. Further details of the annual direct medical cost, including a breakdown by time in LLDAS, are included in Supplementary Table 2.

We next investigated the patient characteristics associated with annual direct medical cost. Among the disease characteristics considered, measures of higher disease activity (AMS >4 or ≥6, or maximum SLEDAI-2K score ≥6 or ≥10) were each associated with increased annual direct medical cost (Table 2). Musculoskeletal or renal disease activity were also associated with increased annual direct medical cost, as was disease flare or organ damage present at study enrolment (Table 2). In terms of treatment-related variables, doses of prednisolone >7.5 mg/day, and use of immunosuppressive or biological agents, were also associated with increased annual direct medical cost (Table 2). Geographic distance from the hospital was found to be significant; residing >35 km from the hospital was associated with a 32.4% decrease in the estimated annual direct medical cost, potentially due to utilization of medical services closer to the patients' residence. Consistent with this hypothesis, patients residing >35 km from the hospital had a significantly lower annual number of specialist visits, medical investigations, hospitalizations and emergency department presentations compared to patients residing closer to the hospital (Supplementary Table 3). Other than a difference in the proportion of time spent in LLDAS, disease- and treatment-related variables did not differ according to distance (Supplementary Table 3).

Among the clinical outcomes evaluated, LLDAS was the only outcome associated with a reduction in annual direct medical cost. Spending ≥50% of the observation period in LLDAS was associated with a 47.0% reduction in cost in univariable analysis, representing an annual decrease of US$4,681; $P<0.001$ (Table 2). We next determined if LLDAS was associated with a reduction in annual direct medical cost after adjusting for other factors. Since LLDAS is a composite definition incorporating aspects of disease activity and treatment, to identify the association of LLDAS with annual direct medical cost, it was important to account for collinearity when constructing the multivariable models. As a result, some of the variables included in Table 2 were not included alongside LLDAS in multivariable modelling. After adjusting for geographic distance, prednisolone dose and baseline organ damage, we determined that spending ≥50% of the observation period in LLDAS was associated with a 25.9% reduction in annual direct medical cost (annual decrease US$1,604; $P = 0.040$) (Table 3). In contrast, significantly increased costs were associated with the presence of baseline organ damage (41.7% increase, $P=0.009$), and corticosteroid use (>7.5-15 mg/day, 55.7% increase, $P=0.02$; > 15 mg/day, 202% increase, $P<0.001$) (Table 3).

DISCUSSION

In this study, we sought to identify whether the recently identified T2T endpoint, LLDAS, was associated with reductions in healthcare utilization and cost. Using prospectively collected clinical data and actual hospital cost data, we estimated a mean annual direct medical hospital cost of US$7,413 per patient per year. We demonstrated that LLDAS, specifically spending ≥50% of the observation period in LLDAS, was associated with reduced direct healthcare costs, while baseline damage and glucocorticoid use were associated with increased costs. LLDAS has now been shown in multiple independent studies to be associated with protection from damage accrual (2, 4), with a remarkably consistent reduction in damage accrual of approximately 50% reported in association with spending ≥50% of a given period in LLDAS. LLDAS has also been shown to be associated with improved health-related quality of life (3). Here, after multivariable analysis, we observed that spending ≥50% of the observation period in LLDAS was associated with a 25.9% reduction in annual direct medical costs. This suggests that using LLDAS as a treatment target in SLE may be associated with reduced healthcare costs that could potentially offset the cost of treatments used to reach this state.

We identified several factors that were associated with increased annual cost of SLE, including renal involvement and the presence of baseline organ damage. Notably, even after adjusting for time spent in LLDAS, baseline organ damage and geographic distance from the hospital, high dose prednisolone (>15mg/day) remained associated with a significant increase in annual direct cost of 202.3%. This potentially reflects the fact that patients on higher prednisolone doses generally have greater disease activity, as well as treatment-related complications requiring further healthcare utilization.

This is the first study of its kind undertaken in Australia, but the annual direct medical costs among SLE patients were consistent with recent studies conducted in Europe (6). Cost-of-illness studies performed in the USA have consistently reported higher annual direct medical cost of SLE , likely related to the higher price of health services in the USA compared to other countries (15).

This study has some limitations. It was conducted using data from a relatively short period of observation (<3 years) and based on a cross-sectional analysis of summary measures. Medication data were sourced from medical records rather than a centralized prescribing system and could not account for whether prescriptions were filled. We were unable to estimate healthcare

utilization external to our hospital network, which may include other hospitals, non-hospital specialist encounters, and primary care. Reduced healthcare utilization documented in patients residing more distant from the hospital are consistent with variation in capture of in-hospital healthcare utilization, prompting us to adjust for this. Furthermore, the scope of this study was limited to analysis of direct medical costs, and by studying care in a tertiary center, our findings may under-represent patients with less severe SLE. Notwithstanding these caveats, the use of prospectively acquired clinical and healthcare utilization and actual cost data are strengths of the current study.

In conclusion, while baseline organ damage and glucocorticoid use were associated with increased direct healthcare utilization and cost in SLE, LLDAS was associated with significantly reduced direct healthcare utilization and cost. While future research could be directed at broader cost estimations and assessment of patterns of LLDAS attainment, these findings provide additional support for the utility of LLDAS as a T2T endpoint in SLE.

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REFERENCES

1. van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, Lerstrom K, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis. 2014;73(6):958-67.

2. Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis. 2016;75(9):1615-21.

3. Golder V, Kandane-Rathnayake R, Hoi AY, Huq M, Louthrenoo W, An Y, et al. Association of the lupus low disease activity state (LLDAS) with health-related quality of life in a multinational prospective study. Arthritis Res Ther. 2017;19(1):62.

4. Petri M, Magder LS. Comparison of Remission and Lupus Low Disease Activity State in Damage Prevention in a United States Systemic Lupus Erythematosus Cohort. Arthritis Rheumatol. 2018.

5. Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. Nat Rev Rheumatol. 2016;12(10):605-20.

6. Doria A, Amoura Z, Cervera R, Khamastha MA, Schneider M, Richter J, et al. Annual direct medical cost of active systemic lupus erythematosus in five European countries. Ann Rheum Dis. 2014;73(1):154-60.

7. Zhu TY, Tam LS, Lee VW, Lee KK, Li EK. The impact of flare on disease costs of patients with systemic lupus erythematosus. Arthritis Rheum. 2009;61(9):1159-67.

8. Golder V, Kandane-Rathnayake R, Hoi AY, Huq M, Louthrenoo W, An Y, et al. Frequency and predictors of the lupus low disease activity state in a multi-national and multi-ethnic cohort. Arthritis Res Ther. 2016;18(1):260.

9. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.

10. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.

11. Ibanez D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol. 2003;30(9):1977-82.

12. Buckley L, Guyatt G, Fink H, McAlindon T. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Care Res (Hoboken). 2017.

13. 'Australian Bureau of Statistics'. Socio-Economic Indexes for Areas (SEIFA) 2011. Canberra: Australian Bureau of Statistics'; 2013.

14. Glick HA, J.A. Doshi, S.S. Sonnad, et al. Economic Evaluation in Clinical Trials. Handbooks in Health Economic Evaluation Series: New York: Oxford University Press; 2007.

15. Gironimi G, Clarke AE, Hamilton VH, Danoff DS, Bloch DA, Fries JF, et al. Why health care costs more in the US: comparing health care expenditures between systemic lupus erythematosus patients in Stanford and Montreal. Arthritis Rheum. 1996;39(6):979-87.

Table 1 - Baseline Demographic and Clinical Characteristics

Baseline Parameter		**Descriptive Statistics (n = 200)** *Number (%) for categorical variables* *Median (IQR) for continuous variables*
Sociodemographic Characteristics		
Age at study commencement (years)		42 (31 - 51)
Female Sex		176 (88.0)
Ethnicity		
	Caucasian	104 (52.0)
	Asian	79 (39.5)
	Other	17 (8.5)
Geographic Distance from Monash Lupus Clinic >35 km		49 (24.5)
Area-level socioeconomic disadvantage (IRSD decile)		6.5 (3 - 9)
SLE Disease Characteristics		
Age at diagnosis		
	<18 years	25 (12.5)
	18 – 45 years	139 (69.5)
	>45 years	36 (18.0)
Time since diagnosis at study commencement (years)		7.0 (3.4 – 15.1)
ACR classification criteria met at study commencement		
	Number of criteria met at enrolment[†]	6 (5 - 7)
***Specific criteria met*:**		
	Anti-nuclear antibody	199 (99.5)
	Immunological disorders	171 (85.5)
	Non-erosive Arthritis	150 (75.0)
	Hematologic disorder	147 (73.5)
	Malar rash	110 (55.0)
	Photosensitivity	85 (42.5)

	Renal disorder	85 (42.5)
	Serositis	81 (40.5)
	Oral ulcers	74 (37.0)
	Discoid rash	32 (16.0)
	Neurologic disorder	18 (9.0)
Autoantibodies present		
	Anti-dsDNA	140 (70.0)
	Anti-Sm	32 (16.0)
Organ damage present at study commencement		
	SDI score	1 (0 – 2)
	Any damage present	110 (55.0)

IQR = Interquartile range, SDI: SLICC-ACR Damage Index

† Where <4 ACR criteria were met at enrolment, patients met the SLICC SLE Classification Criteria only (3.5% of patients).

Table 2 - Factors Associated with Annual Direct Medical Cost

Parameter	Univariable Association with Per Patient Annual Direct Medical Cost[#]			
	Ratio of Geometric Means	**P Value for Association**	**Estimated Increment/ Decrement in Annual Direct Cost (%)**	**Estimated Increment/ Decrement in Annual Direct Cost (US$)**
Sociodemographic Characteristics				
Age at study commencement (years)	1.0	0.846	-0.1	-7
Male Sex	1.04	0.853	4.1	303
Asian Ethnicity	0.90	0.469	-9.9	-757
Geographic Distance from Monash Lupus Clinic >35 km	0.68	0.017	-32.4	-2605
Area-level socioeconomic disadvantage (IRSD decile)	0.99	0.936	-0.2	-13
SLE Disease Characteristics				
Time since diagnosis at baseline (years)	1.0	0.298	0.8	57
Disease activity				
Overall disease activity				
AMS >4	1.31	0.055	31.1	2040
AMS ≥6	1.96	<0.001	96.4	6311
SLEDAI-2K ever ≥6	1.52	0.005	51.6	2820
SLEDAI-2K ever ≥10	1.89	<0.001	89.1	5203
≥50% time spent in LLDAS	0.53	<0.001	-47.0	-4681
Organ system activity[†]:				
Immunological	1.22	0.328	21.7	1351
Mucocutaneous	1.11	0.464	10.9	763
Musculoskeletal	1.57	0.010	57.2	3814
Renal	1.62	0.001	62.5	3450

Hematological	1.16	0.402	15.5	1110
Flares				
Number of mild/moderate flares	1.20	0.003	19.6	1230
Number of severe flares	1.20	0.001	19.7	1337
Treatment				
Annual prednisolone dose (time-adjusted mean)				
Low dose (≤7.5 mg/day)	1.0	NA	NA	
Moderate dose (>7.5 - 15 mg/day)	1.86	<0.001	86.4	5138
High dose (>15 mg/day)	3.84	<0.001	284.3	16908
Treated with hydroxychloroquine	1.20	0.405	20.3	1269
Treated with immunosuppressants[¥]	1.71	<0.001	70.7	3657
Treated with a biological therapy[*]	3.26	<0.001	226	14608
Damage				
Organ damage present at baseline	1.69	<0.001	68.7	3648

[#] Total annual healthcare cost in US$ for each patient was $\log_{10}$-transformed for analysis. The exponentiated regression coefficient represents the relative change in the geometric mean cost of treating SLE compared to the reference group. Percentage (%) increment/decrement represents the percentage change in the geometric mean compared to the reference group. Increment/decrement in US$ was calculated by multiplying the exponentiated constant term for the reference group by the estimated % increment/decrement and then applying a smearing factor to provide an estimate of the absolute change in the arithmetic mean annual healthcare cost in US$. Where the reference category for a parameter is not specified, this is the absence of the parameter (e.g., patients without baseline organ damage in the case of the organ damage parameter). NA = Not applicable.

[†] Limited to organ system disease activity experienced by at least 30 patients.

[¥] Includes any treatment with methotrexate, azathioprine, leflunomide, cyclophosphamide or mycophenolate over the observation period

[*] Includes any treatment with rituximab, belimumab or abatacept over the observation period.

Table 3 – Adjusted Association of LLDAS with Annual Direct Medical Cost (n = 192)

Parameter	Multivariable Association with Per Patient Annual Direct Medical Cost[#, ^]			
	Ratio of Geometric Means	**P Value for Association**	**Estimated Increment/ Decrement in Annual Direct Cost (%)**	**Estimated Increment/ Decrement in Annual Direct Cost (USD)**
SLE Disease Characteristics				
≥50% time spent in LLDAS	0.74	0.040	-25.9	-1604
Treatment				
Annual prednisolone dose				
Low dose (≤7.5 mg/day)	1.0	NA	NA	
Moderate dose (>7.5 – 15mg/day)	1.56	0.020	55.7	3449
High dose (>15 mg/day)	3.0	<0.001	202.3	12520
Damage				
Organ damage present at baseline	1.42	0.009	41.7	2577
Sociodemographic Characteristics				
Geographic Distance from Monash Lupus Clinic >35 km	0.74	0.045	-26.1	-1612

[#] Total annual direct medical cost in US$ for each patient was $\log_{10}$-transformed for analysis. The exponentiated regression coefficient represents the relative change in the geometric mean cost of treating SLE compared to the reference group. Percentage (%) increment/decrement represents the percentage change in the geometric mean compared to the reference group and was calculated as ((exp(coefficient)-1)x100) using a base of 10. Increment/decrement in US$ was calculated by multiplying the exponentiated constant term for the group of patients in the reference group for all parameters by the estimated % increment/decrement and then applying a smearing factor of 1.75 to provide an estimate of the absolute change in the arithmetic mean annual healthcare cost in US$. Where the reference category for a parameter is not specified, this is the absence of the parameter (e.g., patients without baseline organ damage in the case of the organ damage parameter). NA = Not applicable. The full set of variables that were added to the model are included in the table above.

^ In a separate model including the same covariates and outcome variable, we fitted an interaction term between time spent in LLDAS and geographic distance from the Monash Lupus Clinic to assess if there was an evidence to suggest that geographic distance was an effect modifier of the association of LLDAS and cost (data not shown). We did not find any evidence to support geographic distance being an effect modifier of the association of LLDAS with cost ($p = 0.314$).