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Running Head: Economic Evaluation of Lupus Damage in an International Inception Cohort

Title: Economic evaluation of damage accrual in an international SLE inception cohort using a multi-state model approach

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Dr. Clarke holds The Arthritis Society Chair in Rheumatic Diseases at the University of Calgary.

Abstract

Objectives:

There is a paucity of data regarding healthcare costs associated with damage accrual in systemic lupus erythematosus (SLE). We describe costs associated with damage states across the disease course using multi-state modeling.

Methods:

Patients from 33 centres in 11 countries were enrolled in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort within 15 months of diagnosis. Annual data on demographics, disease activity, damage (SLICC/American College of Rheumatology (ACR) Damage Index [SDI]), hospitalizations, medications, dialysis, and selected procedures were collected. Ten-year cumulative costs (Canadian dollars) were estimated by multiplying annual costs associated with each SDI state by the expected state duration using a multi-state model.

Results:

1687 patients participated, 88.7% female, 49.0% of Caucasian race/ethnicity, mean age at diagnosis 34.6 years (SD 13.3), and mean follow up 8.9 years (range 0.6-18.5). Annual costs were higher in those with higher SDIs (SDI ≥ 5: $22 006 2019 CDN, 95% CI $16 662, $27 350 versus SDI=0: $1833, 95% CI $1134, $2532). Similarly, 10-year cumulative costs were higher in those with higher SDIs at the beginning of the 10-year interval (SDI ≥ 5: $189 073, 95% CI $142 318, $235 827 versus SDI=0: $21 713, 95% CI $13 639, $29 788).

Conclusion:

Patients with the highest SDIs incur 10-year cumulative costs that are almost 9-fold higher than those with the lowest SDIs. By estimating the damage trajectory and incorporating annual costs, damage can be used to estimate future costs, critical knowledge for evaluating the cost-effectiveness of novel therapies.

Significance and Innovation

- We provide estimates of annual, five and 10-year cumulative direct costs for SLE patients in an international inception cohort based on their current damage state.
- Patients with high SDIs have 10-year cumulative costs almost 9-fold higher those with no damage (SDI ≥ 5: $189 073, 95% CI $142 318, $235 827 versus SDI=0: $21 713, 95% CI $13 639, $29 788).

Introduction

Organ damage, measured with the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) (1, 2) is an important outcome in systemic lupus erythematosus (SLE), predictive of morbidity and mortality (3-8). Once present, damage is considered permanent. Damage scores increase in an almost linear fashion in the first 10 years of the disease (9). The mean rate of damage accrual was 0.13 SDI units annually in over 2000 patients in the Hopkins' Lupus Cohort (10). An increased rate of damage accrual occurred in patients who were male, older, hypertensive, of African-American race/ethnicity, of lower income or education, and in those with proteinuria or with a positive lupus anticoagulant (10). The Lupus in minorities: nature versus nurture (LUMINA) cohort demonstrated that Hispanics also have more rapid damage accrual and that older age, increased disease activity, corticosteroid use, abnormal illness behavior, and number of fulfilled ACR criteria were damage predictors (11). The SLICC inception cohort enrolled patients between 1999 and 2011 to study long-term clinical outcomes and demonstrated many similar findings to the Hopkins' and LUMINA cohorts; they reported that male sex, older age, hypertension, African-American and Caucasian-American race/ethnicity, increased disease activity, corticosteroid use, and baseline damage

were associated with damage accrual, while protective factors included antimalarial use (7). An Italian cohort of over 500 patients identified disease duration and increased disease activity to be significantly associated with future organ damage (12). Another cohort study of 260 patients in China found that older age and previous organ damage were predictors of further organ damage (8). In addition to the SLICC and LUMINA cohorts, other research has found that corticosteroid use is a major factor in damage accrual, particularly for certain items within the SDI and for damage later in the disease (13). The Hopkins' Lupus Cohort reported that use of ≥ 7.5 mg of prednisone per day substantially increased the risk of cataracts (hazard ratio (HR) 2.41, $p<0.001$), osteoporotic fractures (HR 2.16, $p<0.001$), and cardiovascular damage (HR 1.54, $p=0.041$) (14).

Increased damage is strongly related to mortality. A 2018 systematic review identified seven studies, which demonstrated a significant association between increased baseline SDI or worsening SDI over time and death (pooled HR 1.44, 95% confidence interval (CI) 1.29, 1.61) (6). Damage on the renal subscale of the SDI one year post-diagnosis was a predictor of death within 10 years in a Pakistani cohort (15). Damage on the renal subscale was also associated with a shorter time to death in the LUMINA cohort (HR 1.65, 95% CI 1.03, 2.66) (16). Hence, mitigation of damage is a major therapeutic goal.

Given the irreversibility of damage, with hastened accrual in those of certain race/ethnicity and with higher disease activity and corticosteroid use, and its association with mortality, it is to be expected that damage is an important predictor of long-term healthcare costs (17-20). Although a few studies examine the association between damage and costs, the economic impact of damage has never been assessed in a multi-ethnic, international inception cohort such as the SLICC cohort. Previous research on this cohort used multi-state Markov modeling to estimate progression in damage states, and to determine predictors of damage accrual (7). In this study, we used these inter-state transition probabilities to estimate the expected duration in each SDI state, and the annual direct costs for each state were calculated. Five and 10-year cumulative costs were then estimated by multiplying the annual

costs associated with each damage state with the expected duration in that state, allowing for prediction of long-term costs for damage states for which there are few observations.

Patients and Methods

Inception cohort

The SLICC network is currently comprised of members from 43 academic centers in 16 countries across North America, South America, Asia, Europe, and Australia (21). Between 1999 and 2011, members of this network from 33 centres in 11 countries enrolled patients who fulfilled the ACR revised classification criteria for SLE (22) into an inception cohort within 15 months of their diagnosis; these patients were followed longitudinally. For this study, data collection continued until September 2018. Each patient provided informed consent and research ethics boards at each site approved the study.

At enrolment, data were collected on age, sex, and race/ethnicity, and at enrolment and annually (plus/minus 6 months) on post-secondary education, disease activity (SLE Disease Activity Index-2000 [SLEDAI-2K]) (23), organ damage (SDI) (1), and comorbidities, including smoking, alcohol consumption (with high-risk consumption defined as >10 units per week for women and 15 units per week for men) (24), diabetes, and hypertension (exceeding 140 systolic and 90 diastolic and/or use of antihypertensives). At enrolment and annually, data were also collected on hospitalizations and medications (corticosteroids, antimalarials, immunosuppressives [including azathioprine, cyclophosphamide, methotrexate, cyclosporine, and mycophenolate], biologics, antihypertensives, lipid-lowering agents, antiepileptics, anti-psychotics and other psychoactive drugs, anticoagulants, and antiplatelets) in the year preceding each visit. The cohort was initially designed to assess cardiovascular and neuropsychiatric outcomes and later, renal outcomes. Therefore, data on diagnostic/therapeutic procedures was limited to cardiac investigations/procedures, neuroimaging, dialysis, and renal biopsies.

SLICC/ACR DI (SDI)

Organ damage was assessed using SDI scoring, which considers end-organ damage across 12 domains including ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, premature gonadal failure, diabetes and malignancy (1). This is the only physician-completed validated instrument to measure damage in SLE. Damage does not have to be attributable to SLE per se and can also be secondary to therapies or comorbidities. It must develop after the diagnosis of SLE, and exist for at least six months to be scored (unless otherwise stated).

Statistical Analysis

Multistate Modelling

At each assessment, the SDI was calculated and patients were assigned to one of six damage states in a Markov model (Figure 1). Few transitions occurred between SDI states 5-11, and therefore these states were merged into one, SDI ≥ 5 (7). States can only transition to higher states, as once end-organ damage has occurred it is considered irreversible. Direct transition from one state to a non-adjacent state was not permitted in continuous time although transitions between non-adjacent states could be observed between assessments with the transition assumed to occur through a series of adjacent transitions. The estimation accounts for intermittent observations and the model for correlation between observations within the same patient by assuming that damage evolution depends only on current damage and not on previous history. Transition rates were estimated through maximum likelihood estimation. Further multi-state modeling details are available in (7).

Calculating annual costs

Annual costs were calculated based on health resource utilization over the preceding year, which was collected at each annual follow up visit, and stratified by SDI. A patient could contribute several annual cost observations per a single SDI level if their SDI did not change between annual visits. Conversely, if the SDI changed between annual visits, the patient would contribute cost observations to more than one SDI level. Cost data was only collected

at the annual follow up visits prior to death and not collected over the interval between the last follow up visit and the time of death. As we did not collect costs associated with death or the year prior to death, our cost estimates do not represent costs incurred in the year prior to death and our predictions are only applicable to individuals who would survive the entire predicted period.

Healthcare costs were calculated by multiplying each health resource by its corresponding 2019 Canadian unit cost. As the objective of this research was to compare healthcare costs across different levels of damage rather than to provide country-specific estimates of costs, healthcare prices essentially served as a set of weights to aggregate resources into a single cost measure. This is independent of how different healthcare systems affect costs. We have chosen Canadian prices as they have the advantage of being set in a relatively simple one-payer public system, better reflecting the direct cost of resources than having to use the complex cost-to-charge ratios for systems with more involvement of the private sector.

Cost components included hospitalizations, medications, dialysis, and diagnostic procedures related to cardiovascular, neuropsychiatric, and renal manifestations.

Hospitalizations were costed by multiplying the length of stay by cost per in-patient day, based on data from previous research on hospitalization indications for SLE patients (25). This costing was done using the Case-Mix Group method developed by the Canadian Institute for Health Information (CIHI), adjusting for complexity through resource intensity weights linked with the admission diagnosis. Fee schedules from the provinces of Ontario and Québec (published by the Ontario Health Insurance Plan and the Régie de l'assurance maladie du Québec) were used to cost physician reimbursements during hospitalizations. These provinces were chosen as they represent the two most populous provinces and low and high cost Canadian regions.

Medication costs were obtained from the Québec List of Medications (published by the Régie de l'assurance maladie du Québec). For the less than 3% of medications not available on this list, prices were sourced from the DrugBank website (https://www.drugbank.ca), except for the price of belimumab, which was obtained from the Patented Medicine Prices Review Board of Canada. Generic prices were used whenever possible. Average Canadian 2019 medication prices were derived by multiplying Quebec-based costs by the ratio of a combined Canadian 15-city average price index for healthcare to the corresponding Montreal price index (https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000301).

Dialysis, diagnostic tests, and other procedures were priced according to the Ontario and Quebec fee schedules for physician reimbursement, and to CIHI's Comprehensive Ambulatory Classification System (CACS) for hospital expenses (26).

Adjusting annual costs and predicting long-term costs

Generalized least squares regression modeling with random effects was used to adjust annual costs for each damage state, while minimizing possible confounding of the association between costs and damage. Using the average values of significant covariates, predictions were obtained for adjusted costs, and CIs were calculated using the bootstrapping method, given the non-normal distribution of healthcare costs. Potential confounders included age, sex, education, race/ethnicity, disease duration, geographic region (i.e., North America versus outside North America), calendar year, high risk alcohol use and smoking status.

Given a damage state measured at any time in the patient's disease course, cumulative adjusted costs over the following 5 and 10 years were predicted by multiplying adjusted annual costs by the expected duration in each state for each following year. Annual change in state was determined using transition probabilities estimated after one year. Yearly transition probabilities and state durations were derived from a multi-state model as previously described (7). Year by year calculation allowed for accurate discounting of future

costs, at a yearly rate of 3%, and discounted annual costs were then summed over the five- or 10-year period. Although predicted long-term costs can be compared based on this model, they will only reflect partial adjustment for confounders, since the multi-state models used for predicting transition rates and state durations did not include any adjustment variables.

Results

Patients

1848 patients were recruited. Of these, 1687 patients were included in the analysis (United States, n= 468; Europe, n=455, Canada, n=394; Mexico, n=209; and Korea, n=161), as they had a minimum of one enrollment and one follow up visit, which allowed for determination of costs (Table 1). Almost 89% of patients were female and 49.0% were of Caucasian race/ethnicity and their mean age at diagnosis was 34.6 years (standard deviation (SD) 13.3). The mean disease duration at enrollment was 0.5 years (range 0-1.5 years) and the mean follow up was 8.9 years (range 0.6-18.5 years). At enrollment, 70.8% of patients were on corticosteroids, 67.7% on antimalarials and 41.0% on immunosuppressants. For patients with a disease duration of less than six months, the SDI could not be calculated; at enrolment, SDIs were available on 717 patients, and the mean SDI was 0.32 (SD 0.75) with a range of SDIs from 0 to 6. There were 571 patients with an SDI of 0 at enrollment.

Annual costs and predictors

Annual unadjusted component costs are provided in Table 2. At an SDI ≤ 2, hospitalizations and medications accounted for 95.2% of costs, whereas at an SDI ≥ 3, dialysis was responsible for 52.3% of costs. It should be noted that there are 12,909 cost observations across 1687 patients. As mentioned previously, annual costs are based on all health resource utilization over the preceding year for each patient across all follow up visits. Hence, one patient may have contributed many cost observations to a single SDI state or, may have contributed cost observations to several SDI states.

In the regression model examining the association between annual costs and damage, age (regression coefficient per year -$97, 95% CI -$133, -$62) and Caucasian race/ethnicity (regression coefficient -$860, 95% CI -$1661, -$59) were associated with lower costs.

Annual costs (after adjustment for age and race/ethnicity) were substantially increased in those with higher SDIs (Table 3). For example, annual costs were $22 006 (95% CI $16 662, $27 350) for patients with an SDI ≥ 5 versus $1833 (95% CI $1134, $2532) for those with an SDI of 0.

Transition probabilities and associated state durations

The number of transitions between damage states in shown in supplementary Table 1. The probability of transitioning between SDI states was determined in previous research on the SLICC cohort (7). This was used to determine the expected duration in each state over one year (Table 4). Patients with an SDI state of 0 were much less likely to transition to a higher state (7.7%) than those with an SDI state of 1 (18.2%). Accordingly, patients with an SDI state of 0 were forecasted to spend 3.9% of the next year in a higher SDI state, whereas those with an SDI state of 1 were forecasted to spend 9.4% of the next year in a higher SDI state.

Five and 10-year cumulative costs

Predicted 5-year cumulative costs were greatest in those with the highest SDI. Patients with an SDI ≥ 5 had predicted cumulative costs of $102 658 (95% CI $77 506, $127 809) whereas those with an SDI of 0 had 5-year cumulative costs of $9681 (95% CI $5986, $13 375) (Table 5).

Ten-year cumulative costs were also greatest in those with the highest SDI (Table 5). Patients with an SDI ≥ 5 had predicted 10-year cumulative costs of $189 073 (95% CI $142 318, $235 827) versus $21 713 (95% CI $13 639, $29 788) for patients with an SDI of 0, a relative cost of 8.7 times (Table 5).

Discussion

This study reports annual and long-term cumulative direct costs of SLE, stratified by degree of organ damage, in an international, multi-ethnic inception cohort. Increasing SDIs result in higher healthcare costs. Patients with an SDI ≥ 5 have annual costs approximately 12.0-fold higher than those of patients with an SDI of 0. In the regression model examining the association between annual costs and damage, older patients (regression coefficient -$97 per year) and those of Caucasian race/ethnicity (regression coefficient -$860) had lower healthcare costs. It is speculated that, after adjusting for organ damage, older patients incur lower costs because of less severe disease. Our observation of lower costs in those of Caucasian race/ethnicity is consistent with the literature reporting worse SLE outcomes in populations of non-Caucasian race/ethnicity (27). Similar to the association between damage and annual costs, patients with an SDI ≥ 5 have 10-year cumulative costs approximately 8.7-fold higher than those with an SDI of 0. Our use of multi-state modelling is a powerful predictive tool as it allows for forecasting of long-term costs for damage states for which there are few observations.

Previous studies have investigated the economic impact of organ damage, but none in an international multi-ethnic cohort. In a chart review of 215 SLE patients from Greece, those with an SDI ≥ 2 incurred annual direct costs 197% higher than those with an SDI of 0 (17). This is consistent with our work where those patients with an SDI ≥ 2 incurred annual costs at least 180% higher than those with an SDI of 0. A retrospective cohort study involving over 20 000 Taiwanese patients identified through reimbursement claims estimated the annual cost of the entire cohort at $6733[1] (2019 Canadian dollars), while annual costs for those without organ damage were only $4186 (2019 Canadian dollars) (18). A review of a Korean hospital database, which included 749 patients, also demonstrated that organ damage was a significant predictor of total direct costs (20). Jonsen et al. reported that in 127 Swedish patients, a one-unit increase in SDI was associated with a 28% increase in annual direct costs (19). A study including 715 patients from the United Kingdom, the United States, and

Canada demonstrated that a one-unit increase in the baseline SDI was associated with a 7% increase in 4-year cumulative direct costs (28). In contrast to the data from Jonsen, the study involving 715 patients adjusted for baseline costs in examining the association between baseline SDI and future costs and thus the portion of the baseline SDI that is correlated with baseline cost is removed from the 7% effect of the SDI on future costs. We are unable to provide a comparable calculation for our data regarding the effect of a unit increase in SDI on costs as we have forecasted costs based on a model of disease progression rather than observed progression and we did not use baseline SDI as a linear predictor or estimate the effects of further damage increase beyond an SDI of 5.

Although we have not examined the costs associated with the individual organ domains in the SDI, our study has shown that the majority (52.3%) of expenses for those with an SDI ≥ 3 were from dialysis. In previous research involving the SLICC inception cohort, we have used similar multi-state modelling to estimate long-term direct costs associated with lupus nephritis. We demonstrated that those with lupus nephritis and an estimated glomerular filtration rate (GFR) <30 ml/minute incurred 10-year costs over 15-fold greater than patients without lupus nephritis and an estimated GFR > 60 ml/minute (29). Other research has also reported an association between renal damage and direct costs with one study of 715 patients showing that each unit increase in renal damage was associated with a 24% increase in 4-year direct costs, while there was no association between renal damage and indirect costs (i.e., those due to lost productivity) (30). A Swedish study involving over 1000 patients demonstrated that damage in the renal and ocular domains increased direct costs, while damage in the neuropsychiatric and musculoskeletal domains increased both direct and indirect costs (31).

Our study has some limitations. We did not provide a complete assessment of direct costs, as outpatient physician and emergency room visit data were not collected, nor were procedures beyond those related to cardiovascular, neuropsychiatric, or renal disease. Therefore, we likely underestimated costs, particularly for patients with a lower SDI who

would have a greater proportion of outpatient care, potentially resulting in an overestimation of the cost differential between lower and higher damage states. Nevertheless, we did include the largest cost drivers in our estimations – hospitalizations, medications, and dialysis. Indirect costs could also not be determined. It is also possible that we underestimated the annual costs associated with each SDI state as we assessed health resource utilization in the year preceding the measurement of the SDI. Hence, if the SDI had been lower during a portion of this year, a portion of the annual costs would reflect those incurred while the patient was at a lower SDI. Although we used Canadian prices to aggregate resource utilization as they are set in a relatively simple one-payer system, they do not incorporate price variations across countries and hence may result in conservative estimates of the cost differential between damage states in countries where prices are much higher for complex and specialized services. Further, there were 85 deaths in the cohort and due to our study design, we were unable to collect data on healthcare utilization in the interval between the last annual follow up visit and death in these patients, a period during which significant costs are likely accrued. Therefore, our cost estimates do not represent costs incurred in the year prior to death and our predictions are only applicable to individuals who would survive the entire predicted period. Additionally, the SLICC cohort is recruited through tertiary care academic centers and may not represent the broader SLE patient population.

Preventing organ damage is an important therapeutic target given that damage accrual predicts morbidity, mortality, and quality of life (4, 6, 32, 33). Our study demonstrates there is also a substantial economic imperative to reducing damage. Cost savings can potentially be achieved by aggressive therapy to mitigate damage accumulation, including better control of disease activity while minimizing use of corticosteroids, and greater attention to monitoring and management of risk factors for comorbidities, such as cardiovascular disease. Unfortunately, the excess mortality due to SLE has not been eliminated over the past 20 years (34) and remains at least two-fold greater than that in a matched general population and lupus remains one of the leading causes of death (unrelated to external injury) among

young African-American and Hispanic women in the United States (35). This premature mortality is likely largely attributable to sub-optimal use of existing therapies, such as antimalarials, and relatively few therapeutic advances (36) when compared to other rheumatic diseases, such as rheumatoid arthritis. There is substantial data demonstrating that hydroxychloroquine reduces mortality in SLE (37-39). However, more recent data has shown that this is strongly related to hydroxychloroquine adherence (40) and unfortunately, studies have shown that many patients are nonadherent (41). Furthermore, new guidelines have recommended a reduction in the maximum dose of hydroxychloroquine based on concerns of retinal toxicity (42), but it is unknown if this will compromise efficacy. Regarding new therapies, successful phase two results have been reported for ustekinumab and baricitinib (43, 44). Hence, it is hoped that with improved use of existing therapies and the advent of agents successfully targeting novel therapeutic pathways, damage accumulation will be substantially reduced. Studies, such as ours, which can forecast long-term costs based on damage at disease presentation will contribute to evaluating the cost-effectiveness of existing and novel biologics.

Footnote

[1]Currencies from publications have been converted to 2019 Canadian dollars using purchasing power parities data from the Organisation for Economic Cooperation and Development (https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm) and the consumer price index from Statistics Canada. (http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/econ09a-eng.htm).

References

1. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating

Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 1996;39(3):363-9.
2. Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol. 2000;27(2):373-6.
3. Nived O, Jönsen A, Bengtsson AA, Bengtsson C, Sturfelt G. High predictive value of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for survival in systemic lupus erythematosus. J Rheumatol. 2002;29(7):1398-400.
4. Rahman P, Gladman DD, Urowitz MB, Hallett D, Tam LS. Early damage as measured by the SLICC/ACR damage index is a predictor of mortality in systemic lupus erythematosus. Lupus. 2001;10(2):93-6.
5. Stoll T, Sutcliffe N, Klaghofer R, Isenberg DA. Do present damage and health perception in patients with systemic lupus erythematosus predict extent of future damage?: a prospective study. Ann Rheum Dis. 2000;59(10):832-5.
6. Keeling SO, Vandermeer B, Medina J, Chatterley T, Nevskaya T, Pope J, et al. Measuring Disease Activity and Damage with Validated Metrics: A Systematic Review on Mortality and Damage in Systemic Lupus Erythematosus. J Rheumatol. 2018;45(10):1448-61.
7. Bruce IN, O'Keeffe AG, Farewell V, Hanly JG, Manzi S, Su L, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis. 2015;74(9):1706-13.
8. Wang Z, Li M, Wang Y, Xu D, Wang Q, Zhang S, et al. Long-term mortality and morbidity of patients with systemic lupus erythematosus: a single-center cohort study in China. Lupus. 2018;27(5):864-9.

9. Sutton EJ, Davidson JE, Bruce IN. The systemic lupus international collaborating clinics (SLICC) damage index: a systematic literature review. Semin Arthritis Rheum. 2013;43(3):352-61.
10. Petri M, Purvey S, Fang H, Magder LS. Predictors of organ damage in systemic lupus erythematosus: the Hopkins Lupus Cohort. Arthritis Rheum. 2012;64(12):4021-8.
11. Alarcón GS, McGwin G, Bartolucci AA, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups. IX. Differences in damage accrual. Arthritis Rheum. 2001;44(12):2797-806.
12. 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(11):1197-204.
13. Gladman DD, Urowitz MB, Rahman P, Ibañez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. J Rheumatol. 2003;30(9):1955-9.
14. Al Sawah S, Zhang X, Zhu B, Magder LS, Foster SA, Iikuni N, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. Lupus Sci Med. 2015;2(1):e000066.
15. Rabbani MA, Habib HB, Islam M, Ahmad B, Shah SM, Tahir S, et al. Early renal damage assessed by the SLICC/ACR damage index is predictor of severe outcome in lupus patients in Pakistan. Lupus. 2010;19(13):1573-8.
16. Danila MI, Pons-Estel GJ, Zhang J, Vilá LM, Reveille JD, Alarcón GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford). 2009;48(5):542-5.
17. Bertsias G, Karampli E, Sidiropoulos P, Gergianaki I, Drosos A, Sakkas L, et al. Clinical and financial burden of active lupus in Greece: a nationwide study. Lupus. 2016;25(12):1385-94.
18. Chiu YM, Chuang MT, Lang HC. Medical costs incurred by organ damage caused by active disease, comorbidities and side effect of treatments in systemic lupus erythematosus patients: a Taiwan nationwide population-based study. Rheumatol Int. 2016;36(11):1507-14.

19. Jönsen A, Bengtsson AA, Hjalte F, Petersson IF, Willim M, Nived O. Total cost and cost predictors in systemic lupus erythematosus – 8-years follow-up of a Swedish inception cohort. Lupus. 2015;24(12):1248-56.
20. Park SY, Joo YB, Shim J, Sung YK, Bae SC. Direct medical costs and their predictors in South Korean patients with systemic lupus erythematosus. Rheumatol Int. 2015;35(11):1809-15.
21. Isenberg D, Ramsey-Goldman R, Group S. Systemic Lupus International Collaborating Group--onwards and upwards? Lupus. 2006;15(9):606-7.
22. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725.
23. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum. 1992;35(6):630-40.
24. Butt P, Beirness D, Glicksman L, Paradis C, Stockwell T. Alcohol and health in Canada: A summary of evidence and guidelines for low risk drinking. Canadian Centre on Substance Use and Additction. 2011 [cited; Available from: http://www.ccsa.ca/Resource%20Library/2011-Summary-of-Evidence-and-Guidelines-for-Low-Risk%20Drinking-en.pdf].
25. Clarke AE, Petri MA, Manzi S, Isenberg DA, Gordon C, Senecal JL, et al. An international perspective on the well being and health care costs for patients with systemic lupus erythematosus. Tri-Nation Study Group. J Rheumatol. 1999;26(7):1500-11.
26. Canadian Institute for Health Information. Functional Area Resource Intensity Weight Proportions (Technical notes and glossary). 2019.
27. González LA, Toloza SM, Alarcón GS. Impact of race and ethnicity in the course and outcome of systemic lupus erythematosus. Rheum Dis Clin North Am. 2014;40(3):433-54, vii-viii.
28. Clarke AE, Petri M, Manzi S, Isenberg DA, Gordon C, Senécal JL, et al. The systemic lupus erythematosus Tri-nation Study: absence of a link between health resource use and health outcome. Rheumatology (Oxford). 2004;43(8):1016-24.

29. Barber MRW, Hanly JG, Su L, Urowitz MB, St Pierre Y, Romero-Diaz J, et al. Economic Evaluation of Lupus Nephritis in the Systemic Lupus International Collaborating Clinics Inception Cohort Using a Multistate Model Approach. Arthritis Care Res (Hoboken). 2018;70(9):1294-302.
30. Clarke AE, Panopalis P, Petri M, Manzi S, Isenberg DA, Gordon C, et al. SLE patients with renal damage incur higher health care costs. Rheumatology (Oxford). 2008;47(3):329-33.
31. Jönsen A, Hjalte F, Willim M, Carlsson KS, Sjöwall C, Svenungsson E, et al. Direct and indirect costs for systemic lupus erythematosus in Sweden. A nationwide health economic study based on five defined cohorts. Semin Arthritis Rheum. 2016;45(6):684-90.
32. Mok CC, Ho LY, Cheung MY, Yu KL, To CH. Effect of disease activity and damage on quality of life in patients with systemic lupus erythematosus: a 2-year prospective study. Scand J Rheumatol. 2009;38(2):121-7.
33. Wang C, Mayo NE, Fortin PR. The relationship between health related quality of life and disease activity and damage in systemic lupus erythematosus. J Rheumatol. 2001;28(3):525-32.
34. Jorge AM, Lu N, Zhang Y, Rai SK, Choi HK. Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999-2014). Rheumatology (Oxford). 2018;57(2):337-44.
35. Yen EY, Singh RR. Brief Report: Lupus-An Unrecognized Leading Cause of Death in Young Females: A Population-Based Study Using Nationwide Death Certificates, 2000-2015. Arthritis Rheumatol. 2018;70(8):1251-5.
36. Sciascia S, Radin M, Roccatello D, Sanna G, Bertolaccini ML. Recent advances in the management of systemic lupus erythematosus. F1000Res. 2018;7.
37. Shinjo SK, Bonfá E, Wojdyla D, Borba EF, Ramirez LA, Scherbarth HR, et al. Antimalarial treatment may have a time-dependent effect on lupus survival: data from a multinational Latin American inception cohort. Arthritis Rheum. 2010;62(3):855-62.
38. Alarcón GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alén J, Bastian HM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus:

data from LUMINA, a multiethnic US cohort (LUMINA L). Ann Rheum Dis. 2007;66(9):1168-72.
39. Mok CC, Tse SM, Chan KL, Ho LY. Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort. Lupus. 2018;27(5):722-7.
40. Hsu CY, Lin YS, Cheng TT, Syu YJ, Lin MS, Lin HF, et al. Adherence to hydroxychloroquine improves long-term survival of patients with systemic lupus erythematosus. Rheumatology (Oxford). 2018;57(10):1743-51.
41. Feldman CH, Collins J, Zhang Z, Subramanian SV, Solomon DH, Kawachi I, et al. Dynamic patterns and predictors of hydroxychloroquine nonadherence among Medicaid beneficiaries with systemic lupus erythematosus. Semin Arthritis Rheum. 2018;48(2):205-13.
42. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, Ophthalmology AAo. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-94.
43. Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2018;392(10143):222-31.
44. van Vollenhoven RF, Hahn BH, Tsokos GC, Wagner CL, Lipsky P, Touma Z, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. Lancet. 2018;392(10155):1330-9.

Figures

Figure 1: Multistate Markov model for observed transitions between SDI states

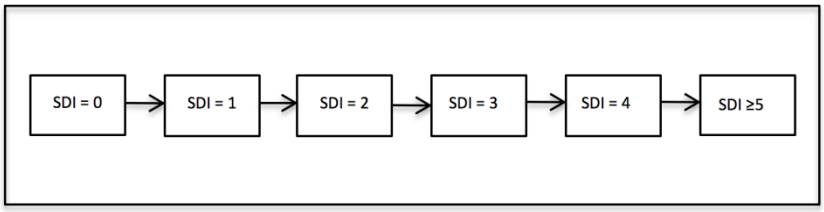

Table 1 – Baseline demographic and clinical manifestations of patients

No. of patients:	1687
Age (years): (Mean and SD)	34.6 (13.3)
Sex (%):	
Female	88.7
Male	11.3
Education (% with any post-secondary)	61.8
Race/Ethnicity (%):	
Caucasian	49.0
Hispanic	15.6
Asian	15.1
African	16.6
Geographic region (%):	
United States	27.7
Europe	27.0
Canada	23.4
Mexico	12.4
Korea	9.5
Disease Duration (years) (mean and range)	0.5 (0-1.5)
ACR Classification Criteria (%):	
Malar Rash	35.9
Discoid Rash	12.2
Photosensitivity	35.7
Oral/nasopharyngeal Ulcers	36.7
Serositis	27.7
Arthritis	75.1
Renal Disorder	28.3
Neurological Disorder	4.7
Hematologic Disorder	62.5
Immunologic Disorder	76.5
Antinuclear Antibody	94.8
SLEDAI-2K (Mean and SD)	5.4 (5.4)
SDI* (Mean and SD)	0.32 (0.75)
SDI* State (N):	
0	571
1	90
2	35
3	16
4	4
≥ 5	1
SDI at first annual follow-up (Mean and SD)	0.44 (0.87)
Medications used at baseline (%):	
Corticosteroids	70.8
Antimalarials	67.7
Immunosuppressants	41.0
Comorbidities/Lifestyle	

Current Smoker (%)	14.8
Alcohol (% with high risk consumption)	1.3
Diabetic (%)	3.5
Hypertensive (%)	34.4

ACR = American College of Rheumatology

SDI = SLICC/ACR Damage index

SLEDAI-2K = SLE Disease Activity Index – 2000

* For patients with a disease duration of less than six months, the SDI cannot be calculated – therefore at enrolment, the SDI was available on 717 patients

Table 2 – Observed annual unadjusted component costs (2019 CDN$), stratified by SDI*

Current** SDI State	Patients (N) ***	Observations (N) [%]	Medications [%]	Hospitalizations [%]	Tests / Procedures [%]	Dialysis [%]	Total
0	1231	7148 [55]	1310 (1029, 1592) [61]	739 (636, 842) [34]	105 (99, 110) [5]	0 [0]	2154 (1851, 2457)
1	630	2532 [20]	1813 (1373, 2254) [57]	1214 (964, 1463) [38]	171 (152, 191) [5]	0 [0]	3198 (2688, 3708)
2	373	1540 [12]	2270 (1704, 2836) [54]	1757 (1342, 2172) [42]	162 (139, 184) [4]	0 [0]	4188 (3479, 4898)
3	237	908 [7]	2185 (1586, 2784) [28]	2317 (1853, 2781) [30]	242 (201, 284) [3]	3070 (2161, 3980) [39]	7815 (6604, 9026)
4	120	379 [3]	2312 (1366, 3258) [19]	3571 (2534, 4608) [30]	208 (163, 252) [2]	5819 (3951, 7687) [49]	11910 (9462, 14358)
≥ 5	97	402 [3]	3278 (2049, 4506) [14]	4852 (3443, 6261) [21]	334 (258, 410) [1]	14927 (11994, 17859) [64]	23390 (19884, 26897)

* Values are the mean (95% confidence interval)

**Current refers to the SDI state at the end of any one-year interval over which costs were calculated

***A single patient may have multiple SDI states during the study duration and may contribute to multiple observations

CDN = Canadian

SDI = SLICC/ACR Damage index

Table 3 – Predicted annual healthcare costs, stratified by SDI*

Current SDI State**	Costs 2019 CDN $	Relative Cost
0	1833 (1134, 2532)	1.0
1	3915 (2888, 4942)	2.1
2	5137 (3901, 6373)	2.8
3	9510 (7497, 11523)	5.2
4	14313 (10385, 18241)	7.8
≥ 5	22006 (16662, 27350)	12.0

* Values are the mean (95% confidence interval)

**Current refers to the SDI state at the end of any one-year interval over which costs were calculated

CDN = Canadian

SDI = SLICC/ACR Damage index

Table 4 – Probabilities of transitioning between SDI states and state durations over 1 year

Current* SDI State	Probability of being in state after 1 year					
	0	1	2	3	4	≥5
0	0.923	0.069	0.007	0	0	0
1	0	0.818	0.162	0.018	0.001	0
2	0	0	0.802	0.179	0.017	0.002
3	0	0	0	0.823	0.152	0.025
4	0	0	0	0	0.738	0.262

≥ 5	0	0	0	0	0	1
	Expected duration in state over 1 year					
	0	1	2	3	4	≥5
0	0.961	0.037	0.002	0	0	0
1	0	0.906	0.087	0.006	0	0
2	0	0	0.897	0.096	0.006	0
3	0	0	0	0.909	0.082	0.009
4	0	0	0	0	0.863	0.137
≥ 5	0	0	0	0	0	1

SDI = SLICC/ACR Damage index

*Current refers to the SDI state at the end of any one year interval over which costs were calculated

Table 5 – Predicted 5-year and 10-year cumulative healthcare costs, stratified by SDI*

SDI State	5-Year Cumulative Costs 2019 CDN $	Relative Cost	10-Year Cumulative Costs 2019 CDN $	Relative Cost
0	9681 (5986, 13375)	1.0	21713 (13639, 29788)	1.0
1	22336 (16560, 28113)	2.3	53845 (39892, 67798)	2.5

2	34677 (26352, 43002)	3.6	83475 (62868, 104082)	3.8
3	56586 (43136, 70036)	5.8	123379 (93105, 153654)	5.7
4	83668 (62060, 105277)	8.6	166495 (124009, 208982)	7.7
≥ 5	102658 (77506, 127809)	10.6	189073 (142318, 235827)	8.7

* Values are the mean (95% confidence interval)

CDN = Canadian

SDI = SLICC/ACR Damage index