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Assessing the Costs of Neuropsychiatric Disease in the Systemic Lupus International Collaborating Clinics (SLICC) Cohort using Multistate Modelling

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Abstract

Objective: To estimate direct and indirect costs (DC, IC) associated with neuropsychiatric (NP) events in the SLICC Inception Cohort.

Methods: NP events were documented annually using ACR NP definitions and attributed to SLE or non-SLE causes. Patients were stratified into one of three NP states (no, resolved, or new/ongoing NP event). Change in NP status was characterized by inter-state transition rates using multi-state modelling. Annual DC and IC were based on healthcare use and impaired productivity over the preceding year. Annual costs associated with NP states and NP events were calculated

by averaging all observations in each state and adjusted through random-effects regressions. Five and 10-year costs for NP states were predicted by multiplying adjusted annual costs per state by expected state duration, forecasted using multistate modelling.

Results: 1697 patients (49% White race/ethnicity) were followed a mean of 9.6 years. NP events (n=1971) occurred in 956 patients, 32% attributed to SLE. For SLE and non-SLE NP events, predicted annual, five, and 10-year DC and IC were higher in new/ongoing versus no events. DC were 1.5-fold higher and IC 1.3-fold higher in new/ongoing versus no events. IC exceeded DC 3.0 to 5.2-fold. Among frequent SLE NP events, new/ongoing seizure disorder and cerebrovascular disease accounted for the largest increases in annual DC. For non-SLE NP events, new/ongoing polyneuropathy accounted for the largest increase in annual DC and new/ongoing headache and mood disorder for the largest increases in IC.

Conclusion: Patients with new/ongoing SLE or non-SLE NP events incurred higher DC and IC.

Introduction

Approximately 50% of patients with SLE experience neurologic and/or psychiatric (NP) events(1,2), ranging from common syndromes such as mild cognitive dysfunction, anxiety, and headache to infrequent manifestations such as psychosis and neuropathy(3). Approximately 30% of these NP events are reported to be directly attributable to SLE(4). NP events in SLE patients negatively impact health-related quality of life(5,6) and increase mortality(1,7), but little is known about their economic impact.

A few studies have reported the direct and indirect costs associated with NPSLE(8–12), but most were limited as they relied on administrative data(8–10), provided only direct(8–10) or short-term(8,10–12) cost estimates, or involved a single centre(11,12). The long-term economic burden has never been assessed in an international, multi-ethnic cohort such as the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort using multistate modelling. Multistate modelling can characterize the transition of SLE patients between onset, remissions, and relapses of different disease states, capturing both the likelihood of moving between states and state durations. We have previously used multistate modelling developed in the SLICC cohort to estimate long-term costs associated with renal involvement(13) and damage accrual(14). Hanly *et al* have recently described dynamic changes in NP events, both attributable (SLE NP events) and not attributable to SLE (non-SLE NP events) using reversible multistate modelling(6). In the current study, we calculated annual direct and indirect costs for each SLE and non-SLE NP state and used the interstate transition probabilities predicted in the models to estimate the expected duration in each state. Five and 10-year cumulative costs were then estimated by multiplying the annual costs associated with each NP state with the expected duration in that state, providing predictions of long-term costs for states with limited observations. We also provide cost estimates for individual SLE and non-SLE NP events.

Patients and Methods

Inception Cohort

Between 1999 and 2011, patients from 31 centres in 11 countries fulfilling the American College of Rheumatology (ACR) Revised Classification Criteria for SLE(15) were enrolled in the SLICC Inception cohort within 15 months of diagnosis and assessed longitudinally. For this study, data collection continued until December 2019. Each patient provided informed consent and research ethics boards at each site approved the study.

At enrolment, data were collected on age, sex, and self-reported race and ethnicity, and at enrolment and annually on disease activity(16), damage(17), NP events (using the ACR case definitions)(18), postsecondary education, smoking, and alcohol consumption(19). At enrolment and annually, data were also collected on hospitalizations and medications (regardless of attribution to SLE) in the year preceding each visit. The cohort was originally created to assess cardiovascular, neuropsychiatric, and renal outcomes and therefore, data on diagnostic/therapeutic procedures were limited.

Beginning in 2015, 18 sites collected supplemental economic data annually on patients still followed in the cohort (Supplemental Figure 1); supplemental data included: 1) additional health resource utilization that was not captured in the pre-existing data collection (i.e., physicians, non-physician healthcare professionals, emergency room visits, laboratory tests, radiological and other diagnostic procedures, outpatient surgeries, and help obtaining medical care) and 2) lost productivity in labour force and non-labour force activity over the year(20,21) preceding the assessment. All healthcare use and all health-related lost productivity were included regardless of attribution to SLE.

Statistical Analysis

Multistate Modelling—At enrolment and annually, patients were assessed for NP events attributed to SLE (SLE NP events) or non-SLE causes (non-SLE NP events). NP events were attributed to SLE based on published attribution decision rules(6) and were attributed if they: 1) had their onset within 10 years of SLE diagnosis and were still present within the enrolment window, or occurred subsequently, 2) had no concurrent non-SLE causes, and 3) were not one of the common NP events in the normal population as described by Ainiala(22). Separate patient level models were developed for SLE and non-SLE NP events, including the following three states (Supplemental Figure 2):

1. No NP event ever.
2. Resolved NP event, i.e., no current NP event but ≥ 1 in the past. State entry was time of resolution of the NP event.
3. New/ongoing NP event with state entry at onset of the event.

At each assessment, patients were assigned to one of three NP states. The SLE NP and non-SLE NP models were estimated independently and all patients were included in both. When fitting the model for SLE NP events, non-SLE NP events were ignored, and vice versa. Therefore, we did not estimate costs for SLE NP events with or without concurrent non-SLE NP events. As costs were only collected at assessments prior to death and not

over the interval between the last follow-up visit and death, death was not included in the economic models although it was allowed for in the multistate modelling. Transition rates were estimated through maximum likelihood estimation using the R(23) package "msm(24)."

Calculating Annual Direct Costs—At each assessment, annual direct costs were based on health resource utilization over the preceding year and annual indirect costs on lost time in labour force and non-labour force activity over the preceding year (depending on the cost dataset available – refer to cost dataset description below). Annual costs associated with each SLE and non-SLE NP state were calculated by averaging costs for all patients contributing an observation to that state.

Healthcare costs were calculated by multiplying each health resource by its corresponding 2021 Canadian unit cost (sources of unit cost for healthcare components are provided in Supplemental Table 1). As the objective of this research was to compare healthcare costs between SLE patients with new/ongoing versus resolved versus no NP events rather than to provide country-specific estimates of costs, healthcare prices and wages essentially served as a set of weights to aggregate resources and lost productivity into a single cost measure. Canadian prices were chosen as the largest proportion of patient observations was from Canada and prices are set in a one-payer universal public system covering the entire Canadian population and therefore better reflect the direct cost of resources.

Calculating Annual Indirect Costs—Total indirect costs consisted of the sum of the following components: 1) absenteeism, 2) presenteeism, and 3) opportunity costs. Absenteeism referred to self-report of time lost from paid labour because of poor health; presenteeism referred to self-report of how productivity, while engaged in labour and non-labour force activities, was affected by health, based on a visual analogue scale anchored at zero percent for health having no impact and 100% for complete inability to work; opportunity costs referred to additional time patients would be working in labour force and non-labour force activities if not ill. Opportunity costs were calculated as the difference between the time patients reported working versus the time worked by an age, sex, and geographic-matched general population(25–28). Indirect costs from labour force activities were valued using age-and-sex-specific wages from Statistics Canada(29). Indirect costs from non-labour force activities were valued using opportunity costs (i.e., age-and-sex specific wages rather than expected earnings of service workers).

Cost Datasets—Based on our method of collecting data on health resource utilization and lost productivity, we have two types of cost data:

1. partial direct costs based on the data provided by the full cohort. These partial direct costs included hospitalizations, medications, selected procedures, and dialysis.
2. complete direct and indirect costs for the cohort subset who completed the annual supplemental economic questionnaire introduced in 2015.

To take full advantage of both cost datasets, we used a multiple imputation strategy to predict all missing values for the patients in the full cohort who did not provide complete direct and indirect costs for all observations. All models for imputing complete direct and indirect costs included partial direct costs and NP state (time-varying) as well as education and geographic location as final covariates, with the direct cost model also including age at diagnosis, and the indirect cost model also including race and ethnicity. Ten sets of imputations were derived from these models, and all subsequent analyses in this setting involved pooling and averaging all estimates across imputed sets, while their variances were computed by applying standard combination rules.

Adjusting Annual Costs and Predicting Five and 10-Year Cumulative Costs— Within each of the three data settings (i.e., partial direct costs for the full cohort, unimputed complete costs for the cohort subset, and imputed complete costs for the full cohort), multivariate random-effects linear regression modelling was used to adjust for possible confounding of demographic variables on the association of annual direct and indirect costs and NP state. Potential covariates included age at diagnosis, sex, race and ethnicity, education, and geographic regions as well as the following time-varying covariates: age, disease duration, smoking, and high-risk alcohol use. Using the average values of significant covariates, predictions were obtained for adjusted annual costs; 95% confidence intervals (CI) were calculated using bootstrapping except in the multiple imputation setting where bootstrapping does not appear to provide realistic variance estimates(30). All statistical computations were done using Stata version 17.

For each NP state, cumulative adjusted costs over the following five and 10 years were predicted by multiplying adjusted annual costs by the expected duration in each state for each of the following years. Annual change in NP state was determined using transition probabilities derived from the multistate model. Future costs were discounted at an annual rate of 3%.

Assessing Costs Associated with Individual SLE and non-SLE NP Events— The increase in annual costs associated with the four most frequent SLE and non-SLE NP events was also estimated. Random-effects linear regression models were developed using the imputed complete costs for the full cohort with annual direct and indirect costs as the outcomes for SLE and non-SLE NP events. In each model, predictors included indicator variables for whether any of the four most frequent events or any other NP events (SLE or non-SLE, depending on the model) had been ongoing at any time over each observed patient-year, as well as other statistically significant covariates, i.e., race and ethnicity and disease duration for direct costs; disease duration, region, and education for indirect costs. This allows cost increases associated with specified new/ongoing NP events to be estimated independently of any co-occurring NP event and compared to no and resolved NP events.

Results

Patients

A total of 1827 patients were recruited in the SLICC Inception Cohort and 1697 provided utilization data on hospitalizations, medications, and selected procedures. Of these 1697

patients, 672 patients were still being followed in 2015 when the annual questionnaire on additional health resource utilization and lost productivity was introduced. In the full cohort of 1697 patients, 88.7% were female subjects, 48.8% were of White race and ethnicity, and their mean age and mean disease duration at cohort enrolment was 35.1 years (standard deviation (SD) 13.3) and 0.5 years (range 0 – 1.3), respectively (Table 1). One thousand nine hundred and seventy-one unique NP events occurred in 956 patients, 32% attributed to SLE. Mood disorder (121 of 624 SLE NP events, 19.4%), seizure disorder (19.2%), cerebrovascular disease (19.1%), and mononeuropathy (7.7%) were the most frequent SLE NP events and headache (940 of 1347 non-SLE NP events, 69.8%), mood disorder (14.8%), anxiety (7.0%), and polyneuropathy (2.8%) were the most frequent non-SLE NP events (Supplemental Tables 2 and 3).

In the subset of 672 patients providing complete economic data, 89.3% were female subjects, 40.9% were of White race and ethnicity, and their mean age and mean disease duration at time of enrolment in the inception cohort was 33.2 (12.0) years and 0.4 (0–1.3) years, respectively. Their mean disease duration at the time of introduction of the economic questionnaire was 10.8 years (range 3.9–19.1). The cohort subset had a larger proportion of Asian patients than the full cohort and Canada, Mexico, and Korea contributed a higher proportion of patients to this subset than the full cohort.

Transition probabilities are shown in Supplemental Table 4.

Partial Direct Costs on Full Cohort

Annual Costs and Predictors—For the 1697 patients, there was a mean follow-up of 9.6 years, yielding 13,987 observations (Table 2; distribution of observations per country in Supplemental Table 5).

In the regression model that examined the association between annual partial direct costs and SLE NP states, older age at diagnosis and White race and ethnicity were associated with lower costs, whereas longer disease duration was associated with higher costs (Supplemental Table 6, **panel A, model 1**). A similar relationship was observed in the model for annual partial direct costs and non-SLE NP states (**panel B, model 1**).

Adjusted annual partial direct costs were higher in those with new/ongoing SLE NP events ($7028 2021 Canadian dollars [CAD]) versus those with no SLE NP events ($4212; difference $2816, 95%CI $1139, $4493) (Supplemental Table 7).

Five and 10-Year Cumulative Costs—For SLE NP events, patients with new/ongoing versus no events at the beginning of the five-year period incurred higher predicted five-year partial direct costs (i.e., new/ongoing ($34,580) versus no events [$23,149; difference $11,431, 95%CI $5293, $17,570]) (Supplemental Table 7). Similarly, patients with new/ongoing versus no events at the beginning of the 10-year period incurred higher predicted 10-year partial direct costs (i.e., new/ongoing ($67,407) versus no events [$48,416; difference $18,992, 95%CI $8774, $29,210]). For the non-SLE NP events, five and 10-year partial direct costs were also higher in those with new/ongoing versus no events.

Complete Direct and Indirect Costs on Cohort Subset

Annual Costs and Predictors—For the 672 patients in the cohort subset completing the economic questionnaire starting in 2015, there was a mean follow-up of 2.7 years, yielding 1594 observations (Table 3). Across all SLE and non-SLE NP states, indirect costs exceeded direct by an average of 4.4-fold; within indirect costs, unpaid labour costs exceeded paid labour costs by an average of 1.6-fold.

In the regression model that examined the association between annual complete direct costs and SLE NP states (Supplemental Table 6, **panel A, model 2**), no additional variables were associated with costs, whereas in the model examining the association between annual complete direct costs and non-SLE NP states (**panel B, model 2**), longer disease duration was associated with higher costs. In the model examining the association between annual indirect costs and SLE NP states (**panel A, model 3**) and non-SLE NP states (**panel B, model 3**), longer disease duration was associated with higher costs, whereas post-secondary education and residing outside of North America were associated with lower costs.

Adjusted annual complete direct costs were higher in those with new/ongoing SLE NP events ($13,825) versus those with no SLE NP events ($7505; difference $6320, 95%CI $1399, $11,241) (Table 4). Adjusted annual indirect costs were also higher in those with new/ongoing ($42,695) versus no SLE NP events ($33,347; difference $9348, 95% CI $1004, $17,692). Similarly, adjusted annual direct and indirect costs were higher in those with new/ongoing non-SLE NP events versus no non-SLE NP events.

Five and 10-Year Cumulative Costs—For the SLE NP events, predicted five-year complete direct costs were higher in those with new/ongoing ($62,071) versus those with no events ($36,948; difference $25,123, 95%CI $6566, $43,680) (Table 4). Similarly, 10-year complete direct costs were higher in those with new/ongoing ($110,682) versus no events ($69,870; difference $40,812, 95%CI $7186, $74,438). Five-year cumulative indirect costs were higher in the new/ongoing ($209,893) versus no SLE NP event ($177,634; difference $32,259, 95%CI $2380, $62,138). For the non-SLE NP events, five and 10-year complete direct and indirect costs were higher in the new/ongoing versus no event.

Imputed Complete Direct and Indirect Costs on Full Cohort

Annual Costs and Predictors—Unadjusted imputed annual direct and indirect costs for the full cohort are shown in Supplemental Table 8. In the regression model that examined the association between imputed annual complete direct costs and SLE NP states (Supplemental Table 6, **panel A, model 4**) and non-SLE NP states (**panel B, model 4**), longer disease duration was associated with higher costs, whereas White race and ethnicity was associated with lower costs. In the model examining the association between imputed annual indirect costs and SLE NP states (**panel A, model 5**) and non-SLE NP states (**panel B, model 5**), White race and ethnicity was associated with higher costs, whereas residing outside of North America was associated with lower costs.

Adjusted imputed annual complete direct costs were higher in those with new/ongoing SLE NP events ($10,471) versus those with no SLE NP events ($6668; difference $3803, 95%CI

$2136, $5471) (Table 5; expressed as US dollars using 2021 purchasing power parity(31) in Supplemental Table 9). Adjusted imputed annual complete direct costs were also higher in the resolved ($9089) versus no SLE NP event ($6668; difference $2421, 95%CI $859, $3983). Adjusted imputed annual indirect costs were higher in those with new/ongoing ($37,197) versus no SLE NP events ($26,248; difference $10,950, 95%CI $376, $21,523). For the non-SLE NP events, adjusted imputed annual complete direct costs were higher in the new/ongoing versus no event and the resolved versus no event. Adjusted imputed annual indirect costs were higher in the new/ongoing versus no event and new/ongoing versus resolved event.

Five and 10-Year Cumulative Costs—For the SLE NP events, imputed five and 10-year complete direct costs were higher in the new/ongoing versus no event and in the resolved versus no event (Table 5). Imputed five and 10-year indirect costs were higher in the new/ongoing versus no event and new/ongoing versus resolved event. For the non-SLE NP events, imputed five and 10-year complete direct costs were higher in the new/ongoing versus no event and in the resolved versus no event. Imputed five-year indirect costs were higher in the new/ongoing versus no event and new/ongoing versus resolved event and imputed 10-year indirect costs were higher in the new/ongoing versus no event, resolved versus no event, and new/ongoing versus resolved event.

Costs of Individual SLE and non-SLE NP events—For SLE NP events, new/ongoing seizure disorder, cerebrovascular disease, and NP event(s) other than the four most frequent (i.e., mood disorder, seizure disorder, cerebrovascular disease, and mononeuropathy), respectively, accounted for increases in annual direct costs of $10,179 (95%CI $7114, $13,245), $3907 (95%CI $920, $6893), and $4383 (95%CI $2272, $6494) (Table 6). Only new/ongoing SLE NP events other than the four most frequent were associated with an increase in annual indirect costs ($8065, 95%CI $22, $16,108).

For non-SLE NP events, new/ongoing headache, polyneuropathy, and NP event(s) other than the four most frequent (i.e., headache, mood disorder, anxiety disorder, and polyneuropathy), respectively, accounted for increases in annual direct costs of $1216 (95%CI $202, $2229), $9168, 95%CI $5392, $12,943), and $8939 (95%CI $5564, $12,314) (Table 6). New/ongoing headache and mood disorder, respectively, were associated with increases in annual indirect costs of $6824 (95%CI $3441, $10,208), and $4660 (95%CI $229, $9091).

Discussion

We have provided the first estimates of annual and long-term costs stratified by patients with NP events attributed to both SLE and non-SLE causes and in varying stages of evolution (new/ongoing versus resolved). For SLE and non-SLE NP events, predicted annual, five, and 10-year direct costs were higher in the new/ongoing versus no events and resolved versus no events. For SLE and non-SLE NP events, annual, five, and 10-year indirect costs were higher in the new/ongoing versus no events and five and 10-year indirect costs were higher in new/ongoing versus resolved events. Direct costs were 1.2 to 1.8-fold higher and indirect costs 1.1 to 1.5-fold higher in patients with new/ongoing versus no NP events and indirect exceeded direct costs between 3.0 and 5.2-fold. The higher direct and indirect costs in

those with new/ongoing versus no event is to be expected based on the significantly poorer health-related quality of life experienced by those with NP lupus, as previously documented in this cohort(6). The relationship between costs and health-related quality of life is likely complex and bi-directional. Although Hanly et al have reported that patients in this cohort with NP events attributed to SLE generally have a more favourable outcome than patients with NP events attributed to non-SLE causes(32), we did not consistently observe lower costs in those with SLE NP events.

While a few studies have assessed costs associated with NPSLE(8–12), only two studies defined NPSLE based on ACR NP cases definitions(10,12), and one of these relied on claims data(10) to identify NP events. Both only included NP events attributable to SLE. Mean annual direct and indirect costs for a clinical cohort in Hong Kong with NPSLE (n=83) were estimated at $16,590 and $9240 (2021 US dollars [USD])(12,31,33), respectively, whereas mean annual direct costs in NPSLE patients identified from a US claims database were $38,408(10). The other NP cost studies(8,9) examined costs associated with damage accrual in the NP domain of the SDI, which includes only a subset of the items in our much broader definition of SLE and non-SLE NP events. For patients with damage in the NP domain of the SDI identified in a US claims database(8), mean annual direct costs were $28,191; for patients identified in Taiwanese National Health Insurance database(9), mean annual direct costs ranged between $2558 for cranial or peripheral neuropathy and $19,949 for recurrent cerebrovascular accidents.

Annual direct and indirect costs in our patients with new/ongoing SLE NP events were $8136 and $28,902 (2021USD) and new/ongoing non-SLE NP events, $6939 and $27,764. While our indirect cost estimates ($28,902 and $27,764) exceeded those in the Hong Kong cohort(12) ($9240), our direct costs estimates ($8136 and $6939) were substantially lower than those from US administrative databases(8,10) ($38,408 and $28,191). Costs are expected to vary widely across studies due to a variety of factors. Direct costs are influenced by both the method of ascertainment (i.e., patient self-report, medical chart review, or insurance claims databases) and source of valuation of healthcare resources, (i.e., single payer national health insurance or private medical insurer). Similarly, indirect costs depend on the method of measuring relevant time inputs (i.e., human capital or friction cost approach), whether presenteeism is accounted for, and valuation of lost productivity.

Our estimates of indirect costs exceeded direct costs across all NP states, which is consistent with other SLE cost-of-illness studies (which do not provide cost estimates specifically for NPSLE)(34).

Annual direct cost increases associated with specified new/ongoing NP events in our cohort ranged from $1216 for non-SLE headaches to $10,179 for SLE-associated seizure disorder and indirect costs increases ranged from $4660 for non-SLE mood disorder to $8065 for SLE NP events other than the four most frequent. It is noteworthy that some ongoing non-SLE NP events such as headaches and mood disorder, despite appearing to require none or relatively modest additional healthcare resources, accounted for significant annual productivity losses (respectively $6824 and $4660).

Our study is limited as we were unable to collect data on direct and indirect costs in the interval between the last annual follow-up visit and death and 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. Further, we did not collect complete direct and indirect costs on the full cohort for the entire observation period. However, as we had collected data on the major sources of direct costs on the full cohort for the entire study and complete direct and indirect costs on a cohort subset, we believed that multiple imputation would allow us to accurately predict complete direct and indirect costs for the full cohort. Costs in the cohort subset were measured later in the disease course when patients were more likely to have accumulated more damage and experienced more NP events. Consistent with this, our estimates based on imputed data were more conservative than when using only unimputed data. Adjusted total costs observed in the cohort subset ranged from 16% to 24% higher than imputed total costs for the full cohort. By combining these imputed costs with interstate transition probabilities predicted in multistate models, we provide the first comprehensive long-term cost estimates for patients with no, active, and resolved NP events.

Additionally, we are not providing country-specific cost estimates for NPSLE. Rather, our purpose was to compare the costs of new/ongoing versus resolved versus no NP event and we used Canadian prices and wages to aggregate resources and lost productivity into a single measure of direct or indirect costs. The use of Canadian prices results in an underestimation (or overestimation) of NP costs in countries where the prices of healthcare services are higher (or lower). Finally, although we assessed costs associated with varying states of NPSLE, all costs incurred by a patient were included in our estimates. Therefore, it was not possible to determine if cost differentials between NP states were directly attributable to an NP event or other SLE manifestations or comorbidities that may be correlated with NP events. Although dialysis, for example, may be a cost item that could be correlated without being causally linked to NP events, it should be noted that unadjusted partial direct costs for the full cohort excluding the portion due to dialysis remained higher in those with new/ongoing and resolved NP events versus no SLE or non-SLE NP events.

Both SLE and non-SLE NP events are important components of the economic costs associated with SLE. It is important to consider non-SLE NP events as patients with SLE may be affected differently or experience different sequelae than persons unaffected by SLE experiencing the event. Accordingly, current models of SLE care should consider allocating more healthcare resources to the detection and treatment of NP events, particularly the most costly, i.e., SLE-associated seizure disorder and cerebrovascular disease and non-SLE polyneuropathy, headache, and mood disorder. Further, the incorporation of economic outcomes in observational studies and clinical trials of NPSLE could help determine if the benefits of interventions are commensurate with their costs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovations

- This is the first study to assess the long-term economic burden of neuropsychiatric (NP) lupus in an international, multi-ethnic inception cohort using multistate modelling to characterize transition between onset, remission, and relapse of NP events.
- For SLE and non-SLE NP events, annual, five, and 10-year direct costs were higher in those with new/ongoing versus no events and resolved versus no events. For SLE and non-SLE NP events, annual, five, and 10-year indirect costs were higher in those with new/ongoing versus no events and five and 10-year indirect costs were higher in new/ongoing versus resolved events.
- Among frequent SLE NP events, new/ongoing seizure disorder and cerebrovascular disease accounted for the largest increases in annual direct costs. For non-SLE NP events, new/ongoing polyneuropathy accounted for the largest increase in annual direct costs and new/ongoing headache and mood disorder for the largest increases in indirect costs.
- The high economic burden associated with NP events in SLE, in addition to the previously documented negative impact on health-related quality of life and mortality, underlines the importance of improving care for this component of SLE.

Table 1.

Demographic and clinical characteristics at time of cohort entry for full sample providing partial direct costs and cohort subset providing complete direct and indirect costs

Characteristic	Full sample, n=1697	Subset, n=672
Age, mean (standard deviation)	35.1 (13.3)	33.2 (12.0)
Sex, % female	88.7	89.3
Education, % any postsecondary	61.8	61.1
Race/ethnicity, %		
White	48.8	40.9
African	16.7	11.5
Hispanic	15.8	18.0
Asian	15.0	26.5
Geographic region, %		
US	27.9	14.6
Europe	26.8	8.2
Canada	23.2	41.4
Mexico	12.6	16.1
Republic of Korea	9.5	19.8
Disease duration, mean (range), years	0.5 (0 – 1.3)	0.4 (0 – 1.3)
SLEDAI–2K score, mean (standard deviation)	5.4 (5.4)	6.1 (5.6)
SDI score at first annual follow up, mean (standard deviation)	0.44 (0.87)	0.36 (0.78)
Medications, %		
Glucocorticoids	70.9	72.3
Antimalarials	67.7	68.4
Immunosuppressants	40.9	42.9
Smoking, ever, %	35.0	30.2
High-risk alcohol consumption, *%	1.3	0.6
Employed, % **		59.8

* Refers to > 15 drinks per week for men and > 10 drinks per week for women(19)

** At the time of the completion of the first economic questionnaire; data only available for the subcohort completing the economic questionnaire

SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 2:

Unadjusted annual partial direct costs (in 2021 Canadian dollars) for the full cohort (n=1697) stratified by SLE and non-SLE NP events. Values are the mean (95% CI).

	SLE NP events			Non-SLE NP events		
Direct Cost Components	**No NP event**	**Resolved NP event**	**New/Ongoing NP event**	**No NP event**	**Resolved NP event**	**New/Ongoing NP event**
Patients, n	1487	235	273	1280	504	620
Observations, n (%)	11155 (80)	1562 (11)	1270 (9)	8169 (58)	2922 (21)	2896 (21)
Direct costs	3948 (3609, 4287)	5054 (4163, 5945)	6916 (5864, 7967)	3559 (3253, 3866)	5405 (4637, 6173)	5472 (4579, 6365)
Hosp	1148 (1032, 1263)	1682 (1211, 2154)	2246 (1797, 2695)	1179 (1040, 1318)	1597 (1285, 1910)	1376 (1156, 1597)
Meds	1833 (1560, 2107)	2219 (1620, 2819)	2459 (1934, 2984)	1629 (1412, 1846)	2237 (1672, 2802)	2485 (1732, 3238)
Tests	72 (66, 78)	85 (68, 102)	162 (138, 186)	76 (69, 83)	64 (54, 73)	117 (102, 132)
Dialysis	895 (743, 1047)	1067 (636, 1498)	2049 (1352, 2746)	676 (527, 826)	1507 (1116, 1898)	1494 (1097, 1890)

Table 3:

Unadjusted annual complete direct, indirect, and total costs (in 2021 Canadian dollars) for the cohort subset (n=672) providing complete cost data stratified by SLE and non-SLE NP events. Values are the mean (95% CI).

	SLE NP events			Non-SLE NP events		
Direct and Indirect Cost Components	**No NP event**	**Resolved NP event**	**New/Ongoing NP event**	**No NP event**	**Resolved NP event**	**New/ongoing NP event**
Patients, n	537	93	60	361	191	167
Observations, n (%)	1250 (78)	214 (13)	130 (8)	822 (52)	403 (25)	369 (23)
Direct costs	7240 (6150, 8331)	9245 (6565, 11926)	10938 (7383, 14493)	6125 (5172, 7078)	9009 (6186, 11832)	10259 (8373, 12145)
Hosp	1156 (824, 1487)	1644 (738, 2550)	1683 (898, 2468)	1153 (709, 1597)	1185 (730, 1641)	1598 (975, 2221)
Meds	2254 (1443, 3065)	2040 (1073, 3008)	3518 (1524, 5512)	1807 (1356, 2259)	2948 (573, 5323)	2813 (2017, 3608)
Physicians	1010 (928, 1092)	1241 (905, 1577)	1376 (1106, 1645)	898 (813, 983)	1114 (955, 1274)	1409 (1170, 1648)
Tests	732 (641, 823)	698 (559, 837)	1108 (822, 1394)	639 (554, 725)	819 (688, 951)	956 (721, 1191)
Dialysis	1203 (657, 1749)	2397 (575, 4220)	2030 (-208, 4268)	850 (293, 1407)	1910 (706, 3113)	2201 (832, 3571)
Other *	886 (759, 1012)	1225 (804, 1645)	1224 (872, 1575)	777 (643, 911)	1033 (747, 1319)	1282 (1017, 1547)
Indirect costs	33108 (30767, 35450)	34444 (28959, 39928)	44571 (38140, 51001)	29820 (27167, 32473)	36095 (32189, 40001)	41984 (37042, 46926)
Paid labour costs	12449 (10674, 14224)	13998 (10437, 17559)	22127 (18150, 26104)	10873 (8961, 12786)	13437 (10741, 16133)	19188 (15259, 23117)
Absenteeism	1621 (722, 2519)	993 (622, 1364)	514 (150, 878)	922 (700, 1144)	1523 (1046, 2000)	2529 (-447, 5505)
Presenteeism	4646 (4101, 5191)	3850 (2615, 5086)	3001 (1672, 4331)	4254 (3631, 4877)	5474 (4369, 6580)	3575 (2711, 4438)
Opportunity	6182 (4441, 7923)	9155 (5107, 13203)	18612 (13881, 23343)	5697 (3627, 7767)	6440 (3284, 9596)	13084 (9911, 16258)
Unpaid labour costs	20659 (19075, 22244)	20446 (15964, 24927)	22444 (17381, 27507)	18947 (16959, 20935)	22658 (19681, 25634)	22796 (19899, 25693)
Presenteeism	7979 (7161, 8798)	7364 (5628, 9100)	8627 (5816, 11439)	6641 (5755, 7527)	9291 (7748, 10834)	9399 (7705, 11093)
Opportunity	12680 (10845, 14515)	13082 (8061, 18102)	13817 (7932, 19702)	12306 (10081, 14531)	13366 (9933, 16800)	13397 (9826, 16968)
Total Costs	40349 (37691, 43007)	43689 (37443, 49935)	55509 (47659, 63359)	35945 (33132, 38759)	45104 (39994, 50214)	52243 (46747, 57740)

*Other includes non-physician healthcare professional, emergency room visits, outpatient surgeries, and help obtaining medical care

Table 4:

Predicted annual and five and 10-year direct and indirect costs (in 2021 Canadian dollars) for the cohort subset (n=672) providing complete cost data stratified by SLE and non-SLE NP events. Values are the mean (95% C).

		No NP event	Resolved NP event	New/ ongoing NP event	Difference between resolved and no NP event	Difference Between ongoing/new and no NP event	Difference new/ ongoing and resolved NP event
SLE NP events							
Direct Costs	**1 year**	7505	10704	13825	3199 (−4140, 10538)	**6320 (1399, 11241)**	3121 (−3260, 9501)
	5 years	36948	51118	62071	14170 (−18588, 46928)	**25123 (6566, 43680)**	10953 (−20059, 41965)
	10 years	69870	96196	110682	26326 (−31628, 84280)	**40812 (7186, 74438)**	14486 (−26529, 55500)
Indirect Costs*	**1 year**	33347	32941	42695	−406 (−7332, 6520)	**9348 (1004, 17692)**	9754 (1006, 18502)
	5 years	177634	175660	209893	−1974 (−32889, 28940)	**32259 (2380, 62138)**	34234 (−3825, 72292)
	10 years	366003	364372	409647	−1630 (−56335, 53706)	43645 (−2387, 89677)	45275 (−5059, 95608)
Non-SLE NP events							
Direct Costs**	**1 year**	6606	9893	11181	3287 (−435, 7010)	**4575 (1145, 8006)**	1288 (−2156, 4733)
	5 years	37984	51051	55364	13067 (−2510, 28645)	**17380 (5974, 28787)**	4313 (−12635, 21261)
	10 years	80277	103034	108532	22757 (−3104, 48617)	**28255 (10588, 45922)**	5498 (−16108, 27104)
Indirect Costs*	**1 year**	30391	35545	40665	5154 (−451, 10759)	**10274 (3493, 17056)**	5120 (−1687, 11927)
	5 years	166771	186798	203940	20027 (−3438, 43492)	**37169 (14976, 59361)**	17142 (−12313, 46597)
	10 years	347053	382680	404533	35627 (−3311, 74565)	**57480 (24978, 89982)**	21853 (−15697, 59402)

*Adjusted for disease duration, education, and residing outside North America

**Adjusted for disease duration

Boldface indicates differences which are significant as the 95% CI does not include 0.

Table 5:

Predicted imputed annual and five and 10-year complete direct and indirect costs (in 2021 Canadian dollars) for the full cohort (n=1697) stratified by SLE and non-SLE NP events. Values are the mean (95%CI).

		No NP event	Resolved NP event	New/ ongoing NP event	Difference between resolved and no NP event	Difference between new/ ongoing and no NP event	Difference between new/ ongoing and resolved NP event
SLE NP events							
Direct Costs *	**1 year**	6668	9089	10471	**2421 (859,3983)**	**3803 (2136, 5471)**	1382 (−602, 3366)
	5 years	35324	46066	50916	**10742 (3781, 17704)**	**15592 (9601, 21584)**	4850 (−3149, 12849)
	10 years	71906	91667	98081	**19761 (7443, 32079)**	**26176 (16707, 35644)**	6415 (−4164, 16993)
Indirect Costs **	**1 year**	26248	27103	37197	855 (−2759, 4469)	**10950 (376, 21523)**	10094 (−2136, 22505)
	5 years	139617	143244	178672	3627 (−11907, 19161)	**39055 (6181, 71930)**	**35428 (363, 70493)**
	10 years	286295	294893	341747	8599 (−18925, 36122)	**55453 (9002, 101904)**	**46855 (480, 93229)**
Non-SLE NP events							
Direct Costs *	**1 year**	6264	8045	8931	**1781 (438,3124)**	**2667 (1471, 3864)**	886 (−514, 2287)
	5 years	34086	41139	44106	**7052 (1491, 12614)**	**10019 (6045, 13994)**	2967 (−3012, 8947)
	10 years	70090	82417	86200	**12327 (3094, 21560)**	**16110 (9913, 22306)**	3783 (−3840, 11405)
Indirect Costs **	**1 year**	24286	29059	35732	4772 (−214, 9759)	**11446 (7532, 15360)**	**6673 (1179, 12168)**
	5 years	134332	152589	174931	18256 (−748, 37260)	**40598 (28356, 52841)**	**22342 (2858, 41826)**
	10 years	279010	311965	340447	32955 (1403, 64507)	**61437 (41757, 81117)**	**28482 (3644, 53320)**

*Adjusted for disease duration and White race and ethnicity

**Adjusted for White race and ethnicity and residing outside North America

Boldface indicates differences which are significant as the 95% CI does not include 0.

Table 6.

Regression models for direct and indirect costs stratified by individual SLE and non-SLE NP events

	Direct	Indirect
SLE NP events		
Mood disorder (new/ongoing *)	-1147 (-3374, 1081)	6495 (-3927, 16916)
Seizure disorder (new/ongoing)	**10179 (7114, 13245)**	9365 (-1469, 20200)
Cerebrovascular disease (new/ongoing)	**3907 (920, 6893)**	4222 (-3460, 11904)
Mononeuropathy (new/ongoing)	1899 (-1699, 5498)	4205 (-5625, 14035)
Other NP event (new/ongoing)	**4383 (2272, 6494)**	**8065 (22, 16108)**
White race/ethnicity	**-2380 (-3452, -1309)**	-
Disease duration	**278 (203, 354)**	**1213 (367, 2059)**
Residing outside of North America **	-	**-12907 (-18658, -7157)**
Postsecondary education	-	**-5866 (-10074, -1657)**
Non-SLE NP events		
Headache (new/ongoing)	**1216 (202, 2229)**	**6824 (3441, 10208)**
Mood disorder (new/ongoing)	-580 (-2424, 1263)	**4660 (229, 9091)**
Anxiety disorder (new/ongoing)	2299 (-218, 4816)	6901 (-194, 13996)
Polyneuropathy (new/ongoing)	**9168 (5392, 12943)**	7448 (-3375, 18270)
Other NP event (new/ongoing)	**8939 (5564, 12314)**	3597 (-3290, 10485)
White race/ethnicity	**-2502 (-3626, -1377)**	-
Disease duration	**282 (202, 363)**	**1276 (796, 1756)**
Residing outside of North America **	-	**-11472 (-18352, -4592)**
Postsecondary education	-	**-5821 (-10333, -1310)**

* Reference group is no event or resolved event

** North America includes Canada, the US, and Mexico

Boldface indicates differences which are significant as the 95% CI does not include 0.

The empty cells refer to variables which were included as potential covariates but were not retained in the final model as they were not significant.