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The socioeconomic burden of SLE

Chak Sing Lau and Anselm Mak

Abstract | Systemic lupus erythematosus (SLE) is a chronic, relapsing–remitting, multisystemic autoimmune inflammatory disorder that predominantly affects women of childbearing age. Much has been written about the clinical course and long-term damage associated with SLE, as well as the reduced life expectancy of patients with this condition. In addition, studies have emphasized the socioeconomic and psychosocial impact of SLE, although the monetary cost of caring for patients with the disorder has only been evaluated in a modest number of studies and a restricted number of countries. SLE has a negative impact on quality of life and is associated with high health-care costs and significant productivity loss. Factors associated with increased cost of SLE include long disease duration, high disease activity and damage, poor physical and mental health, and high education and employment levels. Similarly, high disease activity and damage, poor physical health, certain disease manifestations, as well as poor family and social support are associated with poor health-related quality of life outcomes. SLE incurs a great burden on both the patient and society. Long-term prospective studies should be encouraged to monitor the costs and psychosocial impact of this condition, and to better understand the factors that are associated with poor outcomes.

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The scope of the problem

Few conditions inflict as much physical and functional disability as systemic lupus erythematosus (SLE). There is currently no cure for SLE, and the disease can result in multisystem failure and even death. SLE incurs a significant burden both to patients and to society as a whole. Evidence from the last few decades has shown that uncontrolled disease and infectious complications are responsible for the majority of adverse outcomes in patients with SLE.^{1,2} However, tremendous improvements have been seen in the short-term and medium-term survival of these patients owing to earlier diagnosis, judicious use of potent immunosuppressive agents, meticulous monitoring of disease activity and the availability of powerful antibiotics for the treatment of infective complications.³ Nonetheless, the long-term prognosis of SLE remains poor because of chronic tissue and organ damage pertaining either to the disease itself or its treatment. Unlike infections and disease flares, which are episodic and largely amenable to therapy, SLE damage is mostly irreversible, cumulative and potentially life-threatening.

Early disease damage has been shown to have a significant impact on the long-term survival of patients with SLE. A report from Rahman *et al.*⁴ in Toronto, Canada, has shown that a significantly greater number of patients with early disease damage, defined as the presence of damage at initial assessment, died within 10 years compared with patients who had no early damage. A later prospective study revealed that overall damage accrued as early as 1 year after the diagnosis of SLE could predict mortality.⁵ Of the various organs and tissues that are susceptible to

SLE-related damage, the cardiovascular system is associated with the most substantial long-term morbidity and premature mortality.^{6–8} Notably, among premenopausal women, a group that is usually protected from coronary events, the incidence of myocardial infarction has been shown to be more than 50 times higher in those with SLE compared with healthy individuals.⁶ Based on a 36-year observational study of the University of Toronto Lupus Clinic cohort, Urowitz *et al.*⁹ reported that cardiovascular disease and overall SLE-related damage are strong predictors of all-cause mortality. Despite improvements in disease activity control and overall disease survival over the duration of the study, the authors observed increases both in cumulative organ damage and in the incidence of coronary artery disease, both of which had significant detrimental effects on disease prognosis. Although not as prevalent as cardiovascular disease, other life-threatening damage, such as renal and pulmonary disease, has also been shown to predict mortality.^{4,10} In a recent study reported by Danila *et al.*,¹¹ of all the domains of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), renal damage was found to be the most important predictor of mortality.

Interestingly, although neuropsychiatric disease and osteoporotic fracture have been shown to be highly prevalent in several SLE cohorts, studies of their effects on the mortality of patients with SLE are surprisingly scarce. In a cohort study of 282 Chinese patients with a mean follow-up period of 6.7 years, neuropsychiatric damage was not predictive of mortality.¹² Similarly, fragility fractures, which are reported in 6–20% of patients with SLE in the US, Europe and China,^{13–16} have not been shown to predict mortality, in contrast to observations of

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Competing interests

The authors declare no competing interests.

Key points

- Systemic lupus erythematosus (SLE) has a significant negative impact on a patient's quality of life, and is associated with high health-care costs and loss of productivity
- Increased disease activity and damage, poor physical health, and poor family and social support are associated with a reduced quality of life in patients with SLE
- Patients with certain manifestations SLE, such as disfiguring cutaneous disease, have a worse quality of life than patients without these manifestations
- Health-care costs are higher in patients with a long disease duration, high SLE disease activity and damage, poor physical and mental health, and high education and employment level
- Long-term prospective studies are needed to evaluate the costs of SLE and to assist policymakers in the future elaboration of health-care resource planning and allocation

Box 1 | Definitions of terms used to estimate the socioeconomic costs of SLE [ED: changed to SLE to fit onto 1 line, ok?]

Direct cost: expenditures for diagnosis, treatment, continuing care and rehabilitation.

Indirect cost: loss of productivity due to illness, including both diminished labor market and non-labor or household activity (for example, housekeeping and childcare).

Intangible costs: Expenditures that are more difficult to measure, mainly the assessment of health-related quality of life.

postmenopausal women with osteoporotic fractures in the general population.

A wealth of evidence exists to describe the effects of SLE on the life expectancy of a patient. However, unlike other chronic rheumatic conditions, such as rheumatoid arthritis and osteoarthritis, there is a comparative lack of data on the socioeconomic burden of SLE. Evidence suggests that socioeconomic status is a crucial component of long-term survival in patients with SLE.¹⁷ Thus, it is important to address the magnitude of the problem and understand the factors that might affect the socioeconomic burden of the disease, including the health service costs of caring for a patient with SLE. The relevance of health-care costs is brought to the fore by the recent global economic downturn and the advent of new treatments for SLE. Improved knowledge in this area will allow health-care policymakers to explore specific cost drivers and decide how best to allocate health-care and research resources.

The socioeconomic cost of SLE

Owing to the nature of the condition, estimating the socioeconomic cost of SLE poses a challenge to researchers. SLE is characterized by a chronic remitting-relapsing course and a wide range of disease-associated and unrelated factors that not only entail health-care expenditure, such as physician consultation and diagnostic and therapeutic procedures, but also impose a significant burden on patients' health-related quality of life (HRQOL), work-related disability and other expenditures that are more difficult to measure. Crucially, SLE predominantly affects young women, who constitute the majority of the

non-labor, domestic workforce; such difficult-to-measure yet essential burdens, therefore, need to be addressed properly and factored into the overall cost estimation.¹⁸ A number of cohort studies have shown that overall SLE-related damage is associated with work disability and loss of productivity,^{19–21} and is detrimental to both the physical and mental functioning of a patient.²² The various terms used in evaluating the socioeconomic costs of SLE are defined in **Box 1**, and are further discussed in the Supplementary information online.

Direct and indirect monetary costs

The main findings of the available studies that have investigated the monetary costs of SLE are summarized in **Table 1**. The Tri-Nation study involved over 700 patients from Canada, UK and the US, and was the first prospective study to estimate and compare the cost of caring for patients with SLE, and assess the relationship of this cost to disease characteristics and outcome.^{18,23,24} As well as studies from Canada²⁵ and the UK,²⁶ data from two large-scale studies from Germany²⁷ and the US²⁸ are now available.

Despite the relative paucity of studies, all have shown that substantial costs are incurred in the care of patients with SLE. In the Tri-Nation study, the annual total direct health-care costs (based on the value of CAD\$ in 2002) were CAD\$4,968, CAD\$4,763 and CAD\$5,055 in Canada, the UK and the US, respectively.²⁴ Notably, although patients with SLE in Canada and the UK spent 20% and 13% less on direct resources, respectively, than their US counterparts, they did not experience inferior outcomes in terms of disease damage and physical and mental well-being.²⁴ During a similar period, a study comprising 844 German patients with SLE revealed that the annual direct health-care cost for one patient was €3,191,²⁷ which is relatively similar to that of Canada in the Tri-Nation study.²⁹ In a study from 2008, which included 815 patients with SLE in the US, the annual direct health-care cost for a single patient with SLE was estimated to be approximately US\$13,000, with the indirect cost exceeding US\$8,600.²⁸

Almost all of the related studies have demonstrated that indirect costs constitute the majority of the total cost.^{24–27,30} Sutcliffe and colleagues²⁶ demonstrated that the indirect cost constituted approximately two-thirds of the total cost. In the Tri-Nation study, indirect costs were shown to be between 2.4 and 2.8 times higher than the corresponding direct costs;³⁰ and in Germany, the indirect costs were two times higher than the direct costs of caring for a patient with SLE.²⁷

Factors associated with higher cost

Multiple regression analyses have demonstrated that long disease duration, more-active disease,²⁷ high disease-related damage^{24,26,29} and poor physical and mental health²⁸ were associated with higher direct costs, whereas older age,²⁶ more-active disease,^{24,28} longer disease duration,²⁷ disease-related damage²⁹ and poorer HRQOL²⁶ were associated with higher indirect costs. Interestingly, in one study, higher educational level

[ED: country row removed and added to number of patients to fit table onto 1 page. ok?]

Table 1 Major findings of SLE cost-of-illness studies							
Study	Clarke et al. (1993) ²⁵	Sutcliffe et al. (2001) ²⁶	Clarke et al. (1999) ²³	Clarke et al. (2004) ²⁴	Panopalis et al. (2007) ³⁰	Huscher et al. (2006) ²⁷	Panopalis et al. (2008) ²⁸
Recruitment period	Jan 1990 to Jan 1991	Jul 1995 to Jul 1997	Jun 1995 to Feb 1998	Jul 1995 to Feb 1998	Jul 1995 to Feb 1998	2002	2002–2005
Study type	Cross-sectional analysis (preceding 6 months)	Prospective analysis (6 months)	Cross-sectional analysis (preceding 6 months)	Prospective analysis (4 years)	Prospective analysis (4 years)	Prospective analysis (12 months)	Prospective analysis (12 months)
Country, number of patients	Canada: 164	UK: 105	Tri-Nation study Canada: 229 USA: 268 UK: 211 Total: 778	Tri-Nation study Canada: 162 USA: 157 UK: 166 Total: 485	Tri-Nation study Canada: 162 USA: 157 UK: 166 Total: 485	Germany: 844	USA: 812
Mean age, years	45.0 (range 16.3–85.6)	39.9 (range 18.8–75.3)	Canada: 43.3±13.8 USA: 39±11.9 UK: 40.7±12.1	Canada: 42.4 (95% CI 40.3–44.4) USA: 39.1 (95% CI 37.4–40.8) UK: 40.0 (95% CI 38.2–41.7)	Canada: 42.4 (95% CI 40.3–44.4) USA: 39.1 (95% CI 37.4–40.8) UK: 40.0 (95% CI 38.2–41.7)	42 ^f	48.2±12.8 ^h
Mean duration of SLE, years	13.5 (range 0.1–40.6)	10.5 (range 1–33.5)	Canada: 10.2±7.4 USA: 8.6±6.2 UK: 10.0±7.1	Canada: 9.9 (95% CI 8.7–11.1) USA: 8.6 (95% CI 7.6–9.6) UK: 10.0 (95% CI 9.0–11.1)	Canada: 9.9 (95% CI 8.7–11.1) USA: 8.6 (95% CI 7.6–9.6) UK: 10.0 (95% CI 9.0–11.1)	NA	13.7±8.5
Patients in employment %	44	54.3	NA	NA	Canada: 48.7 USA: 45.3 UK: 52.6	55	48.7
Mean annual direct cost	CAD\$6,023 ^a (2009) US\$7,102	£2,613 ^b (2009) US\$4,784	Canada: CAD\$4,853 ^c (2009 US\$4,953) USA: CAD\$5,285 ^c (2009 US\$4,949) UK: CAD\$4,760 ^c (2009 US\$4,457)	Canada: CAD\$3,961 ^d (2009 US\$3,709) USA: CAD\$5,061 ^d (2009 US\$4,739) UK: CAD\$4,412 ^d (2009 US\$4,131)	NA	€3,191 ^e (2009) US\$3,369	US\$12,643 ⁱ (2009) US\$14,202
Mean annual indirect cost	CAD\$7,071 ^a (2009) US\$8,422	£5,299 ^b (2009) US\$10,241	NA	NA	^e Canada: CAD\$11,024 ^d (2009 US\$10,323) ^e USA: CAD\$15,499 ^d (2009 US\$14,513) ^e UK: CAD\$12,696 ^d (2009 US\$11,889)	€11,220 ^e (2009) US\$11,845	US\$8,659 ⁱ (2009) US\$9,727
Mean annual total cost	CAD\$13,094 ^a (2009) US\$15,524	£7,913 ^b (2009) US\$11,652	NA	NA	NA	€14,411 ^e (2009) US\$15,213	US\$20,924 ⁱ (2009) US\$23,504
Indicators for high direct cost	High creatinine; poor physical function	High disease activity; high disease damage; poor physical function; high education level	NA	NA	NA	High disease activity; short duration of disease; low functional status	High disease activity; long disease duration; poor physical health; poor mental health
Indicators for high indirect cost	Low SLE well-being; weak social support; high education level and employment	High disease activity; poor physical function; high education level	NA	NA	NA	Advanced age; long duration of disease; low functional status	Advanced age; high disease activity; poor physical health; poor mental health

For ease of reference, the monetary cost of SLE reported in these studies is also expressed in USD; exchange rates are correct as of April 2009. ^a1990 Canadian Dollars. ^b1996 Sterling Pounds. ^c1997 Canadian Dollars. ^d2002 Canadian Dollars. ^eSum of the cumulative indirect cost as a result of diminished labor market activity and cumulative indirect cost owing to non-labor market activity (replacement cost, 50%). ^fPatients of working age (<65 years) were studied. ^g2002 Euros. ^hPatients of working age (≥18 and <65 years) were studied. ⁱ2004 US Dollars. Abbreviations: NA, not available; SLE, systemic lupus erythematosus.

was found to incur increased direct health-care costs compared with a lower level of education.²⁶ This phenomenon is probably related to better follow-up and medication compliance amongst patients who are well educated. Because of their higher earning power, the loss of productivity and subsequent indirect cost to the labor market would also be proportionally higher in better-educated patients with SLE.²⁶

Impact of SLE on HRQOL

Most chronic illnesses affect patients' HRQOL, self-esteem, family and marital relationships and psychosocial health. These intangible costs are difficult to evaluate, and most studies have focused mainly on the discrepancy of HRQOL. A number of early studies confirmed that patients with SLE have a poorer HRQOL compared with healthy individuals.^{31–38} The Medical Outcomes Study (MOS) short form (SF)-36 questionnaire is the most commonly used tool to evaluate the HRQOL of patients with SLE.³⁹ The questionnaire consists of eight domains that measure important physical and mental components of health: physical function, role physical, bodily pain, general health, mental health, role emotional, social function and vitality. Significant decrements have been observed in all eight domains of the SF-36 across groups of SLE patients of different ethnicities.^{33–35} In addition, studies have shown that the effects of SLE on HRQOL are comparable to those in other chronic diseases, some of which might be perceived as being more severe than SLE, including AIDS, rheumatoid arthritis, psoriatic arthritis, hypertension, diabetes, post-myocardial infarction and congestive heart failure.^{40–42}

In addition, factors related to patient demographics, disease and therapy have been shown to influence the HRQOL of patients with SLE. For example, a study from the Netherlands showed that patients with SLE who were unemployed had lower HRQOL than those who were employed.⁴³ Similarly, young age at diagnosis, a short disease duration, poor physical health, low family support, a sense of helplessness and use of cytotoxic drugs have been shown to be associated with worse HRQOL in patients with SLE.³⁵

Furthermore, cross-sectional studies have shown that certain manifestations of SLE, such as end-stage renal disease⁴⁰ and cutaneous disease (particularly alopecia and discoid lupus lesions⁴⁵) are associated with poorer HRQOL irrespective of overall disease activity. However, prospective clinical trials, which allow examination of a cause-and-effect relationship, have shown that improvements in overall disease activity are associated with improved HRQOL.^{37,46} Interestingly, although some therapeutic interventions can be equally effective in controlling certain disease complications, their effects on HRQOL can differ. For example, a recent study from Hong Kong showed that induction of immunosuppression using mycophenolate mofetil for the treatment of severe SLE-related nephritis was associated with better HRQOL than oral cyclophosphamide therapy, despite the two interventions having

a similar therapeutic effect.⁴⁷ Disease damage has been shown to be associated with decreased physical, social and mental functioning.^{35,36,48} Furthermore, any new organ damage might predict a further decline in HRQOL.⁴⁸

These observations highlight the importance of measuring HRQOL when evaluating the burden of SLE. Although the SF-36 has several features that make it a suitable instrument for measuring HRQOL in patients with SLE, it is not disease specific. SLE-specific measures are, however, being developed.^{41,49–51} For example, the SLE-specific quality-of-life instrument (SLEQOL) is a 40-item questionnaire in the English language that has been validated for use in patients with SLE in Singapore.⁵¹ Similarly, the LupusQoL, a 34-item questionnaire that covers eight disease-related domains defined by patients as being important,⁵⁰ and the 55-item L-QoL questionnaire⁵¹ have been developed and validated for use in the UK. Using the Rasch model for analysis, the L-QoL was shown to be a valuable instrument for assessing patient-based outcomes in clinical trials in various cohorts of different localities.⁵¹ Until further cultural adaptation and validation is undertaken, however, the use of these instruments remains limited to Singaporean Chinese⁴⁹ and British white populations.^{50,51}

Conclusions and future directions

Improvements in the diagnosis and management of SLE mean that patients are living longer, and the burden of disease at both personal and societal levels is expected to increase. Furthermore, although SLE is less common than other rheumatologic disorders, its predilection for the younger and more productive members of the general population makes it essential that we have a better understanding of the various costs associated with the disease. Although cost-of-illness studies have been criticized for their limitations as a result of possible measurement errors, recall biases and poor comparability across studies, they are a valuable tool to assist policymakers in planning and allocating health-care resources. Early studies have shown that SLE is associated with significant health-care costs and impaired patient quality of life. Longer-term prospective studies are needed to continue to monitor the impact of SLE, especially considering that patient characteristics, disease prognosis, treatment strategies and the financial climate are ever-changing dynamic processes. More importantly, these types of studies are urgently required in the Asia-Pacific region, which houses the majority of the world's SLE patients,⁵² and where the enormous disparity in the needs of patients with SLE and resources available are a major concern.

Review criteria

Full articles published in the English language were sourced from PubMed (from 1966 to February 2009) using the keywords "systemic lupus", "lupus", "healthcare cost", "cost", "quality of life" and "damage". Reference lists of original and review articles retrieved were scanned and relevant articles were reviewed for eligibility.

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