Socioeconomic Impact of Systemic Lupus Erythematosus in Hong Kong: Direct, Indirect Costs and Health-related Quality of Life

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When I walk, it heals

When I stop, it sits

When I go, it comes

Obedient to my blood

- Laura Chester (poet/ novelist, a victim of lupus)

ABSTRACT

Systemic lupus erythematosus (SLE) is a multi-factorial autoimmune disease that primarily affects young women, characterized by a chronic remitting-relapsing (flare) disease course. Central nervous system is one of the most common affect systems in SLE. Neuropsychiatric SLE (NPSLE) is associated with impairment of quality of life, accumulated disease damage, disability and employment. Flare, an increase in disease activity over a defined period, is an important outcome in the assessment of SLE. Uncontrolled disease activity results in cumulative organ damage which is associated with increased mortality.

Cost-of-illness studies measure the monetary burden that a disease imposes on society or individuals. The substantial financial burden of SLE has been demonstrated in a modest number of studies and a restricted number of countries. However, there is no study investigating the relationship between disease costs and NPSLE/flare.

We hypothesized that:

1. SLE is associated with substantial socioeconomic burden as a result of NPSLE and flare;

2. patients with NPSLE or flares may experience more compromised health-related quality of life (HRQoL).

The present thesis was a retrospective cost-of-illness study on Chinese patients in Hong Kong with SLE within working age, aiming to

1. estimate the direct and indirect costs of SLE from a societal perspective;

2. ascertain the relationship between NPSLE and direct and indirect costs;

3. ascertain the relationship between flare and direct and indirect costs;

4. investigate the relationship between HRQoL and NPSLE/flares.

A cohort of 306 patients was recruited. Questionnaire interview, review of medical records and clinical assessments were performed to obtain information regarding disease status, healthcare resources utilization and HRQoL.

The main findings were as follows.

1. The average annual total costs were USD 13,307 (2006 US dollars) per patient. The direct costs dominated the total costs (62%), and the costs of inpatient care contributed 52% of the direct costs. Costs of SLE per subject are higher than those of

other chronic diseases in Hong Kong.

2. Patients with NPSLE incurred significantly higher direct and indirect costs compared to those without NPSLE. The number of NPSLE event was an independent explanatory variable associated with both increased direct and indirect costs.

3. Annual direct costs and indirect costs were significantly higher in those with flares. The number of flare was an independent explanatory variable associated with increased direct costs. Patients with multi-organ flares or renal/neuropsychiatric flares incurred higher direct costs than those with single organ flare or those with minor organ flares.

4. Patients with SLE had significantly lower level of HRQoL compared with Hong Kong general population. The presence of NPSLE and flare only weakly associated with impairment of HRQoL.

In summary, this study has provided support for our hypotheses. The socioeconomic impact of SLE in Hong Kong is considerable. The presence of NPSLE and flare are significantly associated increase disease costs but not impaired HRQoL. These

suggest that management, which can lead to early diagnosis and effectively control disease activity and prevent lupus flares, may reduce disease costs due to both healthcare consumption and loss of productivity.

中文摘要

系統性紅斑狼瘡是一種慢性自身免疫性疾病。SLE 可以影響身體多個器官系統造成臨床上多樣的症狀，中樞神經系統（CNS）是其中最常受累的系統。SLE 的疾病病程有緩解-加重反復出現的特點。目前只有少數文獻研究該疾病對社會或者患者造成的經濟負擔。疾病成本分析通常包括疾病造成的直接（通常指直接醫療成本），間接經濟（患者工作能力的損失）損失和無形的損失（生活品質的受損）。

我們進行了一項關於系統性紅斑狼瘡的疾病成本分析， 目的爲：

1 探討香港系統性紅斑狼瘡患者的疾病成本

2 疾病成本與 CNS 表現之間的關係

3 疾病成本與病情加重之間的關係

4. 生活品質與 CNS 表現和病情加重之間的關係

我們發現：

1.每年每名患者的平均直接經濟損失爲 8,230 美元，而間接經濟損失爲 5,077 美元。與香港其他慢性疾病的疾病成本比較，每名 SLE 患者的疾病成本明顯較高。

2. 有 CNS 表現的 SLE 患者的直接和間接疾病成本則明顯高於沒有的患者。患者曾有過的 CNS 的表現的數目則和疾病的經濟損失成正相關。

3. 如果患者在過去一年曾經有過疾病加重，其造成的經濟損失也會明顯升高。而過去一年疾病加重的次數則和直接經濟損失成正相關。多系統疾病加重，或者主要器官（腎和腦）疾病加重也會明顯增加疾病的直接經濟損失。

4. SLE 患者的生活品質也是明顯低於香港普通人群。但是，相比起沒有 CNS 表現的患者，有 CNS 表現的患者只在總體健康狀況一個方面明顯有較差的生活品質。在過去一年曾有過疾病加重的患者也只有在幾個而不是全部的生活品質範疇比沒有的患者有更爲受損的生活品質。然而，有肌肉骨骼系統疾病加重的患者，例如有關節炎或者關節痛則明顯地比沒有的患者有較差的生活品質。

在這個研究裏，我們發現 SLE 對社會和患者個人都造成了巨大的經濟和精神上的損失。有中樞神經系統表現和病情加重的患者其疾病成本高於沒有的患者，但其生活品質受損並明顯嚴重于沒有的患者。

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I dedicate this thesis to my families. I wish they would be proud of me.

I thank God for all the competence and strength he has given to me. Whatever is done by only me is God's doing.

LIST OF PUBLICATIONS

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2. Zhu TY, Tam LS, Lee VW, Lee KK, Li EK. The impact of flare on disease costs of patients with systemic lupus erythematosus. Arthritis & Rheumatism 2009;61:1159-67.
3. Zhu TY, Tam LS, Lee VW, Lee KK, Li EK. Relationship Between Flare and Health-related Quality Of Life in Patients with Systemic Lupus Erythematosus. The Journal of Rheumatology. 2010: 37: 568-73

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1. Zhu TY, Tam LS, Lee VW, Hwang WW, Li TK, Lee KK, et al. Costs and quality of life of patients with ankylosing spondylitis in Hong Kong. Rheumatology (Oxford) 2008;47:1422-5.
2. Zhu TY, Tam LS, Leung YY, Kwok LW, Wong KC, Yu T, et al. Socioeconomic burden of psoriatic arthritis in Hong Kong: direct and indirect costs and the influence of disease pattern. The Journal of Rheumatology; Epub ahead of print 2010 Apr 1.
3. Tam, LS, Wong, A, Mok, VC, Zhu, YE, Kwok, LW, Li, TK, et al. The relationship between neuropsychiatric, clinical, and laboratory variables and quality of life of Chinese patients with systemic lupus erythematosus. The Journal of Rheumatology 2008 35: 1038-45.
4. Li EK, Zhu TY, Tam LS, Hung VW, Griffith JF, Li TK, et al. Bone microarchitecture assessment by high-resolution peripheral quantitative

computed tomography in patients with systemic lupus erythematosus on corticosteroids. The Journal of Rheumatology 2010. Accepted, in press.

5. Li EK, Tam LS, Zhu TY, Li M, Kwok CL, Li TK, et al. Is combination rituximab with cyclophosphamide better than rituximab alone in the treatment of lupus nephritis? Rheumatology (Oxford) 2009;48:892-8.
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ABBREVIATIONS

ACR	American College of Rheumatology
AMI	Acute myocardial infarction
ANA	Antinuclear antibodies
Anti-ds DNA	Anti-double stranded DNA
AS	Ankylosing spondylitis
BILAG	British Isles Lupus Activity Group
CMS	Clinical management system
CNS	Central nervous system
CVD	Cerebrovascular disease
DM	Diabetes mellitus
ECG	Electrocardiogram
ECLAM	European Consensus Lupus Activity Measurement
EUR	Euro dollar
FCM	Friction cost method
HAQ	Health Assessment Questionnaires
HCA	Human capital approach
HCC	Hepatocellular carcinoma
HKD	Hong Kong dollar
HRQoL	Health-related quality of life
IQR	Interquatile range
LAI	Lupus Activity Index
L-QoL	Systemic Lupus Erythematosus quality of life questionnaire
Lupus QoL	Lupus Quality of Life Scale
NP	Neuropsychiatric
NPSLE	Neuropsychiatric systemic lupus erythematosus
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PAF	Population-attributable fraction
PGA	Physician's global assessment
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SDI	The Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index
SELENA	The Safety of Estrogen in Lupus-Erythematosus National Assessment
SELENA-SLEDAI	The Safety of Estrogen in Lupus-Erythematosus National

	Assessment version of the Systemic Lupus Erythematosus Disease Activity Index
SF-36	Short Form 36
SLAM	Systemic Lupus Activity Measure
SLE	Systemic lupus erythematosus
SLEDAI	The Systemic lupus erythematosusDisease Activity Index
SLEQoL	Systemic Lupus Erythematosus Quality of Life Questionnaire
UK	United Kingdom
US	United States
USD	United States dollars
WTP	Willingness to pay

CHAPTER 1 REVIEW OF THE LITERATURE

1.1 What is systemic lupus erythematosus (SLE)?

Systemic lupus erythematosus (SLE) is a prototypical autoimmune disorder characterized by the production of pathogenic auto-antibodies to components of the cell nucleus in association with a broad range of clinical and laboratory presentations involving almost all organ systems. It is a complex disease characterized by recurrent flares (exacerbations) and subsequent remissions. There is currently no cure for SLE, and the disease can result in multiple organ system failure and even death.

The currently accepted classification scheme for SLE is based on the American College of Rheumatology (ACR) classification criteria for SLE, which was developed in 1971, revised in 1982 and revised again in 1997 (Table1.1) [1]. The classification has excellent sensitivity (>85%) and specificity (>95%) for patients with established disease. However, due to the dynamic nature of the disease represented by periodic involvement of one organ system after another, the sensitivity of the criteria might be significant lower for patients with early disease or disease limited to a few organs [2].

Table 1.1 American College of Rheumatology Revised Classification Criteria for Systemic Lupus Erythematosus*

Criteria	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occurs in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	a. Pleuritis - convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or b. Pericarditis - documented by ECG or rub or evidence of pericardial effusion
Renal disorder	a. persistent proteinuria >0.5 g/day or >3+ if quantization not performed or b. Cellular casts - may be red blood cell, hemoglobin, granular tubular, or mixed
Neurologic disorder	a. Seizures - in the absence of offending drugs or know metabolic derangements (e.g., uremia, acidosis, or electrolyte imbalance) or b. Psychosis - in the absence of offending drugs or know metabolic derangements (e.g., uremia, acidosis, or electrolyte imbalance)
Haematologic disorder	a. Hemolytic anemia with reticulocytosis, or b. Leukopenia - $<4000/mm^3$, or c. Lymphopenia - $<1500/mm^3$, or d. Thrombocytopenia - $<100,000/mm^3$ in the absence of offending drugs
Immunologic disorder	a. Anti-dsDNA - antibody to native dsDNA in abnormal titer, or b. Anti-Sm - presence of antibody to Sm nuclear antigen, or c. Positive finding of antiphospholipid antibodies based on (1) abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) positive test result for lupus anticoagulant using a standard method, or (3) false-positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immunobilization or fluorescent treponemal antibody absorption test

Table 1.1 American College of Rheumatology Revised Classification Criteria for Systemic Lupus Erythematosus *(Continued)*

Criteria	Definition
ANA	Abnormal titer of ANA by immunofluorescence or equivalent assay at any point in time and in the absence of drugs known to be associated with drug-induced lupus syndrome

* Anti-dsDNA = anti-double stranded DNA; ANA = antinuclear antibody; ECG = electrocardiogram.

Adapted from Hochberg MC: Updating the American College of Rheumatology revised classification criteria for systemic lupus erythematosus. Arthritis Rheum 40:1752, 1997.

1.2 Epidemiology of SLE

There are marked disparities in prevalence rates of SLE worldwide. Prevalence are estimated to be 52 per 100,000 in the United States, 21 per 100,000 in Canada, and 25-91 per 100,000 in European countries [3]. Estimated incidence rates in North America, South America, and Europe range from 2 to 8 per 100,000 per year [4]. African-American and Hispanics are affected much more frequently than whites and have a higher disease morbidity [5, 6]. There is a peak age of onset in young women between their late teens and early 40s and women are affected nine times more frequently than men.

The prevalence rate of SLE in Asia is estimated to be 50 to 100 per 100,000 [7]. There is no formal epidemiology survey available in Hong Kong. According to empirical estimation from Mok et al, using the cohort from 2 tertiary hospitals, the point prevalence of SLE is around 58.8 per 100,000 (rates for men and women are 11.7/100,000 and 104/100,000, respectively) [8]. Underestimation is possible because patients with mild disease might be managed by private sectors or general practitioners.

1.3 Etiology and pathogenesis of SLE

The etiology of SLE is unknown but thought to be multifactorial. It may vary from one individual to the next. Several likely possibilities include genetics, environmental influences and hormones. The genetic control of the disease is more compelling in mice. Major histocompatibility complex class II genes on chromosome 17 (similar to human leukocyte antigen -D) and regions on several other chromosomes contribute to susceptibility in strains predisposed to SLE [9]. However, the highest reported concordance rate in monozygotic twins is 57%, suggesting that environmental factors and epigenetic factors are also required [10]. Ultraviolet is the most obvious environmental factor that can exacerbate the disease [11]. Other factors, including Epstein-Barr virus [12], toxic exposure to silica or mercury [13] and drugs [14] are also considered.

Global abnormality in inmmunoregulation is an important aspect in the pathogenesis of SLE. Abnormalities in T cell responses or production of T cell cytokines and/or defective control by regulatory T cell has been identified as an essential role in the development of autoimmunity [15]. Currently, more evidence describing the role of B cell hyperactivity in SLE, including abnormalities in B cell activation, signaling and migration [16]. The development of SLE also requires the failure of multiple immunoregulatory circuits. Such immunological abnormalities are the results of the

interactions between susceptibility genes, gender influences and triggering environmental factors [17].

1.4 Clinical features of SLE

The hallmark of SLE is its diversity of presentation, with accumulation of manifestations over time and waxing-and-waning course. Table 1.2 shows the frequency of various manifestations of SLE at disease onset and during the disease course [18]. Essentially, any organ system can be affected by SLE, with mucocutaneous, musculoskeletal, renal and central nervous system (CNS) being most common. In each organ, different structural components can also be involved with variable frequencies. In addition, constitutional features, including fever, fatigue and weight loss may sometime dominate the clinical features of SLE.

Table 1.2 Frequency of manifestations at onset and at any time during the course of systemic lupus erythematosus, in a large Canadian cohort

	At onset (%)	At any time (%)
Arthralgia	77	85
Constitutional symptoms	53	77
Skin	53	78
Arthritis	44	63
Renal	38	74
Raynaud's phenomenon	33	60
Central nervous system	24	54
Vasculitis	23	56
Mucous membranes	21	52
Gastrointestinal	18	45
Pleurisy	16	30
Lymphadenopathy	16	32
Pericarditis	13	23
Lung	7	14
Nephrotic syndrome	5	11
Azotemia	3	8
Myositis	3	3
Thrombophlebitis	2	6
Cytoid bodies	2	3
Myocarditis	1	3
Pancreatitis	1	2

Adapted from: Gladman DD. Systemic lupus erythematosus: Clinical features. In: Klippel JH, Weyand CM, Wortmann RL, eds. Primer on the rheumatic diseases. 11th ed.: Atlanta:Arthritis Foundation; 1997.

1.4.1 Most commonly involved organ systems

The mucocutaneous system is one of the most commonly affected systems. The most frequent mucocutaneous manifestations of SLE are malar rash (40%), alopecia (24%), and oral ulcers (19%) [19]. The malar rash is an erythematous and edematous eruption, which is precipitated by exposure to sunlight and can last for days to weeks. SLE-associated alopecia may be diffuse or patchy, reversible or permanently scarring as a result of discoid lesions in the scalp. Oral ulcers can affect the mouth (most common), nose and anogenital area.

The involvement of musculoskeletal system affects 53% to 95% of patients. Painful joints are the most common presenting symptom of SLE, with frequencies reported between 76% to 100% [20]. The small joints of the hand and wrist are usually affected, although all joints are at risk. In some cases, painful joints, unaccompanied by the traditional signs of inflammation, are more characteristic; while in other cases, a true arthritis, accompanied by swelling, erythema, heat and decreased range of motion, is present. Unlike rheumatoid arthritis, the arthritis in SLE is less disabling and usually does not cause severe destruction of the joints. It is reported that less than 10% of patients with SLE will develop deformities of the hands [21].

The kidney is considered to be the signature organ affected by SLE and renal involvement is a major cause of morbidity in SLE. Lupus nephritis encompasses diverse patterns of renal disease, including glomerular, tubulointerstitial, and vascular pathology [22]. Almost half of the patients present with asymptomatic urine abnormalities, such as proteinuria and haematuria. About 30% of patients develop nephritic or nephrotic syndrome or both [20]. About 20% of patients progressing to end-stage renal disease require maintenance dialysis or renal transplantation within ten years [23]. Without significant immunosuppression, it is reported that more than 70% of patients with class IV nephritis (diffuse proliferative lupus nephritis) progress to end-stage renal disease within 5 years.

1.5 Neuropsychiatric SLE (NPSLE)

Nervous system involvement in SLE is frequent and a major cause of morbidity and mortality. Clinical features of nervous system involvement include both neurologic (N) and psychiatric (P) presentations, affecting both central and peripheral nervous system. Although the management of SLE has made significant advances during the last few decades, neuropsychiatric SLE (NPSLE) continues to pose challenges on diagnosis, management, for both physicians and scientists [24].

1.5.1 Classification

The diversity and heterogeneity of the manifestations of NPSLE has been long appreciated, although only seizure and psychosis were included as classification criteria of SLE developed by ACR. There is no standardized definitions or classification system of NPSLE until the year of 1999, when an international, multidisciplinary research committee of ACR developed nomenclature, case definitions and diagnosis criteria for 19 NPSLE syndromes (Table 1.3) [25].

Twenty antibodies were described in NPSLE patients, including 11 brain specific antibodies (such as anti-neuronal antibodies, brain-reactive antibodies, anti-neurofilament antibodies, etc.) and 9 systemic antibodies (such as anti-phospholipid /cardiolipin antibodies, lupus anticoagulant, anti-Ro antibodies and anti-Sm antibodies, etc.) [26].

Table 1.3 Neuropsychiatric syndromes in systemic lupus erythematosus as defined by the American College of Rheumatology (ACR) research committee

Central nervous system	Peripheral nervous system
1. Aseptic meningitis	13. Guillain Barre′ syndrome
2. Cerebrovascular disease	14. Autonomic neuropathy
3. Demyelinating syndrome	15. Mononeuropathy
4. Headache	16. Myasthenia gravis
5. Movement disorder	17. Cranial neuropathy
6. Myelopathy	18. Plexopathy
7. Seizure disorders	19. Polyneuropathy
8. Acute confusional state	
9. Anxiety disorder	
10. Cognitive dysfunction	
11. Mood disorder	
12. Psychosis	

Adapted from ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes. Arthritis Rheum 1999;42:599-608

1.5.2 Epidemiology and clinical presentation

The prevalence of NPSLE ranges from 14% to 91% depending on the sampling procedures and diagnostic criteria. It is difficult to compare past studies of prevalence of NPSLE due to the lack of standardized definitions. Results of prevalence and manifestations of NPSLE among 6 recent studies using the 1999 ACR criteria, 2 of which are from cohorts of Chinese patients in Hong Kong, are presented in Table 1.4 [27-32].

Table 1.4 Neuropsychiatric manifestations in systemic lupus erythematosus in 6 selected studies*

Population	Ainiala et al, 2001 Tampere, Finland	Brey et al, 2002 San Antonio, Texas	Sanna et al, 2003 London, UK	Hanly et al, 2004 Halifax, Canada	Mok et al, 2001 New Territories, HK	Tam et al, 2008 New Territories, HK
No. of patients	46	128	323	111	518	291
Age, mean ± SD years	45 ± 13	43	42 ± 13	45	-	42 ± 12
Women (%)	85	94	95	86	89	96
Disease duration, mean ± SD years	14 ± 8	8	11 ± 8	10	-	9.7 (median)
Prevalence of NPSLE (%)	91	80	57	37	19	26
Manifestation of NPSLE (%)						
Aseptic meningitis	2	-	-	1	1	3
Cerebrovascular disease	15	2	18	4.5	19	19
Demyelinating syndrome	2	-	1	3	2	-
Headache	54	57	24	25	4	17
Movement disorder	2	1	-	-	2	-
Myelopathy	-	-	1	-	8	-
Seizure disorders	9	16	8	2	28	27
Acute confusional state	7	-	4	4.5	14	3
Anxiety disorder	13	24	7	1	2	5
Cognitive dysfunction	80	79	11	3	-	4

Table 1.4 Neuropsychiatric manifestations in systemic lupus erythematosus in 6 selected studies *(Continued)*

	Ainiala et al, 2001	Brey et al, 2002	Sanna et al, 2003	Hanly et al, 2004	Mok et al, 2001	Tam et al, 2008
Psychosis	-	5	8	3	11	19
Guillain Barre´ syndrome	-	-	1	-	-	-
Autonomic neuropathy	-	-	-	-	-	-
Mononeuropathy	-	8	2	-	2	12
Myasthenia gravis	2	-	2	-	-	3
Cranial neuropathy	7	2	1	3.5	3	1
Plexopathy	-	-	-	-	-	-
Polyneuropathy	28	22	3	2	1	-

* NPSLE = neuropsychiatric systemic lupus erythematosus

The overall prevalence of NPSLE in these 6 studies ranges from 19% to 91%. In Caucasian population, the most common manifestations are cognitive dysfunction and headache. Most of studies find prevalence of cognitive dysfunction from 17% to 66%, using neuropsychologic assessment techniques as definitions [33]. Cognitive dysfunction appears to have minor negative impact on patients' social function, work capacity or quality of life [34, 35]. Headaches are common in SLE, occurring in a large population of patients, ranging from 30% to 65% [36]. The most common patterns of headaches are migraine without aura, migraine with aura and tension headache [27, 28]. The association between headaches and SLE is controversial. There is only one study reporting an association between headaches and other manifestations of SLE [37]. It is suggested the headaches in SLE, characterized by acute presentation during a lupus flare, are associated with other neurological complications and abnormal laboratory tests, and resolves as lupus activity improves and with corticosteroids therapy [24].

In contrary to Caucasian population, the most common NPSLE manifestations in Chinese population in Hong Kong are seizures and cerebrovascular disease. A lack of routine and standardized assessment of neuropsychologic testings may account for the relatively low prevalence of cognitive dysfunction or anxiety. Seizures are

reported in 6%-15% in other populations with SLE and may be either generalized or focal. Seizures in SLE may be caused by active disease, cicatricial lesions or acute inflammation of any cause. Patients with seizures might have higher level of antiphospholipid antibodies, which are associated with microangiopathy, arterial thrombosis and subsequent cerebral infarction [29]. Ischemic stroke is the most common manifestation of cerebrovascular disease in SLE. Strokes usually occur within the first 5 years of the onset of SLE [38]. Vasculitis, thrombosis, emboli from cardiac vavular lesions, hypertension and accelerated atherosclerosis are considered as etiology of strokes in SLE. Old age, previous history of stroke or transient ischemic attach, antiphospholipid antibodies or cardiac valvular disease are risk factors for strokes in SLE [39].

1.5.3 Management of NPSLE

Management of NPSLE will need to be tailored according to the individual patient's needs. Unfortunately, compared with lupus nephritis, there is a paucity of controlled studies to guide the management of NPSLE and currently, the treatment remains largely empiric or draws upon the experiences from the management of other organ involvement, such as lupus nephritis [40]. Immunosuppressants therapy, such as high-dose oral corticosteroids, cyclophosphamide or azathioprine, along with

symptomatic medications (e.g. antipsychotic, anticonvulsants agents) is beneficial in treating many manifestations of NPSLE. Intravenous corticosteroids or cyclophosphomide is also effective.

1.5.4 Impact and prognosis of NPSLE

A series of cross-sectional studies have demonstrated the adverse impact of NPSLE on a variety of disease outcome, such as the association with quality of life, accumulated disease damage, disability and employment.

Compared with those without NPSLE, patients with NPSLE have lower scores on all domains of quality of life measured by the Short Form 36, which is a generic instrument measuring quality of life, indicating significant reduction of quality of life [30, 41]. This reduction does not depend on the attribution of NPSLE. Jonsen et al reported a higher frequency of disability in patients with NPSLE compared with patients without NPSLE and the general population [42]. NPSLE is also associated with impaired working capacity. Utset el al has shown that NPSLE is an independent predictor of employment status [43]. Compared with general population, patients with NPSLE have an increased relative risk of work incapacity, with relative risk of 4.0 which is higher than those without NPSLE [42]. Patients with NPSLE are also

associated with increase organ damage. It has been reported that neuropsychiatric damage is one of the most common damage category [42]. Also, several studies have found that the organ damage rate is high during the first year after diagnosis in patients with NPSLE [44, 45].

Prospective studies have also demonstrated the negative effect of NPSLE in patients' life. The association of lower level of quality of life and NPSLE over time is independent of progression in cumulative organ damage [46, 47]. A higher number of prior NPSLE episodes is predictors of an unfavorable clinical outcome at second year [48].

The prognosis for patients with NPSLE remains guarded. Previous studies have found that seizures, stroke and coma are particularly poor prognostic indicators [49, 50]. There is no consensus in the literature on the association between NPSLE and mortality. Some studies report increased mortality in patients with NPSLE [51-53], whilst others report no such association [54-56].

1.6 Assessment of SLE

SLE is a chronic disease characterized by remission and relapsing of varying

severity. Disease activity, disease damage and health-related quality of life (HRQoL) are three core outcomes in the assessment of SLE, recommended by the 1998 Outcome Measures in Rheumatoid Arthritis Clinical Trials group [57]. Disease activity is a measure of the reversible manifestations of SLE, whereas disease damage represents irreversible changes. HRQoL represents the functional ability of the patients and includes a variety of domains including physical, social and mental health.

1.6.1 Disease activity index

Several indices are validated and used in the evaluation of disease activity in SLE, most of which are global indices providing one numeric value describing overall disease activity. Commonly used indices include the British Isles Lupus Activity Group (BILAG) index [58], the Safety of Estrogen in Lupus-Erythematosus National Assessment (SELENA) version of the SLE Disease Activity Index (SLEDAI) (SELENA-SLEDAI) [59], the Systemic Lupus Activity Measure (SLAM) [60], the Lupus Activity Index (LAI) [61] and the European Consensus Lupus Activity Measurement (ECLAM) [62] (Table 1.5). Of these indices, the SELENA-SLEDAI and the BILAG index are the predominantly used ones in randomized clinical trials.

Table 1.5 Comparison of the different disease activity indices in systemic lupus erythematosus*

	BILAG [58]	SLEDAI [59]	SLAM [60]	LAI [61]	ECLAM [62]
Origination	United Kingdom	Toronto	Boston	San Francisco	Europe
Year of development	1988	1992	1989	1992	1992
No. of items	86	24	30	14	30
No. of organ systems	8	9	9	8	10
Score	0-72, 5 categories (A-E)	0-105	0-84	0-3	0-10
Time frame	Preceding month	10 days	Preceding month	14 days	Preceding month
Objective/subjective	Both	Objective	Subjective	Both	Both
Fatigue items	Yes	No	Yes	Yes	Yes
Weighted	No	Yes	Yes	Yes	Yes
Laboratory variables	Yes	Yes	Yes	Yes	Yes
Complement levels	No	Yes	No	Yes	Yes
Anti-ds DNA	No	Yes	No	Yes	No
Therapy	Yes	No	No	Yes	No
Relevance to clinical trials	Severity scores available for organ systems and scores vary if item is improving or worsening.	Brief and easy to administer. Heavily weighted for nervous system features.	Scoring fibromyalgia in this index may be a problem.	The modified LAI correlated well with SLEDAI. It is shown sensitive to change.	Maybe the best index if scores need to be calculated retrospectively.

* BILAG = British Isles Lupus Activity Group; SLEDAI= Systemic Lupus Erythematosus Disease Activity Index; SLAM = Systemic Lupus Activity Measure; LAI = Lupus Activity Index; ECLAM = European Consensus Lupus Activity Measurement; anti-ds DNA = anti-double stranded DNA.

The BILAG index

The BILAG scores disease activity in 8 organ-based systems individually occurring in the preceding month [63]. It is a transitional index, which means physicians score the activity of specific organ manifestation as (1) improve, (2) same, (3) worse, (4) new, rather than just present or not. Scoring is based on intention to treat principal instead of a gold standard. Within each organ system, scores generate as A (active), B (beware), C (contentment), D (resolved activity) and E (never Involved). A weighted system (A = 12, B= 5, C = 1, D = 0 and E = 0) can be used to calculate a global score of all the organ systems ranging from 0 to 72 [64]. However, the index is not originally derived to be a global score. The validity of BILAG and good correlation between BILAG and other activity indices or physician's global assessment (PGA) has been documented in previous studies [65-67]. BILAG also shows excellent sensitivity to change when compared with other indices [66]. In view of the transitional feature of this index, BILAG may be very useful in assessment of effectiveness of treatments in clinical trials, both on each organ system or on global disease activity. The index is more complicated when compared with other indices and its performing is time consuming. It also contains subjective items which if not use consistently between studies will interfere with its utility. Proper training is needed for physicians in clinical practice.

The SLEDAI

The original SLEDAI was developed in 1992, including 24 weighted objective clinical and laboratory descriptors assessing disease activity in the preceding 10 days. The weighted system was derived by multiple regression analysis from clinicians' judgment about the features' contribution to the overall disease activity [68]. Each manifestation is assessed only as "present" or "absent". The total score ranges from 0 to 105, with higher score indicating higher disease activity. It has been shown as valid, reliable and sensitive to change [66, 67, 69]. The SELENA-SLEDAI is a modification of the original SLEDAI by the investigators from the SELENA trial (Table 1.6) [59]. It modifies several descriptor definitions of the original instrument in an attempt to improve clarification and attribution for the individual items, as well as to better capture changes in disease activity. Such modifications include: excluding seizures that are caused by old, irreversible CNS damage, expanding visual disturbances to include scleritis and episcleritis, excluding hypertension-related cerebrovascular accident, and adding new-onset or recent increase proteinuria. The SLEDAI is criticized to have heavily weighted for the CNS which are not that frequent. It does not include several severe or lift-threatening manifestations, such as pulmonary hemorrhage or hemolytic anemia, and it does not

take into account the severity of the manifestations [70]. All these limitations account for its less suitability for use in clinical trials compared with the BILAG. However, The SLEDAI is brief and easy to use, which may improve the correlation between different studies. Furthermore, results from Arce-Salinas et al have indicated that the SLEDAI score can be calculated retrospectively from the data in clinical charts [71].

Table 1.6 The Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) [59]

Descriptor	Definition	Weighted Score
Seizure	Recent onset. Exclude metabolic, infectious or drug cause.	8
Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.	8
Organic brain syndrome	Syndrome Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.	8
Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.	8
Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.	8
Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.	8
Cerebrovascular accident	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.	8
Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.	8

Table 1.6 The Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) (*Contintued*)

Descriptor	Definition	Weighted Score
Arthritis	More than 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).	4
Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.	4
Urinary casts	Hemo-granular or red blood cell casts.	4
Haematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.	4
Proteinuria	>0.5 gm/24 hours. New onset or recent increase of more than 0.5 gm/24 hours.	4
Pyuria	>5 white blood cells/high power field. Exclude infection.	4
New rash	New onset or recurrence of inflammatory type rash.	4
Alopecia	New onset or recurrence of abnormal, patchy or diffuse loss of hair.	4
Mucosal ulcers	New onset or recurrence of oral or nasal ulcerations.	4
Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.	4
Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.	4
Low complement	Decrease in total complement (C) CH50, C3, or C4 below the lower limit of normal for testing laboratory.	2
Increased double stranded DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.	2
Fever	>38°C. Exclude infectious cause.	1
Thrombocytopenia	<100,000 platelets/mm^3.	1
Leukopenia	<3000 White blood cell/mm^3. Exclude drug causes.	1

1.6.2 Lupus flare

The assessment of lupus activity encompasses the concept of "flare", an increase in disease activity over a defined period [72]. Flare in SLE appears to be a common lexicon used by both the rheumatologists and patients. However, there is no consensus on the definitions at present. Various approaches have been proposed.

Petri et al defined flare as a $\geqq$ 1.0cm change on a 3cm visual analog scale of PGA of disease activity [73]. The PGA includes only reversible disease activity. Cumulative damage and health status are not included. They found an incidence of flare of 0.65 flares per patients-year in a cohort of 185 patients. The result was similar with a later study by Zonna-Nacach et al who reported an incidence of 0.69 per patient-year in a cohort of Mexican patients [74]. Based on this definition, Petri et al found that the corresponding cutoff on SLEDAI was 3 or more. This was in accordance with a separated study by Gladman et al, in which results suggested that an increase in a SLEDAI score of more than 3 was a flare, a SLEDAI score that was within 3 points of the previous score was persistent disease, and a SLEDAI score of 0 was remission [75].

Using the BILAG, Ehrenstein et al proposed that a severe flare of lupus was defined

as a new score of A in any organ system and a moderate flare as a score of B in any oran system which previously scored C, D or E [76]. Using this definition, they found that the most common "A" (severe) flare observed was polyarthritis. Ehrenstein et al's definitions were further used and confirmed by Gordon et al [77].

The investigators from the SELENA clinical trial did not think it is sufficient using activity indices alone to capture all the flares in SLE. They devised a new definitions system separating mild/moderate flare from severe flare (Table 1.7) [59]. The SELENA flare definitions encompass disease activity indices scores, disease activity scenarios and have a special emphasis on treatment.

Flare in lupus is an important outcome. Uncontrolled disease activity and toxicity of the subsequent treatments result in irreversible damage which is associated with an increased risk of morbidity and mortality. Flare has been shown as the major cause of admission [78]. Stoll, et al concluded that death and the long-term accumulation of damage were strongly predicted by a high total disease activity over time and especially associated with the number of BILAG A (most active disease) flare [79]. In contrary to the so-called "minor" organ flare, i.e, constitutional, musculoskeletal, and mucocutaneous [73], major organ flares, such as renal or neuropsychiatric (NP)

flare, have been shown to be associated with poor prognosis. Renal flares were significantly associated with the risk of doubling plasma creatinine and death or dialysis [80]. Ward, et al concluded that the occurrence of seizure increased the risk of death in patients with SLE [49]. Results from Hanly, et al showed that NP disease was related to more frequent use of corticosteroids and immunosuppressants [30].

Table 1.7 The Safety of Estrogen in Lupus-Erythematosus National Assessment Trial flare tool*

Mild/moderate flare	Sever flare
Change in SELENA-SLEDAI instrument score of 3 points or more (but not to more than 12)	Change in SELENA-SLEDAI instrument score to greater than 12 points
New/worse:	New/worse:
Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus	CNS-SLE
Nasopharyngeal ulcers	Vasculitis
Pleuritis	Nephritis
Pericarditis	Myositis
Arthritis	Platelet $<$ 60 000/mm^3
Fever (SLE)	Haemolytic anemia; Hb $<$ 70 g/l or decrease in Hb $>$ 30 g/l
Increase in prednisone, but not to $>$0.5 mg/kg/day	Requiring: double prednisone, or prednisone increase to $>$ 0.5 mg/kg/day, or hospitalisation
Added NSAID or hydroxychloroquine for SLE activity	Increase in prednisone to $>$0.5 mg/kg/day
$\geq$1.0 increase in PGA score, but not to more than 2.5	New cyclophosphamide, azathioprine, methotrexate for SLE activity
	Hospitalisation for SLE
	Increase in PGA score to greater than 2.5

* Adapted from Petri M. Disease activity assessment in SLE: do we have the right instruments? Ann Rheum Dis 2007;66 Suppl 3:iii61-4. SELENA-SLEDAI = The Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus ErythematosusDisease Activity Index; CNS = Central nervous system; SLE = systemic lupus erythematosus; Hb = haemoglobin; NSAID = non-steroidal anti-inflammatory drug; PGA = physician's global assessment.

1.6.3 Disease damage index

The survival has significantly improved in patients with SLE. However, the expanded life expectancy means that patients with SLE are facing with considerable morbidity due to disease progression, side effects of medications and comorbid conditions. Therefore, assessment of cumulative organ damage in this group of patient has become a crucial outcome.

The System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) was developed to assess organ damage in SLE (Table 1.8) [81, 82]. The index is a physician-rated index that consists of 41 items across 12 organ systems with a total score of 49 (higher score indicating more damage). It includes co-morbidities associated with disease itself, as well as with toxicity attributable to treatment. Damage is defined as any irreversible change occurring since the onset of SLE, irrespective of attribution, and presenting for at least 6 months or being associated with an immediate pathological scar indicative of damage (e.g., a myocardial infarction). Once an item is scored, it will remain positive even if the manifestation resolves.

Table 1.8 System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus* [82]

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	0,1
Retinal change or optic atrophy	0,1
Neuropsychiatric	
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	0,1
Seizures requiring therapy for 6 months	0,1
Cerebrovascular accident ever (score 2 if > 1)	0,1,2
Cranial or peripheral neuropathy (excluding optic)	0,1
Transverse myelitis	0,1
Renal	
Estimated or measured glomerular filtration rate<50%	0,1
Proteinuria >3.5 gm/24hours	0,1
Or end-stage renal disease (regardless of dialysis or transplantation)	or 3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P_2)	0,1
Pulmonary fibrosis (physical and radiograph)	0,1
Shrinking lung (radiograph)	0,1
Pleural fibrosis (radiograph)	0,1
Pulmonary infarction (radiograph)	0,1
Cardiovascular	
Angina or coronary artery bypass	0,1
Myocardial infarction ever (score 2 if > 1)	0,1,2
Cardiomyopathy (ventricular dysfunction)	0,1
Valvular disease (diastolic murmur, or systolic murmur >3/6)	0,1
Pericarditis for 6 months, or pericardiectomy	0,1
Peripheral vascular	
Claudication for 6 months	0,1
Minor tissue loss (pulp space)	0,1
Significant tissue loss ever (e.g. loss of digit or limb) (score 2 if > 1site)	0,1,2
Venous thrombosis with swelling, ulceration, or venous stasis	0,1
Gastrointestinal	
Infarction or resection of bowel below duodenum spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site)	0,1,2

Table 1.8 System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus *(Continued)*

Item	Score
Mesenteric insufficiency	0,1
Chronic peritonitis	0,1
Stricture or upper gastrointestinal tract surgery ever	0,1
Musculoskeletal	
Muscle atrophy or weakness	0,1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	0,1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0,1
Avascular necrosis (score 2 if > 1)	0,1,2
Osteomyelitis	0,1
Skin	
Scarring chronic alopecia	0,1
Extensive scarring or panniculum other than scalp and pulp space	0,1
Skin ulceration (excluding thrombosis) for > 6 months	0,1
Premature gonadal failure	0,1
Diabetes (regardless of treatment)	0,1
Malignancy (exclude dysplasia) (score 2 if > 1 site)	0,1,2

* Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur 6 months apart to score 2. The same lesion cannot be scored twice.

The index has been shown as valid and reliable when used by 10 physicians from five countries in the assessment of 10 actual patients with SLE [82]. It has also been shown to have good agreement with prospective and retrospective measurement [83]. Damage is common in patients with SLE. In most cohorts, approximately 50% of patients will have at least one item of damage [70]. Musculoskeletal damage from osteonecrosis and osteoporosis is the most common organ damage [84]. The SDI is associated with increase mortality for those with high scores early in the course of the disease [85, 86]. Results from a prospective study found that damage increases over time and a substantial portion of that increase was attributable to corticosteroid therapy [87]. Higher disease activity at baseline predicts an increase in the SDI score [79, 88].

Specifically, in a prospective cohort consisting 242 Chinese patients with SLE in Hong Kong, 37% patients had organ damage at enrollment and the number increased to 55% after 3 years follow-up [89]. Eighty-four patients in the cohort had further damage accrued. The increase in SDI scores over time was primarily caused by the increase in the renal, musculoskeletal and gonadal damage. The number of major disease flares and the use of cyclophosphamide were independent predictors of damage accrual. A study by Mok et al also revealed that the accrual of disease

damage during the first year after the diagnosis of SLE could predict mortality [90].

1.7 Health-related quality of life (HRQoL)

1.7.1 What is health-related quality of life?

Health-related quality of life (HRQoL) is a multi-dimensional construct concerned with the health status, attitudes, values, and perceived levels of satisfaction and general well-being (physical, functional, social and emotional well-being) with respect to either specific health conditions or life as a whole from the individual's perspective. HRQoL are mostly measured by questionnaires/instrument. Generic HRQoL questionnaires are designed to be applicable across all diseases or conditions and across a wide range of populations, whereas specific HRQoL questionnaires are designed to be applicable to a particular health condition or population. Measures of HRQoL provide unique information regarding an individual's report of the impact of disease and treatment, as well as treatment side effects and other health-related data. Such information is important for evaluating treatment efficacy and interpreting clinical outcomes.

1.7.2 The Short Form 36 (SF-36)

The Short Form 36 (SF-36) is a widely-used generic HRQoL questionnaire. It was

developed by the Rand Corporation in the United States for use in the Health Insurance Experiment/Medical Outcomes Study [91]. It has 36 items and takes approximately 7 to 10 minutes to self-administer. Alternative forms are available as 1- and 4-week recall periods. It has 8 subscales measuring 8 domains of quality of life: physical functioning, role limitation due to physical problems, role limitation due to emotional problems, bodily pain, social functioning, mental health, vitality and general health perception. Each scale consists of 2 to 10 items, and each item is rated on a two- to six-point Likert scale. Each subscale score is calculated by summation and transformation of all the scores of items belonging to the same scale, ranging from 0 (poorest) and 100 (optimal). In additional, the SF-36 can be summarized into 2 summary scores: the physical health summary scale and mental summary scale [92]. The 2 summary scales give an overall assessment of quality of life related to physical and mental health, respectively [92]. The SF-36 has been translated into Chinese and validated for Chinese adults in Hong Kong and normative values of the SF-36 questionnaire of Chinese adult population in Hong Kong have been published [93, 94].

1.7.3 HRQoL in SLE

HRQoL in SLE has been identified as a different entity to that of disease activity and

damage and an important outcome of SLE. Several studies in both Caucasian and Chinese population have demonstrated impaired HRQoL of patients with SLE compared to healthy controls [95-97]. The poorer HRQoL in SLE is comparable to that found in other severe chronic diseases, like rheumatoid arthritis [98, 99], acquired immunodeficiency syndrome [100], chronic heart failure [101] and myocardial infarction [101].

Several generic HRQoL instruments have been used in the assessment of SLE, including, the SF-36, the SF-20 (a shorter predecessor of the SF-36), the Euroqol Quality of Life Scale 5-Dimension, and the Quality of Life Scale. The SF-36 is the most commonly used instrument in the evaluation of HRQoL of SLE. Significant impairment has been observed in all 8 domains of the SF-36 [102]. However, there are concerns regarding the generic feature of the SF-36. It may not be specific enough to identify certain issues that are important to SLE. Sleep disturbance and sexual dysfunction are 2 frequent affected domains for SLE but absent from the common generic instruments [103, 104]. Some environmental or personal factors important to patients with SLE, such as support and attitudes of other persons, body image, self-confidence and reproductive ability, are not covered by standard generic instrument [105]. This has led to the development of several SLE-specific HRQoL

instruments. Some features of several SLE-specific questionnaires are summarized in Table 1.9. However, use of these instruments remains limited to Singaporean Chinese and British white population. Cross-cultural validation is needed before these instruments used in the population in Hong Kong.

Table 1.9 Adult systemic lupus erythematosus-specific health-related quality of life measures

	SLEQoL [106]	Lupus QoL [107]	L-QoL [108]
Origination	Singapore	UK	UK
Year of development	2005	2006	2009
No. of items	40	34	25
Review period	1-week	4-weeks	N/A
Score	40-280	0-100	N/A
Higher score indicating poorer HRQoL	Yes	No	Yes
Administration time to completion	N/A	<10 minutes	<5 minutes
Domains	Physical functioning, activities, symptoms, treatment, mood and self-image.	Physical health, pain, planning, intimate relationships, burden to others, emotional health, body image and fatigue.	Unidimensional measure overall impact of SLE and its treatment on the patient.

SLEQoL = Systemic Lupus Erythematosus Quality of Life Questionnaire; Lupus QoL = Lupus Quality of Life Scale; L-QoL = Systemic Lupus Erythematosus quality of life questionnaire; HRQoL = health-related quality of life; N/A = not available.

In cross-sectional studies, factors which have been identified associated with poorer HRQoL include older age [98], fatigue [109, 110], fibromyagia [111, 112], end-stage renal disease [113], neuropsychiatric involvement [32], psychological distress [114], and social support [97]. Some longitudinal studies suggest improvement in HRQoL in patients with SLE during follow-up [115], whilst some longitudinal studies suggest SLE patients with established disease changed little over time [112]. In a 2-year prospective study in Hong Kong, Mok et al found that there was a significant further impairment in mental health but not in physical health in patients with SLE, and new damages predicted a further decline in HRQoL [116].

The relationship between disease activity, damage and HRQoL, results remain controversial. Some studies found correlations between these three domains [58, 117-119], whereas some did not [32, 96, 120, 121]. It appears that the investigators who used either the SLAM or the BILAG were more likely to find a relationship. This is probably because these 2 measures include items that reflect quality of life as well as disease activity. A review by McElhone et al concludes that there is no or only week correlation between disease activity/damage and HRQoL [102]. Therefore, all these three aspects of SLE, disease activity, disease damages and HRQoL should be measured in a patient with SLE to obtain the comprehensive assessment of the

disease.

1.8 Management of SLE

The management of SLE requires a comprehensive assessment of disease activity and damage and tailoring of the treatment according to involved organ and severity [20]. Patients with mild disease without major organ involvement may need no treatment or only intermittent courses of anti-inflammatory medications. Those with more severe disease involving damage to major organ may require high doses of corticosteroids in combination with other medications such as immunosuppressants. The treatment of severe SLE usually consists of a period of intensive immunosuppressive therapy (induction therapy) followed by a longer period of less intensive maintenance therapy. The goal of induction therapy is to halt injury, recover function and induce remission by controlling immunologic activity. The objective of maintenance therapy is to consolidate remission and prevent flares by using medications that are convenient and associated with a lower risk for complications [20]. Most of the patients with SLE require long-term use of medications, which lead to the concern about the toxicities related to the treatment. Corticosteroid toxicity is a major problem in SLE. Other toxicities includes but not limit to hepatotoxicity and lymphoproliferative diseases related to azathioprine use, hepatotoxicity and infection

related to mycophenolate mofetil use, malignancies related to cyclophosphamide use and renal insufficiency related to cyclosporine use [122].

1.8.1 Emerging Biological therapies in SLE

Advances in knowledge about the pathogenesis of SLE have led to the development of targeted therapies that are more effective and less toxic. Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells [123]. Results from uncontrolled trials have shown substantial and long-lasting remission in patients with various manifestations of SLE, refractory to conventional or even novel therapies such as mycophenolate mofetil [124-126], one of which was conducted in our Rheumatology centre. The underlying mechanism of rituximab remains unclear. Acute infusion reaction has been mostly reported, usually mild to moderate. Other serious adverse events include infection, neutropenia, thrombocytopenia and asthenia. Although the use of rituximab appears to be promising, there are still concerns, such as about the optimal treatment regimen (i.e. frequency, use of concomitant therapies), and the potential for retreatment after relapse without developing neutralizing antibodies [127]. Large randomized controlled trials with longer observation period will be needed in the future.

More recently, a range of new treatments for SLE have been introduced, such as a anti-CD22 agent (epratuzumab) [128], anti-B-Lymphocyte stimulator agent (belimumab) [129], B-cell anergy (abetimus sodium) [130], anti-CD-20 agent (ocrelizumab) [131]. In general, the emerging therapies, showing promising results in short-term trials, are all well tolerated with rates of adverse events similar to those of conventional therapies. Additional large, long-term randomized, placebo-controlled trials of these emerging novel therapies are needed in order to further establish their efficacy, toxicity and safety in the treatment of such a complex disease as SLE.

1.9 Mortality in SLE

Although no new treatments for SLE have been introduced in the past 30 years, the mortality of patients with SLE continues to decrease. The 5-year survival has improved from 50% in 1955 to 88% - 96% nowadays; and 77% - 85% patients survive for 10 years and 75% survive for 20 years [132]. Urowitz et al reported a significant decreased in mortality from 14% to 1.8% during 36 years [133], however, these patients still have three- to fivefold increased mortality compared with the general population. Factors related to mortality include last disease onset (> 50 years old) [134], female[135, 136] and African-Americans and Hispanics [137, 138]. Deaths occurring early in the course of disease are more attributed to active disease,

particularly renal disease [134, 139-141], infections [142-144]and NPSLE [139] in most cohort studies. Deaths occurring later in the course of disease are more likely related to the results of complications from disease progression itself or from toxicity of its therapies [134].

1.10 What is cost-of-illness study?

Cost-of-illness studies measure the monetary burden that a disease or diseases impose on society caused by morbidity and premature mortality, in terms of the consumption of health care resources and losses of productivity. Cost of illness study is the earliest form of economic evaluation in the healthcare sector. In 1967, Rice first outlined a methodological framework for calculating costs of illness/disability/death in great detail [145]. Later in 1982, Hodgson and Meiners provided guidelines for those intended to perform cost-if-illness studies [146]. Numerous cost-of-illness studies have been conducted over the past 3 decades.

1.11 Framework of a cost-of-illness study

The costs can be measured within the framework of direct, indirect and intangible costs associated with the illness. The specific focus of a study may make one or the other unnecessary. Table 1.10 lists an example of costs categories.

Table 1.10 An example of framework of a cost-of-illness study

Direct medical costs	Medications
	Medication monitoring
	Medication administration
	Patient counseling and consultations
	Diagnostic tests
	Hospitalizations
	Clinic visits
	Emergency department visits
	Home medical visits
	Ambulance services
	Nursing services
Direct nonmedical costs	Travel costs to receive health care (e.g., bus, gas, taxi)
	Nonmedical assistance related to condition (e.g., meals-on-wheels, homemaking service)
	Hotel stays for patient or family for out-of-town care
	Child care services for children of patients
Indirect costs	Lost productivity for patient
	Lost productivity for unpaid caregiver (e.g., family member, neighbor, friend)
	Lost productivity because of premature mortality
Intangible costs	Pain and suffering; fatigue; anxiety.

Adapted from Rascati K.L Measuring and Estimating Costs, in Essentials of Pharmacoeconomics. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2009.

1.11.1 Direct costs

Direct costs represent the opportunity costs of all kinds of resources used for treating an illness. Opportunity cost is defined by Hodgson and Meiners as "the value of the forgone opportunity to use in a different way those resources that are used or lost due

to illness" [146]. Direct costs usually include direct medical costs and direct nonmedical costs. The first one refers to the medically related inputs used directly to provide the treatment, examples including costs associated with the diagnosis, treatment, continuing care, emergency care and rehabilitation; while the latter one refers to costs to patients and their families that are directly associated with an illness but are not medical in nature, examples including transportation costs, costs of household expenditures and informal care.

One challenge with calculating direct costs is to find the true cost of the resources. The amount charged to the payer is not necessarily synonymous with the true cost of the resource. The market price is the best reflection of the true costs but it is not always available [147]. Another challenge is calculating the costs of hospitalization (inpatient care), which usually contribute large percentage of direct costs. In order from least to most precise, four methods for estimating costs of hospitalization are per diem, disease-specific per diem, diagnosis-related group and micro-costing. The first three methods are also called gross-costing approach, in which the cost of a resource is calculated by dividing total costs of the resource by the total number of the resource produced in a period of time [148]. Micro-costing usually involves a review of patients' hospital record to obtain what specific services (e.g. medications,

technology services, and procedures) are used and assigning a unit cost to each service. In this case, micro-costing provides more useful information.

1.11.2 Indirect costs

Indirect costs represent productivity losses related to morbidity and mortality. Indirect costs usually account for large proportion of total costs in most cost-of-illness studies. However, it has long been an issue for debate, in that either ethical issues to place a value on losses of productivity, or how to calculate these losses [149, 150]. There are mainly three approaches to estimate indirect costs: the human capital approach (HCA), the friction cost method (FCM) and the willingness to pay (WTP) method [149].

One assumption underlying in the HCA is that a worker's wage equals the value of his marginal product contributed to the economy. The HCA uses wages as a proxy measure of the output of work time to evaluate the losses of productivity during the time absent from work. The HCA can also include the value of household work, usually calculated as the costs of hiring a replacement from the labor market. The FCM assumes that the short-term work loss caused by one employee can be made up by another one or the employee himself/herself, and employees absent from work for

a long period can be replaced from the internal labor market or by an unemployed individual (concept of worker replacement). Therefore, productivity losses due to short-term absence from work will not be considered using the FCM and for long-term absence, the FCM limits costs to a friction period (the amount of time before the losses of productivity are restored), the length of which depend on the availability of qualified individual within companies and on the labor market and on the level of unemployment. Furthermore, all non-labor activities will not be pertinent using the FCM. The WTP method determines how much an individual is willing to pay to reduce the chance of an adverse health outcome. It can be conducted through face-to-face interviews, mail, and telephone or via the internet.

There is no consensus on which method should be used in calculating indirect costs. Each method has its advantages and disadvantages [148]. The HCA is the most common approach used and has been given a foundation in economic theory [151], but it's frequently criticized for overestimating indirect costs in an economy with less than full employment. The FCM, claiming capable to measure the actual losses to the society, requires extensive data to estimate the friction period that are unlikely to be available at country level, and the results using the FCM may change over time even within the same economy. The WTP method, which can value both the indirect and

intangible costs of a disease, is often difficult to implement in cost-of-illness studies but a more preferable method in cost-benefit analysis.

1.11.3 Intangible costs

Intangible costs refer to patients' psychological pain, discomfort, anxiety and depression, and suffering related to an illness or the treatment of an illness [148]. This type of costs is very difficult to quantify in monetary term and therefore it is often omitted from cost-of-illness studies. However, they are usually presented in the form of quality of life or HRQoL.

1.12 Perspective of a cost-of-illness study

Perspective of a cost-of-illness study describes which costs are relevant base on the purpose of the study [146]. Societal perspective is the most appropriate and comprehensive perspective when performing a cost-of-illness study. Using societal perspective, all types of costs are relevant, including all direct costs as well as losses of productivity, irrespective of who pays for them eventually. Other perspectives, such as the perspective of the institution, the healthcare system, the government and the payer, provide information about costs to the particular group. A cost-of-illness study is not limited to a single perspective.

1.13 Prevalence- versus incidence-base studies

The difference between prevalence-based and incidence-based studies depends on the nature of epidemiological data used for the analysis. The incidence-base cost-of-illness studies estimate the discounted, life-long costs, based on all cases with onset of disease within the period of study, usually a year. The prevalence-based studies focus on the costs of an illness in one period, usually a year, and on a cohort of typical patients, irrespective of the onset of the disease [146].

For an acute disease, results generated by using prevalence- or incidence-based studies will not differ much, because costs are mostly restricted to one year. However, for a chronic disease, results from the prevalence-based method are usually higher than those from the incidence-based method. This is largely because that some future costs are discounted in the incidence-based studies, but not in the prevalence-based studies. The underlying premise of discounting is that there is a time-value associated with money, which is that money received today is worth more than the same amount of money received next year. Modifications for this time value are estimated using a discount rate, which is usually between 3% and 6%.

The incidence-based studies are less common because this type of studies requires long term follow-up and involves more assumptions regarding nature history and evolution of the disease. In contrary, the prevalence-based studies require collecting data during a define period and nothing to be assumed about the survival rate, mortality rate, or morbidity rate. Although attempts have been made to estimate lifetime costs using prevalence-base costs, the estimates may not be as accurate as using actual lifelong follow-up data because of some potential changes in the future, such as medical technology changes. In a review by Tarricone, it is proposed that prevalence-based cost-of-illness studies can be particularly useful when the study is aiming to plan cost containment policies or draw policy-makers interests for a certain condition. If the study is aiming to consider preventive measures or analyze the management of the illness from the onset till recovery/death, incidence-based studies will be particular useful [152].

1.14 Top-down versus bottom-up approach

Cost-of-illness studies can also be top-down or bottom-up designed. The top-down approach is an epidemiological approach, using the total costs of disease in a population (e.g., the national healthcare expenditures) [153] and a population-attributable fraction (PAF) to calculated costs for a specific disease. The

PAF represents the proportion of medical care for a certain disease to another. However, because there may be multiple confounding variables related to both 2 diseases, the PAF might be biased if not controlled for these confounders. Furthermore, the use of the total costs of a disease in a population, like the national healthcare expenditures, is likely to either underestimate or overestimate the costs.

Bottom-up approach first estimates the quantity of health resources used and then estimates the unit costs of the resources used. Using this method, patient and disease characteristics can be related to resource use and costs. This approach was developed by Rice in 1967 [145] and it's more commonly used in cost-of-illness studies. It is recommended by Tarricone to use bottom-up approach in cost-of-illness studies [152].

1.15 Value and debates of cost-of-illness studies

One major limitation of cost-of-illness studies is that they only measure the expenditure, therefore incapable of telling whether the costs are worth paying for. A high cost of an illness might be reflecting the inefficiency of the use of resources, while a low cost might also be due to insufficient access to resources. Because of variable costing methods available, the costs can vary considerable depending on

which approach is employed, making the comparison among literatures difficult. Although it's claimed that cost-of-illness studies can provide information for the economic assessment of a certain treatment, this form of studies actually provides very limited knowledge about what health gains are attainable from specific treatment or a prevention program, compared with cost-effectiveness, cost-benefit or cost-utility analysis.

Nonetheless, in another perspective, although not an economic evaluation, determining economic burden of an illness provides valuable information that can support the policy-making decisions, if the design of the studies is capable of measuring the true costs to the society. Cost-of-illness studies are also valuable in determining the magnitude of a problem and identifying areas for future investigation. It can identify how costs are distributed among the healthcare system and other sector, such as the patients and the family. In view of these, although debates continue, cost-of-illness are frequently used by organization, such as World Health Organization [154], and the United States National Institute of Health [155].

1.16 Cost-of-illness studies in Hong Kong

Several cost-of-illness studies have been performed in Hong Kong, including studies

about costs of tobacco-related diseases [156-158], obesity [159], stroke [160], informal caregivers for elderly [161], chronic hepatitis B [162], palliative care for hepatocellular carcinoma [163], epilepsy [164], acute myocardial infarction [165], type-2 diabetes mellitus [166], osteoporosis [167], ankylosing spondylitis [168] and psoriatic arthritis [169]. All these studies differed in study design and methodologies, however, most of them did not provide clear statements regarding the perspective of the study, prevalence- or incidence-base design, or top-down or bottom-up approach. Table 1.11 summarized main results from studies using prevalence-based bottom-up design and with enough data capable for comparisons.

Table 1.11 Main findings from several cost-of-illness studies performed in Hong Kong*

	AS [168]	PsA [169]	Type-2 DM [166]	Epilepsy † [164]	AMI [165]	HCC ‡ [163]
Year	2008	2010	2007	1999	2005	2001
No. of subjects	145	125	204	745	95	204
Mean age	40	47	63	-	67	57
Employ, %	67%	55%	-	-	-	-
Biggest contributor to direct costs	Diagnostic examination (32%)	Hospitalization (27%)	Hospitalization (43%)	Outpatient visits (39%)	Hospitalization (70%)	Hospitalization (60%)
Mean annual direct costs* (2006 USD)	3,487	4,141	1,445	317	8,889	3,654
Mean annual indirect costs (2006 USD)	5,633	3,127	226	461	-	2,853

Table 1.11 Main findings from several cost-of-illness studies performed in Hong Kong *(Continued)*

	Mild OA [167]	Severe OA [167]	Prothesis OA§[167]	Chronic HB [162]	Compensated cirrhosis [162]	Decompensate cirrhosis [162]	HCC# [162]
Year	2003	2003	2003	2004	2004	2004	2004
No. of subjects	219	290	65	232	112	55	89
Mean age	-	-	-	-	-	-	-
Employ, %	27%	46%	5%	-	-	-	-
Biggest contributor to direct costs	Private outpatient	Hospitalization	Surgery	Laboratory tests (32%)	Hospitalization (49%)	Hospitalization (65%)	Hospitalization (58%)
Mean annual direct costs (2006 USD)	1,544	5,306	32,269	834	1,361	7,715	16,087
Mean annual indirect costs (2006 USD)	436	877	2,098	-	-	-	-

*: Costs were adjusted for inflation using consumer price index, in 2006 USD (purchasing power parity). AS = ankylosing spondylitis; PsA = psoriatic arthritis; DM = diabetes mellitus; AMI = acute myocardial infarction; HCC = hepatocellular carcinoma; OA = osteoarthritis; HB = hepatitis B; USD = United States dollar.

†: Study assessed total costs of epilepsy from 1992 to 1996, without indicating which year of value was use to present results. Reference period was 1996.

‡: The study only assessed costs of palliative care for patients with terminal non-operatable HCC.

§: Results were original displayed as costs among patients with first year prosthesis and subsequent year prosthesis, but without indicating the number of patients in each category. Average costs of these 2 groups were used here.

#: Costs of operation/procedures were also included, but not costs of liver transplant.

1.17 Cost-of-illness studies in SLE

There are several cost-of-illness studies in SLE [170-179]. Table 1.12 summarized the main findings of these studies. More detail description about these studies can be found in Appendix 1.

Clarke et al performed the first cost-of-illness study in SLE, using a cohort of 164 Canadian patients [179]. Both direct and indirect costs for patients with SLE were substantial and most of these costs were attributable directly to SLE. Indirect costs comprised 54% of total costs. Also, hospitalization among patients with SLE were 4 times more frequent than that among the sex- and age-matched general population in the study region, and the number of outpatients visits to physicians was 2 times higher. Full-time employee reported 48% to 80% of their work loss days and 65% to 89% of their income loss attributable to SLE. Higher serum creatinine and a poorer level of physical functioning were the best predictors of higher direct costs. A poorer well-being score, a combination of low education and unemployment, a weaker level of social support (measured by the Interpersonal Support Evaluation List) were the best predictors of higher indirect costs. These results were consistent with that of another study by Clarke et al using regression trees procedures to analyze the costs predictors in the same cohort [180]. Clarke et al concluded that direct costs are more

likely to arise from organic complications which induce functional disability. Measures that lead to earlier diagnosis and better management might be useful in reducing direct costs. On the other hand, predictors for indirect costs appear more amendable. Strengthening social support can improve patients' ability to cope with and resist the stress imposed by the disease, potentially improve patients' health outcome, while simultaneously reducing disease costs.

Table 1.12 Major findings of cost-of-illness studies in systemic lupus erythematosus

	Clarke et al. (1993) [179]	Sutcliffe et al. (2001) [170]	Clarke et al. (1999) [175]	Clarke et al. (2000) [177]
Country	Canada	United Kingdom (UK)	Canada, UK and United States (US)	Canada, UK and US
No. of subjects	164	105	Canada: 229; US: 268; UK: 211. Total: 708	648
Period of recruitment	January 1990 to January 1991	June to September, 1995	July 1995 to July 1997	July 1995 to July 1997
Study design	Prospective (1-year)	Prospective (1-year)	Cross-sectional	Cross-sectional
Mean annual direct costs (2006 USD)	1989 costs: 7,397 1990 costs: 9,067	5,592	Canada: 5,629; US: 5,415; UK: 5,158	-
Mean annual indirect costs (2006 USD)	1989 costs: 8,685 1990 costs: 9,153	Human Capital Approach (HCA): 11,340	-	1,517 (Friction Costs Method [FCM]) - 24,075 (HCA)
Predictors for high direct costs	Impaired physical function, high serum creatinine.	Young age, high education level, high disease activity, more disease damage, impaired physical function.	-	-
Predictors for high indirect costs	Low level of global well-being, impaired physical function, low level of social support, high education level and unemployment.	High education level, high disease activity, impaired physical function.	-	-

Table 1.12 Major findings of cost-of-illness studies in systemic lupus erythematosus *(Continued)*

	Clarke et al. (2004) [176]	Panopalis et al.(2007) [172]	Huscher et al. (2006) [174]	Panopalis et al. (2008) [171]
Country	Canada, UK and US	Canada, UK and US	Germany	US
No. of subjects	Canada: 231; US: 269; UK: 215. Total: 715	Canada: 231; US: 269; UK: 215. Total: 715	844	812
Period of recruitment	June 1995 to February 1998	June 1995 to February 1998	2002	September 2002 to December 2003
Study design	Prospective (4-year)	Prospective (4-year)	Cross-sectional	Cross-sectional
Mean annual direct costs (2006 USD)	Canada: 3,812; US: 4,872; UK: 4,247	-	4,269	13,493
Mean annual indirect costs (2006 USD)	-	HCA: Canada: 10,611; US: 14,918; UK: 12,221 FCM: Canada: 1,517; US: 1,116; UK: 1,202	HCA: 19,280 FCM: 8,720	9,241
Predictors for high direct costs	-	-	High disease activity, poor function, short disease duration.	Young age, high disease activity, long disease duration, poor physical and mental health.
Predictors for high indirect costs	-	-	Poor function, long disease duration, old age.	Old age, high disease activity, poor physical health, poor mental health.

* Costs were adjusted for inflation using consumer price index (derived from Statistic Department of each country), in 2006 US dollars (USD).

Using the same cohort, Lacaille et al performed a sub-analysis to investigate the impact of disease activity, treatment, and disease damage on direct and indirect costs of SLE [173]. Disease activity was measured using the SLEDAI. A global disease severity index, ranging 0 to 6, was developed to assess disease damage, in which severity was assessed in three systems – renal involvement, CNS involvement and haematologic involvement. Particularly, CNS involvement was scored on a scale of 0 to 2. A score of 2 required the presence in the past of seizure, stroke, psychosis, or organic brain syndrome. The presence of a motor, sensory, autonomic or cranial neuropathy received a score of 1, and the absence of any of these signs/symptoms received a score of 0. For treatment index, patients received a score of 3 if receiving immunosuppressants, a level of 2 if receiving high dose prednisone, 1 if receiving low dose of prednisone and 0 if receiving neither immunosuppressants nor prednisone. Lacaille et al found that the SLEDAI score did not associated with direct costs or indirect costs and the treatment index only associated with indirect costs. Disease damage strongly associated with costs, and it was an independent predictor associated with both direct and indirect costs. However, not all the subset of the severity index presented the same ability as a cost predictor. Haematologic subscale did not influence costs. Renal subscale associated with only direct costs. CNS subscale significantly associated with both direct and indirect costs. Results from this

study suggested the CNS involvement in SLE as an important costs determinant and drew attention to the need for greater study of NPSLE.

The Tri-Nation study was the first prospective study to estimate and compare costs of SLE among three countries, Canada, United States (US), and United Kingdom (UK) [172, 175, 176]. Over 700 patients were recruited at baseline and surveyed semi-annually over 4 years for healthcare resources utilization and health status. Canadian prices were applied for each health resource across countries. Clarke et al reported the baseline direct costs assessment in 1999 [175]. Differences were observed in the utilization pattern of each resource category. Canadians were older but scored more favorably in most of the domains of the SF-36 compared with the Americans and British, and had more disease damage compared with the British. Canadian saw more specialists than the British, the British more general practitioners. Canadians and Americans used more emergency facilities, Americans more laboratory/imaging tests. Canadians had higher hospitalization costs than Americans. However, overall annual direct costs per patient did not vary significantly among three countries.

Using the Tri-Nation cohort at baseline, indirect costs of women with SLE were also

calculated by Clarke et al [177]. A total of 648 women were in this study to assess diminished labor market and non-labor market productivity over the preceding 6 months. Canadian wages were applied. The study measured indirect costs due to both diminished labor and non-labor (non-paid household work and daily living activities) market productivity, as well as the costs of time provided by family and friends in delivering healthcare or aiding the patient in receiving healthcare. Costs were calculated using the FCM and 4 different approaches using the HCA (approaches varied in whether including non-labor market productivity and the wage level used to value productivity). Average annual indirect costs calculated by the FCM was $1,424 (1997 Canadian dollars) and ranged from $10,463 to $22,604 by the HCA, depending on the value assigned to labor and non-labor work. When the time women lost from household work was included, the annual indirect costs of SLE would be twice as much as that when household work was not valued. It suggests that long-term absence from labor market, as well as diminished non-labor market productivity will be of great importance, especially in the population affected by chronic diseases or more likely to be engaged in non-labor market, such as patients with SLE. Costing methods that fail to consider these losses of productivity will probably underestimate the impact of a disease or diseases on a patient's productivity [181].

The cross-country comparisons of cumulative direct and indirect costs and health outcome (expressed as disease damaged measured by SDI) were performed [176]. After 4-year follow-up, despite significant higher direct costs in patients in the US, which is 20% and 13% higher than that in Canada and the UK respectively, these patients did no experience superior health outcomes. Patients in the US also had significantly higher cumulative indirect costs due to diminished labor market activity than those in Canada and the UK [172]. These results further demonstrated that the high direct costs observed in the American patients did not guarantee better health outcome or improved productivity.

Also using the Tri-Nation cohort, a study was performed to elucidate the relationship between renal damage and disease costs and quality of life [178]. Four-year cumulative direct and indirect costs and quality of life (mean annual change in the SF-36) were compared between patient with and without renal damage (according to the SDI scoring). The results showed that the renal subscale of the SDI was a significant independent predictor for high direct costs. Patients with end-stage renal disease incurred significantly higher direct costs than those without renal damage. Cumulative indirect costs and annual change in the SF-36 physical and mental health

summary scores did not differ between patients with and without renal damage.

Apart from the Tri-Nation group, costs of SLE were also assessed by three large cohorts in the UK [170], Germany [174] and US [171]. Results from these studies were consistent with previous findings, which was that SLE has a considerable economic impact on the society, the healthcare system as well as the individuals. Indirect costs of SLE usually represent a larger proportion of total costs than direct costs.

1.17.1 Cost predictors

Cost-of-illness studies usually identify cost predictors, which are variables associated with high direct or indirect costs. The value of identifying cost predictors is that by modifying or controlling these variables, costs of a disease may possibly be reduced, avoided, or delayed. Several cost predictors have been identified (Table 1.12). Disease activity and disease damage are the 2 most frequently shown cost predictors.

1.18 Summary and future directions in cost-of-illness studies in SLE

Albeit the relative paucity of SLE cost data, early studies have shown the considerable financial burden that SLE imposed to the society and patients. Almost

all these studies have shown that indirect costs contributed the majority of total costs and costs of hospitalization represented the largest component of direct costs.

All these cost-of-illness studies in SLE are prevalence-based bottom-up designed, and mostly using societal perspective. Most of the cohorts are clinic-based, except the study by Panopalis et al (2008) having had community-based sources [171]. Survey was the most common tool to derive details about healthcare resources utilization, and the economic section of the Stanford Health Assessment Questionnaires (HAQ) was the most frequently used [182]. The HAQ was developed for the assessment of arthritis although the economic section of HAQ can be applied to other diseases. However, using this method, the accuracy of the data relies largely on the patients' memory. Reviewing medical notes may generate more accurate data, but it's more feasible when the patient seeks healthcare through a single provider. Gross-costing approach to calculate hospitalization costs was employed in all previous cost-of-illness studies in SLE. As discussed, this method generates less information. Micro-costing method is recommended if data is available. HCA was used in most of the studies to calculate indirect costs. For those using 2 methods, indirect costs were much lower when calculating using the FCA compared with HCA [174, 177].

So far, all cost-of-illness studies in SLE were conducted in Canada, the US, UK or Germany, mostly Caucasian population. There is no data regarding the socioeconomic burden of SLE in Asia-Pacific region, which in fact houses the majority of the world's SLE patients [7]. Cost-of-illness studies should always be country specific, because there is great variation in the organization of care, treatment patterns, and absolute or relative cost of individual facilities across countries [183]. Particularly, for Hong Kong, which has a dual healthcare system different from most western countries and of course, very limited healthcare budget but huge demands, how to prioritize the existing available resources is a major concern. Knowledge about the economic consequences of SLE can provide information about the magnitude of the problem and assisting in allocating healthcare resources and research.

Furthermore, previous cost-of-illness studies have found high disease activity or damage predicts high disease costs [170, 171, 173]. Renal damage has also been shown associated with high direct costs [178]. However, no study has ever investigated the relationship between disease costs and NPSLE or lupus flare. CNS is one of the major organs frequently affected by SLE. However, compared with renal

system, less attention has been drawn to the CNS involvement in SLE and there is relatively fewer data about the ideal treatment strategy of NPSLE. Previous studies have demonstrated the adverse impact of NPSLE on HRQoL and its association with more accumulated disease damage, higher disability and impaired productivity. Lupus flare is an important outcome variable. Preventing flare and prolonging remission are major management principals in SLE. Death and the long-term accumulation of damage were strongly predicted by a high total disease activity over time and especially associated with the number of severe flare [79]. Major organ flares, such as renal or NP flare, have been shown to be associated with poor prognosis [30, 49, 80]. Altogether, it is probably that NPSLE and lupus flare are associated with increased disease costs and impaired HRQoL and it will be of great interest investigating the relationship between disease costs or HRQoL and NPSLE or lupus flare. However, currently, there are no such analyses available.

1.19 The healthcare system in Hong Kong

1.19.1 The public sector

Hong Kong has a dual healthcare system, both public and private sector. Hong Kong's health care is largely administered by the Government, which provides comprehensive health care from primary to tertiary care, including medications,

investigations, ambulatory care, hospitalization, and operations. Public hospitals and clinics deliver most of the medical services, especially specialty clinics and inpatient care, with a market share of more than 90% [184, 185]. The public healthcare services are heavily subsidized by the Government and are available to all residents with no means test and no medical insurance required. The public is charged nominal fees for medical treatment provided by the Government, with patients usually paying HKD 45 (1 HKD = 0.13 USD, market exchange rate) for an attendance at a general clinic, HKD 60 for an attendance at a specialist clinic, and HKD 100 per inpatient day for general wards *(Hospital Authority Suppl No.4 To Gazette No. 13/2003)*. For genuine hardship, all fees can be waived.

The Department of Health and the Hospital Authority are 2 major branches responsible for the delivery of healthcare. The Department of Health oversees the health of the community through promotive, preventive, curative and rehabilitative services. The Hospital Authority is responsible for the formulation of health policies and monitoring the performance of the Authority. It manages 41 public hospitals / institutions, 48 specialist outpatient clinics and 74 general outpatient clinics.

From 1994, the clinical management system (CMS) was implemented by the

Government, providing single logon access to almost all the available clinical information in the public healthcare system, from clinic to hospital care [186]. The CMS keeps records of all kinds of public healthcare resources used, including ambulatory, hospital, emergency resources, medication and laboratory/radiologic facilities. Therefore, the number of each kind of public healthcare facilities could be easily retrieved.

1.19.2 The private sector

The private healthcare system consists of 13 private hospitals and numerous private physicians, which are run on a profit basis. The private hospitals are relatively small in number, size, and custom, and used mainly by expatriates and wealthy Chinese. Ninety-five percent of the private physicians operate solo practices [187]. Fees and charges of private healthcare services vary considerably, depending on the region and the reputation of the doctors.

CHAPTER 2 HYPOTHESES AND AIMS

Systemic lupus erythematosus (SLE) is a prototypical chronic autoimmune disease, with a predisposition to affect young women during reproductive age. SLE incurs significant burden on the society and the individual, economically, physically and mentally. Central nervous system is one of the most commonly involved major organs in SLE. Neuropsychiatric SLE (NPSLE) is associated with accumulated disease damage, disability and unemployment. Flare, an increase in disease activity over a defined period, is an important outcome in the assessment of SLE. Uncontrolled disease activity results in cumulative organ damage which is associated with increased mortality.

Cost-of-illness studies measure the economic burden an illness or illnesses impose on the society or individuals in terms of the consumption of healthcare resources and production losses. Despite paucity of data, several cost-of-illness studies have all demonstrated substantial direct and indirect costs in patients with SLE. Increased in disease activity and damage have shown associated with high disease costs. However, currently, there are no analyses regarding the relationship between disease costs or health-related quality of life (HRQoL) and NPSLE or lupus flare. In view of the

adverse impact of NPSLE and lupus flare demonstrated by other studies, it is probably that NPSLE and lupus flare are associated with increased disease costs and impaired HRQoL.

In the present study, we hypothesized that:

1. SLE is associated with substantial economic burden as a result of NPSLE and flare.

2. Patients with NPSLE or flares may experience more compromised HRQoL.

This thesis is concerned with a cost-of-illness study in Chinese patients with SLE in Hong Kong. The aims of the study are described as follows.

1. To estimate the direct costs related to utilization of both healthcare and non-healthcare resources, as well as the indirect costs associated with losses of productivity, in a cohort of Chinese patients with SLE in Hong Kong, from a societal perspective.
2. To ascertain the relationship between NPSLE and direct and indirect costs.
3. To evaluate the impact of lupus flares on direct/ indirect costs.
4. To determine the impact of SLE on patients' HRQoL and to investigate the relationship between NPSLE/flare and HRQoL.

CHAPTER 3 METHODOLOGIES

3.1 Study design and selection of patients

It was a retrospective, non-randomized survey. A convenient sample consisting of 306 patients meeting at least 4 of the 11 the 1997 American College of Rheumatology revised criteria for systemic lupus erythematosus (SLE) [1] were recruited from the Rheumatology Clinic of the Prince of Wales Hospital (PWH) between January 2006 and August 2007. All participants were Chinese, within working age ($\geqq$18 years old, <65 years old for male and <60 for female), and were followed at the PWH at regular intervals (every 3 to 4 months) according to a standardized assessment protocol including (a) disease activity assessment according to the Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) at each visit [68]; (b) yearly disease damage assessment according to the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) [82]. Patients who were not capable to respond to a questionnaire (e.g., aphasia as a result of stroke, presence of dementia) were excluded. Consecutive eligible subjects were identified by the investigator (TYZ) from a review of the medical notes and then invited to participate. Only one patient

was excluded due to presence of mute. Less than 5 patients were excluded due to not within working and less than 10 patients refused to participate. The characteristics between those participated and those refused could not be compared due to loss of data.

Situated in Shatin, PWH was officially opened in 1984. It is one of the acute general public hospitals managed by the Hospital Authority, as well as the teaching hospital of the Medical Faculty of the Chinese University of Hong Kong. With around 1,200 beds and a total workforce of around 3,500, it is the regional hospital of the Eastern New Territories serving a population of over 1 million (17% of the total population of Hong Kong in 2006) in Shatin, Tai Po and North District.

The study was conducted according to the Declaration of Helsinki. The protocol was approved by the Joint Chinese University of Hong Kong - New Territories East Cluster clinical research ethics committees. Written informed consents were obtained from each participant prior to entry to the study.

3.2 Procedures

All participants completed structured questionnaire interviews conducted by the

investigator (TYZ). The questionnaire was specially designed according to our study aims and the characteristics of the Hong Kong healthcare system. It included items pertaining to demographics and health status, employment outcomes and patients' out of pocket expenses over the preceding 12 months. The same questionnaire had been used in a cost-of-illness study on patients with ankylosing spondylitis and psoriatic arthritis [168, 169]. Complete physical assessment was performed in all subjects by their treating rheumatologists. The protocol driven clinic visit and associated laboratory tests were not included in the cost estimation.

3.3 Measures

3.3.1 Demographic variables

Demographic information collected included age, gender, marital status (categorized as being currently married, divorced, widowed, and single), and education (reported as the number of years of receiving formal education).

3.3.2 Disease status

Disease duration represented the interval between disease diagnosis and study entry. Disease diagnosis was defined as the date the patient first met 4 of the 1997 American College of Rheumatology revised diagnostic criteria [1] as ascertained by

a rheumatologist. Assessment of disease activity and disease damage, using the SELENA-SLEDAI and SDI respectively, was performed in all participants by their treating rheumatologists. For the detail description about the SELENA-SLEDAI and SDI, please refer to **CHAPTER 1.6**. Briefly, the SELENA-SLEDAI is a valid and reliable disease activity measure in SLE [68]. It contains 24 descriptors in 9 organ systems, including clinical and laboratory measures. The total SELENA-SLEDAI score falls between 0 (no activity) and 105 (maximum activity). The SDI is a validated physician-rated index that consists of 41 items in 12 organ systems/domains [82]. Damage is defined as any irreversible change occurring since onset of SLE and presenting for at least 6 months. The total SDI scores range from 0 (no damage) to 49 (maximum damage).

Physical and mental health status was assessed by the physical component summary scale (PCS) and mental component summary scale (MCS) of the Short Form 36 (SF-36). For more details about the assessment of the SF-36, please refer to **CHAPTER 1.7** and **CHAPTER 7**.

3.3.3 Employment outcomes

Participants were queried about their employment status over the preceding 12

months. Employment outcomes were categorized as employed, unemployed due to SLE, unemployed not due to SLE and housewife. Participants were considered employed if they reported that they had been at work for pay or profit or they had formal job attachment. Whether unemployment was related to SLE was indicated by participants. Participants also reported their current occupation, or last occupation before unemployment (categorized as professional/supervisory workers, clerical and secretarial workers, service workers, miscellaneous non-production workers and production worker). The categorization was in accordance with that in *Report of Wage and Payroll Statistics, Census and Statistics Department* in Hong Kong. In the mentioned questionnaire, participants also provided information regarding: a) sick leave taken in the preceding 12 months (for those who were employed); b) whether they were unemployed due to SLE and the duration of unemployment (for those who were SLE-related unemployed); c) the number of days off from household work or daily activities due to SLE in the preceding 12 months (for those who were non-SLE-related unemployed or housewives).

3.4 Cost estimates

We recorded both direct and indirect cost, in a societal perspective, which means all costs would be relevant, irrespective of who paid for them. As to intangible costs,

given the difficulty to accurately quantify them in monetary term, we conveyed them as health-related quality of life (HRQoL), measured by the SF-36, and discussed separately in **CHAPTER 7**. The cost framework used in our study was summarized in Table 3.1. Details relating to costs of the disease were collected for the preceding 12 months, consisting of use of all types of hospital or clinic services. Results were shown in 2006 US dollar (USD, Purchasing Power Parity).

Given the complexity of SLE, it is difficult to distinguish utilization of healthcare resources as a result of SLE versus other condition. Therefore, costs estimated in our study reflected all costs of resources incurred by participants, rather than the additional costs that were related to a consequence of SLE.

Table 3.1 Cost framework used in our study

Direct costs	Visits to healthcare provider
	Diagnostic examination
	Blood test
	Urine test
	Radiological examination
	Medications
	Visits to emergency room
	Inpatient care
	Private hospital/clinic service
	Patients' out-of-pocket expense
	Health product
	Non-traditional therapy
	Aid device
	Non-healthcare resource
	Transportation
	Household helper
	Alteration of house
Indirect costs	Due to sick leave
	Due to systemic lupus erythematosus-related unemployment
	Due to days off from household work or daily activities
Intangible costs	Health-related quality of life

3.4.1 Direct costs to the public healthcare

In view of the dual healthcare system in Hong Kong, utilizations of public and private healthcare resources would be collected in different methods. Utilization of public healthcare resources was derived by reviewing medical notes. Public healthcare resources referred to a) all visits to healthcare providers (such as rheumatologist, nephrologist, dermatologist, general practitioner, psychologist,

psychiatrists, physiotherapist, occupational therapists, etc), b) all diagnostic examinations (including, blood test, urine test and radiological examinations), c) all kinds of medications taken in the preceding year, d) visit to the emergency room, and e) inpatient care (including acute and rehabilitation hospitalization).

Direct costs to the public healthcare were initially recorded as units of service and then assigned a dollar value per unit of service. Details pertaining to the unit price for various services were shown in Appendix 2. Because public healthcare were heavily subsidized, nominal charges were not a good measure of costs. Thus, we used per diem charge to non-eligible persons issued by the Hospital Authority as a measure of costs to the public healthcare. Other sources of unite price included Department of Pathology, Department of Radiology, Department of Pharmacy and Department of Accounting of Prince of Wales Hospital. For the estimates of costs of inpatient care, we used micro-costing method. Costs of inpatient care comprised of professional charge (rate of charge issued by Hospital Authority), all diagnostic examinations and all medications received during hospitalization.

3.4.2 Direct costs to the private healthcare

We did not have access to the private hospital/clinic records and the costs of private

healthcare facilities varied considerable. Also, we found it very difficult for participants recalling the details, such as types and numbers of use, regarding the utilized private healthcare facilities. Therefore, if the patient utilized a private facility, we recorded the total fees reported by the patient.

3.4.3 Patients' out-of-pocket expenses

Patients' out-of-pocket expenses in the preceding year were reported by the patients, including costs of: a) health products (including traditional Chinese medicine); b) non-traditional therapies (e.g. hydrotherapy, acupuncture, massage); c) aid devices and d) direct non-healthcare resources, including transportation expenses to the healthcare providers, private household helper and adaptation to houses. These expenses were without coverage by the government's reimbursement.

3.4.4 Indirect costs

The Human Capital Approach, which uses wages as a proxy measure of the output of work time to value the individual's lost work hours, was used to calculate productivity losses [149]. Indirect costs represented the wages forgone due to SLE over the preceding year, which included annual sick leave due to SLE, unemployment due to SLE, and days off from household work or daily activities due

to SLE. They were calculated by multiplying the patient's wages by the time lost from work/activities. All wages were obtained from *Report of Wage and Payroll Statistics, Census and Statistics Department (fiscal year 2005-2006).*

For those who were still employed, the number of self-reported days of SLE-related sick leaves was multiplied by the gender- and occupation (category)-matched daily wage. For those who stated they would be employed if they did not have SLE, productivity losses due to unemployment were the product of the duration (months) of unemployment multiplied by the gender- and occupation-matched monthly wages. For those who were unemployed but not due to SLE and housewives, productivity loss due to days off from household work or daily activities was also measured, using replacement cost approach, which imputes market values to perform equivalent duties at home. Productivity losses for this group of patients were calculated by multiplying the self-reported number of days that the individual was unable to attend household work or daily activities by the daily income of a gender-matched general worker in Hong Kong.

3.4.5 Intangible costs

Intangible costs were conveyed as HRQoL measured by the SF-36. Details about the

measurement and the results were described in **CHAPTER 7**.

3.5. Sample size calculation

The sample size is estimated by the Crochan's formula [188, 189]. Based on our preliminary data, the estimated standard deviation of SLEDAI in systemic lupus erythematosus is 2.86. We take a margin of error for the mean being estimated to be 0.2 as acceptable and the alpha value be 0.05, a total sample size of 126 would be sufficient. We decided to recruit all the available patients fulfilling the inclusion criteria in our centre in order to generate a larger and representative sample.

3.6 Statistical analyses

Statistical analyses were performed using the Statistics Package for Social Sciences (SPSS for Windows, version 13.0, SPSS Inc, Chicago, IL). Results were expressed as mean ± SD for normally distributed data. For non-normally distributed data, median and IQR (or range) were expressed. Continuous variables were compared by the independent samples *t*-test (with normal distribution) or Mann-Whitney *U* test (with non-normal distribution). Categorical variables were compared by chi-square test. Sensitivity analysis was not employed in this study. For more detail about the statistical analyses methods, please refer to following chapters.

CHAPTER 4 DIRECT AND INDIRECT COSTS OF SYSTEMIC LUPUS ERYTHEMATOSUS IN HONG KONG

4.1 INTRODUCTION

Economic questions are now of great interest to the practice of rheumatic diseases [190]. Recent data have shed additional light on the major economic impact of musculoskeletal diseases on patients' daily life and on society [147, 191-195]. As to systemic lupus erythematosus (SLE), a multi-factorial autoimmune disease that primarily affects young women, the data on economic evaluation is scanty. Because of the frequent disease activity exacerbations and the consequently accumulated organ damage, one may expect that SLE affects the patients both physically and psychologically, and incurs a significant economic burden to the society as well as to the patients.

Several previous studies in western societies have demonstrated substantial disease costs among patients with SLE, both direct costs associated with healthcare resources consumption and indirect costs due to loss of productivity [171, 175, 179, 180]. However, there is no data regarding the socioeconomic impact of SLE in Asia-pacific area or in Hong Kong. Cost-of-illness studies are always country-specific. It is

impossible to apply the results of one study in a given country to another country, because there is great variation in the healthcare system, treatment patterns and the amount of available recourses.

We performed a retrospective non-randomized cost-of-illness study from 2006 to 2007 in a tertiary rheumatology specialty centre in Hong Kong on patients with SLE. The study identified the direct and indirect costs of patients with SLE in a societal perspective in Hong Kong. Results are reported here.

4.2 METHODS

4.2.1 Study design, patients, data collection and cost estimates

Please refer to **CHAPTER 3**.

4.2.2 Statistical analyses

Results were expressed as mean ± SD for normally distributed data. For non-normally distributed data, median and IQR (or range) are expressed. Number of cases and percentage was used where appropriate.

Both univariate and multivariate linear regression analyses (stepwise selection) were

used to determine the predictors of increased direct costs. Because 36.9% of patients had no indirect costs, the combination of logistic regression and a linear regression model was preferable as to determine predictors of increased indirect costs. This approach to analyzing data with clumping at zero has been demonstrated by Chang et al [196]. Briefly, a logistic regression was used to model probability of a zero indirect costs and a stepwise multiple linear regression was used to model the non-zero continuous indirect costs. Due to skewness of the costs data, the costs results were log-transformed (base=10) for the linear regression model. The possible predictors included gender, age, disease duration, education level, the Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores and the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) scores, scores of physical and mental component summary scales of the Short Form 36 (PCS and MCS). Because marital status did not show influence on costs estimates in univariate analysis, similar to previous studies in SLE, it was not included in the prediction models. The p value for a variable to remain in the model was <0.05. Selection of final model was based on the adjusted R^2 and an evaluation of the residual plots. A sensitivity analysis was performed to indicate whether the test was sensitive to outliers (a case was an outlier

if it was 3 SDs away from the mean). Assumptions were checked before performing the linear regression, including no outliers, independent data points and normally distributed residuals with mean = 0 and a constant variance. No assumptions were violated. Multi-collinearity was checked using the statistics of tolerance which is one of the functions of multiple linear regression analysis in the SPSS programme. Tolerance lies between zero to one. A value close to zero indicates that a variable is almost a linear combination of the other independent variables. Values above 0.6 would be recommended but since most likely there will be some correlation between variables, 0.4 and above would be acceptable [197]. In our analyses, all tolerances for tested variables were above 0.6. This argument also applied to **CHAPTER 5** and **CHAPTER 6**.

4.3 RESULTS

4.3.1 Demographics and clinical profile

Three hundred and six patients were recruited, with a male to female ratio of 1:25. The mean (SD) age was 41 (11) years and the mean (SD) disease duration was 9.6 (6.9) years (median 8.7) (Table 4.1). The mean (SD) education level was 10 (4) years. Three percent patients reported education level as less than primary school, 15% as primary school, 55% as secondary school and 27% as college graduate or

postgraduate degree.

At the time of the assessment, 107 (35%) patients had inactive disease with a SELENA-SLEDAI score of 0. The remaining 199 patients had mild to moderate disease activity, with a mean (SD) SELENA-SLEDAI of 3.77 (2.69) (median 3, range 1-16). One hundred and seventy-eight (58%) patients had a SDI of 0. The remaining 128 patients had a mean (SD) SDI of 1.70 (1.03) (median 1, range 1-7). The most common organ damages, in order of frequency, were neuropsychiatric damage (11.8%), ocular (8.2%), musculoskeletal (6.9%), pulmonary (6.9%), premature gonadal failure (6.5%), renal (5.2%) and skin (4.9%) damage.

Table 4.1 Demographics and clinical profile (ever) of patients* (n=306)

	Value
Demographics	
Age, mean ± SD years	41 ± 11
Women	294 (96)
Education level, mean ± SD years	10 ± 4
Married	170 (56)
Employed	142 (46)
Disease characteristics	
Age at diagnosis, mean ± SD years	32 ± 12
Disease duration, mean ± SD years	9.6 ± 6.9
SELENA–SLEDAI score, mean ± SD	2.5 ± 2.8
SDI score, mean ± SD	0.71 ± 1.07
American College of Rheumatology criteria profile	
Malar rash	133 (43)
Discoid lesion	40 (13)
Photosensitivity	97 (32)
Oral ulcer	94 (31)
Arthritis	235 (77)
Serositis	85 (28)
Renal disease	182 (59)
Neuropsychiatric disease	83 (27)
Haematologic	256 (84)
Leukopenia	160 (52)
Lymphopenia	199 (65)
Thrombocytopenia	91 (30)
Hemolytic anemia	25 (8)
Immunological	290 (95)
Anti-ds DNA positive	232 (76)
Anti-Smith positive	66 (22)
Anti-Ro positive	170 (56)
Anti-La positive	57 (19)
ANA positive	301 (98)

* Values are the number (percentage) unless otherwise indicated. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; anti-ds DNA= anti–double-stranded DNA; ANA = antinuclear antibody.

4.3.2 Healthcare resources, productivity and costs

The number of visits to healthcare providers over preceding 12 months varied between 1 to 36, with a mean (SD) visit of 7.25 (4.72) (median 6, range 1-36). Rheumatologists visit were the most commonly seen healthcare provider during the study period, followed by ophthalmologists and general practitioners. Details of visits to healthcare provider are shown in Table 4.2. For the 94 respondents who visited other providers, 26 visited obstetricians and gynaecologists (median number 2), 20 visited surgeons (1.5), 8 visited orthopedists (2.5), 7 each visited gastroenterologists (2), otolaryngologists (1) and neurologists (3.0) respectively. Other less visited health providers included cardiologists (by 3 patients), hepatologists (by 3 patients), endocrinologists (by 3 patients), haematologists (by 1 patient) and oncologists (by 1 patient).

During the study period, 96.7% patients were on medications and 73% on prednisone and 55% on anti-malaria drugs. Thirty-one percent patients were on immunosuppressants, including azathioprine (n=68, 71%), cyclophosphamide (n=11, 11%), mycofenolate mofetil (n=6, 6%), cyclosporin A (n=9, 9%), leflunomide (n=8, 8%), methotrexate (n=3, 3%).

Table 4.2 Visits to healthcare provider in the preceding year

	No. of patients with at least one visit		Mean (SD) no. of visits in 12 months	Median
	n	%		
Rheumatologist	306	100	4.66 (2.54)	4
Nephrologist	5	2	0.06 (0.51)	0
Dermatologist	26	8	0.23 (0.93)	0
Opthalmologist	114	37	0.59 (1.08)	0
General practitioner	65	21	0.54 (1.39)	0
Allied health professional	8	3	0.19 (1.72)	0
Psychologist	5	2	0.04 (0.31)	0
Other provider	94	31	0.95 (2.16)	0

The number of diagnostic examinations per patient-year varied from 5 to 159 with a median of 27.5 (mean 35.8 ± 24.5). All the participants reported blood tests (mean number of tests 30.4 ± 16.8, median 25, range 5-108) and 44.8% patients needed urine tests (mean number of tests 10.9 ± 10.8, median 6, range 1-51). Eighty-five patients (27.8%) needed radiological examinations, most of which were plain X-ray examinations. The more expensive tests were used for relatively small numbers of patients (only 9% patients had at least one of ultrasound, computed tomography or magnetic resonance imaging investigation).

Eighty-three (27%) patients had emergency room visits, with a mean number of 1.6 ± 1.1 (median 1, range 1-6). A total number of 197 inpatient care (including

rehabilitation hospital) were recorded by 82 patients (27%) with a mean duration of 21 ± 40 days (median 7.5, range 1-260). The main cause of hospitalization was clinical active SLE (40%), followed by infection (14%, including human papillomavirus infection). Five patients needed rehabilitation hospitalization with a mean duration of 42.8 ± 34.2 days (median 42, range 7-82). Five operations were recorded, 3 of which were musculoskeletal and 2 gastrointestinal surgery.

Utilization of private hospital/clinic services were recorded in 51 (17%) patients. Eighty-seven percent of patients recorded out-of-pocket expenses, mainly on health products (110/306, 36%), and non-traditional therapy (58/306, 19%). Seven percents patients used self-paid aid devices, mostly on crutch or wheelchair. Expenses on household helper and alteration of houses reported by only 12 (4%) and 5 (2%) patients, respectively.

More than half of the patients were unemployed. Among those who were still working, 85% needed to take sick leave with a mean duration of 14 ± 32 days (median 6). For those who were unemployed, the majority indicated that they were work disable because of SLE (72/164 patients, 44%), 85% of which had been unemployed for over 12 months. For those who were unemployed but not due to SLE

(42/164 patients, 26%) and housewives (40/164 patients, 25%), days off from daily activities or household work due to SLE were reported by 24% and 30% patients respectively, both with a median duration of 0 days. Ten patients were still full-time students.

We determined the average total costs of the 306 patients with SLE to the society as USD 13,307 (2006 US dollars, purchasing power parity) per patient-year (Table 4.3). The direct costs dominated the total costs (62%). Costs were not distributed normally. One hundred and thirteen (36.9%) patients incurred no indirect costs and 10 patients had very high indirect costs over the preceding 12 months (>USD 30,000). Eleven patients incurred high direct costs (>USD 30,000), with 2 incurred extremely high direct costs (>USD 150, 000). The costs of inpatient care contributed 52% of the direct costs. These were followed by the costs of diagnostic examinations (16%), patients' out-of-pocket expenses (15%) and costs of healthcare provider visits (10%). Costs of medications and emergency room visits represented a relatively small percentage.

Table 4.3 Annual costs for patients with systemic lupus erythematosus (in 2006 US dollars)*

	Mean	SD	Percentage of direct costs (%)	Percentage of total costs (%)	Median	IQR
Visits to healthcare provider	848	544	10.3	6.4	670	546
Diagnostic examination	1,302	805	15.8	9.8	1,070	783
Laboratory examination	1,227	737			994	681
Radiological examination	74	216			0	34
Medications	330	495	4.0	2.5	171	283
Emergency room visits	47	99	0.6	0.4	0	103
Inpatient care	4,312	16,474	52.4	32.4	0	1,775
Private hospital/clinic services	125	507	1.5	0.9	0	0
Patient out-of-pocket expenses	1,267	2,402	15.4	9.5	190	1,335
Health products	687	1,586			0	651
Non-traditional therapy	310	958			0	0
Aid devices	22	312			0	0
Non-healthcare costs	248	989			25	120
Transportation	81	155			22	81
Household help	154	971			0	0
Alteration of house	13	135			0	0
Direct costs	8,230	16,785		61.8	3,697	6,021

Table 4.3 Annual costs for patients with systemic lupus erythematosus *(Continued)*

	Mean	SD	Percentage of direct costs (%)	Percentage of total costs (%)	Median	IQR
Due to sick leave	1,229	3,068			511	609
Due to SLE-related unemployment	18,613	8,320			15,314	13,991
Due to days off from household work or daily activities	4,315	5,743			1,187	9,232
Indirect costs	5,077	8,890		38.2	332	7,177
Total costs	13,307	20,197			6,300	13,935

*: 1 US dollar = 5.527 HK dollar, purchasing power parity, exchange rate derived from United Nation Statistics Division. IQR = interquatile range; SLE = systemic lupus erythematosus.

Most of the direct costs were paid by the government while the patients only paid for about 17% of the direct costs (including the patients' out-of-pocket expenses and costs of private hospital/clinic services). These proportions were associated with disease severity. For those patients without organ damage (SDI=0), patients' self-paid expenses were approximately 20% of the direct costs. This percentage decreased as disease damage score increased. For those patients with SDI score of more than 5, the patients' self-paid expenses contributed only 3% of the direct costs. The most expensive healthcare resources, like the inpatient costs or operations, were largely paid by the government.

A conservative approach was used to estimate the total direct medical costs of SLE imposed on Hong Kong society. Assuming the prevalence as 58.8 per 100,000, we estimated that around 4,036 people are suffering from SLE (2006 Hong Kong population: 6,864,346). Total annual direct costs for diagnosed SLE patients in Hong Kong were estimated to be USD 33.2 million (2006 USD, 1 USD = 5.527 HKD, purchasing power parity). The total healthcare expenditure in fiscal year 2005/2006 in Hong Kong was HKD 71,414 million. Hence, direct costs for diagnosed SLE patients contributed up to 0.26% of total Hong Kong health expenditure.

4.3.3 Costs predictors

Table 4.4 shows results of univariate and multivariate regression analysis of direct costs predictors. Univariate analysis showed that younger age, shorter disease duration, higher disease activity and more disease damage, poorer physical and mental health status (i.e., lower scores on the SF-36 PCS and MCS) were associated with increased direct costs. Multivariate regression analysis was performed on log-transformed direct costs. Older age and longer disease duration predicted lower direct costs, whereas more disease damage and poorer physical health status independently predicted higher direct costs. Analyses were not sensitive to outliers.

Table 4.5 shows results of the combination of logistic regression and linear regression analysis of indirect costs. The logistic regression modeled the likelihood of a patient incurring indirect costs as apposed to not incurring. Patients with younger age, poorer physical and mental health status were more prone to incur indirect costs. Stepwise multivariate linear regression analysis showed that lower education level, poorer physical and mental health status predicted higher amount of indirect costs that a patient incurred. Analyses were not sensitive to outliers.

Table 4.4 Univariate analyses and multivariate linear regression (stepwise selection) analyses of direct cost predictors*

	Univariate analyses		Multivariate regression analyses		
	Unadjusted coefficient (95% CI)	P value	Adjusted coefficient (95% CI)	P value	Adjusted R^2
Female gender	0.036 (-0.214, 0.285)	0.778			0.188
Age (1 year increase)	-0.005 (-0.009, 0)	**0.029**	-0.006 (-0.010, -0.002)	**0.007**	
Education level (1 year increase)	0.004 (-0.007, 0.016)	0.456			
Disease duration (1 year increase)	-0.012 (-0.019, -0.005)	**0.001**	-0.015 (-0.022, -0.008)	**<0.0001**	
SELENA–SLEDAI score (1 point increase)	0.023 (0.006, 0.040)	**0.009**			
SDI score (1 point increase)	0.085 (0.040, 0.129)	**<0.0001**	0.109 (0.064, 0.153)	**<0.0001**	
PCS (1 point increase)	-0.013 (-0.019, -0.008)	**<0.0001**	-0.012 (-0.017, -0.007)	**<0.0001**	
MCS (1 point increase)	-0.005 (-0.009, 0)	**0.034**			

* Due to the skewness of direct costs data, a log10 was performed prior to the regression analysis. Numbers in bold represent $p < 0.05$. 95% CI = 95% confidence interval; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PCS = physical component summary scale of the Short Form 36; MCS = mental component summary scaleof the Short Form 36.

Table 4.5 Combination of logistic regression and linear regression (stepwise selection) analyses of indirect cost predictors*

	Logistic regression		Linear regression of log_{10} indirect costs				
	Adjusted odds ratio (95% CI)	P value	Unadjusted coefficient (95% CI)	P value	Adjusted coefficient (95% CI)	P value	Adjusted R^2
Female gender	0 (0,0)	0.998	0.100 (-0.384, 0.585)	0.683			0.203
Age (1 year increase)	0.966 (0.939, 0.994)	**0.019**	0.022 (0.011, 0.032)	**<0.0001**			
Education level (1 year increase)	1.029 (0.960, 1.013)	0.417	-0.061 (-0.090, -0.033)	**<0.0001**	-0.056 (-0.082, -0.029)	**<0.0001**	
Disease duration (1 year increase)	1.031 (0.989, 1.074)	0.151	-0.008 (-0.026, 0.009)	0.346			
SELENA–SLEDAI score (1 point increase)	0.999 (0.910, 1.096)	0.984	0.022 (-0.019, 0.063)	0.285			
SDI score (1 point increase)	0.953 (0.737, 1.232)	0.711	0.137 (0.031, 0.243)	**0.012**			
PCS (1 point increase)	0.961 (0.933, 0.990)	**0.009**	0.029 (-0.040, -0.017)	**<0.0001**	-0.025 (-0.036, -0.014)	**<0.0001**	
MCS (1 point increase)	0.972 (0.950, 0.994)	**0.014**	-0.015 (-0.024, -0.005)	**0.003**	-0.012 (-0.021, -0.003)	**0.010**	

* Due to the skewness of indirect costs data, a log10 was performed prior to the linear regression analysis. Numbers in bold represent $p < 0.05$. 95% CI = 95% confidence interval; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; PCS = physical component summary scale of the Short Form 36; MCS = mental component summary scale of the Short Form 36.

4.4 CONCLUSIONS

In conclusion, SLE incurs substantial socioeconomic impact in Hong Kong, not only because of high amount of healthcare resources delivered in taking care of patients with this condition, but also because of considerable losses of productivity due to work capacity impairment. More disease damage and poorer physical and mental health status are associated with increased direct and indirect costs and they are, to a large extent, modifiable clinical characteristics. Treatments that can delay disease progression to the more advanced status and restore physical and mental health will help avoid, offset or delay these considerable costs to the individual and the society. Our results provide a baseline for the economic evaluation for such treatment.

CHAPTER 5 SYSTEMIC LUPUS ERYTHEMATOSUS WITH NEUROPSYCHIATRIC MANIFESTATIONS INCURS HIGH DISEASE COSTS

5.1 INTRODUCTION

Kidney and central nervous system (CNS) are 2 major organs that frequently affected by systemic lupus erythematosus (SLE) [89, 198, 199]. Clinical features of neuropsychiatric SLE (NPSLE) are diverse and heterogeneous, including both central and peripheral nervous systems. The prevalence of NPSLE varied greatly from 37% to 95% [27-29, 40]. Cognitive dysfunction and headaches are the most commonly reported symptoms in Caucasians. In Chinese, Mok et al reported that 23% patients experienced NPSLE in a longitudinal study in Hong Kong and seizure and cerebrovascular diseases (CVD) were the most common manifestations [200]. Zhou et al reported the prevalence of NPSLE in a hospitalized Chinese population as 12.2% and headache and seizure the most common manifestations [201]. The lower prevalence and different pattern of NPSLE in Chinese may be due to variance in genetic factors, study designs and clinical practice. NPSLE has been identified as a poor prognostic indicator and it's associated with poor quality of life [30, 41, 202]. It has been reported that 47% of the NPSLE patients were readmitted to hospital

because of recurrent NPSLE within 4.5 years, while 10% died due to NPSLE [203]. Jonsen et al reported a higher frequency of disability in NPSLE patients compared with patients without NPSLE and the general population [42].

SLE has been shown associated with significant economic burden to the society and individual and disease activity or organ damage as predictors of high costs. Estimated by Clarke et al, renal damage is associated with increased disease costs in SLE [178]. However, no studies investigate the relationship between NPSLE and disease costs. We have estimated the annual direct and indirect costs of SLE in Hong Kong in a cost-of-illness study. Here we ascertained the relationship between NPSLE and the disease costs. The results are presented here.

5.2 METHODS

5.2.1 Study design, patients, data collection and cost estimates

Please refer to **CHAPTER 3**.

5.2.2 Assessment of NPSLE

Patients' medical records were reviewed by the attending rheumatologists to retrospectively record the total number of NPSLE event since onset of SLE. The

occurrence of neuropsychiatric (NP) manifestation was determined using the 1999 ACR nomenclature and standard definitions for NPSLE (**CHAPTER 1.5**) [25]. This consists of 19 NPSLE syndromes, namely aseptic meningitis, CVD, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis, Guillain-Barre´ syndrome, autonomic neuropathy, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.

5.2.3 Statistical analysis

Results were expressed as mean ± SD for normally distributed data. For non-normally distributed data, median and interquartile/range were expressed as well. Mann-Whitney *U* test was used to compare healthcare resources utilization and disease costs between patients with and without NPSLE. Kruskal–Wallis test was used to test for differences in disease costs among patients with seizure/ CVD/headache, which were the most commonly seen events in our study. . When a Kruskal–Wallis test revealed significant results, Mann–Whitney *U* test by Bonferroni adjustment was used for multiple comparisons (for triple comparisons, $p<0.016$ was considered significant).

Both univariate and multivariate linear regression analyses (stepwise selection) were used to determine the predictors increased direct costs. The combination of a logistic regression and a linear model was used to determine predictors of increase indirect costs [196]. Due to skewness of the costs data, the results were log-transformed (base=10) for the linear regression model. The possible predictors included gender, age, disease duration, education level, the Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) scores, scores of physical and mental component summary scales of the Short Form 36 (PCS and MCS), and the number of NPSLE event since disease onset. Because the number of NPSLE event was included into the regression analyses, we used a modified the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) score (modified SDI, excluding NP domain of the SDI) as a possible predictor. The p value for a variable to remain in the model was <0.05. Selection of final model was based on the adjusted R^2 and an evaluation of the residual plots. A sensitivity analysis was performed to indicate whether the test was sensitive to outliers (a case was an outlier if it was 3 SDs away from the mean).

5.3 RESULTS

5.3.1 Demographics, clinical and NPSLE profile

Table 5.1 summarizes demographics and clinical profile of the cohort, cross-classified by the presence of NPSLE. There were no significant differences in demographics and clinical characteristics between patients with and without NPSLE, except that patients with NPSLE had higher score of SDI and a higher prevalence of having had positive anti-Ro antibodies.

Eighty-three (26.8%) patients had a total of 116 NPSLE events ever. Most patients had 1 NPSLE event (64/83, 77%). Twenty patients had 2 NPSLE events and 5 patients had more than 2. The last NP events occurred within past 3 years and 1 years in 29 (35 %) and 14 (17%) of these patients. Table 5.2 shows the frequency of various NPSLE events since disease onset. The most common manifestations were seizures, CVD and headache.

Table 5.1 Demographics and clinical characteristics (ever) of patients with and without neuropsychiatric systemic lupus erythematosus

	Without NPSLE (n=223)	With NPSLE (n=83)	p value
Age, mean ± SD years	41.5 ± 11.6	40.4 ± 11.1	0.461
Female	216 (97)	78 (94)	0.318
Education level, mean ± SD years	10.3 ± 4.4	10.5 ± 3.8	0.950
Employed	107 (48)	35 (42)	0.371
Disease duration, mean ± SD years	9.6 ± 6.9	9.7 ± 6.9	0.891
SELENA-SLEDAI score, mean ± SD	2.50 ± 3.00	2.33 ± 2.28	0.726
SDI score, mean ± SD	0.60 ± 0.98	1.01 ± 1.24	**0.001**
Modified SDI score, mean ± SD	0.55 ± 0.93	0.60 ± 0.99	0.553
Organ manifestations			
Malar rash	91 (41)	42 (51)	0.153
Discoid lesion	31 (14)	9 (11)	0.570
Photosensitivity	73 (33)	24 (29)	0.582
Oral ulcer	68 (30)	26(31)	0.890
Arthritis	167 (75)	68 (82)	0.225
Serositis	57 (26)	28 (34)	0.196
Renal disease	137 (61)	45 (54)	0.295
Haematologic	190 (85)	75 (90)	0.264
Leukopenia	113 (51)	47 (57)	0.370
Lymphopenia	144 (65)	55 (66)	0.893
Thrombocytopenia	65 (29)	26 (31)	0.779
Hemolytic anemia	16 (7)	9 (11)	0.348
Immunological	210 (94)	80(96)	0.571
Anti-ds DNA positive	172 (77)	60 (72)	0.373
Anti- Smith positive	48 (22)	18 (22)	1.000
Anti-Ro positive	115 (52)	55 (66)	**0.028**
Anti-La positive	43 (19)	14 (17)	0.742
ANA positive	221 (99)	80 (96)	0.293

* Values are the number (percentage) unless otherwise indicated. Numbers in bold represent $p<0.05$. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; anti-dsDNA = anti–double-stranded DNA; ANA = antinuclear antibody.

Table 5.2 Neuropsychiatric manifestations since disease onset in 306 patients with systemic lupus erythematosus

	No.	No. (%) of patients with NPSLE
NPSLE event	116	83 (27.1)
Seizure	25	18 (5.9)
Generalized	24	17 (5.6)
Partial	1	1 (0.3)
Cerebrovascular disease	24	20 (6.5)
Stroke	14	11 (3.6)
Transient ischemic attack.	7	7 (2.3)
Multifocal disease	1	1 (0.3)
Sinus thrombosis	2	2(0.7)
Headache	19	19 (6.2)
Migraine	14	14 (4.6)
Tension	2	2 (0.7)
Nonspecific headache	3	3 (1.0)
Psychosis	7	7 (2.3)
Aspetic meningitis	6	5 (1.6)
Mood disorder	11	10 (3.3)
Major depression	1	1 (0.3)
Depressive features	6	6 (2.0)
Mixed features	4	4 (1.3)
Acute confusional state	4	4 (1.3)
Polyneuropathy	4	4 (1.3)
Cognitive dysfunction	3	3 (1.0)
Mononeuropathy	3	3 (1.0)
Myasthenia gravis	3	3 (1.0)
Anxiety disorder	2	2 (0.7)
Myelopathy	2	2 (0.7)
Acute inflammatory demyelinating polyradiculopathy	1	1 (0.3)
Neuropathy,cranial	1	1 (0.3)
Plexopathy	1	1 (0.3)

NPSLE = neuropsychiatric systemic lupus erythematosus.

5.3.2 Healthcare resources utilization and disease costs and NPSLE

Patients with and without NPSLE had similar numbers of visits to healthcare providers and emergency room (Table 5.3). Patients with NPSLE used more radiological examinations than those without NPSLE. Although patients with NPSLE had longer inpatient care duration, it did not reach significance level. The employment rate was not different between these 2 groups (48% for patients without NPSLE and 42% for those with NPSLE, p=0.371). There was no significant different in duration of annual sick leave / unemployment / days off from household task or daily activities limitation between the 2 groups.

Annual direct costs was nearly twice of patients with NPSLE compared to those without NPSLE (p<0.001) (Table 5.4). Most of the direct costs components did not differ between the 2 groups. However, patients with NPSLE incurred significant higher annual medication costs (p=0.020), mostly due to the higher percentage of using NP drugs in those with NPSLE (35% compared to 10% of those without NPSLE, p<0.0005). Patients with NPSLE also incurred higher annual indirect costs (p=0.024). There was no significant difference in indirect costs due to sick leave (mean ± SD [median] costs: USD 1,107 ± 2,414 [USD 443] [2006 US dollars, purchasing power parity] for patients without NPSLE and USD 1,575 ± 4,482 [USD

635] for those with NPSLE, p=0.122), due to SLE-related unemployment (USD 18,616 ± 8,575 [USD 12,281] for patients without NPSLE and USD 18,607 ± 8,015 [USD16,522] for those with NPSLE, p=0.943) and due to days off from household work or daily activities (USD 2,881 ± 4,418 [USD 791] for patients without NPSLE and USD 8,905 ± 7,561 [USD 14,374] for those with NPSLE, p=0.230) between the 2 groups.

Patients with only seizure (n=12)/ CVD (n=11)/ headache (n=15) were then selected for comparison (Table 5.5). Compared with those with headache, patients with CVD had higher annual direct costs. However, disease costs did not differ between patients with seizure and CVD or between patients with seizure and headache.

Table 5.3 Utilization of healthcare resources in patients with and without neuropsychiatric systemic lupus erythematosus*

	Without NPSLE (n=223)	With NPSLE (n=83)	p-value
No. of visits to healthcare providers	7.11 ± 4.60 (6)	7.64 ± 5.04 (7)	0.271
Rheumatologist	4.57 ± 2.37 (4)	4.90 ± 2.93 (4)	0.427
Nephrologist	0.04 ± 0.36 (0)	0.08 ± 0.77 (0)	0.728
Dermatologist	0.27 ± 1.04 (0)	0.13 ±0.56 (0)	0.577
Opthalmologist	0.58 ± 1.12 (0)	0.61 ± 1.00 (0)	0.632
Government general clinic	0.61 ± 1.54 (0)	0.35 ± 0.83 (0)	0.729
Allied health professional	0.19 ± 1.89 (0)	0.18 ± 0.16 (0)	0.499
Psychologist	0.02 ± 0.21 (0)	0.08 ± 0.47 (0)	0.095
Others	0.83 ± 2.05 (0)	1.29 ± 2.39 (0)	**0.049**
No. of diagnosis examinations			
Blood test	29.7 ± 16.6 (24)	32.3 ± 17.5 (26)	0.168
Urine test	5.3 ± 9.3 (0)	3.9 ± 8.3 (0)	0.372
Radiological examination‡	0.40 ± 1.00 (0)	0.71 ± 2.21 (0)	**0.041**
Visit to the emergency room, No. (%)	56 (25)	27 (33)	0.197
No. of visits to emergency room	0.45 ± 0.98 (0)	0.41 ± 0.70 (0)	0.195
Inpatient care, No. (%)	55 (25)	27 (33)	0.192
Duration of inpatient care, days	3.85 ± 16.5 (0)	10.4 ± 33.4 (0)	0.168

* Values are the mean ± SD (median) unless otherwise indicated.

‡ Including radiographs, ultrasounds, computed tomography scans, and magnetic resonance imaging.

Table 5.4 Annual direct and indirect costs for patients with and without neuropsychiatric systemic lupus erythematosus*

	Without NPSLE (n=223)	With NPSLE (n=83)
Visits to healthcare provider		
Mean ± SD	823 ±511	915 ± 624
Median (IQR)	633 (506)	712 (669)
Diagnostic examinations		
Mean ± SD	1,262 ± 774	1,408 ± 877
Median (IQR)	1,064 (809)	1,136 (742)
Medications		
Mean ± SD	309 ± 512	388 ± 443†
Median (IQR)	165 (238)	238 (402)
Emergency room visits		
Mean ± SD	49 ±108	43 ± 73
Median (IQR)	0 (103)	0 (103)
Inpatient care		
Mean ± SD	3,012 ± 13,023	7,804 ± 23,094
Median (IQR)	0 (436)	0 (3,580)
Private hospital/clinic services		
Mean ± SD	124 ± 538	127 ± 414
Median (IQR)	0 (0)	0 (0)
Patients out-of-pocket expenses		
Mean ± SD	1,131 ± 2,117	1,631 ± 3,024
Median (IQR)	145 (1,090)	308 (2,018)
Direct costs		
Mean ± SD	6,710 ± 13,428	12,316 ± 23,165†
Median (IQR)	3,357 (5,958)	5032 (9,605)
Indirect costs		
Mean ± SD	4,414 ± 8,449	6,859 ± 9,813†
Median (IQR)	276 (1,912)	640 (11,972)

* Results are in 2006 US dollars, purchasing power parity, 1 US dollar = 5.527 Hong Kong dollar. NPSLE = neuropsychiatric systemic lupus erythematosus; IQR = interquatile range, US = United States.

†: $P<0.05$

Table 5.5 Annual direct and indirect costs for patients with the most common neuropsychiatric systemic lupus erythematosus event*

	With Seizure (n=12)	With CVD (n=11)	With Headache (n=15)
Visits to healthcare provider			
Mean ± SD	647 ± 262	1,300 ± 1,231	801 ± 3,820
Median (IQR)	628 (430)	970 (1,139)	673 (463)
Diagnostic examinations			
Mean ± SD	1,393 ± 529	1,606 ± 1,050	1,564 ± 1,125
Median (IQR)	1,406 (865)	1,390 (1,363)	1,002 (1,380)
Medications			
Mean ± SD	502 ± 464	438 ± 350	177 ± 184
Median (IQR)	368 (668)	239 (612)	117 (245)
Emergency room visits			
Mean ± SD	43 ± 53	56 ± 54	35 ± 85
Median (IQR)	0 (103)	103 (103)	0 (0)
Inpatient care			
Mean ± SD	17,741 ± 48,758	12,846 ± 16,696	1,535 ± 2,935
Median (IQR)	0 (10,707)	3,094 (21,687)	0 (2,709)
Private hospital/clinic services			
Mean ± SD	45 ± 157	382 ± 833	83 ± 219
Median (IQR)	0 (0)	0 (543)	0 (0)
Patients out-of-pocket expenses			
Mean ± SD	1,548 ± 3,833	3,091 ± 4,317	782 ± 1,389
Median (IQR)	328 (1,207)	2,035 (5,491)	130 (1,309)
Direct costs			
Mean ± SD	21,1920 ± 48,025	19,719 ± 16,866	4,977 ± 4,851
Median (IQR)	4,905 (13,624)	17,771 (21,967) †	2,957 (3,550)
Indirect costs			
Mean ± SD	6,640 ± 11,371	5,332 ± 8,687	2,723 ± 6,279
Median (IQR)	446 (17,941)	640 (14,375)	511 (942)

* Results are in 2006 US dollars, purchasing power parity, 1 US dollar = 5.527 Hong Kong dollar. Including patients with only seizure/CVD/headache. CVD = cerebrovascular disease; IQR = interquatile range; US= United States.

†: Comparison between patients with CVD and headache, $p<0.005$, using Mann–Whitney *U* test ($p<0.016$ was considered significant after adjustment of multiple comparisons).

5.3.3 Costs predictors

The results of multiple regression analyses for annual direct costs are shown in Table 5.6. Multiple regression analysis of direct costs showed that younger age, shorter disease duration, higher disease damage (other than NP damage), poorer physical health status and higher number of NPSLE events since disease onset were independently associated with increased direct costs. Analyses were not sensitive to outliers.

Results of the combination of logistic regression and linear regression as to determine the predictors of indirect costs are shown in Table 5.7. Logistic regression showed that younger age, poorer physical and mental health status were associated with patients incurring indirect costs. Lower level of education, poorer physical and mental health status and higher number of NPSLE events since disease onset were independent predictors for increased amount of indirect costs. Analyses were not sensitive to outliers.

Table 5.6 Univariate analyses and multivariate linear regression (stepwise selection) analyses of direct cost predictors*

	Univariate analyses		Multivariate regression analyses		
	Unadjusted coefficient (95% CI)	P value	Adjusted coefficient (95% CI)	P value	Adjusted R2
Female gender	0.036 (-0.214, 0.285)	0.778			0.189
Age (1 year increase)	-0.005 (-0.009, 0)	**0.029**	-0.005 (-0.009, -0.001)	**0.018**	
Education level (1 year increase)	0.004 (-0.007, 0.016)	0.456			
Disease duration (1 year increase)	-0.012 (-0.019, -0.005)	**0.001**	-0.015 (-0.022, -0.008)	**<0.0001**	
SELENA–SLEDAI score (1 point increase)	0.023 (0.006, 0.040)	**0.009**			
Modified SDI score (1 point increase)	0.067 (0.016, 0.118)	**0.010**	0.093 (0.043, 0.144)	**<0.0005**	
Total number of NPSLE event (1 event increase)	0.132 (0.061, 0.203)	**<0.0001**	0.111 (0.044, 0.178)	**0.001**	
PCS (1 point increase)	-0.013 (-0.019, -0.008)	**<0.0001**	-0.011 (-0.016, -0.007)	**<0.0001**	
MCS (1 point increase)	-0.005 (-0.009, 0)	**0.034**			

* Due to the skewness of direct costs data, a log10 was performed prior to the regression analysis. Numbers in bold represent $p<0.05$. 95% CI = 95% confidence interval; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; NPSLE = neuropsychiatric systemic lupus erythematosus; PCS = physical component summary scale of the Short Form 36; MCS = mental component summary scale of the Short Form 36.

Table 5.7 Combination of logistic regression and linear regression (stepwise selection) analyses of indirect cost predictors*

	Logistic regression		Linear regression of log_{10} indirect costs				
	Adjusted odds ratio (95% CI)	P value	Unadjusted coefficient (95% CI)	P value	Adjusted coefficient (95% CI)	P value	Adjusted R^2
Female gender	0 (0)	0.998	0.100 (-0.384, 0.585)	0.683			0.220
Age (1 year increase)	0.968 (0.940, 0.996)	**0.025**	0.022(0.011, 0.032)	**<0.0001**			
Education level (1 year increase)	1.028 (0.959, 1.102)	0.431	-0.061 (-0.090, -0.033)	**<0.0001**	-0.056 (-0.082, -0.030)	**<0.0001**	
Disease duration (1 year increase)	1.031 (0.989, 1.075)	0.145	-0.008 (-0.026, 0.009)	0.346			
SELENA–SLEDAI score (1 point increase)	1.002 (0.913, 1.099)	0.968	0.022 (-0.019, 0.063)	0.285			
Modified-SDI score (1 point increase)	0.909 (0.680, 1.215)	0.518	0.120 (-0.005, 0.245)	0.061			
Total number of NPSLE event (1 event increase)	1.212 (0.795, 1.847)	0.371	0.199 (0.043, 0.355)	**0.013**	0.162 (0.021, 0.304)	**0.025**	
PCS (1 point increase)	0.962 (0.934, 0.991)	**0.011**	-0.029 (-0.040, -0.017)	**<0.0001**	-0.023 (-0.035, -0.012)	**<0.0001**	
MCS (1 point increase)	0.973 (0.951, 0.995)	**0.017**	-0.015 (-0.024, -0.005)	**0.003**	-0.012 (-0.021, -0.003)	**0.009**	

* Due to the skewness of indirect costs data, a log10 was performed prior to the linear regression analysis. Numbers in bold represent $p<0.05$. CI = confidence interval; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; NPSLE = neuropsychiatric systemic lupus erythematosus; PCS = physical component summary scale of the Short Form 36; MCS = mental component summary scale of the Short Form 36.

5.4 CONCLUSIONS

In conclusion, our study shows that patients with NPSLE incur both higher annual direct and indirect costs. The total number of NPSLE event since disease onset independently predicted high direct and indirect costs. Unlike lupus nephritis, much less is known about the ideal treatment of NPSLE and current therapeutic approach is still empirical and based on clinical experience [204]. Our study suggests that the improvements in the management of NPSLE may avoid or delay the high costs associated with NP manifestation and more attention should be drawn to this area.

CHAPTER 6 THE IMPACT OF FLARE ON DISEASE COSTS OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

6.1 INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterized by periods of fluctuating disease activity. The British Isles Lupus Activity Group (BILAG) index [58] and the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (SELENA-SLEDAI) [59] are 2 disease activity indices primarily used in the clinical studies of SLE. The assessment of lupus activity encompasses the concept of a flare, which is an increase in disease activity over a defined period [72]. However, there is no general consensus on the definition of lupus flare, and various tools have been used [73, 75, 205, 206]. Using an increase of 1.0 cm on a 3-cm visual analog scale of the physician's global assessment (PGA) of disease activity as a gold standard of flare, the corresponding cutoff is 3 points or more on the SELENA–SLEDAI and 4 points or more on the BILAG [207]. Since indices alone may not capture overall changes in disease activity, SELENA trial investigators developed the SELENA flare tool, which incorporates 2 indices of disease activity (PGA and SELENA–SLEDAI), clinical manifestations,

and treatment to define both mild/moderate flares and severe flares [59].

Lupus flare is an important outcome variable and has been shown to be a major cause of admission [78]. Disease activity and toxicity of the consequent treatments result in irreversible damage that is associated with an increased risk of morbidity and mortality [127]. Major organ flares such as renal or neuropsychiatric (NP) flares have been shown to be associated with poor prognosis [30, 49, 80].

Previous studies on the economic impact of SLE focus on the relationship between disease activity/damage and costs. Higher disease activity/damage has been shown to be associated with both higher direct and indirect costs [170, 171, 173, 174]. However, to our knowledge, no study has focused on the relationship between costs and flares. Whether the severity or specific clinical manifestations of flares would influence disease costs has not been studied.

In the current study, we evaluated both direct and indirect costs of SLE patients with and without flares from a societal perspective. We also investigated the impact of the severity and clinical manifestations of flares on direct/indirect costs. In view of the evidence that major organ flares are significantly related to poor prognosis, we

selected 2 major organ flares, renal and NP flares, to find out whether major organ flares were more costly than other flares.

6.2 METHODS

6.2.1 Study design, patients, data collection and cost estimates

Please refer to **CHAPTER 3**.

6.2.2 Definitions of flare

Patients' medical records were reviewed by an investigator (TYZ) to derive the total number and manifestations of lupus flares during the preceding 12 months. A revised SELENA flare tool that excluded the component of PGA was used to define flares [59]. Mild/moderate flares were defined as 1 or more of the following: 1) change in SELENA–SLEDAI score of > 3 points but $\leqq$ 12 points; 2) new/worse discoid lesions, photosensitivity, profundus, cutaneous vasculitis, bullous lupus, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, and/or fever (SLE); 3) increase in prednisone not to exceed 0.5 mg/kg/day; or 4) added nonsteroidal anti-inflammatory drugs (NSAIDs) or hydroxychloroquine for SLE. Severe flares were defined as 1 or more of the following: 1) change in SELENA–SLEDAI score of > 12 points; 2) new/worse neuropsychiatric SLE (NPSLE), vasculitis, nephritis,

myositis, platelet count < 60,000/mm^3, or haemolytic anaemia (haemoglobin [Hb] < 70 g/l or decrease in Hb > 30 g/l), which required either a doubling of or increase in prednisone dosage to > 0.5 mg/kg/day or hospitalization; 3) increase in prednisone to > 0.5 mg/kg/day; 4) new immunosuppressants for SLE activity; or 5) hospitalization for SLE.

The definitions of the individual organ flares are listed below. Renal flare was defined as 1 of the following [208, 209]: 1) a reproducible (2 samples at least 1 week apart) increase in 24-hour urine protein levels to > 1 gm if the baseline value was < 0.2 gm, to > 2 gm if the baseline value was 0.2–1 gm, or to more than twice the baseline value if the baseline value was > 1 gm; 2) a reproducible increase in serum creatinine level of > 20% or at least 25 μmoles/liter, whichever was greater, accompanied by proteinuria (> 1 gm/24 hours), haematuria (≧ 4 red blood cells [RBCs]/high-powered field [hpf]), and/or RBC casts; or 3) new, reproducible haematuria (≧ 10 RBCs/hpf) or an increase in haematuria by 2 grades compared with baseline, associated with > 25% dysmorphic RBCs, exclusive of menses, accompanied by either a 0.8-gm increase in 24-hour urinary protein levels or new RBC casts.

NP flare was defined according to the case definition system for central nervous system lupus syndromes by the 1999 American College of Rheumatology nomenclature [25]. This includes a detailed glossary and diagnostic guidelines for 19 NP syndromes, namely aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis, Guillain-Barre´ syndrome, autonomic neuropathy, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.

Other clinical features of flares were grouped into the following organs/systems: musculoskeletal, mucocutaneous, haematologic, vasculitic, and serositis. They was defined according to the definitions of the descriptors of the SELENA–SLEDAI instrument [59, 68] (Table 6.1). Flares with only serologic manifestations (increased anti–double-stranded DNA [anti-dsDNA] titre and depressed complement levels) without medical intervention were excluded in the analyses.

Single-organ flares referred to flares involving only 1 organ/system, whereas multiorgan flares involved more than 1 organ/system (excluding immunologic

manifestations).

Table 6.1 Clinical features of flares (other than renal and neuropsychiatric flare)

Type of flares	Definitions
Musculoskeletal flares	Arthritis and/or myositis. Myositis was defined as proximal muscle aching or weakness associated with elevated muscle enzyme, electromyographic changes, or a biopsy showing myositis.
Mucocutaneous flare	Included any of the following: malar rash, discoid rash, photosensitivity, or oral ulcer.
Haematologic flare	Any one of the following: hemolytic anemia, leukopenia (white cell count $<4.0 \times 10^9$/L), and thrombocytopenia (platelet count $<100 \times 10^9$/L) on at least 2 occasions that were not due to the effects of medications.
Vasculitic flare	Any of the following: ulceration, gangrene, tender finger nodules, periungual, infarction splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
Serositis flare	Pleurisy and/or pericarditis. Pleurisy was defined as pleuritic chest pain with pleural rub or effusion, or pleural thickening. Pericarditis was defined as pericardial pain with at least one of the following: rub, effusion, or electrocardiogram confirmation.

6.2.3 Statistical analysis

Results were expressed as the mean ± SD for normally distributed data. For non–normally distributed data, the median and interquartile range (IQR) were expressed. A 2-sample t-test, chi-square test, or Mann-Whitney *U* test was used to

compare demographics, clinical features, health care resource use, and disease costs between patients with and without flares. P values less than 0.05 were considered significant. A Kruskal-Wallis test was used to test for differences in costs between patients grouped by severity/organ involvement/manifestations of flares. When a Kruskal-Wallis test revealed significant results ($p<0.05$), a Mann-Whitney *U* test by Bonferroni adjustment was used for multiple comparisons (for triple comparisons, p values less than 0.016 were considered significant).

Both univariate and multivariate linear regression analyses (stepwise selection) were used to determine the predictors increased direct costs. The combination of logistic regression and a linear model was used to determine predictors of increase indirect costs [196]. Due to skewness of the costs data, the results were log-transformed (base=10) for the linear regression model. The possible predictors included gender, age, disease duration, education level, SELENA-SLEDAI scores, the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) scores, scores of physical and mental component summary scales of the Short Form 36 (PCS and MCS) and the number of flare in the preceding 12 months. The p value for a variable to remain in the model was <0.05. Selection of final model was based on the adjusted R^2 and an evaluation of the residual plots. A

sensitivity analysis was performed to indicate whether the test was sensitive to outliers (a case was an outlier if it was 3 SDs away from the mean).

6.3 RESULTS

6.3.1 Demographics and clinical profiles

Table 6.2 shows the demographics and clinical characteristics (ever) at the time of the assessment of the whole cohort, as well as the 2 groups subdivided according to whether they experienced a flare in the preceding year. Compared with those without flares, patients with flares were younger, had shorter disease duration, and had higher disease activity at the time of the assessment. Regarding the clinical features, patients with flares had a higher prevalence of having had discoid lesions and being anti-dsDNA positive. No significant differences in the prevalence of major organ manifestations and the SDI score were observed between the 2 groups.

Table 6.2 Baseline demographics and clinical characteristics (ever) of patients with and without flares in the preceding year

	Without flares (n=244)	With flares (n=62)	P
Age, mean ± SD years	42.5 ± 11.4	36 ± 10	**<0.0005**
Female	236 (97)	58 (94)	0.271
Education level, mean ± SD years	10.1 ± 4.4	11.3 ± 3.5	0.115
Disease duration, mean ± SD years	10.2 ± 7.0	7.4 ± 5.8	**0.002**
SELENA-SLEDAI score, mean ± SD	2.15 ± 2.64	3.63 ± 3.20	**<0.0005**
SDI score, mean ± SD	0.73 ± 1.06	0.63 ± 1.07	0.279
Organ manifestations			
Malar rash	107 (44)	26 (42)	0.786
Discoid lesion	27 (11)	13 (21)	**0.039**
Photosensitivity	77 (32)	20 (32)	0.916
Oral ulcer	73 (30)	21 (34)	0.547
Arthritis	192 (79)	43 (69)	0.120
Serositis	68 (28)	17 (27)	0.944
Renal disease	139 (57)	43 (69)	0.076
Neuropsychiatric disease	62 (25)	21 (34)	0.181
Haematologic	208 (85)	57 (92)	0.167
Leukopenia	124 (51)	36 (58)	0.308
Lymphopenia	161 (66)	38 (61)	0.489
Thrombocytopenia	70 (29)	21 (34)	0.425
Hemolytic anemia	19 (8)	6 (10)	0.627
Immunological	230 (94)	60 (97)	0.428
Anti-ds DNA positive	179 (73)	53 (86)	**0.047**
Anti-Smith positive	47 (19)	19 (31)	0.052
Anti-Ro positive	134 (55)	36 (58)	0.656
Anti-La positive	50 (21)	7 (11)	0.097
ANA positive	241 (99)	60 (97)	0.801

* Values are the number (percentage) unless otherwise indicated. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; anti-dsDNA = anti–double stranded DNA; ANA = antinuclear antibody.

6.3.2 Lupus flare profiles

During the preceding year, 74 episodes of flare were recorded in 62 (20.3%) of 306 patients. The overall flare rate was 0.24 episodes per patient-year. Fifty (80.6%) of 62 patients had 1 flare and 12 (19.4%) of 62 had 2 flares. Renal flare was the most common (0.09 episodes/patient-year), followed by mucocutaneous flare (0.04 episodes/patient-year), musculoskeletal flare (0.04 episodes/patient-year), haematologic flare (0.04 episodes/patient-year), NP flare (0.03 episodes/patient-year), vasculitic flare (0.03 episodes/patient-year), and serositis flare (0.01 episodes/patient-year). Seven patients had 8 NP flares during the preceding year. Four of 8 were cerebrovascular diseases (3 were strokes and 1 was a transient ischemic attack), 2 were seizure disorders, 1 was a migraine, and 1 was a myelopathy.

For those with 1 flare, 18 (36%) of 50 patients had a mild/moderate flare and 32 (64%) of 50 had a severe flare. For those with 2 flares, 1 (8%) of 12 had 2 mild/moderate flares, 6 (50%) of 12 had 1 mild/moderate flare and 1 severe flare, and 5 (42%) of 12 had 2 severe flares. The majority of these patients had a single-organ flare (54 [87%] of 62). Among patients with single-organ flare, 23 (42.6%) of 54 patients had a renal flare, 4 (7.2%) of 54 patients had an NP flare, 10 (18.5%) of 54 patients had a mucocutaneous flare, 8 (14.8%) of 54 patients had a

musculoskeletal flare, and 7 (13.0%) of 54 patients had a haematologic flare. Eight (12.9%) of 62 patients had a multiorgan flare involving 2–5 organ systems (median 2). The commonly involved organ systems included the kidney (5 [62.5%] of 8 patients), brain (4 [50%] of 8 patients), haematologic system (4 [50%] of 8 patients), vasculitis (3 [37.5%] of 8 patients), and musculoskeletal system (2 [25%] of 8 patients).

6.3.3 Flare, health care resources utilization, and costs

Table 6.3 shows the health care resources use of patients with and without flares. More visits to rheumatologists were observed in patients with flares. Seventy-six percent of patients with flares had urine tests compared with 37% of those without flares ($p < 0.0001$). The proportion of patients having imaging tests was also higher in those with flares (28% versus 50%; $p = 0.001$). A higher proportion and longer duration of inpatient care were seen in patients with flares. For those with flares, the major reason for hospitalization was flare (58%), followed by infection (14%). For those without flares, infection was the major reason for hospitalization (30%).

All of the patients with flares required medication treatment in the preceding 12 months, compared with 96% of those without flares ($p = 0.105$). Use of NSAIDs,

corticosteroids, immunosuppressants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, antibiotics, and prophylaxis for steroid-induced osteoporosis was more common in patients with flares (Table 6.4). The use of health products, nontraditional therapies, aids, and private hospital/clinic facilities did not differ between patients with and without flares.

Table 6.3 Healthcare resources use with regard to patients with and without flares during the preceding year*

	Without flare (n=244)	With flare(s) (n=62)	P
Number of visits to healthcare providers	6.9 ± 4.8 (5)	8.8 ± 4 (9)	**<0.0001**
Rheumatologist	4.23 ± 2.19 (4)	6.37 ± 3.07 (5.5)	**<0.0001**
Nephrologist	0.07 ± 0.57 (0)	0 (0)	0.257
Dermatologist	0.23 ± 0.93 (0)	0.23 ± 0.95 (0)	0.888
Opthalmologist	0.61 ± 1.15 (0)	0.52 ± 0.74 (0)	0.906
Government general clinic	0.46 ± 1.17 (0)	0.85 ± 2.02 (0)	0.053
Allied health professional	0.24 ± 1.93 (0)	0 (0)	0.149
Psychologist	0.03 ± 0.28 (0)	0.06 ± 0.4 (0)	0.271
Others	1 ± 2.22 (0)	0.74 ± 1.88 (0)	0.210
Number of diagnostic examinations			
Blood test	28 ± 45 (24)	40 ± 21 (3.5)	**<0.0001**
Urine test	4 ± 8 (0)	9 ± 12 (3.5)	**<0.0001**
Radiological examinations‡	0.27 ± 0.74 (0)	1.31 ± 2.69 (0.5)	**<0.0001**
Visit to emergency room, %	21	52	**<0.0001**
Number of visits to emergency room	0.29 ± 0.7 (0)	1.03 ± 1.33 (1)	**<0.0001**
Inpatient care, %	16	69	**<0.0001**
Duration of inpatient care, days	3.1 ± 16 (0)	15.6 ± 37.3 (4.5)	**<0.0001**

* Values are the mean ± SD (median) unless otherwise indicated. Numbers in bold represent $p<0.05$.

‡ Including radiographs, ultrasounds, computed tomography scans, and magnetic resonance imaging.

Table 6.4 Medications taken (ever) by patients with and without flares in the preceding year*

	Without flare (n=244)	With flare(s) (n=62)	P
NSAIDs	91 (37)	33 (53)	**0.023**
Anti-malaria drugs	134 (55)	35 (57)	0.828
Corticosteroids	163 (67)	60 (97)	**<0.0001**
Immunosuppressant	62 (25)	34 (55)	**0.011**
ACEI / ARB	70 (29)	30 (48)	**0.003**
Anti-osteoporosis	117 (48)	46 (74)	**<0.0001**
Antibiotics	46 (19)	19 (31)	0.043
Gastrointestinal drugs†	95 (39)	36 (58)	**0.007**
Cardiovascular system drugs‡	77 (32)	19 (31)	0.890
Neuropsychiatric drugs§	38 (16)	13 (21)	0.309

* Values are the number (percentage). Numbers in bold represent $p<0.05$. NSAIDs = non-steroidal anti-inflammatory drugs; ACEI = angiotensin converting enzyme inhibitor; ARB = Angiotensin II Receptor Blockers.

† Including: diuretics, anti-arrhythmic drugs, Beta-adrenoceptor blocking drugs, hypertension and heart failure drugs (excluding ACEI/ARB), nitrates, calcium-channel blockers, anticoagulants and protamine, antiplatelet drugs, lipid-regulating drugs, fibrinolytic drugs, antifibrinolytic drugs and haemostatics.

‡ Including: antacids and simethicone, antispasmodics drugs, ulcer-healing drugs, adsorbents and bulk-forming drugs, antimotility drugs, laxatives, local preparations for anal and rectal disorders and drugs affecting intestinal secretions.

§ Including: hypnotics and anxiolytics, antipsychotic drugs, antipsychotic depot injections, antimanic drugs, antidepressants drugs, drugs in nausea and vertigo, analgesics, anti-epileptics, drugs for dementia, and drugs used in Parkinsonism and related disorders.

The employment rate was not significantly different between these 2 groups (46% for patients without flares and 47% for those with flares; $p = 0.948$). For those who were employed, a higher proportion (93% versus 66%; $p = 0.003$) and longer duration (median [IQR] 4 [10] days versus 15 [23] days; $p < 0.0005$) of annual sick leave were observed in patients with flares. There was no difference in the duration of unemployment between the 2 groups for those who were unemployed because of SLE (median duration 12 months for both; $p = 0.202$). The number of days off from household work or daily activities did not differ between the 2 groups (median [IQR] duration 0 [0] days versus 0 [30] days; $p = 0.299$).

Annual direct costs were nearly 3-fold higher for patients with flares compared with those without flares ($p < 0.0005$) (Table 6.5). Patients with flares incurred significantly higher costs in all of the components of direct costs, except in the category of costs of private hospital/clinic services. For both groups, the costs of inpatient care represented the largest component, accounting for 40% (patients without flares) and 70% (patients with flares) of total direct costs. Annual indirect costs were significantly higher in those with flares ($p = 0.017$). For those who were employed, higher indirect costs due to sick leave were also observed in patients with flares. Indirect costs due to SLE-related unemployment and days off from household

work or daily activities did not differ between the 2 groups.

In univariate analysis, variables significantly associated with direct costs included age, disease duration, SELENA–SLEDAI score, SDI score, PCS and MCS scores, and the total number of flares in the preceding 12 months (Table 6.6). In multivariate analysis, shorter disease duration, more disease damage, poorer physical health status and higher number of flares in the preceding year were independent explanatory variables associated with increased direct costs.

However, the number of flares did not influence the indirect costs. Logistic regression showed that it was age, physical and mental health status determined a patient incurring indirect costs (Table 6.7). The increased amount of incurred indirect costs was associated with older age, lower level of education, more disease damage and poorer physical and mental health status, as shown in the univariate linear regression analyses, and independently predicted by lower education level and poorer physical and mental health status, as shown in the multivariate linear regression analysis. A sensitivity analysis was performed and the tests were not sensitive to the outliers.

Table 6.5 Annual costs for patients with and without flares (in 2006 US dollars)

	Without flare (n=244)	With flare(s) (n=62)
Visits to healthcare provider		
Mean ± SD	805 ± 560	1,017 ± 440†
Median (IQR)	633 (504)	1,013 (566)
Diagnostic examinations		
Mean ± SD	1,180 ± 686	1,780 ± 1,035†
Median (IQR)	989 (636)	1,564 (1,232)
Medications		
Mean ± SD	317 ± 515	381 ± 404‡
Median	164 (245)	265 (322)
Emergency visits		
Mean ± SD	31 ± 79	108 ± 140†
Median (IQR)	0 (0)	103 (206)
Inpatient care		
Mean ± SD	2,425 ± 12,581	11,737 ± 25,615†
Median (IQR)	0 (0)	3,469 (12,759)
Private hospital/clinic services		
Mean ± SD	115 ± 499	164 ± 539
Median (IQR)	0 (0)	0 (0)
Patient out-of-pocket expenses		
Mean ± SD	1,161 ± 2,329	1,685 ± 2,649‡
Median (IQR)	140 (1,210)	317 (2,167)
Indirect costs due to sick leave		
Mean ± SD	1,509 ± 7,363	5,014 ± 17,078‡
Median (IQR)	0 (1360)	0 (5,042)
Indirect costs due to SLE-related unemployment		
Mean ± SD	24,201 ± 49,091	24,225 ± 49,126
Median (IQR)	0 (0)	0 (8,497)
Indirect costs due to days off from household work or daily activities		
Mean ± SD	1,398 ± 9,273	2,577 ± 13,002
Median (IQR)	0 (0)	0 (0)
Total direct costs		
Mean ± SD	6,034 ± 12,899	16,873 ± 25,510†
Median (IQR)	2,872 (4,106)	9,441 (12,364)

Table 6.5 Annual costs for patients with and without flares (in 2006 US dollars) *(Continued)*

	Without flare (n=244)	With flare(s) (n=62)
Total indirect costs		
Mean ± SD	4,905 ± 8,872	5,756 ± 8,999‡
Median (IQR)	322 (7,040)	1,013 (10,061)

* 1 US dollar = 5.527 Hong Kong dollars, purchasing power parity. US = United States; IQR = interquartile range.

† $P < 0.005$.

‡ $P < 0.05$.

Table 6.6 Univariate analyses and multivariate linear regression (stepwise selection) analyses of direct cost predictors*

	Univariate analyses		Multivariate regression analyses		
	Unadjusted coefficient (95% CI)	p-value	Adjusted coefficient (95% CI)	p-value	Adjusted R2
Female gender	0.036 (-0.214, 0.285)	0.778			0.300
Age (1 year increase)	-0.005 (-0.009, 0)	**0.029**			
Education level (1 year increase)	0.004 (-0.007, 0.016)	0.456			
Disease duration (1 year increase)	-0.012 (-0.019, -0.005)	**0.001**	-0.013, (-0.020, -0.007)	**<0.0001**	
SELENA–SLEDAI score (1 point increase)	0.023 (0.006, 0.040)	**0.009**			
SDI score (1 point increase)	0.085 (0.040, 0.129)	**<0.0005**	0.097 (0.056, 0.139)	**<0.0001**	
Number of flares (1 flare increase)	0.366 (0.280, 0.451)	**<0.0001**	0.318 (0.234, 0.402)	**<0.0001**	
PCS (1 point increase)	-0.013 (-0.019, -0.008)	**<0.0001**	-0.008 (-0.013, -0.004)	**<0.0005**	
MCS (1 point increase)	-0.005 (-0.009, 0)	**0.034**			

* Due to the skewness of direct costs data, a log10 was performed prior to the regression analysis. Numbers in bold represent $p<0.05$. 95% CI = 95% confidence interval; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; NPSLE = neuropsychiatric systemic lupus erythematosus; PCS = physical component summary scale of the Short Form 36; MCS = mental component summary scale of the Short Form 36.

Table 6.7 Combination of logistic regression and linear regression (stepwise selection) analyses of indirect cost predictors*

	Logistic regression		Linear regression of log_{10} indirect costs				
	Adjusted odds ratio (95% CI)	p-value	Unadjusted coefficient (95% CI)	p-value	Adjusted coefficient (95% CI)	p-value	Adjusted R^2
Female gender	0 (0, 0)	0.998	0.100 (-0.384, 0.585)	0.683			0.203
Age (1 year increase)	0.968 (0.940, 0.996)	**0.027**	0.022 (0.011, 0.032)	**<0.0001**			
Education level (1 year increase)	1.031 (0.990, 1.075)	0.142	-0.061 (-0.090, -0.033)	**<0.0001**	-0.056 (-0.082, -0.029)	**<0.0001**	
Disease duration (1 year increase)	1.029 (0.960, 1.103)	0.414	-0.008 (-0.026, 0.009)	0.346			
SELENA–SLEDAI score (1 point increase)	0.995 (0.906, 1.093)	0.919	0.022 (-0.019, 0.063)	0.285			
SDI score (1 point increase)	0.948 (0.733, 1.227)	0.687	0.137 (-0.105, 0.243)	**0.012**			
Number of flare (1 flare increase)	1.187 (0.675, 2.087)	0.551	0.113 (-0.105, 0.332)	0.308			
PCS (1 point increase)	0.962 (0.934, 0.992)	**0.012**	-0.029 (-0.040, -0.017)	**<0.0001**	-0.025 (-0.036, -0.014)	**<0.0001**	
MCS (1 point increase)	0.972 (0.950, 0.995)	**0.015**	-0.015 (-0.024, -0.005)	**0.003**	-0.012 (-0.021, -0.003)	**0.010**	

* Due to the skewness of indirect costs data, a log10 was performed prior to the linear regression analysis. Numbers in bold represent $p<0.05$. 95% CI = 95% confidence interval; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; NPSLE = neuropsychiatric systemic lupus erythematosus; PCS = physical component summary scale of the Short Form 36; MCS = mental component summary scale of the Short Form36.

6.3.4 Severity, organ involvement and manifestations of flare and costs

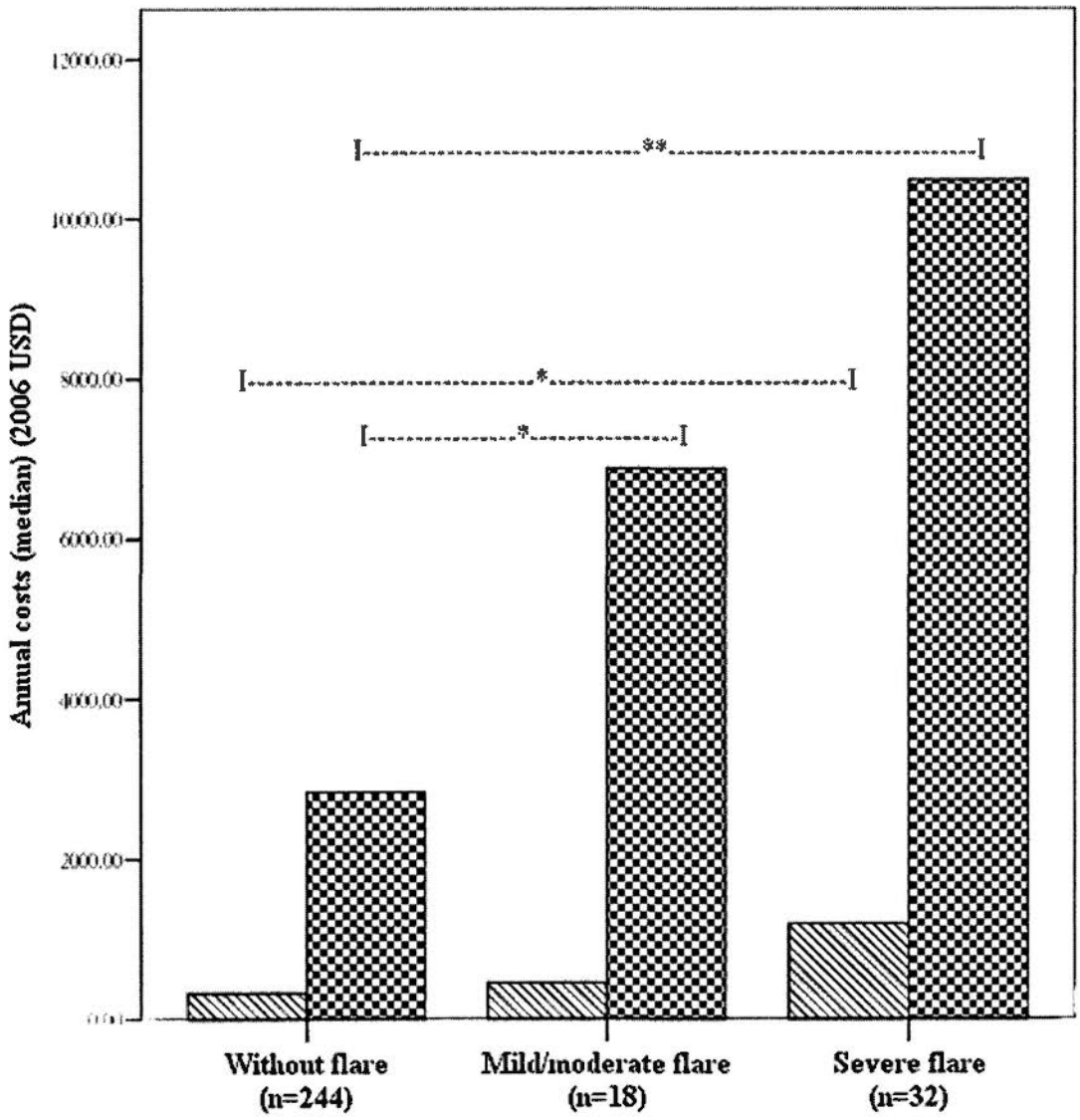
Patients with 1 flare were then grouped into 2 groups: those with a mild/moderate flare (n=18) and those with a severe flare (n=32). Patients with mild/moderate and severe flare incurred significantly higher direct costs compared with those without flare (Figure 6.1A). Patients with severe flares also incurred higher indirect costs compared with those without flares. But direct and indirect costs did not differ between patients with mild/moderate and severe flares (P = 0.086 for direct costs; p = 0.099 for indirect costs).

Patients with multi-organ flares incurred significantly higher direct costs compared with those without flares and those with single organ flare (Figure 6.1B). Their indirect costs were also higher than those without flare, but this became insignificant after correction for multiple comparisons (P = 0.044).

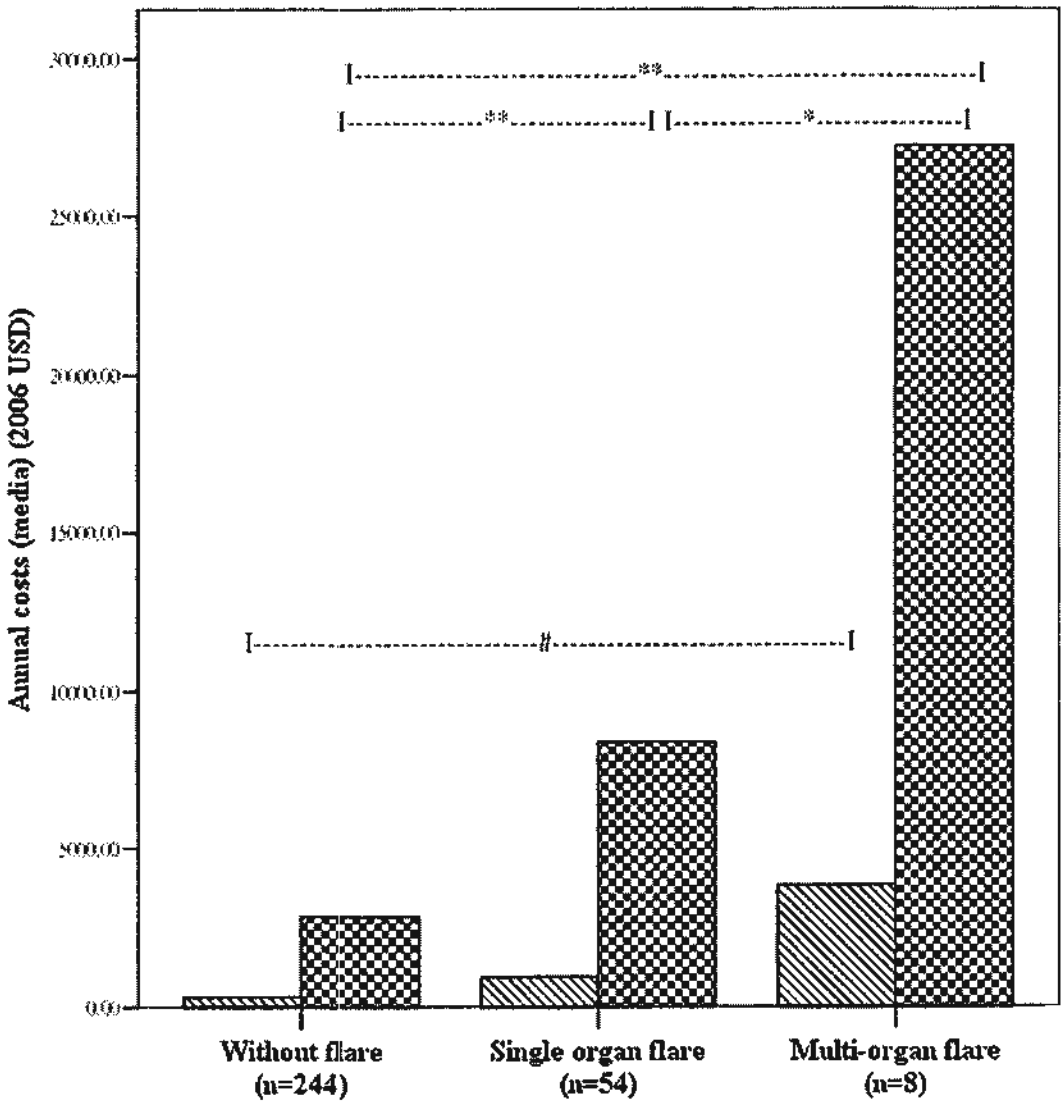
Patients with single organ flares were then divided into 2 groups: those with renal/NP flares (n=27) and those with other manifestations (n=27). Patients with renal/NP flares generated higher direct costs than those with other manifestations and those without flares (Figure 6.1C). However, indirect costs did not differ among these 3 groups.

Figure 6.1 Annual direct and indirect costs by A, severity, B, organ involvement, and C, manifestations of flares

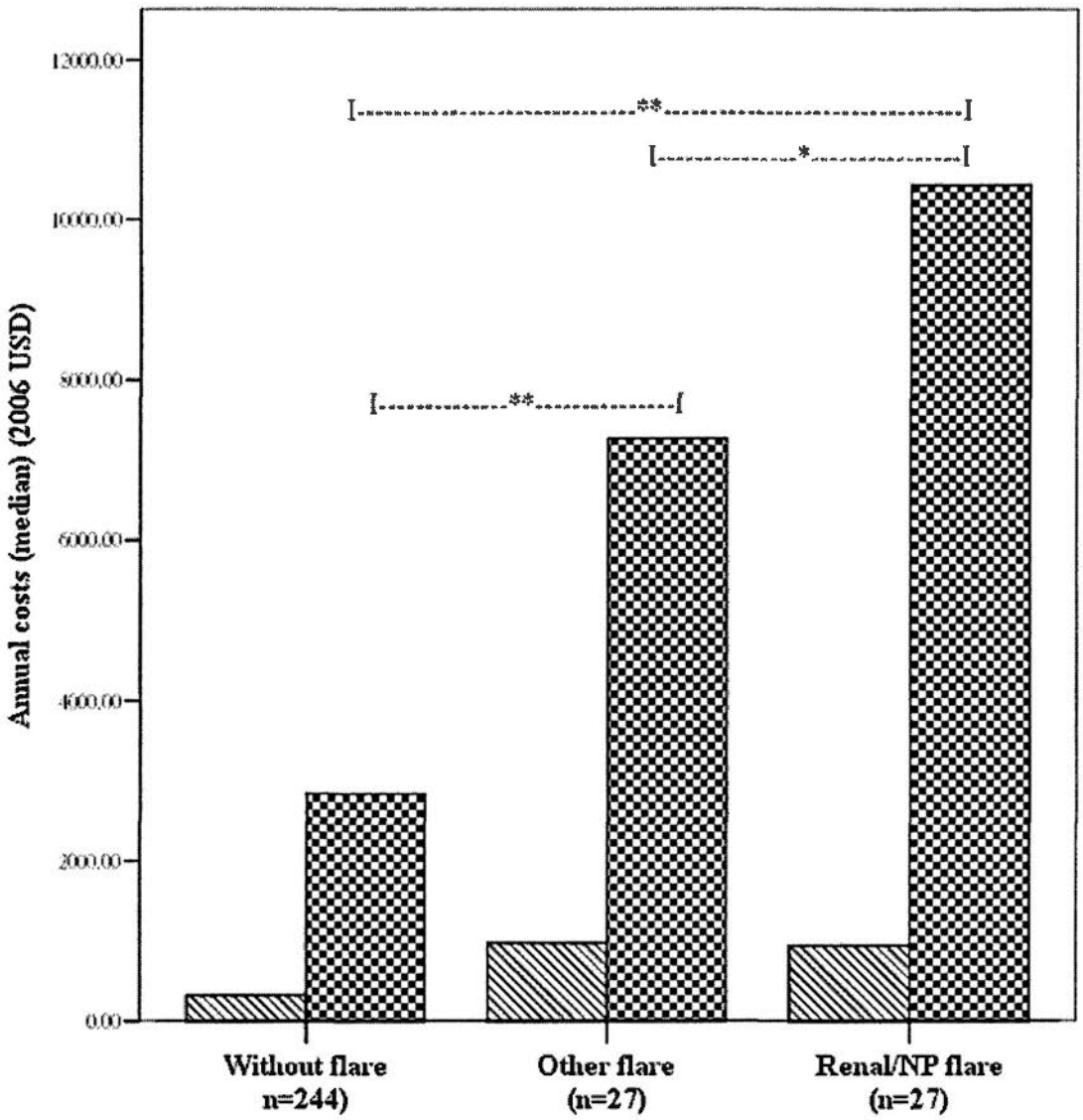
A:



B:


Annual costs (media) (2006 USD)
3000.00
2500.00
2000.00
1500.00
1000.00
500.00
0.00
**
**
*
#
Without flare
(n=244)
Single organ flare
(n=54)
Multi-organ flare
(n=8)

C:



Hatched bars are the indirect costs; stippled bars are the direct costs. * P< 0.005; ** P< 0.0005; # P = 0.044 (P<0.016 was considered significant after the Bonferroni adjustment). USD = US dollars; NP = neuropsychiatric.

6.4 CONCLUSIONS

In summary, we have shown that patients with flares use more healthcare resources and incur higher direct and indirect costs compared with those without flares. The total number of flares is an independent explanatory variable associated with direct costs of SLE. Major organ flares incur higher disease costs than minor organ flares. These results further support the important role of preventative care in the management of SLE. Therapies that can effectively control disease activity and prevent flares, especially those that could prevent renal or NP flares may be cost-effective in view of the high costs associated with active disease affecting these organs. Our results provide some preliminary data for the economic evaluation of such therapies in the future.

CHAPTER 7 HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: WITH SPECIAL EMPHASIS ON THE INFLUENCE OF NEUROPSYCHIATRIC INVOLVEMENT AND FLARE

7.1 INTRODUCTION

We have demonstrated that systemic lupus erythematosus (SLE) imposed substantial economic burden on the society and the individuals and patients with neuropsychiatric SLE (NPSLE) and lupus flares incurred significantly higher disease costs than their counterparts. As mentioned, a complete cost-of-illness study should include direct and indirect costs as well as intangible costs. Intangible costs usually refer costs of pain and suffering imposed by a disease or diseases. It is challenging to accurately quantify intangible costs in monetary terms. Usually, they are in the form of health-related quality of life (HRQoL) measures.

HRQoL is a multi-dimensional concept including physical, functional, social and emotional well-being [91]. A number of studies have demonstrated that patients with SLE have poorer HRQoL compared with healthy controls, both in Caucasian and Chinese population [95-97]. The Short Form 36 (SF-36) is the most commonly used tool to assess HRQoL of patients with SLE. Factors which have been identified

associated with poorer HRQoL include older age [98], fatigue [109, 110], fibromyagia [111], end-stage renal disease [113], neuropsychiatric involvement [32], psychological distress [114], social support [97]. Although studies have attempted to elucidate the relationship between disease activity, damage and HRQoL, results remain controversial [32, 111, 118, 120].

The relationship between flare and HRQoL in patients with SLE has been explored in Doria et al's study, in which lower level of general health and physical function measured by the SF-36 were found [96]. However, the definition of flare used in Doria et al's study appears to be empirical and might not be comprehensive enough to adequately capture all the changes in disease activity.

In this study, we used the cohort recruited for the cost-of-illness study of SLE, aiming to investigate the HRQoL of this cohort. With special emphasis, we also investigate whether the presence of NPSLE event since disease onset or the presence of lupus flares in the preceding year would influence the patients' HRQoL.

7.2 METHODS

7.2.1 Patients and procedures

Three participants from the cost-of-illness study cohort failed to provide the results of the SF-36, leaving 303 patients for the analyses of this study. For more details about the study design and study procedures, please refer to **CHAPTER 3**.

7.2.2 Assessment of NPSLE and definitions of lupus flares

Please refer to **CHAPTER 5.2.2 and 6.2.2.**

7.2.3 Assessment of HRQoL

HRQoL was assessed using the SF-36 (standard version 1.1, recall period of preceding 4 weeks). Participants completed the SF-36. The SF-36 is a generic instrument of HRQoL assessment [91]. The SF-36 has eight subscales measuring eight domains of quality of life: physical function, role limitation due to physical problems, bodily pain, general health, vitality, social function, role limitation due to emotional problems, and mental health. Each subscale consists of 2 to 10 items, and is calculated by summation and transformation of all the scores of items belonging to the same subscale, ranging from 0 (poor) and 100 (optimal). In additional, the physical health summary scale and mental health summary scale summarize the eight SF-36 subscales into 2 summary scales that give an overall assessment of quality of life related to physical and mental health, respectively [92]. These 2

summary scales facilitate interpretation and statistical analyses in clinical trials and longitudinal studies. The SF-36 has been translated into Chinese and validated for Chinese adults in Hong Kong. Normative values of the SF-36 subscales and summary scales of Chinese adult population in Hong Kong have been published [93, 94].

7.2.4 Statistical analysis

Chi-square test, Student's t-test and Mann-Whitney *U* test were used for comparison between 2 groups. Comparisons for continuous variables between 3 groups were analyzed using one-way ANOVA with Bonferroni adjustment. Multiple linear regression analysis (stepwise selection) was used to identify the independent variables associated with the subscales and summary scales of the SF-36. The following variables would be entered into the regression analysis: age (years), female gender, education level (years), disease duration (years), the Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score, the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) score, total number of NPSLE since disease onset, cerebrovascular disease (CVD) ever, number of flares during the preceding

year, severe flare ever, multi-organ flare ever and musculoskeletal flare ever in the preceding year. Assumptions were checked before performing the linear regression, including no outliers, independent data points and normally distributed residuals with mean = 0 and a constant variance. No assumptions were violated.

7.3 RESULTS

7.3.1 Demographics and clinical characteristics

Of the 303 participants, only 12 were men (4%). The mean (SD) age of the entire group was 41.1 (11.5) years. Table 7.1 summarizes the demographics and clinical characteristics (ever) of patients, cross-classified by the presence of NPSLE event since disease onset and flares in the preceding year. Patients with NPSLE had more organ damage than those without NPSLE, due to damages in central nervous system. Higher prevalence of having had positive anti-Ro antibodies was also observed in patients with NPSLE. Compared to those without flares, patients with flares were younger, had shorter disease duration, and had higher disease activity at the time of the assessment. No significant differences in the prevalence of major organ manifestations (ever) and the SDI score were observed between the 2 groups, except that patients with flares had higher prevalence of having had discoid lesions.

Table 7.1 Demographics and clinical characteristics (ever) of patients, cross-classified by the presence of NPSLE event since disease onset and flares in the preceding year

	Without NPSLE (n=220)	With NPSLE (n=83)	P	Without flares (n=242)	With flares (n=61)	P	Entire group (n=303)
Age, mean ± SD years	41.4 ± 11.6	40.4 ± 11.1	0.649	42.4 ± 11.4	36.2 ± 10.3	**<0.0005**	41.1 ± 11.5
Female	213 (97)	78 (94)	0.321	234 (97)	57 (93)	0.245	294 (96)
Education level, mean ± SD years	10.3 ± 4.4	10.5 ± 3.8	0.808	10.2 ± 4.4	11.3 ± 3.5	0.115	10.4 ± 4.3
Employed	104 (47)	35 (42)	0.441	111 (46)	28 (46)	1.000	139 (46)
Disease duration, mean ± SD years	9.6 ± 6.9	9.7 ± 6.9	0.888	10.2 ± 7.1	7.4 ± 5.8	**0.003**	9.6 ± 6.9
SELENA-SLEDAI score, mean ± SD	2.52 ± 3.01	2.33 ± 2.28	0.782	2.17 ± 2.64	3.67 ± 3.21	**<0.0005**	2.5 ± 2.8
SDI score, mean ± SD	0.60 ± 0.98	1.01 ± 1.24	**0.002**	0.74 ± 1.07	0.64 ± 1.11	0.279	0.71 ± 1.07
Modified SDI score, mean ± SD	0.55 ± 0.94	0.60 ± 0.99	0.563	-	-	-	0.57 ± 0.95
Organ manifestations							
Malar rash	90 (41)	42 (51)	0.153	106 (44)	26 (42)	0.868	132 (44)
Discoid lesion	31 (14)	9 (11)	0.569	27 (11)	13 (21)	**0.036**	40 (13)
Photosensitivity	73 (33)	24 (29)	0.494	77 (32)	20 (33)	0.885	97 (32)
Oral ulcer	68 (31)	26(31)	1.000	73 (30)	21 (34)	0.520	94 (31)
Arthritis	166 (76)	68 (82)	0.283	191 (79)	43 (70)	0.160	234 (77)
Serositis	57 (26)	28 (34)	0.198	68 (28)	17 (28)	0.971	85 (28)
Renal disease	135 (61)	45 (54)	0.294	138 (57)	42 (69)	0.093	180 (59)
Neuropsychiatric disease	-	-	-	62 (26)	21 (34)	0.168	83 (27)

Table 7.1 Demographics and clinical characteristics (ever) of patients, cross-classified by the presence of NPSLE event since disease onset and flares in the preceding year *(Continued)*

	Without NPSLE (n=220)	With NPSLE (n=83)	P	Without flares (n=242)	With flares (n=61)	P	Entire group (n=303)
Haematologic manifestations	187 (85)	75 (90)	0.151	206 (85)	56 (92)	0.173	262 (87)
Leukopenia	111 (51)	47 (57)	0.368	122 (50)	36 (59)	0.229	158 (51)
Lymphopenia	141 (64)	55 (66)	0.788	159 (66)	37 (61)	0.461	196 (65)
Lymphopenia	141 (64)	55 (66)	0.788	159 (66)	37 (61)	0.461	196 (65)
Thrombocytopenia	64 (29)	26 (31)	0.788	70 (29)	20 (33)	0.555	90 (30)
Hemolytic anemia	16 (7)	9 (11)	0.350	19 (8)	6 (10)	0.615	25 (8)
Immunological manifestations	207 (94)	80(96)	0.570	228 (94)	59 (97)	0.434	287 (95)
Anti-ds DNA positive	171 (77)	60 (72)	0.370	178 (74)	52 (85)	0.056	230 (76)
Anti- Smith positive	46 (21)	18 (22)	0.876	46 (19)	18 (30)	0.073	64 (21)
Anti-Ro positive	112 (51)	55 (66)	**0.020**	132 (55)	35 (57)	0.691	167 (55)
Anti-La positive	43 (20)	14 (17)	0.742	50 (21)	7 (12)	0.101	57 (19)
ANA positive	219 (99.5)	80 (96)	0.180	239 (99)	60 (98)	0.386	299 (99)

* Values are the number (percentage) unless otherwise indicated. Numbers in bold represent $p<0.05$. NPSLE = neuropsychiatric systemic lupus erythematosus; SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; anti-dsDNA = anti–double-stranded DNA; ANA = antinuclear antibody.

7.3.2 NPSLE and lupus flare profile

A total of 116 NPSLE events since disease onset were recorded in 83 patients. For more details about the profile of NPSLE events, please refer to **CHAPTER 5.3.1** and Table 5.2.

A total of 72 episodes of flare were recorded in 61 (20.1%) of 303 patients in the preceding year. The overall rate of lupus flare was 0.24 episodes per patientyear. Fifty (82.0%) out of 61 patients had 1 flare and 11 (18.0%) of 61 had 2 flares. Renal flare was the most common, followed by mucocutaneous, musculoskeletal and haematologic flare (Table 7.2). For those with 1 flare, 18 (36%) out of 50 patients had mild/moderate flare and 32 (64%) of 50 had severe flare. For those with 2 flares, 1 (9%) out of 11 patients had 2 mild/moderate flares; 6 (56%) of 11 had 1 mild/moderate flare and 1 severe flare; 4 (36%) out of 11 had 2 severe flares. The majority of these patients with flare had single-organ flare (53/61, 87%). Among patients with single-organ flare, 22 (42%) of 53 patients had renal flare, 4 (8%) had NP flare, 10 (19%) had mucocutaneous flare, 8 (15%) had musculoskeletal flare, and 7 (13%) had haematologic flare. Eight out of 61 (12.9%) patients had multiorgan flare involving 2 to 5 organ systems (median 2).

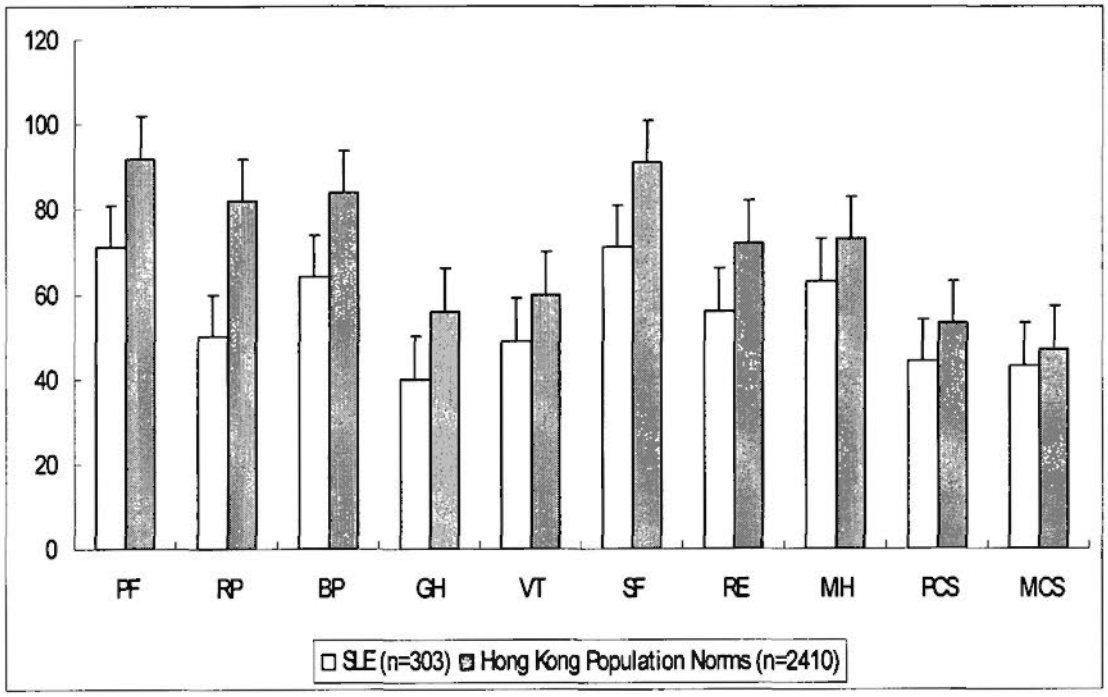
Table 7.2 Clinical features of lupus flares in the preceding year

	No. of episodes	Rate of flare (per patient-year)
All flares	72	0.24
Renal flares	28	0.09
Neuropsychiatric flares	8	0.03
Other flares		
Mucocutaneous	16	0.05
Musculoskeletal	11	0.04
Heamatologic	10	0.03
Vasculitis	9	0.03
Serositis	2	0.01

7.3.3 HRQoL compared with Hong Kong population norms

In SLE patients, the SF-36 subscales and 2 component scores were both significantly lower than the Hong Kong population norms, indicating poorer HRQoL across all the domains of SF-36 in this cohort (Figure 7.1). In male patients with SLE, only role-physical were significantly lower compared to sex-matched controls ($p = 0.021$).

Figure 7.1 Comparison of the Short Form 36 scores between patients with systemic lupus erythematosus (SLE) and the Hong Kong population norms* [93, 94]



* Significant difference ($p<0.0001$) were found in all subscales and summary scales. PF = physical function; RP = role limitation due to physical problems; BP = bodily pain; GH = general health; VT = vitality; SF = social function; RE = role limitation due to emotional problems; MH = mental health; PCS = physical health summary scale; MCS = mental health summary scale.

7.3.4 NPSLE and the SF-36 scales

Patients with NPSLE had more compromised HRQoL in some, but not all, of the domains of the SF-36. Affected domains included physical function, general health, social function, role limitation due to emotional problems and physical health summary scale (Table 7.3). When comparing the SF-36 scales among patients with seizure, CVD and headache, significant differences were only found between patients

with the latter 2 NPSLE events, where patients with CVD had lower level of social function and more role limitation due to physical/emotional problems.

7.3.5 Lupus flare and the SF-36 scales

Table 7.4 summarizes the SF-36 subscales and summary scales of the study population, cross-classified by the number of flares, severity of flares (for those with 1 flare only), number of involved organs of flares, and manifestations of flares (for those with single-organ flares only). Patients with flares in the preceding year had significantly lower scores in the areas of role limitation due to physical problems, general health, social function, and role limitation due to emotional problems compared with those without flare. Physical health summary scale was also lower in patients with flare, but there was no difference in mental health summary scale between these 2 groups. The number of flares, the severity of flares (mild/moderate versus severe), and the number of organs involved (single-organ versus multiorgan flare) did not influence the domains of HRQOL measured by the SF-36. For those with single-organ flares, patients with musculoskeletal flares had lower levels of physical function, bodily pain, social function, and physical health summary scale compared to those with other flares. However, patients with renal/NP flares did not have significantly poorer level of HRQOL measured by the SF-36.

Table 7.3 Mean ± SD for the SF-36 subscales and summary scales for the study population, cross-classified by the presence of NPSLE event since disease onset*

	Without NPSLE (n=220)	With NPSLE (n=83)	With seizure (n=12)	With CVD (n=11)	With headache (n=15)
Subscales					
Physical function	46 ± 11	42 ± 12†	45 ± 7	40 ± 10	47 ± 11
Role limitation due to physical problems	42 ± 12	42 ± 12	42 ± 13‡	34 ± 11§§	53 ± 6
Bodily pain	48 ± 11	46 ± 11	45 ± 13	42 ± 9	45 ± 9
General health	37 ± 10	34 ± 10†	30 ± 9	34 ± 10	35 ± 6
Vitality	47 ± 10	46 ± 10	45 ± 11	47 ± 12	47 ± 10
Social function	46 ± 10	42 ± 12†	44 ± 11	39 ± 9§	48 ± 7
Role limitation due to emotional problems	43 ± 14	39 ± 14†	40 ± 15	33 ± 14§	50 ± 10
Mental health	43 ± 11	43 ± 12	42 ± 12	44 ± 12	47 ± 6
Summary scales					
Physical health summary	44 ± 10	42 ± 9†	42 ± 7	38 ± 8	46 ± 8
Mental health summary	44 ± 11	42 ± 12	42 ± 12	42 ± 11	48 ± 6

* SF-36 = Short Form 36; NPSLE = neuropsychiatric systemic lupus erythematosus; CVD = cerebrovascular diseases.

†: P<0.05, comparison between patients with and without NPSLE.

‡: P<0.05, comparison between patients with seizure and headache.

§: P<0.016, §§: P<0.0001, comparison between patients with CVD and headache. P<0.016 was considered significant after adjustment of multiple comparisons.

Table 7.4 Mean ± standard deviation for the Short Form 36 subscales and summary scales for the study population, cross-classified by the presence of flares in the preceding year and the severity or manifestations of flares*

			Number of flares		Severity of flare		Number of involved organ		Manifestations of flares		
	Without flare (n=242)	With flares (n=61)	1 flare (n=50)	2 flare (n=11)	Mild/ moderate flare (n=18)	Severe flare (n=32)	Single organ flares (n=53)	Multi-organ flares (n=8)	Other flares (n=19)	Renal/NP flares (n=26)	Musculo-skeletal flares (n=8)
Subscales											
Physical function	73 ± 26	66 ± 30	65 ± 30	59 ± 31	64 ± 25	66 ± 32	68 ± 28	52 ± 40	74 ± 14	68 ± 33	48 ± 26‡
Role limitation due to physical problems	55 ± 44	31 ± 38††	34 ± 39	20 ± 31	39 ± 40	30 ± 40	32 ± 39	25 ± 35	37 ± 40	30 ± 39	28 ± 36
Bodily pain	65 ± 25	58 ± 28	59 ± 27	53 ± 35	50 ± 28	65 ± 25	56 ± 28	70 ± 29	63 ± 28	60 ± 27	30 ± 16‡
General health	41 ± 22	35 ± 20†	35 ± 21	32 ± 20	34 ± 18	36 ± 22	35 ± 21	32 ± 18	41 ± 19	34 ± 23	27 ± 13
Vitality	50 ± 20	47 ± 23	49 ± 22	38 ± 23	45 ± 22	52 ± 22	47 ± 23	49 ± 19	52 ± 19	46 ± 26	39 ± 21
Social function	73 ± 24	64 ± 26†	65 ± 26	59 ± 26	61 ± 28	68 ± 26	65 ± 26	58 ± 30	74 ± 22	65 ± 26	44 ± 24‡
Role limitation due to emotional problems	59 ± 44	45 ± 45†	46 ± 46	39 ± 42	43 ± 47	48 ± 46	43 ± 45	54 ± 47	58 ± 46	38 ± 46	25 ± 39
Mental health	64 ± 19	62 ± 20	63 ± 19	55 ± 20	60 ± 21	65 ± 19	62 ± 21	63 ± 14	68 ± 19	60 ± 22	53 ± 18

Table 7.4 Mean ± standard deviation for the Short Form 36 subscales and summary scales for the study population, cross-classified by the presence of flares in the preceding year and the severity or manifestations of flares *(Continued)*

			Number of flares		Severity of flare		Number of involved organ		Manifestations of flares		
	Without flare (n=242)	With flares (n=61)	2 flare (n=50)	2 flare (n=11)	Mild/ moderate flare (n=18)	Severe flare (n=32)	Single organ flares (n=53)	Multi-organ flares (n=8)	Other flares (n=19)	Renal/NP flares (n=26)	Musculo-skeletal flares (n=8)
Summary scales											
Physical health summary	45 ± 9	41 ± 9†	41 ± 9	40 ± 11	40 ± 9	41 ± 9	41 ± 9	38 ± 8	43 ± 8	42 ± 10	34 ± 7‡
Mental health summary	44 ± 11	42 ± 12	43 ± 12	38 ± 13	41 ± 12	44 ± 13	42 ± 12	44 ± 13	46 ± 11	43 ± 12	36 ± 9

* NP = neuropsychiatric.

†: $p<0.05$, ††: $p<0.005$, significant differences found between patients with and without flares.

‡: $p<0.01$, significant differences found between patients with musculoskeletal flares and other flares.

7.3.6 Multivariate analyses

Results of the multivariate regression are shown in Table 7.5. We found no relationship between the SF-36 scales and education level, disease duration, severe flare, and multiorgan flare in the preceding year.

Older age independently predicted poorer level of HRQoL in the domains of physical function, role limitation due to physical problems and bodily pain. Females had significantly more impairment in social function. The relationships between the SF-36 scales and disease damage or disease activity were weak. Higher disease activity was associated with lower level of general health, whereas higher disease damage associated with lower level of physical function. The presence of NPSLE events did not influence HRQoL significantly, with only weak association with general health and social function. The presence of CVD was associated with role limitation due to physical/mental problems. The increased number of lupus flares in the preceding year was only independently associated with more role limitation due to physical problems. Musculoskeletal flare in the preceding year appeared to have significantly influences on HRQoL, independently associated with impairment of most of the subscales of the SF-36, except role limitation due to physical problems and mental health.

Independent variables associated with poorer physical health summary were older age, higher level of disease damage and disease activity, and musculoskeletal flare in the preceding year. The independent variable associated with poorer mental health summary score was musculoskeletal flare in the preceding year.

However, it should be noted that all these multivariate models only expressed limited percentage (1% - 10%) of variance of scales/subscales of the SF-36.

7.4 CONCLUSIONS

In summary, patients with SLE experience significant compromised HRQoL across all health domains measured by the SF-36. The presence of NPSLE event since disease onset or lupus flares in the preceding year does not have substantial influence on HRQoL. The worsening HRQoL we have observed does not seem to directly depend on disease activity or damage. Musculoskeletal manifestations, such as arthritis/arthralgia, might be the unique clinical manifestation able to influence HRQoL in patients with SLE.

Table 7.5 Results from final regression models showing coefficients (95% confident interval) for independent variables associated with the Short Form 36 subscales and summary scales*

	Physical function	Role limitation due to physical problems	Bodily pain	General health	Physical health summary
Age (per year)	-0.16 (-0.26, -0.05)	-0.14 (-0.26, -0.02)	-0.14 (-0.24, -0.03)		-0.13 (-0.22, -0.04)
Female					
SELENA-SLEDAI score (per unit)				-0.52 (-0.92, -0.12)	-0.49 (-0.86, -0.12)
SDI score (per unit)	-2.03 (-3.20, -0.87)				-1.47 (-2.43, -0.51)
Number of NPSLE event (per event)				-2.04 (-3.71, -0.36)	
CVD ever		-7.45 (-12.87, -2.02)			
Number of flare (per flare)		-5.96 (-8.69, -3.23)			
Musculoskeletal flare ever	-9.43 (-15.97, -2.90)		-14.63 (-21.09, -8.17)	-6.29, (-12.32, -0.26)	-9.15 (-14.57, -3.73)
Adjusted R^2	0.088	0.077	0.072	0.048	0.102

Table 7.5 Results from final regression models showing coefficients (95% confident interval) for independent variables associated with the Short Form 36 subscales and summary scales *(continued)*

	Vitality	Social function	Role limitation due to emotional problems	Mental health	Mental health summary
Age (per year)					
Female		-6.22 (-12.31, -0.14)			
SELENA-SLEDAI score (per unit)					
SDI score (per unit)					
Number of NPSLE event (per event)		-2.39 (-4.16, -0.62)			
CVD ever			-8.79 (-15.14, -2.45)		
Number of flare (per flare)					
Musculoskeletal flare ever	-6.13 (-12.02, -0.25)	-12.89 (-19.20, -6.57)	-10.33 (-18.75, -1.91)		-8.11 (-15.06, -1.18)
Adjusted R^2	0.011	0.074	0.037		0.014

* SELENA-SLEDAI = the Safety of Estrogen in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; NPSLE = neuropsychiatric systemic lupus erythematosus; CVD = cerebrovascular disease.

CHAPTER 8 DISCUSSION

8.1 Costs of systemic lupus erythematosus in Hong Kong

We have performed the first cost-of-illness study in systemic lupus erythematosus (SLE) in Hong Kong, and also the first one in the Asian-pacific region, using a cohort of Chinese patients, including both direct and indirect costs from a societal perspective. We have estimated the average annual total costs incurred by patients with SLE as USD 13,307, 62% of which were attributable to direct costs.

8.1.1 Comparison among different countries

There are limited literatures pertaining to the costs of SLE. Figure 8.1 summarizes the comparisons of direct and indirect costs between our study and studies conducted in other countries. Direct comparison of our results with those of other studies in other countries would be difficult because of different years of evaluation, the cost framework, and the methods of costs calculation and the pattern of practice. However, such comparisons might help put our results in perspective. Direct costs in our study were quite comparable with those in United Kingdom (UK) and Canada. Costs of SLE in United States appear to be significantly more expensive than those in other countries. Prices are an possible explanation because studies have found that

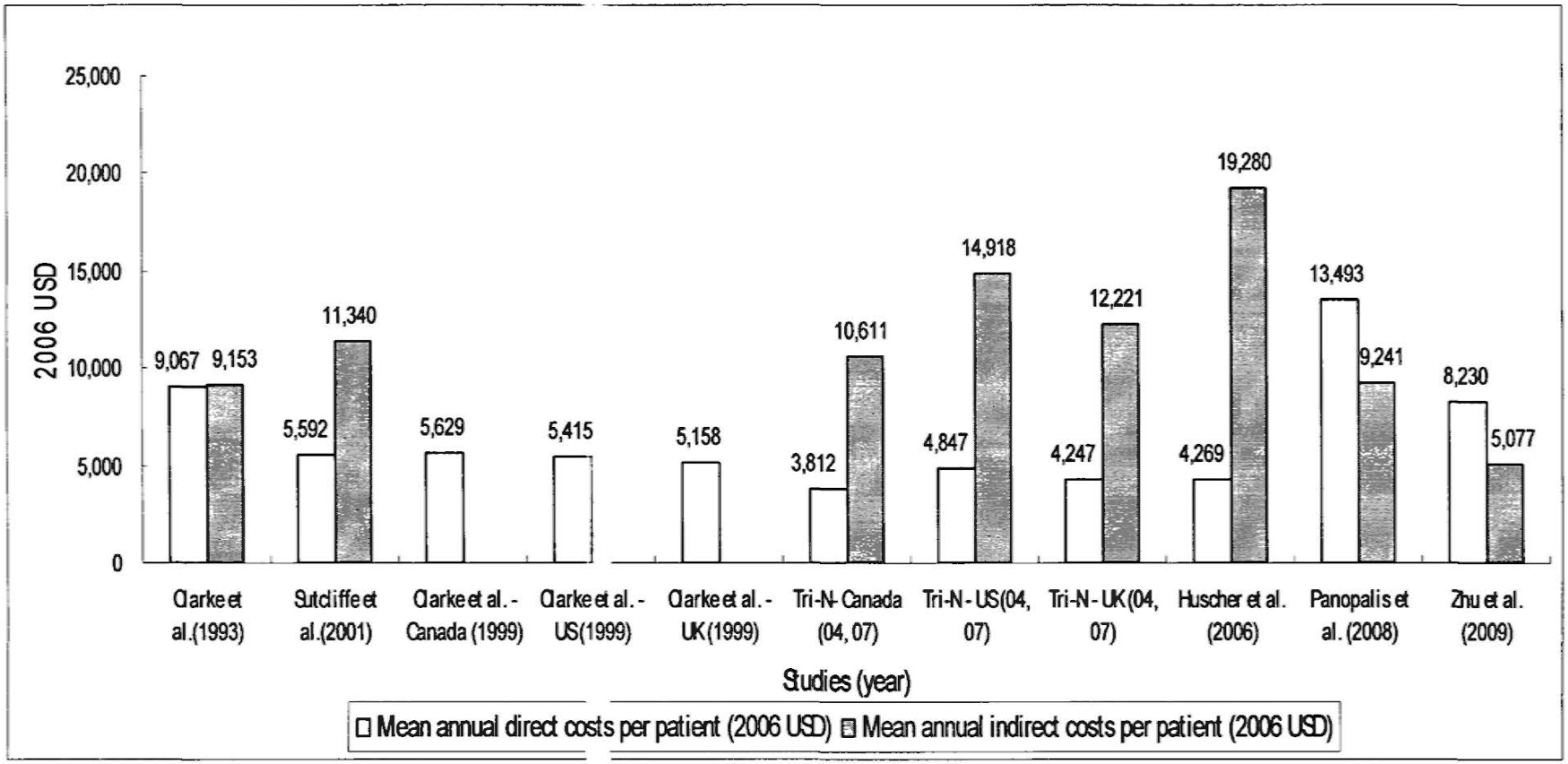
American prices are often much higher than those in other countries [210, 211]. The employment rate across different studies was quite comparable. The mean duration of sick leave taken per year in our study was similar to that in Canada by Clarke et al (1993) (14 days in our study versus 13 days in Clarke et al's) [179]. The proportion of patients having SLE-related unemployment was also similar to that in UK (24% in our study versus 22% in Sutcliffe et al's) [170]. However, higher proportion of indirect costs contributing to total costs which was frequently found in previous studies was absent from our study. But such comparison must be made with caution because there is significantly variation in wage rate across different countries. Such as, in Huscher et al's study in Germany, the average daily wage used was €95, compared with €38 (1EUR = 7.38 HKD, market exchange rate) used in our study [174].

Consistent with previous studies, inpatient care costs represent the largest proportion of direct costs. However, the costs of medications were relatively low in our cohort - only 4% of direct costs. But we may have underestimated the costs of medication since the unit price issued by the government may not reflect the true costs or market prices of the drugs. Besides, not all the drugs were included into the government hospital's drug formulary and subsidized by the government in Hong

Kong. New and high-cost drugs (e.g. mycophenolate mofetil) are not within the reimbursed system and patients have to pay for these drugs by themselves, which resulted in limited usage of these drugs.

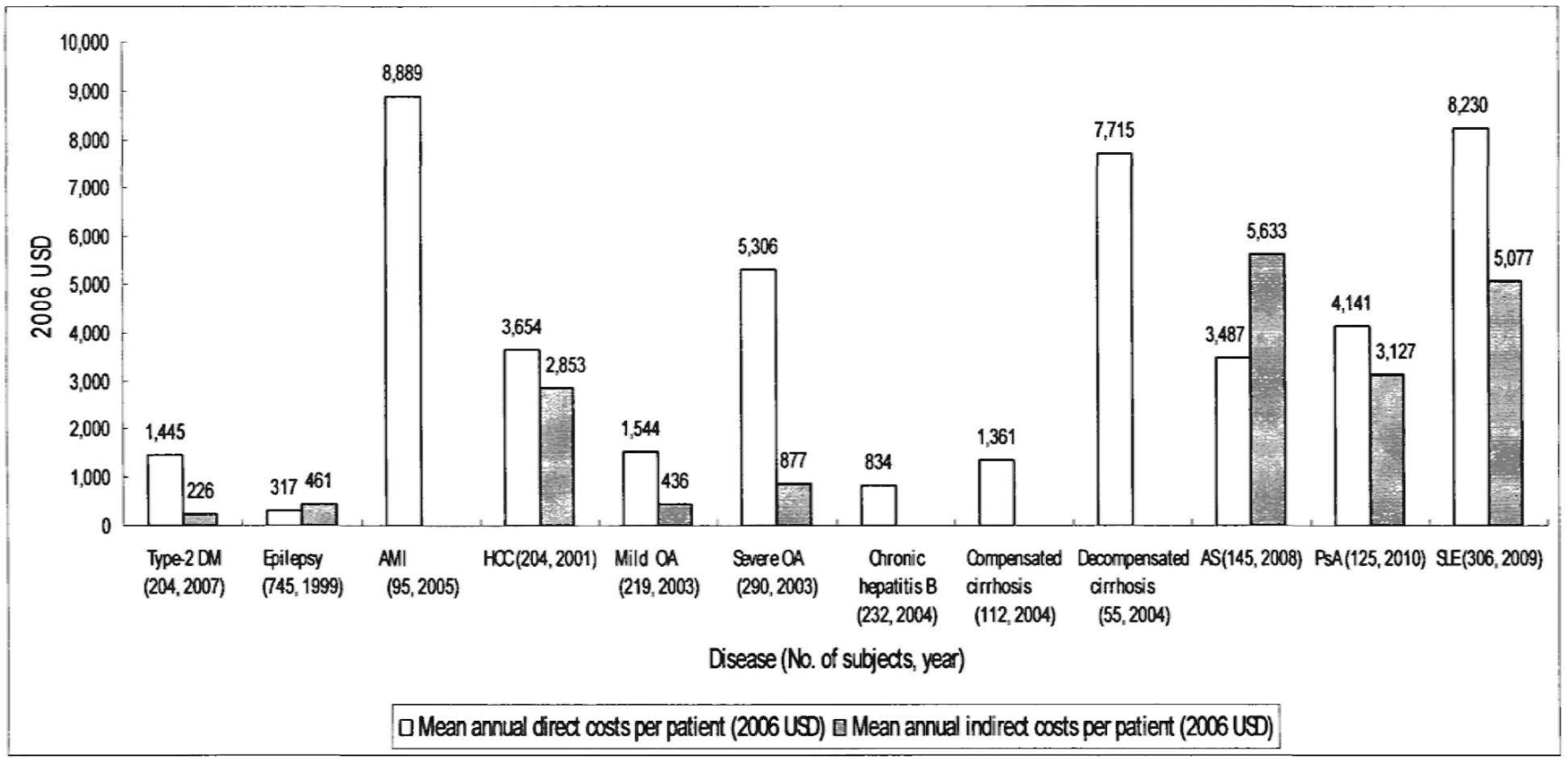
In a study by Huscher et al using a German national database, costs of several rheumatic diseases were compared [174]. In Huscher et al's study, direct costs of SLE were quite comparable with that of ankylosing spondylitis (AS) and psoriatic arthritis (PsA) but lower than that of rheumatoid arthritis, and indirect costs of different rheumatic diseases were quite comparable. We have also conducted cost-of-illness studies in AS and PsA in Hong Kong using similar methodologies as that in SLE [168, 169]. As shown in Figure 8.2, direct costs of SLE were higher than those of AS and PsA. This difference was due to, in large part, differences in the costs of inpatient care. Hospitalization rate was significantly higher in SLE than that in AS or PsA (27% in SLE, compared with 16% in PsA and 6% in AS).

Figure 8.1 Comparisons of average annual direct and indirect costs per subject between our study and studies conducted in other countries*



* Costs were adjusted for inflation using consumer price index (derived from Statistic Department of each country), in 2006 US dollars (USD).
UK = United Kingdom, US = United States; Tri-N = Tri-nation study (Clarke et al [2004] and Panopalis et al [2007])

Figure 8.2 Comparisons of average annual disease costs per patient among several cost-of-illness studies in chronic diseases in Hong Kong*



* Costs were adjusted for inflation using consumer price index, in 2006 USD (purchasing power parity). AS = ankylosing spondylitis; PsA = psoriatic arthritis; DM = diabetes mellitus; AMI = acute myocardial infarction; HCC = hepatocellular carcinoma; OA = osteoarthritis; USD = United States dollars.

8.1.2 Comparison with costs of other chronic diseases in Hong Kong

Figure 8.2 shows the comparisons of average annual disease costs per patient among several cost-of-illness studies in chronic diseases in Hong Kong. Besides the great variance of methodologies employed in each study, prevalence of diseases should also be taken into account when considering the impact of SLE on the society comparing with other chronic diseases. The average annual direct costs per patient with SLE were significantly higher than most of these other chronic diseases, even comparable with acute myocardial infarction which is an acute fetal disorder with relatively high prevalence and multiple comorbidities. However, the prevalence of SLE may be the lowest among these chronic diseases. The prevalence of SLE in Hong Kong is 0.0588%, in comparison with 0.44% of epilepsy [159], 10% of chronic hepatitis B infection [157], 10-22% of type-2 diabetes [161] and 30% of osteoarthritis (among population aged above 70 years) [162]. Therefore, when taken the prevalence into consideration, the total costs of SLE population in Hong Kong may be lower than those of other chronic diseases population with higher prevalence. For example, estimated by Chan et al, direct medical costs of type-2 diabetes contributed up to 3.9% of total Hong Kong healthcare expenditure [161], compared with only 0.26% that SLE contributed to by our conservative estimation.

Although the total societal costs imposed by SLE may not be as substantial as the costs imposed by other chronic disease, an economic point that needs to be emphasized is that SLE is a condition affecting young women during their prime time of life, the peak of their productivity and their reproductive potential. Also, the advances in early diagnosis and effective treatment of SLE have prolonged patients' life-expectancy, leading to more cumulative organ damage. Although we managed to calculate the productivity losses due to work disability in these patients, we cannot directly assess the economic costs of loss of reproductive potential, which is a frequently seen complication in SLE. The physical and psychological burden incurred by SLE on patients and their families may be more considerable than that only expressed by numbers. One might expect that the burden incurred by SLE is more devastating than that when someone 75 years old develops congestive heart failure.

8.1.3 Productivity losses in SLE

Work productivity was also impaired in patients with SLE. More than half of the patients were unemployed and 22% of the patients reported SLE-related unemployment, in comparison with around 4.4% unemployment rate in the whole population in Hong Kong in 2006 (data from Census and Statistic Department). In

our study, we used the Human Capital Approach (HCA) to calculate indirect costs. Although it may be arguable that the Friction Cost Method (FCM) may actually capture the real productivity loss to the society, we could not find a reliable estimate of the duration of the friction period in Hong Kong at the time of the study. On the other hand, given that chronic diseases usually have prolonged effect on work productivity, using the FCM to calculate indirect costs of chronic diseases would probably incur underestimation. This has been found in Clarke et al's study, where they used 2 methods to calculate indirect costs in women with SLE [172]. They found that approximate half of the differences in costs calculated by these 2 methods were due to extending the market work losses beyond the friction period. Furthermore, the FCM excluded indirect costs generated from non-labor market. However, diseases like SLE predominantly affecting young women, who are more likely to be engaged in non-market work, might have considerable impact on household work or daily activities. Discriminating these patients may lead to underestimate the impact of SLE on productivity.

8.1.4 Cost predictors

We also identified costs predictors in our study. Regression analysis showed that the strongest independent predictor for increased direct costs were younger age, shorter

disease duration, more disease damage and poorer physical health status. Logistic regression analysis showed that age, physical and mental health status predicted whether patient incurred indirect costs and the increased amount of incurred indirect costs were independently predicted by lower education level, poorer physical and mental health as shown in linear regression analysis. We found some disparities compared with previous studies. In the study in UK, higher levels of education incurred high indirect costs, which was opposite to our study [170]. Although patients with more education may have higher earning capacity and thus time lost from these patients would be valued highly, patients with lower levels of education may be more likely to be unemployed when affected by SLE, which was shown in our study (mean education year for employed and unemployed patients: 12 versus 9, $p<0.0005$).

Younger age was found associated with increased indirect costs in our study, whereas in the study in United States, it was older age predicting high indirect costs [171]. There is no evidence showing that older patients being offered less care than the younger patients. In our study, there was no difference in the number of visits to healthcare providers between older patients (with age $\leqq$ 42) and younger patients (with age >42, 42 as the median age of the cohort). Older patients visited more

general practitioners (mean number of visit: 0.73 vs. 0.35, p=0.034) and other providers (1.25 vs. 0.65, p=0.015), which can be explained by the higher possibilities of having had complications of SLE when disease progresses. On the other hands, younger patients used more diagnostic examinations, including blood tests (mean number: 33 vs. 28, p=0.001) and urine tests (mean number: 6 vs. 4, p=0.020). There are no differences in the use of emergency room and inpatient care. The higher costs found in younger patients could be partially explained by the higher disease activity (mean value of SELENA-SLEDAI: 2.9 vs. 2.0, p=0.007) and more disease damage (mean value of SDI: 0.86 vs. 0.56, p=0.001) in these patients.

Disease costs depend, to a large extent, on the cumulative disease damage rather than the disease activity, as shown in our and other studies [173]. Disease activity measured by the Safety of Estrogen in Lupus-Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) was not associated with either direct or indirect costs in the multivariate analysis. Such negative association was not completely unexpected given the potential reversibility of disease activity. However, it is evident that uncontrolled disease activity will result in irreversible cumulative disease damage, which has been frequently shown as an important costs predictor. Therefore, control

of disease activity might be effective in view of the high costs associated disease damage.

8.2 Neuropsychiatric SLE and disease costs

We have also shown that SLE patients with neuropsychiatric SLE (NPSLE) incurred substantially higher direct and indirect costs than those without NPSLE, and the number of NPSLE event was an independent costs predictor of both direct and indirect costs. The costs of NPSLE are obviously substantially higher than other chronic diseases shown in Figure 8.2. Our results provide additional highlights of the scope of impact imposed by NPSLE.

8.2.1 The prevalence of NPSLE

The overall prevalence of NPSLE in our cohort (27%) is lower than that in Caucasians (37%-91%) [27-29, 40, 212]. The most common manifestations in our cohort are seizure disorder and cerebrovascular disease, in contrast to the series in Caucasians in which cognitive dysfunction, headache and mood disorder are among the most common manifestations. Besides genetic, immunologic, geographic difference, the retrospective assessment in our study may also lead to underestimation of the number of NPSLE. Second, formal neuropsychological test

for subtle cognitive dysfunction is not our routine practice at clinic visits because of cumbersomeness of these tests, which may also explain the relatively low prevalence of cognitive dysfunction in our cohort. However, the prevalence and pattern of NPSLE of our cohort is similar to previous studies on Chinese cohorts (19%-23%) [31, 200], which also omitted the neuropsychological assessment.

8.2.2 High disease costs associated with NPSLE

NPSLE has been shown to be associated with significant physical and psychological burden in patients with SLE [32, 49, 212]. Our results suggest that NPSLE also incurs considerable economic burden and the number of NPSLE is an independent explanatory variable associated with increased direct and indirect costs. Previous studies reported that 21-47% of NPSLE patients show recurrence or onset of new NPSLE symptoms requiring continued outpatient or inpatient management [203, 213]. Patients with NPSLE need more technical examinations for accurate diagnosis and more aggressive management strategies, which may explain the high direct costs. Given the potential for neuropsychiatric (NP) involvement to affect psychosocial function [214, 215], which refers to the emotional, behavioral and social aspects of a person's functioning, it is possible that it's an important mechanism for its influence on indirect costs of SLE.

There was only one previous study investigating the relationship between disease costs and NP involvement in patients with SLE. Lacaille *et al* used a simple scoring method to assess the impact of the central nervous system (CNS) involvement on disease costs, where a score of 2 required the presence in the past of seizure, stroke, psychosis or organic brain syndrome, a score of 1 the presence of a motor, sensory, autonomic or cranial neuropathy and the absence of any of these received a score of 0. Their results showed that CNS involvement were predictors of the short term direct costs and indirect costs of SLE [173]. However, such definitions might be too brief to capture the diversity of NP involvement in SLE. Compared with Lacaille et al, our assessment of NPSLE is more standard and comprehensive, by using the 1999 American College of Rheumatology nomenclature and standard definitions for NPSLE, which includes a broad range from subtle abnormalities of neurocognitive functions to overt manifestations.

8.3 Flare and disease costs

To our knowledge, this is the first attempt to elucidate the impact of flare on the costs of SLE. We have shown that patients with flares use more health care resources and incurred both higher direct and indirect costs compared with their counterparts. They

paid more visits to health care providers and the emergency room, had a higher hospitalization rate, required more diagnostic examinations, and received more corticosteroids and immunosuppressants. After being adjusted for other demographics and disease characteristics, the number of flares in the preceding year was an independent explanatory variable associated with increased direct costs in SLE.

8.3.1 Flare rate

The overall flare rate of our cohort was lower compared with previous studies [73, 207, 216]. Although this could be due to differences in the definition used, there are several other possible explanations. First, the validity of the retrospective assessment of flare at a specific visit has been shown to be poor [217]. Second, the study period in our study is shorter (1 year). Third, although all of the patients were followed at our hospital at regular intervals, it is possible that patients would not seek medical consultation for some minor and short-term flares. Furthermore, we excluded flares with only active serologic manifestations. Although one study has shown the high probability of flares in the next 5 years for patients with serologically active but clinically quiescent disease [218], it is our routine practice that we do not launch treatment for these patients. Therefore, it is appropriate to exclude these flares from

our analysis.

8.3.2 High disease costs associated with flare

Sutcliffe et al reported that greater disease activity measured by the Systemic Lupus Activity Measure (SLAM) was associated with high direct and indirect costs [170]. A study in United States also found that disease activity measured by the Systemic Lupus Activity Questionnaire (SLAQ) was an independent predictor of direct health care and productivity costs [171]. It has to be noted that the SLAM and SLAQ both contain items concerning the patients' self-reported well-being (physical and mental) and these items (physical health or mental health) have been found significantly associated disease costs. On the other hand, the SELENA-SLEDAI is a completely objective instrument. In our study, the SELENA–SLEDAI was associated with direct costs in univariate analyses, but after being adjusted by other covariates, it became insignificant. Although this may be due to different measures, it may also be explained by the chronic and fluctuating course of SLE that makes an activity score at a single time point not a good indicator of the overall disease activity [173]. Therefore, calculating disease activity over time may be more desirable [219]. The adjusted mean SLEDAI 2000 update (SLEDAI-2K), determined by the calculation of the area under the curve of the SLEDAI-2K over time, has been shown to be strongly

associated with mortality [220]. Future studies may use this measure to investigate whether disease activity over time is a stronger predictor of costs than disease activity at a single time point.

Since flare is defined as an increase in disease activity, we consider the total number of flares during the study period as a summary of the overall disease activity. In our study, the number of flares was significantly associated with the SELENA–SLEDAI score ($r = 0.219$, $p = 0.0005$). The number of flares was significantly related to direct costs, both in the univariate and multivariate models.

In our study, severe flares did not incur significantly higher direct/indirect costs compared with mild/moderate flares. However, we might underestimate the number of mild/moderate flares because a patient might not seek medical consultation for a minor and short-term flare. Multiorgan flares in our study were more costly than single-organ flares. However, it must be noted that the number of patients with multiorgan flares is relatively small. Such a comparison may be inconclusive. Flares involving major organs require more aggressive and intensive treatment [80, 221], which concurs with our results that patients with renal/NP flares incur higher direct costs compared with other organ flares. There was no difference in direct costs

between patients with renal and NP flares, which is probably due to the small number of patients with NP flares (n = 4).

8.3.3 Definitions of lupus flare

There is no generally accepted definition of lupus flare at present, although various approaches have been used in clinical trials. The definitions of flares we used in this study were adopted from the SELENA flare tool, which has been shown to be reliable and valid [222]. The limitations of using the disease activity index (the SELENA-SLEDAI) alone to define flares have been discussed, including a lack of descriptors for several types of activity, such as hemolytic anemia and mononeuritis multiplex [222]. Although we incorporated disease activity index and disease activity scenarios and treatment changes that might be missed by the indices used to define flares, concerns should be raised. Some clinical manifestations of disease activity scenarios were not specified in the definitions, such as acute or subacute cutaneous lupus or mild/moderate haematologic abnormalities for the definitions of mild/moderate flare; or acute lupus pneumonitis, interstitial pneumonitis, pulmonary hypertension, pulmonary hemorrhage, and myocarditis for the definitions of severe flare. However, some of these manifestations might have been identified by the changes in treatments, which were individual items of the definitions.

8.4 Health-related quality of life in SLE: focus on the relationship with NPSLE and lupus flares

In this study, we have demonstrated significantly poorer health-related quality of life (HRQoL) in patients with SLE than that of the Hong Kong population. This finding is consistent with that from previous studies. Overall, Patients with SLE experience significantly worse HRQoL affecting all health domains in comparison with healthy controls or patient with orther chronic conditions [102]. However, the presence of NPSLE or flare has only week relationship with the impairment of HRQoL.

8.4.1 Flare and HRQoL

We previously found that there was no relationship between disease activity measured by SELENA-SLEDAI and HRQoL measured by the Short Form 36 (SF-36) in a cohort of patients with SLE [32]. In our study, we found that the SELENA-SLEDAI score was only significantly associated with general health measured by the SF-36. This is consistent with previous studies which also found no or only a weak relationship between disease activity measured at a single time point and HRQoL in patients with SLE [102]. Flares – overall changes in disease activity – appear to have a stronger relationship with HRQoL, but this would probably be

associated with the presence of musculoskeletal flare. The relationship between flare and HRQoL in patients with SLE was also studied by Doria, et al, who found that a higher number of flares was associated with lower levels of general health and physical function measured by the SF-36 [96]. They also proposed that arthritis/arthralgia was the unique clinical manifestation able to influence the HRQOL. Our results are consistent with these findings, in that we found musculoskeletal flare is the only variable that has consistent and relatively stronger relationship with most of the health domains measured by the SF-36. Joint pain, even without a true arthritis, worsens HRQoL by requiring large amount of energy to cope with it or by representing as a persistent signal of active disease [96].

8.4.2 NPSLE and HRQoL

We have shown that SLE patients with NPSLE incurred substantially higher direct and indirect costs than those without NPSLE. In this study, we did no observe strong relationship between NPSLE and HRQoL, which appears to be opposite to previous studies. However, it should be noted that the definitions of NPSLE used in those previous studies are diverse and may not be the same as those in our study. Furthermore, most of these previous studies did not consider some important confounders, such as musculoskeletal manifestations. In our study, although patients

with NPSLE had lower level of HRQoL in some domains, this might be probably due to some confounders, such as the presence of musculoskeletal flares. Higher prevalence of having had musculoskeletal flares in the preceding year in patients with NPSLE was observed in our cohort (3% versus 5%), albeit not statistically significant. After adjusted by other demographics and clinical characteristics, the presence of NPSLE event was only independently associated with poorer general health and social function, and the presence of CVD ever was independently associated with more limitation due to physical/emotional problems. It is possible that HRQoL measured by the SF-36 in patient with SLE may not be substantially influenced by the presence of NPSLE event. During the long disease course of SLE, NPSLE can occur at any time. Although NPSLE events can result in irreversible accumulative damage, patients may gradually habituate to the impact imposed by NPSLE and also, to their compromised quality of life. Such negative relationship has also been observed in patient with renal damage where patients' HRQoL was not affected by the presence of renal damage [178]. It is possible that active NPSLE could have more influence on HRQoL. However, such relationship cannot be explored in this cross-sectional study.

When overt manifestations of NPSLE appear to have limited influence on HRQoL,

other studies have shown that higher level of anxiety and depression are significantly associated with compromised HRQoL in patients with SLE [32, 96]. It is possible that in patient with mild disease activity, the effect of NPSLE on HRQoL could be marked by such factors as anxiety and depression.

8.4.3 HRQoL instrument

As a generic instrument, the SF-36 has shown construct validity and responsiveness in measuring HRQoL in patients with SLE. However, HRQoL research in patients with chronic illnesses strives to use disease-specific instruments to obtain the optimal measure of HRQoL in specific patient groups. The SF-36 is not disease-specific and therefore it may contain irrelevant items and/or lack items that are important for SLE [223] (**CHAPTER 1.7.3**). Several SLE-specific HRQoL questionnaires have been developed recently, such as the SLE-specific quality of life instrument [106], the Lupus Quality of Life [107], and the SLE Quality of Life Questionnaire [108]. However, the use of these instruments remains limited to Singaporean Chinese and British Caucasian populations. Further cultural adaptation and validation have to be undertaken before they can be applied to the Chinese population in Hong Kong.

8.5 Limitations

8.5.1 Sample and generalizability

We recruited patients within working age in view of the controversies regarding the calculation of indirect costs among patients outside the labor market. There is no currently no accepted consensus regarding whether and how to calculate the indirect costs of children and the elderly who are outside the labor market. In fact, this has been one of the ethical objections against the use of cost-of-illness study because if the relative economic burden of diseases includes productivity losses, and if these data are used in priority setting, then more resources will be devoted to the care of people of working age or in certain occupation. Considering the statistics of our center, over 94% and over 97% are within working age for female (mean age 42) and male (mean age 43) patients, respectively. Although we might be at risk of discriminating the elderly, in order to generate a more homogenous sample, we recruited patients only within working age.

The study was clinic-based, which can provide more detailed data and was easy to assemble. Although without detail statistics, clinic-based cohort may over-represent more severe diseases since mild or inactive diseases would be mainly managed by the general practitioners in the community. Other methods for obtaining resource use include from community-based cohorts, general practices, enrollees in large managed

care organizations and national surveys [224]. Each method has limitations. Community-based cohort, general practices and national random sample have the ability to recruit a more representative patient population than a clinic sample. However, community-based cohorts are difficult to assemble and therefore, very rare. In population surveys, the diagnosis of SLE relies on self-reported illness. In community-based cohorts and managed care organizations, the diagnosis mainly depends on administrative data. For a disease like SLE, it is unwise to rely on self-defined illness or diagnosis by a non-rheumatology specialist because of the high risk of including a variety of inflammatory and non-inflammatory rheumatic and non-arthritis conditions. Resource use and work disability can vary considerably among these conditions, national survey and administrative data lead to less precise costs estimates than clinic-based cohorts.

The demographics and clinical characteristics of our cohort are quite comparable with previous SLE study cohort in Hong Kong, including one cohort recruited from the rheumatology clinics of Queen Mary and Tuen Mun Hospital in Hong Kong [32, 89, 200]. Queen Mary Hospital is a regional acute hospital and a territory-wide tertiary and quaternary referral centre offering services to the residents from west of Hong Kong Island. Tuen Mun Hospital provides a comprehensive range of acute and

ambulatory healthcare services to residents of the Tuen Mun and Yuen Long districts and the northern region of New Territories West. Although this was a single center study, given the primarily public healthcare system in Hong Kong, the treatment patterns or healthcare delivery patterns should be similar across different centers. Therefore, our cohort should be representative in general and our results could be generalized to the SLE population in Hong Kong.

8.5.2 Limitations of study design

There are several limitations regarding the design of this cost-of-illness study. First, the retrospective design and recall bias may affect the accuracy of the data. It should be noted that the recall period in our study is long (12 months). The major advantage and reason we choosing retrospective design is that they are less expensive and time consuming than those performed prospectively because all relevant events have already occurred at the time the study is initiated. The primary public Hong Kong healthcare system facilitates the retrospective assessment by providing access to sufficient and detailed data on resources consumption. The largest part of the disease costs, i.e., the public health care resources, was obtained by chart review that was solid and accurate. However, the data derived from patients' self-reported questionnaires were subjected to recall bias. Prospective studies with diaries being

given to patients and/or caregivers may be more robust to recall bias, although more expensive and time-consuming. The reliability of self-report data has been demonstrated in a previous study by Clarke et al [179], by analyzing the data as a series of matched pairs, which is government and patient report of number of physician visits. Clarke et al found that the difference was equal to zero.

Second, patients with end-staged renal disease or on dialysis mainly attended by nephrologists are excluded from the cohort. Because patients were recruited from the outpatient clinic, most of the participants were with only mild disease activity or damage. Third, if affordable, some patients may be treated by private sectors through the whole disease course. However, under the well established public healthcare system of Hong Kong, we believe this is a minority and should not influence the results. Fourth, as we measured all costs incurred by patients with SLE, we could not distinguish which proportion of costs were directly attributable to SLE. Similarly, although we have shown that NPSLE is associated with high disease costs, we cannot determine the proportion of disease costs of NPSLE attributable to the neuropsychiatric manifestations or to the treatment. Furthermore, we did not measure the productivity loss because of the time spent nursing patients provided by families and friends (social help), as suggested by some previous studies [171, 177]. However,

we found it very difficult for the patients indicating the amount of time when they receiving social help. Finally, because of international differences in patients' demographics, treatment practices and healthcare systems, our results may not be generalizable to other populations of SLE.

8.5.3 Limitations of the assessment of NPSLE

The total number of NPSLE events since disease onset was determined retrospectively by reviewing medical records. It is possible that minor NP involvement might be left out from assessment. Without psychological tests and cognitive assessment, we might have underestimated the prevalence of psychological and cognitive involvement. Because patients were recruited from the outpatient clinic, most of the participants were with mild disease activity or damage, and we could not assess the costs of patients with active NPSLE.

8.5.4 Limitations of the assessment of lupus flare

The major concern regarding the assessment of lupus fare is the retrospective assessment, validity of which still needs to be further established. The number of flares might have been underestimated as minor or short-term flares might have been omitted from analyses because the assessment was retrospectively made through

reviewing medical notes. Although we have shown that patients with flares received more medications, we could not tell from our results whether these medications were initiated during the preceding 12 months or were prescribed because of the flares.

8.5.5 Limitations of the assessment of HRQoL

An important limitation is the difference in the assessment timeframe between the SF-36 and lupus flare. The SF-36 assesses HRQoL in the preceding 4 weeks, but we recorded lupus flare in the preceding 12 months. Patients who last experienced a flare 13 months ago will not be considered to have had a flare. This one-year cutoff was arbitrary. However, we still found a significant correlation between the presence of flares and the deterioration in some domains of the SF-36. It is possible that the influence of flares on patients' HRQoL might last longer than the duration of flares themselves.

Because we did not record information about time to the last flare, we could not determine whether a recent lupus flare would have a greater influence on HRQoL than an old flare. And it would be of great interest to investigate the perturbation of HRQOL after a lupus flare. The comparisons of HRQoL between patients with and without flares are not conclusive due to the small number of patients with flares.

Reliable conclusions cannot be based on comparisons between such uneven groups. An investigation to replicate our findings using a larger patient group is needed. We used a convenience sample of patients with SLE and there may have been some selection bias or overestimation of patients' HRQoL. Finally, we did not assess fibromyalgia, which has been shown to have high prevalence in patients with SLE and as a major contributor to patients' HRQoL in SLE [111].

CHAPTER 9 CONCLUSIONS OF THE THESIS

This project was a retrospective comprehensive cost-of-illness study conducted from 2006 to 2007. A total of 306 patients with systemic lupus erythematosus (SLE) within working age were recruited. Results from this cost-of-illness study showed that SLE incurs substantial socioeconomic impact in Hong Kong, in terms of healthcare resources utilization, losses of productivity due to work capacity impairment and significantly compromised HRQoL. The aims of the study were achieved and the hypotheses framed were answered as follows.

9.1 Answers to the hypotheses

1. SLE is associated with substantial socioeconomic burden as a result of NPSLE and flare.

Hypothesis accepted.

Patients with NPSLE incur both higher annual direct and indirect costs than those without NPSLE. The total number of NPSLE event since disease onset is independent explanatory variable significantly associated with increase direct and indirect costs. Patients with flares in the preceding year use more health care resources and incur higher direct and indirect costs compared with those without

flares. The total number of flares is an independent explanatory variable associated with direct costs of SLE, but not with indirect costs. Major organ flares such as renal and NP flares incur higher direct costs than other organ flares.

2. Patients with NPSLE or flares may experience more compromised HRQoL.

Hypothesis cannot be accepted.

Although patients with NPSLE and lupus flares had lower scores in several domains of HRQoL measured by the Short Form 36 in univariate analyses, the presence of NPSLE event or lupus flares does not have substantial influence on HRQoL in multivariate analyses.

9.2 Summary and implications

The advances in early diagnosis and management of SLE have enabled the affecting patients to live longer. Physicians are now facing the challenge imposed by the cumulative organ damage and morbidity related to this condition. Although SLE is less common than other rheumatic diseases, it has a predilection for affecting young women during their prime of life, physically, mentally, socially and economically. Understanding the financial costs of SLE may help us highlight the profound influence imposed by this condition and identify future areas for research work on

this condition.

Our project is the first cost-of-illness study in the Asian-pacific area aiming to investigate the economic burden of SLE. We have found substantial financial burden to the society and the individuals in patients with SLE. Per-patient costs of SLE are higher than those of other chronic conditions in Hong Kong.

Direct costs are primarily determined by factors related to disease status, such as disease duration, disease damage, neuropsychiatric manifestations and lupus flares, while indirect costs arise mainly from patients' health status (physical and mental health), which are influenced, at least in part, by the disease progression and cumulative damage. On the other hands, clinical variables only weakly correlate with impairment of HRQoL, and the only clinical characteristic we found associated with HRQoL is musculoskeletal manifestations. The high disease costs associated with lupus flares provide further support for the important role of preventative care in the management of SLE. Overall, these suggest that treatments, which can lead to early diagnosis and effectively control disease activity and prevent organ damage and lupus flares, may improve patients' outcome and simultaneously reduce disease costs due to both healthcare consumption and productivity losses.

Nowadays, the improvement in understanding the pathogenesis of SLE has led to the development of new therapies specifically targeting the immune system and being more effective and less toxic. Some of these therapies have claimed to be able to control disease activity and prevent flare. At the mean time, costs of these therapies are likely to be much higher than conventional therapies. However, given the substantially high costs associated with SLE, the high costs associated with lupus flare and NPSLE, and the significantly worsening HRQoL in SLE, it could be anticipated that the potential benefits of these therapies will be commensurate with their costs. Future economic evaluations, using cost-effective analysis, cost-benefit analysis or cost-utility analysis, will give us more information regarding the economic properties of these novel therapies. Our project provides a baseline for such evaluations.

9.3 Future directions

We have demonstrated that patients with NPSLE incur significant higher disease cost than those without and it seems to be the only clinical characteristic that can independently predict increase indirect costs. This finding highlights the substantial impact of NPSLE and justifies more future investigation onto this area.

Future longitudinal studies are needed to continue to monitor the influence of this condition, in view of the dynamic process of disease course and disease prognosis. The relationship between disease costs and NPSLE and lupus flares, as found in our project, can only be further well-established in prospective studies. Furthermore, a cost-of-illness study can not tell whether the money is worth paying for. Causal association between expenditure and health outcomes can only be made from longitudinal studies.

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CHAPTER 11 APPENDIX

Appendix 1 Major findings of cost-of-illness studies in systemic lupus erythematosus

	Clarke et al. (1993)	Sutcliffe et al. (2001)	Clarke et al. (1999)	Clarke et al. (2000)
Country	Canada	United Kingdom (UK)	Canada, UK and United States (US)	Canada, UK and US
No. of subjects	164[†]	105	Canada: 229; US: 268; UK: 211. Total: 708	648
Period of recruitment	January 1990 to January 1991	June to September, 1995	July 1995 to July 1997	July 1995 to July 1997
Study design	Prospective (1-year)	Prospective (1-year)	Cross-sectional	Cross-sectional
Recall period	Preceding 6 months	Preceding 6 months	Preceding 6 months	Preceding 6 months
Framework of direct costs	Physician visits, diagnostic tests, medications, emergency room visits, hospitalization, rehabilitation facility, transportation, baby sitter, miscellaneous.	Physician visits, diagnostic tests, medication (and dialysis), aids devices, emergency room visits, hospitalization (and day-care surgery).	Physician visits, diagnostic tests, medication (and dialysis), aids devices, emergency room visits, outpatient surgery, hospitalization (acute and non-acute care)	-
Framework of indirect costs	Productivity losses due to SLE-related unemployment; due to lost work hour; due to household chores limitations.	Productivity losses due to lost work hour, due to SLE-related unemployment, due to household chores limitations. Productivity of extra work hour if SLE-free.	-	Productivity loss due to limitations of 1) labor market activity (lost work hour, extra work hour if SLE-free, unpaid labor - domestic and volunteer work); 2) non-labor market activity (household work)

	Clarke et al. (1993)	Sutcliffe et al. (2001)	Clarke et al. (1999)	Clarke et al. (2000)
Indirect costs calculation method	Human Capital Approach (HCA)	HCA	-	HCA and Friction Costs Method (FCM)
Mean age, years	45.0 (range 16.3 - 85.6)	39.9 (range 18.8 - 75.3)	Canada: 43.3 (SD 13.8) US: 39.0 (SD 11.9) UK: 40.7 (SD 12.1)	41 (SD 13)
Female, %	88	94	Canada: 91%; US: 95%; UK: 95%	100%
Mean disease duration, year	13.5 (range 0.1 - 40.6)	10.5 (range 1-33.5)	Canada: 10.2 (SD 7.4) US: 8.6 (SD 6.2) UK: 10.0 (SD 7.1)	9.6 (SD 6.9)
Employed, %	44	54.3% (at study entry) and 52% (at 6 months)	-	48%
Annual sick leave, % or duration	First 6 months: average 13 days for full-time employees. Second 6 months: average 16 days for full-time employees.	63.1% and average 10.5 days at study entry; 55.5% and average 8.2 days at 6 months for employed patients	-	-
Hospitalization, %	First 6 months: 18% Second 6 months: 15%	27% at study entry and 17% at 6 months	-	-
Duration of hospitalization, days	First 6 months: average 9.5 days for those hospitalized. Second 6 months: average 18 days for those hospitalized	Average 8 and 9 days at study entry and at 6 months respectively	-	-

	Clarke et al. (1993)	Sutcliffe et al. (2001)	Clarke et al. (1999)	Clarke et al. (2000)
Largest contributor to annual direct costs (%)	1989 costs: Hospitalization (36%) 1990 costs: Hospitalization (56%)	Hospitalization (38%)	Canada: hospitalization (40%) US: hospitalization (26%) UK: hospitalization (39%)	-
Mean annual direct costs (2006 USD)	1989 costs: 7,397 1990 costs: 9,067	5,592	Canada: 5,629 US: 5,415 UK: 5,158	-
Mean annual indirect costs (2006 USD)	1989 costs: 8,685 1990 costs: 9,153	11,340	-	1,517 - 24,075
Predictors for high direct costs	Impaired physical function, high serum creatinine.	Young age, high education level, high disease activity, more disease damage, impaired physical function.	-	-
Predictors for high indirect costs	Low level of global well-being, impaired physical function, low level of social support, high education level and unemployment.	High education level, high disease activity, impaired physical function.	-	-

Appendix 1 Major findings of cost-of-illness studies in systemic lupus erythematosus *(Continued)*

	Clarke et al. (2004)	Panopalis et al.(2007)	Huscher et al. (2006)	Panopalis et al. (2008)
Country	Canada, UK and US	Canada, UK and US	Germany	US
No. of subjects	Canada: 231; US: 269; UK: 215. Total: 715	Canada: 231; US: 269; UK: 215. Total: 715	844	812
Period of recruitment	June 1995 to February 1998	June 1995 to February 1998	2002	September 2002 to December 2003
Study design	Prospective (4-year)	Prospective (4-year)	Cross-sectional	Cross-sectional
Recall period	Preceding 6 months	Preceding 6 months	Preceding 4 months for visits to doctors and out-of-pocket expenditures; preceding 12 months for other data	Preceding 12 months
Framework of direct costs	Physician visits, diagnostic tests, medication (and dialysis), aids devices, emergency room visits, outpatient surgery, hospitalization (acute and non-acute care).	-	Physician visits, medication, non-medication treatments, surgery, imaging tests, hospitalization (acute and rehabilitation), patients' out-of-pocket expenses.	Hospitalization (acute and long-term care), physician visits, emergency room visits, outpatient surgical procedures, medication, renal dialysis.
Framework of indirect costs	-	Productivity loss due to limitations of 1) labor market activity (lost work hour, extra work hour if SLE-free, unpaid labor - domestic and volunteer work); 2) non-labor market activity (household work).	Productivity loss due to sick leave and early retirement.	Restricted to patients within working age. Productivity costs associated with work productivity changes, determined by subtracting annual income at the time of study from annual income at the time of diagnosis.

	Clarke et al. (2004)	Panopalis et al.(2007)	Huscher et al. (2006)	Panopalis et al. (2008)
Indirect costs calculation method	-	HCA and FCM	HCA and FCM	HCA
Mean age, years	Canada: 42.4 (95% CI 40.3-44.4) US: 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) US: 39.1 (95% CI 37.4-40.8) UK: 40.0 (95% CI 38.2-41.7)	42	48.2 (SD 12.8)
Female, %	-	Canada: 93.5% US: 95.1% UK: 94.8%	90%	92.6%
Mean disease duration, year	Canada: 9.9 (95% CI 8.7-11.1) US: 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) US: 8.6 (95% CI 7.6-9.6) UK: 10.0 (95% CI 9.0-11.1)	-	13.7 (SD 8.5)
Employed, %	-	Canada: 48.7% US: 45.3% UK: 52.6%	55	48.7%
Annual sick leave, % or duration	-	Mean (95% CI) days: Canada: 9.1 (6.2 - 12.0) US: 7.0 (4.5 - 9.5) UK: 8.1 (6.1 - 10.0)	30%, average duration 64.8 days.	-

	Clarke et al. (2004)	Panopalis et al.(2007)	Huscher et al. (2006)	Panopalis et al. (2008)
Hospitalization, %	-	-	20%	21%
Duration of hospitalization, days	-	-	Average duration 21.1 days	-
Largest contributor to annual direct costs (%)	Canada: medications (33%) US: medications (30%) UK: hospitalization (35%)	-	Hospitalization (48%)	Acute care hospitalization (48.7%)
Mean annual direct costs (2006 USD)	Canada: 3,812 US: 4,872 UK: 4,247	-	4,269	13,493
Mean annual indirect costs (2006 USD)	-	HCA: Canada: 10,611; US: 14,918, UK: 12,221; FCM: Canada: 1,517; US: 1,116 UK: 1,202.	HCA: 19,280 FCM: 8,720	9,241
Predictors for high direct costs	-	-	High disease activity, poor function, short disease duration	Young age, high disease activity, long disease duration, poor physical health, poor mental health
Predictors for high indirect costs	-	-	Poor function, long disease duration, old age	Old age, high disease activity, poor physical health, poor mental health

* Costs were adjusted for inflation using consumer price index (derived from Statistic Department of each country), in 2006 US dollars (USD). UK = United Kingdom, US = United States; CI = confidence interval; SD = standard deviation; HCA = human capital approach; FCM = friction costs method.

† Results of 1990 costs were based on 155 patients.

Appendix 2 Source of unit price used in the study

Item	Source	Remark
Visit to healthcare provider	The gazetted rate issued by the Hospital Authority (supplement No. 4 to Gazette No. 13/2003)	Hong Kong Dollar (HKD) 215 - 700 per visit
Pathology examinations (blood tests, urine tests)	Department of Pathology, Prince of Wales Hospital	Details about list of charges available on intranet homepage of Prince of Wales Hospital
Radiologic examinations	Department of Radiology, Prince of Wales Hospital	HKD 190 – 3,100 per examination per region. Details about list of charges available upon request to Department of Radiology
Inpatient care	The gazetted rate issued by the Hospital Authority (supplement No. 4 to Gazette No. 13/2003)	HKD 3,300 per day (served as professional charge in our study)
Emergency room visit	The gazetted rate issued by the Hospital Authority (supplement No. 4 to Gazette No. 13/2003)	HKD 570 per visit
Medications	Department of Pharmacy, Prince of Wales Hospital	
Surgical procedure	The gazetted rate issued by the Hospital Authority (supplement No. 4 to Gazette No. 13/2003)	Charges depend on the scale of procedures.

CHAPTER 12 ORIGINAL PUBLICATIONS

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Concise Report

Systemic lupus erythematosus with neuropsychiatric manifestation incurs high disease costs: a cost-of-illness study in Hong Kong

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Objective. To determine the direct and indirect costs of SLE in Hong Kong, and to ascertain the relationship between neuropsychiatric SLE (NPSLE) and disease costs.

Methods. A retrospective, cross-sectional, non-randomized cost-of-illness study was performed in a tertiary rheumatology specialty centre in Hong Kong. Participants completed questionnaires on sociodemographics, employment status and out-of-pocket expenses. Healthcare resources consumption was recorded by chart review. The occurrence of NPSLE since onset of SLE was determined using the 1999 ACR nomenclature and standard definitions. Mann–Whitney U-test was used to compare disease costs between patients with and without NPSLE. Multiple linear regression was used to determine the predictors of the costs.

Results. Three hundred and six Chinese patients were recruited, with a mean age of 41 years and mean disease duration of 9.6 years. A total of 108 NPSLE events were recorded by 83 patients. The most common manifestations were seizure and cardiovascular disease. The mean annual total costs were USD 13 307 per patient. The direct costs dominated the total costs, and the costs of inpatient care contributed 52% of the direct costs. Patients with NPSLE incurred significantly higher direct and indirect costs compared with those without NPSLE. The number of NPSLE events was an independent explanatory variable associated with both direct and indirect costs.

Conclusion. The economic impact of SLE in Hong Kong is considerable and patients with NPSLE incur higher disease costs compared with those without NPSLE. Improvement in prevention of end-organ damage, especially neuropsychiatric manifestation, may reduce costs of SLE patients.

KEY WORDS: Systemic lupus erythematosus, Neuropsychiatric lupus, Cost of illness.

Introduction

SLE is a multi-factorial autoimmune disease that primarily affects young women. The patients may suffer frequent disease activity exacerbations and the consequently accumulated organ damage [1–3]. CNS is one of the most commonly involved organs in SLE. Clinical features of neuropsychiatric SLE (NPSLE) are diverse and heterogeneous, including both central and peripheral nervous systems [4]. NPSLE has been identified as a poor prognostic indicator and it is associated with poor quality of life [5–7]. High hospitalization rate and high frequency of disability in NPSLE patients has been shown previously [8, 9]. Despite the magnitude of the condition, in contrast to other rheumatic diseases, studies evaluating the economic impact of SLE are scanty [10–13]. None of the studies investigates the relationship between NPSLE and disease costs and no data are available regarding the economic impact of Chinese patients with SLE. We performed a retrospective, non-randomized cost-of-illness study from 2006 to 2007 in a tertiary rheumatology specialty centre in Hong Kong on Chinese patients with SLE. The study identified the direct, indirect and total costs of patients with SLE in a societal perspective. We also ascertained the relationship between NPSLE and the disease costs.

Methods

Patients and procedures

It was a retrospective non-randomized survey. Three hundred and six consecutive Chinese patients with an SLE diagnosis according to the 1997 ACR revised criteria for the classification of SLE [14] were recruited between January 2006 and August 2007 from the Rheumatology Clinic of the Prince of Wales Hospital in Hong Kong. Patients who were not capable of responding to a questionnaire (e.g. presence of dementia) were excluded. The Ethics Committee of the Chinese University of Hong Kong approved this study, and all patients provided written informed consent.

After informed consent, a questionnaire was administered by a trained interviewer. The questionnaire consisted of information on sociodemographics, employment status, out-of-pocket expenses and non-healthcare facilities utilization. All participants also underwent examination by their treating rheumatologists. Disease activity and damage was assessed using the SLEDAI [15] and the SLICC/ACR Damage Index (SDI) [16, 17], respectively. A modified damage index (modified-SDI), which excluded the neuropsychiatric (NP) domain, was used to indicate disease damage other than NP.

After the interview, patients' medical records were reviewed by the attending rheumatologists to retrospectively record the total number of NPSLE events since the onset of SLE. The occurrence of NP manifestation was determined using the 1999 ACR nomenclature and standard definitions for NPSLE [4].

Costs assessment

Hong Kong's healthcare system is dual partite, with government hospitals and private hospitals [18, 19]. Government hospitals deliver most of the medical services with a market share of 94% [19]. They are heavily subsidized and available to all residents with no private means or medical insurance required. Private hospitals in Hong Kong are relatively small in number, size and custom. Charges of private hospitals vary considerably [18]. In Hong Kong, patients with chronic diseases mainly rely on government hospitals while utilization of private hospital services represents a relatively small percentage [20, 21]. In this study, we recorded both government and private medical services by different methods. Expenses on private hospital facilities were reported by patients as a part of patients' out-of-pocket expenses. Utilization of

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government hospital services was derived by chart review. We used average per diem cost estimated by the government authority [21].

Costs were determined from the societal perspective, which meant all costs were relevant. Direct costs represented all the health resources utilization delivered to the patients because of SLE in the previous 12 months, including direct healthcare resources as well as non-healthcare resources. Direct healthcare resources comprised: (i) all visits to healthcare providers, including general practitioners, specialists, physiotherapists, occupational therapists, psychologists and other healthcare providers; (ii) all technical examinations including blood tests, urine tests, imaging tests such as conventional radiographic examinations, CT scan, MRI, ultrasound imaging; (iii) all drugs taken; (iv) emergency room visits; (v) costs of inpatient care (including rehabilitation hospitalization); and (vi) patients' out-of-pocket expenses for health products, non-traditional therapies (such as hydrotherapy, acupuncture and massage), aid devices and private hospital facilities. Direct non-healthcare resources comprised: (i) transportation fee to the healthcare providers; (ii) private household help; and (iii) adaptation to houses.

Indirect costs represented the productivity loss due to SLE. Human capital approach (HCA) was used to calculate productivity loss [22]. For those who were employed, indirect costs were the product of the days of annual sick leave and the mean sex- and job-specific monthly salary of full-time workers in Hong Kong. For those who were unemployed due to SLE, the lost wages based on the mean sex- and job-specific monthly salary of the previous job was calculated as the productivity loss. For those who were housewives or non-SLE-related unemployed, productivity loss was calculated as the product of the number of days off household tasks or daily activity limitation and the sex-specific average annual salary of full-time workers in Hong Kong. Wages were derived from *Wage and Payroll Statistics, Census and Statistic Department of Hong Kong*.

Statistical analyses

Statistical analyses were performed using The Statistics Package for Social Sciences (SPSS for Windows, version 13.0, 2006, SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± S.D. for normally distributed data. For non-normally distributed data, median and range are expressed as well. Mann–Whitney U-test was used to compare disease costs between patients with and without NPSLE. Kruskal–Wallis test was used to test for differences in clinical features or costs among patients with seizure/cerebrovascular diseases (CVD)/headache. When a Kruskal–Wallis test revealed significant results, Mann–Whitney U-test by Bonferroni adjustment was used for multiple comparisons (for triple comparisons, $P < 0.01$ was considered significant).

Univariate correlation and multiple linear regression analyses were used to determine the predictors of direct costs and indirect costs. Because of the skewed nature of costs data, logarithm (base = 10) transformed data were used. The possible predictors included gender, age, disease duration, educational level, SLEDAI scores and the number of NPSLE events since disease onset. Because the number of NPSLE events was included into the regression analyses, we used a modified-SDI score (excluding NP domain of SDI) as a possible predictor.

Results

Sociodemographics, clinical and NPSLE profile

Three hundred and six patients were recruited, with a male to female ratio of 1:25, a mean (S.D.) age of 41 (11) years and a mean (S.D.) disease duration of 9.6 (6.9) years (median 8.7, range 0.1–37). At the time of the assessment, 107 (35%) patients had inactive disease with a SLEDAI of 0. The remaining 199 patients were with a mean (S.D.) SLEDAI of 3.77 (2.69) (median 3, range 1–16). One hundred and ninety-four (63%) patients had a modified-SDI of 0. The remaining 112 patients had a mean (S.D.) modified-SDI of 1.35 (1.04) (median 1, range 1–6).

Eighty-three (26.8%) patients had had a total of 108 NPSLE events. Most patients had had one NPSLE event (64/83, 77%). Fifteen patients had had two NPSLE events and four patients had had more than two. The last NP event occurred within the past 3 years and 1 year in 29/83 (35%) and 14/83 (17%) of these patients, respectively. The most common manifestations were seizures (25 episodes), CVD (24 episodes), headache (19 episodes), mood disorder (11 episodes) and psychosis (seven episodes).

Healthcare resources and costs

During the preceding 1 year, the mean ± S.D. visits to healthcare providers was 7.25 ± 4.27. Visits to rheumatologists were the most frequently seen, followed by ophthalmologists and general practitioners. Ninety-seven percent of the patients were on medications, of which 73% were on prednisone, 55% on antimalarial drugs and 31% on immunosuppressants, including AZA ($n = 68$, 71%), cyclophosphamide ($n = 11$, 11%), mycophenolate mofetil ($n = 6$, 6%), CSA ($n = 9$, 9%), LEF ($n = 8$, 8%) and MTX ($n = 3$, 3%).

The number of technical examinations per patient-year varied from 5 to 159 with a median of 27.5 (mean 35.8 ± 24.5). All the participants reported blood tests (mean 30.4 ± 16.8, median 25, range 5–108) and 44.8% of patients needed urine tests (mean 10.9 ± 10.8, median 6, range 1–51). Eighty-five patients (27.8%) needed image tests, but only 9% of patients had at least one of ultrasound, CT or MRI investigation.

Eighty-three (27%) patients had emergency room visits, with a mean number of 1.6 ± 1.1 (median 1, range 1–6). A total number of 197 inpatient care days were recorded by 82 patients (27%) with a mean duration of 21 ± 40 days (median 7.5, range 1–260). The main cause of hospitalization was clinically active SLE (40%), followed by infection (14%, including HPV infection). Five patients needed rehabilitation hospitalization with a mean duration of 42.8 ± 34.2 days (median 42, range 7–82).

Fifty-three percent of the patients recorded out-of-pocket expenses, mainly on health products (110/306, 36%), non-traditional therapy (58/306, 19%) and private doctor visits (52/306, 17%). Seven percent of the patients used self-paid aid devices, mostly on crutch or wheelchair. Expenses on household help and alteration of houses were reported by only 12 (4%) and 5 (2%) patients, respectively.

More than half of the patients were unemployed. Among those who were still working, 85% needed to take sick leave with a mean duration of 14 ± 32 days (median 6 days). For those who were unemployed, the majority indicated that they were work disabled because of SLE (44%), 85% of which had been unemployed for >12 months. For those who were unemployed but not due to SLE (26%) and homemakers (25%), days off from daily activities or household work due to SLE were reported by 24 and 30% patients, respectively, both with a median duration of 0 days.

We determined the average total costs of the 306 patients with SLE to the society as USD 13 307 per patient-year (Table 1). The direct costs dominated the total costs (62%), and the costs of inpatient care contributed 52% of the direct costs. These were followed by the costs of technical examinations (16%), patients' out-of-pocket expenses (14%) and costs of healthcare provider visits (10%). The costs of drugs and emergency room visits represented a relatively small percentage.

Annual costs and NPSLE

There is no significant difference in age, disease duration, employment rate, SLEDAI score and SDI score between patients with and without NPSLE (Table 2). Patients with and without NPSLE had a similar number of visits to healthcare providers and

TABLE 1. Annual costs for patients with SLE (expressed in 2006 USD, 1 USD = 5.527 HKD[a])

	Mean (s.d.)	Percentage of direct costs	Percentage of total costs	Median	Range
Visits to healthcare provider	848 (544)	0.10	0.06	670	127–4472
Technical examination	1302 (805)	0.16	0.10	1070	194–4793
Blood test	1227 (737)			994	194–4793
Imaging	74 (216)			0	0–1853
Drugs	330 (495)	0.04	0.02	171	0–5392
Emergency room visits	47 (99)	0.01	0.00	0	0–628
Inpatient care	4312 (16474)	0.52	0.32	0	0–170961
Patients' out-of-pocket expenses	1144 (2166)	0.14	0.09	72	0–14981
Health products	687 (1586)			0	0–13027
Non-traditional therapy	310 (958)			0	0–8685
Aid devices	22 (312)			0	0–5428
Private doctor visit	125 (507)			0	0–5428
All direct healthcare costs	7983 (16724)	0.97	0.60	3589	640–172408
Transportation	81 (155)			22	0–1737
Household help	154 (971)			0	0–7968
Alteration of house	13 (135)			0	0–1809
All direct non-healthcare costs	248 (989)	0.03	0.02	25	0–8185
Direct costs	8230 (16785)		0.62	3697	646–172463
Due to sick leave	1229 (3068)			511	77–23448
Due to SLE-related unemployment	18613 (8320)			15314	870–34261
Due to days off from household task or daily activities limitation	4315 (5743)			1187	79–14441
Indirect costs	5077 (8890)		0.38	332	0–34261
Total cost	13307 (20197)			6300	646–195910

[a]Purchasing power parities conversion factor of 2006 was used and conversion factor of USD is 1 : 1 (data from United Nation Statistics Division).

TABLE 2. Disease profile, healthcare resource use, direct and indirect costs for patients with and without NPSLE (costs were expressed in 2006 USD, 1 USD = 5.527 HKD[a])

	0 NPSLE (n = 223)	⩾1 NPSLE (n = 83)	With seizure[b] (n = 12)	With CVD[b] (n = 11)	With headache[b] (n = 15)
Age[b], mean ± s.d., years	42 ± 12	40 ± 11	38 ± 10	38 ± 10	37 ± 11
Female, %	97	94	83	100	100
Employed, %	48	42	50	46	60
Disease duration[b], mean ± s.d., years	9.6 ± 6.9	9.7 ± 6.9	9.4 ± 6.3	10.3 ± 9.2	7.6 ± 4.4
SLEDAI score					
Mean ± s.d.	2.5 ± 3.0	2.3 ± 2.3	2.8 ± 2.7	2.8 ± 3.5	2.3 ± 1.7
Median (range)	2 (0–16)	2 (0–10)	2 (0–8)	3 (0–9)	2 (0–5)
SDI score					
Mean ± s.d.	0.6 ± 0.9	1.0 ± 1.2	0.9 ± 1.2	2.2* ± 1.9	0.3 ± 0.6
Median (range)	0 (0–5)	1 (0–7)	0 (0–3)	2 (0–7)	0 (0–2)
No. of healthcare provider visits[b], mean ± s.d.	7 ± 5	8 ± 5	6 ± 3	10 ± 10	7 ± 3
No. of emergency room visits[b], mean ± s.d.	0.4 ± 1.0	0.4 ± 0.7	0.4 ± 0.5	0.6 ± 0.5	0.3 ± 0.8
Inpatient care, %	25	33	42	64	27
Duration of inpatient care, days					
Mean ± s.d.	3.9 ± 16.5	10.4 ± 33.4	26.2 ± 742	16.9 ± 25.5	1.9 ± 3.6
Median (range)	0 (0–199)	0 (0–260)	0 (0–260)	5 (0–77)	0 (0–11)
Annual costs of visits to healthcare provider					
Mean ± s.d.	823 ± 511	915 ± 624	647 ± 262	1300 ± 1231	801 ± 3820
Median (range)	633 (127–3415)	712 (253–4472)	628 (336–1133)	970 (253–4472)	673 (253–1646)
Annual costs of technical examination					
Mean ± s.d.	1262 ± 774	1408 ± 877	1393 ± 529	1606 ± 1050	1564 ± 1125
Median (range)	1064 (194–4793)	1136 (344–4643)	1406 (581–2236)	1390 (507–3591)	1002 (628–3874)
Annual costs of drugs					
Mean ± s.d.	309 ± 512	388# ± 443	502 ± 464	438 ± 350	177 ± 184
Median (range)	165 (0–5392)	238 (0–2743)	368 (11–1383)	239 (17–956)	117 (0–520)
Annual costs of emergency room visits					
Mean ± s.d.	49 ± 108	43 ± 73	43 ± 53	58 ± 54	35 ± 85
Median (range)	0 (0–628)	0 (0–314)	0 (0–103)	103 (0–103)	0 (0–309)
Annual costs of inpatient care					
Mean ± s.d.	3012 ± 13023	7804 ± 23094	17741 ± 48758	12846 ± 16696	1535 ± 2935
Median (range)	0 (0–157635)	0 (0–170961)	0 (0–170961)	3094 (0–52985)	0 (0–8562)
Annual costs of patients out-of-pocket expenses					
Mean ± s.d.	1072 ± 2053	1338 ± 2447	868 ± 1556	3128 ± 4696	824 ± 1319
Median (range)	9 (0–13027)	217 (0–14981)	270 (0–5428)	1954 (0–14981)	127 (0–4342)
Annual costs of direct non-healthcare costs					
Mean ± s.d.	184 ± 698	420 ± 1508	725 ± 2350	345* ± 571	41 ± 49
Median (range)	22 (0–7614)	33 (0–8185)	22 (0–8185)	181 (0–2026)	14 (0–136)
Annual total direct costs					
Mean ± s.d.	6710 ± 13428	12316# ± 23165	21 1920 ± 48025	19719 ± 16866	4977 ± 4851
Median (range)	3357 (646–158218)	5032 (906–172463)	4905 (1167–172463)	17771* (3688–61776)	2957 (906–14352)
Annual total indirect costs					
Mean ± s.d.	4414 ± 8449	6859# ± 9813	6640 ± 11371	5332 ± 8687	2723 ± 6279
Median (range)	276 (0–34261)	640 (0–32834)	446 (0–29219)	640 (0–23294)	511 (0–22706)
Annual total cost					
Mean ± s.d.	11124 ± 16205	19174# ± 27540	28560 ± 54371	25051 ± 22752	7715 ± 7113
Median (range)	5113 (646–158218)	13003 (906–195910)	5992 (1167–195910)	19561* (3688–85070)	4353 (906–24391)

[a]Purchasing power parities conversion factor of 2006 was used and conversion factor of USD is 1 : 1 (data from United Nation Statistics Division). [b]Including patients with only seizure/CVD/headache events. *Comparison between patients with CVD and headache, $P < 0.005$ using Mann–Whitney U-test ($P < 0.01$ was considered significant after adjustment of multiple comparisons). #$P < 0.05$ using Mann–Whitney U-test.

TABLE 3. Univariate analyses and multivariate linear regression analyses of cost predictors

	Univariate analyses		Multivariate regression analyses			
	Coeff.	*P*-value	Coeff.	95% CI	*P*-value	R^2
Direct costs						
Female gender	−0.053	0.958	0.410		0.448	
Age, years	−0.144	**0.012**[a]	−0.073		0.200	
Education level	0.072	0.212	0.055		0.314	
Disease duration	−0.231	**<0.0005**	−0.017	(−) 0.024, (−) 0.010	**<0.0001**	0.15
SLEDAI score	0.153	**0.007**	0.018	(−) 0.002, 0.034	**0.027**	
Modified-SDI score	0.043	0.453	0.106	0.056, 0.157	**<0.0001**	
Number of NPSLE	0.187	**0.001**	0.134	0.066, 0.202	**<0.0005**	
Indirect costs						
Female gender	−2.197	**0.028**	−1.332	(−) 2.520, (−) 0.143	**0.028**	
Age, years	−0.027	0.643	−0.006		0.626	
Education level	0	1	0.015		0.646	
Disease duration	−0.020	0.734	0.008		0.667	0.04
SLEDAI score	0.102	0.076	0.045		0.304	
Modified-SDI score	0.058	0.308	0.006		0.965	
Number of NPSLE	0.144	**0.012**	0.412	0.066, 0.758	**0.020**	

[a]Numbers in bold represent $P < 0.05$.

emergency rooms. Although patients with NPSLE had a longer inpatient care duration, this did not reach a significant level ($P = 0.074$). Annual direct costs were nearly twice of patients with NPSLE compared with those without NPSLE ($P < 0.001$). Most of the direct costs components did not differ between the two groups. However, patients with NPSLE incurred significant higher annual drug costs ($P = 0.020$), mostly due to the higher percentage of them using neuropsychiatric drugs (35% compared with 10% of those without NPSLE, $P < 0.0005$). Patients with NPSLE also incurred higher annual indirect costs ($P = 0.024$). However, there was no significant different in unemployment rate, duration of annual sick leave/unemployment/days off from household task or daily activities limitation between the two groups.

Patients with only seizure ($n = 12$)/CVD ($n = 11$)/headache ($n = 15$) were then selected for comparison. Compared with those with headache, patients with CVD had more disease damage, higher annual direct non-healthcare costs, higher direct costs and total costs. However, the clinical features and costs did not differ between patients with seizure and CVD or between patients with seizure and headache.

Multivariate regression analyses

The results of multiple regression analyses for annual direct and indirect costs are shown in Table 3. Regression analyses of direct costs showed that disease damage (other than NP damage), disease activity and NPSLE events were independent explanatory variables positively associated with increased direct costs, whereas disease duration was negatively associated with increased direct costs. The independent explanatory variables associated with increased indirect costs was the number of NPSLE events and gender.

Discussion

Our study is the first full economic evaluation on Chinese patients with SLE, and also the first study to determine how NPSLE can influence disease costs. Our results show that SLE has a substantial economic impact on the patients and government in Hong Kong, and the number of NPSLE patients is an independent costs predictor of both direct and indirect costs. Such information will be important in view of the improvement in the survival and prolongation of life of the condition and limited healthcare resources.

The assessment of NPSLE in our study was standard and comprehensive, using the 1999 ACR nomenclature and standard definitions for NPSLE, which includes a broad range from subtle abnormalities of neurocognitive functions to overt manifestations. Previous studies have shown that NPSLE is associated with a high mortality rate and carries a significant physical and psychological burden in patients with SLE [23–25]. Our results show that NPSLE also incurs considerable economic burden and the number of NPSLE patients is an independent explanatory variable associated with increased direct and indirect costs. Patients with NPSLE need more technical examinations for accurate diagnosis and more aggressive management strategies, which may explain the high direct costs. Given the potential for NP involvement to affect psychosocial function [26, 27], which refers to the emotional, behavioural and social aspects of a person's functioning, it is possible that it is an important mechanism for its influence on indirect costs of SLE. We also compared costs between patients with seizure, CVD and headache, which were the most common NPSLE events in our cohort. Our results showed that patients with CVD generated higher direct costs compared with those with headache. However, such comparison may be of limited value due to the relatively small number of patients with seizure/CVD/headache.

The overall prevalence of NPSLE in our cohort (27%) is lower than that in Caucasians (37–91%) [24, 28–31]. The most common manifestations in our cohort are seizure disorder and CVD, in contrast to the series in Caucasians in which cognitive dysfunction, headache and mood disorder are among the most common manifestations. Besides genetic, immunological and geographic differences, the retrospective assessment in our study may also lead to an underestimation of the number of NPSLE patients. Secondly, formal neuropsychological testing for subtle cognitive dysfunction is not our routine practice at clinic visits because of cumbersomeness of these tests, which may explain the relatively low prevalence of cognitive dysfunction in our cohort. However, the prevalence and pattern of NPSLE of our cohort is similar to previous studies on Chinese cohorts (19–23%) [32, 33]. Our study shows that patients with NPSLE incur both higher annual direct and indirect costs. Unlike lupus nephritis, much less is known about the ideal treatment of NPSLE and the current therapeutic approach is still empirical and based on clinical experience [34]. Our data provide suggestion that improvements in the management of NPSLE may avoid or delay the high costs associated with NP manifestation, and more attention should be drawn to this area.

We determined the average total cost of patients with SLE to the Hong Kong society as USD 13 307 per patient-year. There are no previous cost-of-illness studies of SLE in Hong Kong. Direct comparison of our results with those of other studies in other countries would be difficult because of different years of evaluation, the cost matrix, and the methods of calculation and the pattern of practice. Consistent with previous studies, inpatient care costs represent the largest proportion of direct costs.

The costs of drugs were relatively low in our cohort—only 4% of direct costs. But we may have underestimated the costs of medication since the unit price issued by the government may not reflect the true costs or market prices of the drugs. Besides, differences in the healthcare system may affect the summary costs estimation. Not all the drugs were included into the government hospital's drug formulary and subsidized by the government in Hong Kong. New and high-cost drugs (e.g. mycophenolate mofetil) are not within the reimbursed system and patients have to pay for these drugs by themselves, which may also contribute to the low drug costs in our cohort.

There are limitations to this study. First, the retrospective design may affect the accuracy of the data, particularly that the recall period is long (12 months). Secondly, patients with end-staged renal disease or on dialysis mainly attended by nephrologists are excluded from the cohort. Thirdly, if affordable, some patients may be treated by private sectors through the whole disease course. However, under the well-established public healthcare system of Hong Kong, we believe that this is a minority and should not influence the results. Furthermore, because patients were recruited from the outpatient clinic, most of the participants were with mild disease activity or damage, and we could not assess the costs of patients with active NPSLE. Finally, because of international differences in patients' sociodemographics, treatment practices and healthcare systems, our results may not be generalizable to other populations of SLE.

In conclusion, we performed the first cost-of-illness assessment of Chinese SLE in Hong Kong. The results of our study show that SLE has considerable socioeconomic impact on the society and the individual. Patients with NPSLE incur significantly higher annual direct and indirect costs compared with those without NPSLE. Disease activity, organ damage and the number of NPSLE events are independent explanatory variables associated with increased disease costs. Effective control of disease activity and prevention of end-organ damage, especially NP manifestation, may reduce costs in patients with SLE.

Rheumatology key messages

- SLE has considerable socioeconomic impact on the society and the individual in Hong Kong.
- Patients with NPSLE incur higher disease costs compared with those without NPSLE.

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ORIGINAL ARTICLE

The Impact of Flare on Disease Costs of Patients With Systemic Lupus Erythematosus

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Objective. **To evaluate both direct and indirect costs of systemic lupus erythematosus (SLE) patients with and without flares from a societal perspective, and to investigate the impact of the severity and clinical manifestations of flares on direct/indirect costs.**

Methods. **A retrospective cost-of-illness study was performed on 306 SLE patients. Participants completed questionnaires on sociodemographics, employment status, and out-of-pocket expenses. Health resources consumption was recorded by chart review and patient self-reported questionnaire. The total number of flares and involved organs during the preceding 12 months were recorded. Multiple linear regression was performed to determine the cost predictors.**

Results. **Patients with flares were younger, had shorter disease duration, and had higher disease activity at the time of the assessment. The overall incidence of lupus flares was 0.24 episodes per patient-year. Patients with flares used more health care resources and incurred significantly higher annual direct and indirect costs. The mean total costs per patient-year were 2-fold higher for patients with flares ($22,580 versus $10,870 [2006 US dollars]; $P < 0.0005$). Multiple regression analysis showed that the number of flares was an independent explanatory variable associated with increased direct costs. Patients with multiorgan flares or renal/neuropsychiatric flares incurred higher direct costs compared with those with single-organ flares or with other organ flares.**

Conclusion. **Patients with flares incur higher direct and indirect costs compared with those without flares. Major organ flares incur higher disease costs than other organ flares. Treatments that effectively control disease activity and prevent flares, especially major organ flares, may reduce the high costs associated with flare in SLE.**

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, multisystem, autoimmune disease characterized by periods of fluctuating disease activity. The British Isles Lupus Activity Group (BILAG) index (1) and the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (2) are 2 disease activity indices primarily used in the clinical studies of SLE. The assessment of lupus activity encompasses the concept of a flare, which is an increase in disease activity over a defined period (3). However, there is no general consensus on the definition of flare, although various tools have been used (4–7). Using an increase of 1.0 cm on a 3-cm visual analog scale of the physician's global assessment (PGA) of disease activity as a gold standard of flare, the corresponding cutoff is 3 points or more on the SELENA–SLEDAI and 4 points or more on the BILAG (8). Since indices alone may not capture overall changes in activity, SELENA trial investigators developed the SELENA flare tool, which incorporates 2 indices of disease activity (PGA and SELENA–SLEDAI), clinical manifestations, and treatment to define both mild/moderate and severe flares (2).

Flare is an important outcome variable and has been shown to be a major cause of admission (9). Disease activity and toxicity of the consequent treatments result in irreversible damage that is associated with an increased risk of morbidity and mortality (10). Stoll et al concluded that death and the long-term accumulation of damage were strongly predicted by a high total disease activity over time, and especially associated with the number of BILAG A (most active disease) flares (11). Contrary to the so-called minor organ flares, i.e., constitutional, musculoskeletal, and mucocutaneous (4), major organ flares such as renal or neuropsychiatric (NP) flares have been shown to be associated with poor prognosis. Renal flares were significantly associated with the risk of doubling plasma creatinine level and death or dialysis (12). Ward et al concluded that the occurrence of seizures increased the risk of death in

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patients with SLE (13). Results from Hanly et al showed that NP disease was related to more frequent use of corticosteroids and immunosuppressants (14).

Previous studies on the economic impact of SLE focus on the relationship between disease activity/damage and costs. Higher disease activity/damage has been shown to be associated with both higher direct and indirect costs (15–18). However, to our knowledge, no study has focused on the relationship between costs and flares. Whether the severity or specific clinical manifestations of flares would influence disease costs has not been studied.

In the current study, we evaluated both direct and indirect costs of SLE patients with and without flares from a societal perspective. We also investigated the impact of the severity and clinical manifestations of flares on direct/indirect costs. In view of the evidence that major organ flares are significantly related to poor prognosis, we selected 2 major organ flares, renal and NP flares, to find out whether major organ flares were more costly than other flares.

PATIENTS AND METHODS

Patients and procedures. A convenience sample of 306 Chinese patients with a diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) revised criteria (19), who had been followed at the Rheumatology Clinic of the Prince of Wales Hospital in Hong Kong, were recruited between January 2006 and August 2007. All of the participants were within working age (≥18 years; <65 years for men and <60 years for women) and were followed at the Prince of Wales Hospital at regular intervals (every 3 to 4 months) according to a standardized assessment protocol, including 1) disease activity assessment according to the SELENA–SLEDAI at each visit (20) and 2) yearly disease damage assessment according to the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (21). Patients who were not capable of responding to a questionnaire (e.g., presence of dementia) were excluded. The Ethics Committee of the Chinese University of Hong Kong approved this study, and all of the patients provided written informed consent.

A questionnaire including sociodemographics, employment outcomes, and patients' out-of-pocket expenses was administered by a trained interviewer. The same questionnaire had been used in a cost-of-illness study of patients with ankylosing spondylitis (22). Clinical and laboratory assessments were also performed in all of the subjects by their treating rheumatologists, including the SELENA–SLEDAI and the SDI. The SELENA–SLEDAI is a valid and reliable disease activity measure of SLE (20) that contains 24 descriptors in 9 organ systems, including clinical and laboratory measures. The total SELENA–SLEDAI score falls between 0 (no activity) and 105 (maximum activity). The SDI, a validated physician-rated index that consists of 41 items in 12 organ systems/domains, was used to measure accumulated damage (21). Damage was defined as any irreversible change occurring since the onset of SLE and presenting for at least 6 months. The total SDI scores range from 0 (no damage) to 49 (maximum damage).

Definitions of flare. Patients' medical records were then reviewed by an investigator (TYZ) to derive the total number and manifestations of flares during the preceding 12 months. A revised SELENA flare tool that excluded the component of PGA was used to define flares (2). Mild/moderate flares were defined as 1 or more of the following: 1) change in SELENA–SLEDAI score of >3 points but ≤12 points; 2) new/worse discoid lesions, photosensitivity, profundus, cutaneous vasculitis, bullous lupus, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, and/or fever (SLE); 3) increase in prednisone not to exceed 0.5 mg/kg/day; or 4) added nonsteroidal antiinflammatory drugs (NSAIDs) or hydroxychloroquine for SLE. Severe flares were defined as 1 or more of the following: 1) change in SELENA–SLEDAI score of >12 points; 2) new/worse NPSLE, vasculitis, nephritis, myositis, platelet count <60,000/mm^3, or anemia (hemoglobin level <7 mg/dl), which required either a doubling of or increase in prednisone dosage to >0.5 mg/kg/day; 3) increase in prednisone to >0.5 mg/kg/day; 4) new immunosuppressants for SLE activity; or 5) hospitalization for SLE.

The definitions of the individual organ flares are listed below. Renal flare was defined as 1 of the following (23,24): 1) a reproducible (2 samples at least 1 week apart) increase in 24-hour urine protein levels to >1 gm if the baseline value was <0.2 gm, to >2 gm if the baseline value was 0.2–1 gm, or to more than twice the baseline value if the baseline value was >1 gm; 2) a reproducible increase in serum creatinine level of >20% or at least 25 μmoles/liter, whichever was greater, accompanied by proteinuria (>1 gm/24 hours), hematuria (≥4 red blood cells [RBCs]/high-powered field [hpf]), and/or RBC casts; or 3) new, reproducible hematuria (≥10 RBCs/hpf) or an increase in hematuria by 2 grades compared with baseline, associated with >25% dysmorphic RBCs, exclusive of menses, accompanied by either a 0.8-gm increase in 24-hour urinary protein levels or new RBC casts.

NP flare was defined according to the case definition system for central nervous system lupus syndromes by the 1999 ACR nomenclature (25). This includes a detailed glossary and diagnostic guidelines for 19 NP syndromes, namely aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis, Guillain-Barré syndrome, autonomic neuropathy, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy.

Other clinical features of flares were grouped into the following organs/systems: musculoskeletal, mucocutaneous, hematologic, vasculitic, and serositis. Each organ/system flare was defined according to the definitions of the descriptors of the SELENA–SLEDAI instrument (2,20) (for details, see Supplemental Appendix A, available in the online version of this article at http://www3.interscience.wiley.com/journal/77005015/home). Flares with only serologic manifestations (increased anti–double-stranded DNA [anti-dsDNA] titer and depressed complement levels) without medical intervention were not included in the analyses.

Single-organ flares referred to flares involving only 1

Table 1. Baseline sociodemographics and clinical characteristics (ever) of patients with and without flares in the preceding year*

	Without flares (n = 244)	With flares (n = 62)	*P*	Entire group (n = 306)
Age, mean ± SD years	42.5 ± 11.4	36 ± 10	< 0.0005	41 ± 11
Women	236 (97)	58 (94)	0.271	294 (96)
Education level, mean ± SD years	10.1 ± 4.4	11.3 ± 3.5	0.115	10 ± 4
Disease duration, mean ± SD years	10.2 ± 7.0	7.4 ± 5.8	0.002	9.6 ± 6.9
SELENA–SLEDAI score, mean ± SD	2.15 ± 2.64	3.63 ± 3.20	< 0.0005	2.5 ± 2.8
SDI score, mean ± SD	0.73 ± 1.06	0.63 ± 1.07	0.279	0.71 ± 1.07
Organ manifestations				
Malar rash	107 (44)	26 (42)	0.786	133 (44)
Discoid lesion	27 (11)	13 (21)	0.039	40 (13)
Photosensitivity	77 (32)	20 (32)	0.916	97 (32)
Oral ulcer	73 (30)	21 (34)	0.547	94 (31)
Arthritis	192 (79)	43 (69)	0.12	235 (77)
Serositis	68 (28)	17 (27)	0.944	85 (28)
Renal disease	139 (57)	43 (69)	0.076	182 (60)
Neuropsychiatric disease	62 (25)	21 (34)	0.181	83 (27)
Hematologic	208 (85)	57 (92)	0.167	265 (87)
Leukopenia	124 (51)	36 (58)	0.308	160 (52)
Lymphopenia	161 (66)	38 (61)	0.489	199 (65)
Thrombocytopenia	70 (29)	21 (34)	0.425	91 (30)
Hemolytic anemia	19 (8)	6 (10)	0.627	25 (8)
Immunologic	230 (94)	60 (97)	0.428	290 (95)
Anti-dsDNA positive	179 (73)	53 (86)	0.047	232 (76)
Anti-Sm positive	47 (19)	19 (31)	0.052	66 (22)
Anti-Ro positive	134 (55)	36 (58)	0.656	170 (56)
Anti-La positive	50 (21)	7 (11)	0.097	57 (19)
ANA positive	241 (99)	60 (97)	0.801	301 (98)

* Values are the number (percentage) unless otherwise indicated. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; anti-dsDNA = anti–double-stranded DNA; ANA = antinuclear antibody.

organ/system, whereas multiorgan flares involved more than 1 organ/system (excluding immunologic manifestations).

Cost assessment. Hong Kong's health care system is largely administered by the government, which provides all residents with comprehensive health care from primary to tertiary care, including medications, investigations, ambulatory care, hospitalization, and operations. The public is charged nominal fees for medical treatment provided by the government. Government hospitals and clinics deliver most of the medical services, especially specialty clinics and inpatient care, with a market share of more than 90% (26,27). There are also private hospitals in Hong Kong that are run on a profit basis. They are relatively small in number, size, and custom, and used mainly by expatriates and wealthy Chinese. Fees and charges of private hospitals vary considerably (27). In Hong Kong, patients with chronic diseases mainly rely on government hospitals, whereas use of private hospital services represents a relatively small percentage (28). We recorded both government and private medical services by different methods. Use of private hospital facilities was reported by the patients. Use of government hospital services was derived by chart review. We used average per diem costs (both hospital and ambulatory services) estimated by the government authority as a measure of costs of both government and private medical services. The unit costs of some major services have been described elsewhere (22).

We assessed both direct and indirect costs from a societal perspective. Details relating to direct costs were collected for the previous 12 months, consisting of 1) all visits to health care providers, 2) all diagnostic examinations, 3) medications taken, 4) emergency room visits, 5) costs of inpatient care (including rehabilitation hospitalization), 6) costs of private hospital/clinic facilities (including costs of visits, medications, investigations, and hospitalizations), and 7) patients' out-of-pocket expenses for health products, nontraditional therapies (hydrotherapy, acupuncture, and massage), aid devices, transportation fee to the health care providers, private household helper, and adaptation to houses.

Indirect costs represented the productivity loss due to SLE, which included annual sick leave due to SLE, unemployment due to SLE, and days off from household work or daily activities due to SLE. In the mentioned questionnaire, participants were asked to indicate 1) sick leave taken in the preceding 12 months (for those who were still employed), 2) whether they were unemployed due to SLE and the duration of unemployment (for those who were unemployed), and 3) the number of days off from household work or daily activities due to SLE. The human

Table 2. Health care resources use with regard to patients with and without flares during the preceding year*

	Without flares (n = 244)	With flares (n = 62)	P
No. of visits to health care providers	6.9 ± 4.8 (5)	8.8 ± 4 (9)	< 0.0001
Rheumatologist	4.23 ± 2.19 (4)	6.37 ± 3.07 (5.5)	< 0.0001
Nephrologist	0.07 ± 0.57 (0)	0 (0)	0.257
Dermatologist	0.23 ± 0.93 (0)	0.23 ± 0.95 (0)	0.888
Ophthalmologist	0.61 ± 1.15 (0)	0.52 ± 0.74 (0)	0.906
Government general clinic†	0.46 ± 1.17 (0)	0.85 ± 2.02 (0)	0.053
Allied health	0.24 ± 1.93 (0)	0 (0)	0.149
Psychologist	0.03 ± 0.28 (0)	0.06 ± 0.4 (0)	0.271
Others	1 ± 2.22 (0)	0.74 ± 1.88 (0)	0.210
No. of diagnostic examinations			
Blood test	28 ± 45 (24)	40 ± 21 (35)	< 0.0001
Urine test	4 ± 8 (0)	9 ± 12 (3.5)	< 0.0001
Imaging tests‡	0.27 ± 0.74 (0)	1.31 ± 2.69 (0.5)	< 0.0001
Visit to the emergency room, %	21	52	< 0.0001
No. of visits to the emergency room	0.29 ± 0.7 (0)	1.03 ± 1.33 (1)	< 0.0001
Inpatient care, %	16	69	< 0.0001
Duration of inpatient care, days	3.1 ± 16 (0)	15.6 ± 37.3 (4.5)	< 0.0001

* Values are the mean ± SD (median) unless otherwise indicated.
† A standard clinic consists of a general outpatient department and a family health center, with or without a maternity ward.
‡ Including radiographs, ultrasounds, computed tomography scans, and magnetic resonance imaging.

capital approach, which uses wages as a proxy measure of the output of work time to value the individual's lost work hours, was used to calculate productivity loss (29). In our study, wages were derived from Wage and Payroll Statistics, Census and Statistic Department of Hong Kong.

Statistical analyses. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 13.0 (SPSS, Chicago, IL). Results are expressed as the mean ± SD for normally distributed data. For non–normally distributed data, the median and interquartile range (IQR) are expressed. A 2-sample *t*-test, chi-square test, or Mann-Whitney U test was used to compare sociodemographics, clinical features, health care resource use, and disease costs between patients with and without lupus flares. *P* values less than 0.05 were considered significant. A Kruskal-Wallis test was used to test for differences in costs between patients grouped by severity/organ involvement/manifestations of flare. When a Kruskal-Wallis test revealed significant results, a Mann-Whitney U test by Bonferroni adjustment was used for multiple comparisons (for triple comparisons, *P* values less than 0.01 were considered significant). Stepwise multiple linear regression analysis was used to determine the cost predictors. Log_{10} transformation of costs was performed to fit the normative assumptions. The possible cost predictors included the patient's age, education level, disease duration since diagnosis, SELENA–SLEDAI, SDI, and the number of flares during the past 12 months. A sensitivity analysis was performed to indicate whether the test was sensitive to outliers (a case was an outlier if it was 3 SDs away from the mean).

RESULTS

Sociodemographics and clinical profiles. Table 1 shows the sociodemographics and clinical characteristics (ever) at the time of the assessment of the whole cohort, as well as the 2 groups subdivided according to whether they experienced a flare in the preceding year. Compared with those without flares, patients with flares were younger, had a shorter disease duration, and had higher disease activity at the time of the assessment. Regarding the clinical features, patients with flares had a higher prevalence of having had discoid lesions and being anti-dsDNA positive. No significant differences in the prevalence of major organ manifestations and the SDI score were observed between the 2 groups.

Lupus flare profiles. During the preceding year, 74 episodes of flare were recorded in 62 (20.3%) of 306 patients. The overall flare rate was 0.24 episodes per patient-year. Fifty (80.6%) of 62 patients had 1 flare and 12 (19.4%) of 62 had 2 flares. Renal flare was the most common (0.09 episodes/patient-year), followed by mucocutaneous flare (0.04 episodes/patient-year), musculoskeletal flare (0.04 episodes/patient-year), hematologic flare (0.04 episodes/patient-year), NP flare (0.03 episodes/patient-year), vasculitic flare (0.03 episodes/patient-year), and serositis flare (0.01 episodes/patient-year). Seven patients had 8 NP flares during the preceding year. Four of 8 were cardiovascular accidents (3 were strokes and 1 was a transient ischemic attack), 2 were seizure disorders, 1 was a migraine, and 1 was a myelopathy.

For those with 1 flare, 18 (36%) of 50 patients had a mild/moderate flare and 32 (64%) of 50 had a severe flare. For those with 2 flares, 1 (8%) of 12 had 2 mild/moderate flares, 6 (50%) of 12 had 1 mild/moderate flare and 1 severe flare, and 5 (42%) of 12 had 2 severe flares. The majority of these patients had a single-organ flare (54 [87%] of 62). Among patients with single-organ flare, 23 (42.6%) of 54 patients had a renal flare, 4 (7.2%) of 54 patients had an NP flare, 10 (18.5%) of 54 patients had a mucocutaneous flare, 8 (14.8%) of 54 patients had a mus-

Table 3. Medications taken (ever) by patients with and without flares in the preceding year*

	Without flares (n = 244)	With flares (n = 62)	P
NSAIDs	91 (37)	33 (53)	0.023
Anti-malaria drugs	134 (55)	35 (57)	0.828
Corticosteroids	163 (67)	60 (97)	< 0.0001
Immunosuppressants	62 (25)	34 (55)	0.011
ACE inhibitors/ARBs	70 (29)	30 (48)	0.003
Anti-osteoporosis	117 (48)	46 (74)	< 0.0001
Antibiotics	46 (19)	19 (31)	0.043
Gastrointestinal drugs†	95 (39)	36 (58)	0.007
Cardiovascular system drugs‡	77 (32)	19 (31)	0.890
Neuropsychiatric drugs§	38 (16)	13 (21)	0.309

* Values are the number (percentage). NSAIDs = nonsteroidal antiinflammatory drugs; ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers.
† Including diuretics, anti-arrhythmic drugs, β-adrenoceptor–blocking drugs, hypertension and heart failure drugs (excluding ACE inhibitors/ARBs), nitrates, calcium-channel blockers, anticoagulants and protamine, antiplatelet drugs, lipid-regulating drugs, fibrinolytic drugs, antifibrinolytic drugs, and hemostatics.
‡ Including antacids and simethicone, antispasmodic drugs, ulcer-healing drugs, adsorbents and bulk-forming drugs, antimotility drugs, laxatives, local preparations for anal and rectal disorders, and drugs affecting intestinal secretions.
§ Including hypnotics and anxiolytics, antipsychotic drugs, antipsychotic depot injections, antimanic drugs, antidepressant drugs, drugs for nausea and vertigo, analgesics, antiepileptics, drugs for dementia, and drugs used in parkinsonism and related disorders.

culoskeletal flare, and 7 (13.0%) of 54 patients had a hematologic flare. Eight (12.9%) of 62 patients had a multiorgan flare involving 2–5 organ systems (median 2). The commonly involved organ systems included the kidney (5 [62.5%] of 8 patients), brain (4 [50%] of 8 patients), hematologic system (4 [50%] of 8 patients), vasculitis (3 [37.5%] of 8 patients), and musculoskeletal system (2 [25%] of 8 patients).

Flare, health care resources utilization, and costs. Table 2 shows the health care resources use of patients with and without flares. More visits to rheumatologists were observed in patients with flares. Seventy-six percent of patients with flares had urine tests compared with 37% of those without flares ($P < 0.0001$). The proportion of patients having imaging tests was also higher in those with flares (28% versus 50%; $P = 0.001$). A higher proportion and longer duration of inpatient care were seen in patients with flares. For those with flares, the major reason for hospitalization was flare (58%), followed by infection (14%). For those without flares, infection was the major reason for hospitalization (30%).

All of the patients with flares required medication treatment in the preceding 12 months, compared with 96% of those without flares ($P = 0.105$). Use of NSAIDs, corticosteroids, immunosuppressants, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, antibiotics, and prophylaxis for steroid-induced osteoporosis was more common in patients with flares (Table 3). The use of health products, nontraditional therapies, aids, and private hospital/clinic facilities did not differ between patients with and without flares.

The employment rate was not significantly different between these 2 groups (46% for patients without flares and 48% for those with flares; $P = 0.948$). For those who were employed, a higher proportion (93% versus 66%; $P =$

Table 4. Annual costs for patients with and without flares (in 2006 US dollars)*

	Without flares (n = 244)	With flares (n = 62)
Visits to health care provider		
Mean ± SD	805 ± 560	1,017 ± 440†
Median (IQR)	633 (504)	1,013 (566)
Diagnostic examinations		
Mean ± SD	1,180 ± 686	1,780 ± 1,035†
Median (IQR)	989 (636)	1,564 (1,232)
Medications		
Mean ± SD	317 ± 515	381 ± 404‡
Median (IQR)	164 (245)	265 (322)
Emergency visits		
Mean ± SD	31 ± 79	108 ± 140†
Median (IQR)	0 (0)	103 (206)
Inpatient care		
Mean ± SD	2,425 ± 12,581	11,737 ± 25,615†
Median (IQR)	0 (0)	3,469 (12,759)
Private hospital/clinic services		
Mean ± SD	48 ± 169	115 ± 516
Median (IQR)	0 (0)	0 (0)
Patient out-of-pocket expenses		
Mean ± SD	1,161 ± 2,329	1,685 ± 2,649‡
Median (IQR)	140 (1,210)	317 (2,167)
Indirect costs due to sick leave		
Mean ± SD	1,509 ± 7,363	5,014 ± 17,078‡
Median (IQR)	0 (1,360)	0 (5,042)
Indirect costs due to SLE-related unemployment		
Mean ± SD	24,201 ± 49,091	24,225 ± 49,126
Median (IQR)	0 (0)	0 (8,497)
Indirect costs due to days off from household work or daily activities		
Mean ± SD	1,398 ± 9,273	2,577 ± 13,002
Median (IQR)	0 (0)	0 (0)
Total direct costs		
Mean ± SD	6,034 ± 12,899	16,873 ± 25,510†
Median (IQR)	2,872 (4,106)	9,441 (12,364)
Total indirect costs		
Mean ± SD	4,905 ± 8,872	5,756 ± 8,999‡
Median (IQR)	322 (7,040)	1,013 (10,061)
Total costs		
Mean ± SD	10,870 ± 16,094	22,580 ± 29,943†
Median (IQR)	4,539 (12,689)	14,276 (19,423)

* 1 US dollar = 5.527 Hong Kong dollars. The purchasing power parities conversion factor of 2006 was used and the conversion factor of US dollars is 1:1. IQR = interquartile range.
† $P < 0.005$.
‡ $P < 0.05$.

Table 5. Multiple linear regression model of annual direct and indirect costs*

	Univariate analysis		Multivariate regression analysis		
	Coefficient	P	Coefficient	P	R^2
Direct costs					
Age	−0.152	0.008			
Education level	0.062	0.277			
Disease duration	−0.212	< 0.0005	−0.013	< 0.0005	
SELENA–SLEDAI score	0.156	0.006			0.280
SDI score	0.122	0.033	0.114	< 0.0005	
Number of flares	0.448	< 0.0001	0.340	< 0.0001	
Indirect costs†					
Age	−0.027	0.643			
Education level	0	1			
Disease duration	−0.020	0.734			
SELENA–SLEDAI score	0.102	0.076			
SDI score	0.058	0.308			
Number of flares	0.136	0.017			

* Due to the skewness of direct and indirect costs data, a $\log_{10}$ was performed prior to the regression analysis. SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus: National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.
† None of these variables was an independent predictor of indirect costs in the multivariate analysis.

0.003) and longer duration (median [IQR] 4 [10] days versus 15 [23] days; $P < 0.0005$) of annual sick leave were observed in patients with flares. There was no difference in the duration of unemployment between the 2 groups for those who were unemployed because of SLE (median duration 12 months for both; $P = 0.202$). The number of days off from household work or daily activities did not differ between the 2 groups (median [IQR] duration 0 [0] days versus 0 [30] days; $P = 0.299$).

Patients with flares incurred approximately twice the average annual total costs of those without flares ($22,580 versus $10,870 [2006 US dollars] per patient; $P < 0.0005$) (Table 4). Annual direct costs were nearly 3-fold higher for patients with flares compared with those without flares ($P < 0.0005$). Patients with flares incurred significantly higher costs in all of the components of direct costs. For both groups, the costs of inpatient care represented the largest component, accounting for 40% (patients without flares) and 70% (patients with flares) of total direct costs. Annual indirect costs were also significantly higher in those with flares ($P = 0.017$). For those who were employed, higher indirect costs due to sick leave were also observed in patients with flares. Indirect costs due to SLE-related unemployment and days off from household work or daily activities did not differ between the 2 groups.

In univariate analysis, variables significantly associated with direct costs included age, disease duration, SELENA–SLEDAI score, SDI score, and the total number of flares (Table 5). In multivariate analysis, disease duration, SDI score, and the total number of flares were independent explanatory variables associated with increased direct costs. The total number of flares was the only variable significantly associated with increased indirect costs in univariate analysis (Table 5). However, none of these variables were independent predictors of indirect costs in the multivariate analysis. A sensitivity analysis was performed and the tests were not sensitive to the outliers.

Severity, organ involvement, and manifestations of flares and costs. Patients with 1 flare were then grouped into 2 groups: those with a mild/moderate flare (n = 18) and those with a severe flare (n = 32). Patients with mild/moderate and severe flares incurred significantly higher direct costs compared with those without flares (Figure 1A). Patients with severe flares also incurred higher indirect costs compared with those without flares. However, direct and indirect costs did not differ between patients with mild/moderate and severe flares ($P = 0.082$ for direct costs and $P = 0.099$ for indirect costs).

Patients with multiorgan flares incurred significantly higher direct costs compared with those without flares and those with single-organ flares (Figure 1B). Their indirect costs were also higher than those for patients without flares, but this became insignificant after correction for multiple comparisons ($P = 0.044$).

Patients with single-organ flares were then divided into 2 groups: those with renal/NP flares (n = 27) and those with other manifestations (n = 27). Patients with renal/NP flares generated higher direct costs than those with other manifestations and those without flares (Figure 1C). However, indirect costs did not differ among these 3 groups.

DISCUSSION

To our knowledge, this is the first study to elucidate the impact of flares on the costs of SLE. We have shown that patients with flares use more health care resources and incurred both higher direct and indirect costs compared with their counterparts. They paid more visits to health care providers and the emergency room, had a higher hospitalization rate, required more diagnostic examinations, and received more corticosteroids and immunosuppressants. After being adjusted for other sociodemographics and disease characteristics, the number of flares

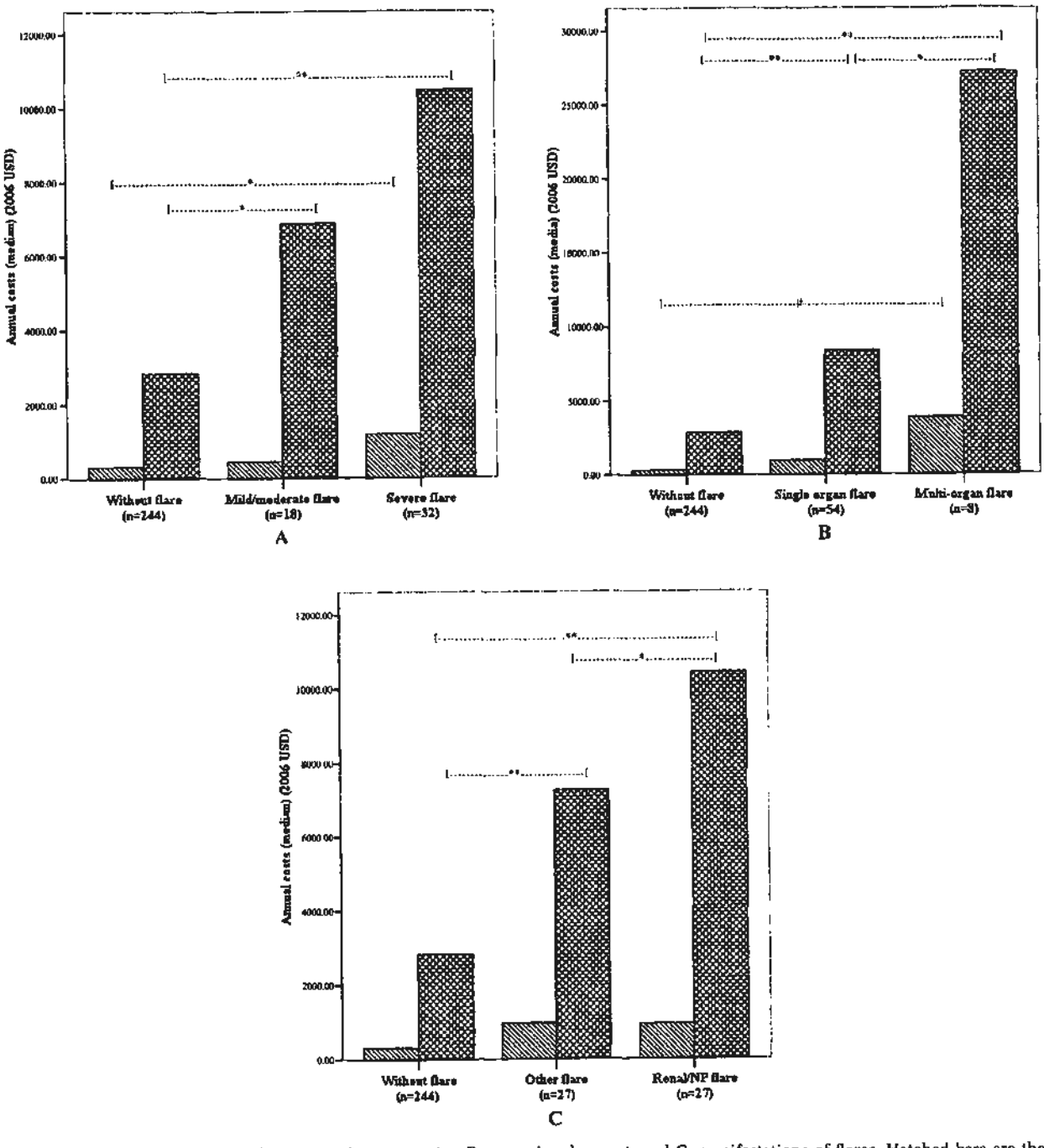

Figure 1. Annual direct and indirect costs by **A**, severity, **B**, organ involvement, and **C**, manifestations of flares. Hatched bars are the indirect costs; stippled bars are the direct costs. * $P < 0.005$; ** $P < 0.0005$; # $P = 0.044$ ($P < 0.01$ was considered significant after the Bonferroni adjustment). USD = US dollars; NP = neuropsychiatric.

was an independent explanatory variable associated with increased direct costs in SLE.

There is no generally accepted definition of lupus flare at present, although various approaches have been used in clinical trials (5–7). In our study, we defined flare by encompassing 1) the SELENA–SLEDAI score, 2) clinical disease activity scenarios that may not be captured by the SELENA–SLEDAI descriptors, and 3) change in treatments. Therefore, this should be a comprehensive definition of flare.

The overall flare rate of our cohort was lower compared with previous studies (4,8,30). Although this could be due to differences in the definition used, there are several other possible explanations. First, the validity of the retrospec-

tive assessment of flare at a specific visit has been shown to be poor (31). Second, the study period in our study is shorter (1 year). Third, although all of the patients were followed at our hospital at regular intervals, it is possible that patients would not seek medical consultation for some minor and short-term flares. Furthermore, we excluded flares with only active serologic manifestations. Although one study has shown the high probability of flares in the next 5 years for patients with serologically active clinically quiescent disease (32), it is our routine practice that we do not launch treatment for these patients. Therefore, it is appropriate to exclude these flares from our analysis.

Sutcliffe et al reported that greater disease activity measured by the Systemic Lupus Activity Measure was associated with high direct and indirect costs (18). A recent study also found that disease activity measured by the Systemic Lupus Activity Questionnaire was an independent predictor of direct health care and productivity costs (17). In our study, the SELENA–SLEDAI was associated with direct costs in univariate analyses, but after being adjusted by other covariates, it became insignificant. Although this may be due to different measures, it may also be explained by the chronic and fluctuating course of SLE that makes an activity score at a single time point not a good indicator of the overall disease activity (16). Therefore, calculating disease activity over time may be desirable (33). The adjusted mean SLEDAI 2000 update (SLEDAI-2K), determined by the calculation of the area under the curve of the SLEDAI-2K over time, has been shown to be strongly associated with mortality (34). Future studies may use this measure to investigate whether disease activity over time is a stronger predictor of costs than disease activity at a single time point.

Since flare is defined as an increase in disease activity, we consider the total number of flares during the study period as a summary of the overall disease activity. In our study, the number of flares was significantly associated with the SELENA–SLEDAI score ($r = 0.219$, $P < 0.0005$). The number of flares was significantly related to direct costs, both in the univariate and multivariate models, and it is the only variable significantly associated with indirect costs in the univariate analysis.

In our study, severe flares did not incur significantly higher direct/indirect costs compared with mild/moderate flares. However, we might underestimate the number of mild/moderate flares because a patient might not seek medical consultation for a minor and short-term flare. Multiorgan flares in our study were more costly than single-organ flares. However, it must be noted that the number of patients with multiorgan flares is relatively small. Such a comparison may be of limited value. Flares involving major organs require more aggressive and intensive treatment (12,35), which concurs with our results that patients with renal/NP flares incur higher direct costs compared with other organ flares. There was no difference in direct costs between patients with renal and NP flares, which is probably due to the small number of patients with NP flares ($n = 4$).

There are several limitations to this study. The retrospective design may result in inaccuracies of the data, especially for the long recall period (12 months). However, the largest part of the disease costs, i.e., the government health care resources, was obtained by chart review that was solid and accurate. Our indirect costs did not capture the productivity loss because of the time spent nursing patients. However, we included productivity loss in nonpaid work such as housework and daily activity, which are of great importance (36). Although we have shown that patients with flares received more medications, we could not tell from our results whether these medications were initiated during the preceding 12 months or were prescribed because of the flares. Furthermore, because of differences in the patients' sociodemographics, disease features, treatment practices, and health care systems, our results may not be generalizable to other populations of SLE.

In summary, we have shown that patients with flares use more health care resources and incur higher direct and indirect costs compared with those without flares. The total number of flares is an independent explanatory variable associated with direct costs of SLE. Major organ flares such as renal and NP flares incur higher disease costs than other organ flares. Therapies that can effectively control disease activity and prevent flares, especially those that could prevent renal or NP flares, may be cost-effective in view of the high costs associated with active disease affecting these organs. Our results provide some preliminary data for the economic evaluation of such therapies in the future.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Li had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Zhu, Tam, Vivian W.-Y. Lee, Kenneth K.-C. Lee, Li.

Acquisition of data. Zhu, Li.

Analysis and interpretation of data. Zhu, Tam, Li.

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Relationship Between Flare and Health-related Quality of Life in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To investigate (1) the relationship between flares and health-related quality of life (HRQOL) in Chinese patients with systemic lupus erythematosus (SLE) in Hong Kong; and (2) the influence of severity of flare, number of organs involved in flares, and manifestations of flares on HRQOL.

Methods. A retrospective study was performed on 303 patients with SLE. Participants completed the Medical Outcomes Survey Short-Form 36 (SF-36) and underwent clinical and laboratory examination to evaluate disease activity and damage. The total number and manifestations of flares during the preceding year were assessed retrospectively. Multiple linear regression analysis was used to identify the independent variables associated with impairment of HRQOL.

Results. Patients with flares were younger, had a shorter disease duration, and had higher disease activity at the time of the assessment. A total of 72 episodes of flares were recorded in 61 patients in the preceding year. Patients with flares had significantly lower scores in the areas of role limitation due to physical problems, general health, social function, and role limitation due to emotional problems compared with those without flare. The physical health summary scale was also lower in patients with flares. In the multivariate analysis, the presence of musculoskeletal flare was independently associated with all scales of the SF-36, except bodily pain and mental health.

Conclusion. The low level of patients' HRQOL is mostly associated with the presence of musculoskeletal involvement. (First Release Feb 1 2010; J Rheumatol 2010;37:568–73; doi:10.3899/jrheum.090876)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
LUPUS FLARE
HEALTH-RELATED QUALITY OF LIFE
SF-36

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with a broad spectrum of clinical and laboratory manifestations. It is characterized by a chronic remitting-relapsing disease course that imposes a considerable burden of healthcare expenditure, as well as on patients' health-related quality of life (HRQOL). HRQOL is a multidimensional concept including physical, functional, social, and emotional well-being[1]. Studies have demonstrated that patients with SLE have poorer HRQOL compared with healthy controls, both in Caucasian and Chinese populations[2-4]. The Medical Outcomes Survey Short-form 36 (SF-36) is the tool most commonly used to assess HRQOL of patients with SLE. Factors related to patients' demographics, disease, and therapy have been identified that are associated with HRQOL in patients with SLE[5-7].

Flare is an important outcome in SLE because uncontrolled disease activity and toxicity of therapies will result in disease damage, which is a major determinant of longterm prognosis[8-10]. Flare can be quantified using the existing disease activity indices. Using an increase of 1.0 cm on a 3-cm visual analog scale of the physician's global assessment (PGA) as a "gold standard," flare corresponds to an increase of 3 points or more on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[11]. The Safety of Estrogen in Lupus Erythematosus: National Assessment (SELENA) flare tool, which includes both activity indices, clinical manifestations, and treatment strategies, has been devised to separate "mild/moderate" flare from "severe" flare[12].

The relationship between flare and HRQOL in patients with SLE has been explored by Doria, *et al*, in which lower level of general health and physical function measured by the SF-36 were found[3]. However, the definition of flare used in that study appears to be empirical and might not be comprehensive enough to adequately identify all the changes in disease activity. In this retrospective study, we investigate the relationship between flare and HRQOL in Chinese

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patients with SLE in Hong Kong. The influence on HRQOL of severity of flares, number of organs involved in flares, and major organ [renal or neuropsychiatric (NP)] or musculoskeletal flares are also explored.

MATERIALS AND METHODS

Patients and procedures. This was a retrospective nonrandomized study. We recruited a convenience sample of 303 consecutive patients from a study aiming to estimate direct and productivity losses of patients with SLE, conducted from January 2006 to August 2007, from the Rheumatology Out-patient Clinic of the Prince of Wales Hospital, Hong Kong[13]. All patients fulfilled the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE[14] and were followed at the Prince of Wales Hospital at regular intervals (every 3 to 4 months) according to a standardized protocol including (1) disease activity assessment at each followup visit according to the SLEDAI[15]; and (2) yearly disease damage assessment according to the SLE International Collaborating Clinics/ACR Damage Index (SDI)[16].

The Ethics Committee of the Chinese University of Hong Kong approved this study, and all patients provided written informed consent.

Participants underwent clinical and laboratory assessments by their treating rheumatologists. Disease activity was assessed by SLEDAI, which evaluates disease activity in 9 organ systems. The total SLEDAI score ranges from 0 (no activity) to 105 (maximum activity)[15]. Disease damage was measured by the SDI, which evaluates damage on 12 organ systems. The total SDI score ranges from 0 (no damage) to 47 (maximum damage)[16,17].

The SF-36 (standard version 1.1). Participants completed the SF-36, a generic instrument for HRQOL assessment that is widely used in the general population as well as various disease populations[1]. The SF-36 has 8 subscales measuring 8 domains of quality of life: physical function, role limitation due to physical problems, bodily pain, general health, vitality, social function, role limitation due to emotional problems, and mental health. Each subscale consists of 2 to 10 items, and each item is rated on a 2- to 6-point Likert scale. Each subscale score is calculated by summation and transformation of all the scores of items belonging to the same subscale, ranging from 0 (poor) to 100 (optimal). In addition, the physical health summary and mental health summary summarize the 8 SF-36 subscales into 2 summary scales that give an overall assessment of quality of life related to physical and mental health, respectively[18]. The SF-36 has been translated into Chinese and validated for Chinese adults in Hong Kong. Normative values of the SF-36 questionnaire of a Chinese adult population in Hong Kong have been published[19,20].

Definitions of flare. The total number and the manifestations of flares during the preceding 12 months were assessed retrospectively by the investigator (TYZ). A revised SELENA flare tool that excluded the component of PGA was used to define flare[12]. Mild/moderate flares were defined as one or more of the following: (1) change in SLEDAI score > 3 points but ≤ 12; (2) new/worse discoid lesion, photosensitive, profundus, cutaneous vasculitis, bullous lupus, nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, fever (SLE); (3) increase in prednisone use, but not to > 0.5 mg/kg/day; and (4) added nonsteroidal antiinflammatory drugs (NSAID) or hydroxychloroquine for SLE. Severe flares were defined as one or more of: (1) change in SLEDAI score > 12; (2) new/worse NP-SLE, vasculitis, nephritis, myositis, platelets < 60,000/mm^3, anemia with hemoglobin < 7 mg/dl, requiring doubling of or increase in prednisone dosage to > 0.5 mg/kg/day; (3) increase in prednisone to > 0.5 mg/kg/day; (4) new immunosuppressants for SLE activity; and (5) hospitalization for SLE.

Clinical features of flares were grouped into the following organs/systems: renal, NP, musculoskeletal, mucocutaneous, hematologic, vasculitic, and serositis. Definitions of renal flare were as described[13]. NP flare was defined using the case definition system for central nervous system lupus syndromes by the 1999 ACR nomenclature and standard definitions[21]. This includes 19 NP syndromes, namely aseptic meningitis, cerebrovascular disease, demyelinating syndrome, headache, movement disorder, myelopathy, seizure disorder, acute confusional state, anxiety disorder, cognitive dysfunction, mood disorder, psychosis, Guillain-Barré syndrome, autonomic neuropathy, mononeuropathy (single/multiplex), myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy. Definitions of other organ/system flare were according to the definitions of the SLEDAI[12,15]. Flares with only serological manifestations [increased anti-double-stranded DNA (anti-dsDNA) titer and depressed complement levels] without medical intervention were not included into the analysis. Single-organ flare referred to flares involving only one organ while multiorgan flares involve more than one (excluding immunological manifestations).

Statistical analysis. Results were expressed as mean ± SD for normally distributed data. Non-normally distributed data were expressed as median (interquartile range). Chi-square test, Student t test, and Mann-Whitney U test were used for comparisons between 2 groups. Univariate logistic or multinomial logistic regression was used to analyze the relationship among HRQOL measured by the SF-36 and the presence of flare in the preceding year and the severity or manifestations of flares. Multiple linear regression analysis (stepwise selection) was used to identify the independent variables associated with the subscales and summary scales of the SF-36. The following variables would be entered into the regression analysis: age, female sex, education level (years), disease duration (years), SLEDAI score, SDI score, number of flares, severe flare ever, multiorgan flare ever, and musculoskeletal flare ever in the preceding year. Because only 2 scales, i.e., mental health and mental health summary, were normally distributed, for the rest of the scales, log 10 transformation would be performed before entering the regression analysis. All analysis was performed using the Statistical Package for the Social Sciences for Windows, version 13.0 (SPSS 2006; SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and clinical characteristics. Of the 303 participants, only 12 were men (4%). The mean (SD) age of the entire group was 41.1 (11.5) years. Table 1 summarizes the demographic and clinical characteristics (ever) of participants cross-classified by whether they experienced a flare in the preceding year. Compared to those without flares, patients with flares were younger, had a shorter disease duration, and had higher disease activity at the time of the assessment. No significant differences in the prevalence of major organ manifestations (ever) and the SDI score were observed between the 2 groups, except that patients with flares had higher prevalence of having had discoid lesions.

Lupus flare profiles. A total of 72 episodes of flare were recorded in 61 (20.1%) of 303 patients in the preceding year. The overall rate of lupus flare was 0.24 episodes per patient-year. Fifty (82.0%) out of 61 patients had 1 flare and 11 (18.0%) of 61 had 2 flares. Renal flare was the most common, followed by mucocutaneous, musculoskeletal and hematologic flare (Table 2). For those with 1 flare, 18 (36%) out of 50 patients had mild/moderate flare and 32 (64%) of 50 had severe flare. For those with 2 flares, 1 (9%) out of 11 patients had 2 mild/moderate flares; 6 (56%) of 11 had 1 mild/moderate flare and 1 severe flare; 4 (36%) out of 11 had 2 severe flares. The majority of these patients with flare had single-organ flare (53/61, 87%). Among patients with single-organ flare, 22 (42%) of 53 patients had renal flare, 4 (8%) had NP flare, 10 (19%) had mucocutaneous flare, 8

Table 1. Demographic and clinical characteristics (ever) of patients with and without flares in the preceding year. Values are number (%) unless otherwise indicated.

Characteristics	Without Flares, n = 242	With Flares, n = 61	p	Entire Group, n = 303
Age, mean ± SD yrs	42.4 ± 11.4	36.2 ± 10.3	< 0.0005	41.1 ± 11.5
Female	234 (97)	57 (93)	0.245	291 (96)
Education level, mean ± SD yrs	10.2 ± 4.4	11.3 ± 3.5	0.115	10.4 ± 4.3
Disease duration, mean ± SD yrs	10.2 ± 7.1	7.4 ± 5.8	0.003	9.6 ± 6.9
SLEDAI score, mean ± SD	2.17 ± 2.64	3.67 ± 3.21	< 0.0005	2.5 ± 2.8
SDI score, mean ± SD	0.74 ± 1.07	0.64 ± 1.11	0.279	0.72 ± 1.08
Organ manifestations				
Malar rash	106 (44)	26 (43)	0.868	132 (44)
Discoid lesion	27 (11)	13 (21)	0.036	40 (13)
Photosensitivity	77 (32)	20 (33)	0.885	97 (32)
Oral ulcer	73 (30)	21 (34)	0.520	94 (31)
Arthritis	191 (79)	43 (70)	0.160	234 (77)
Serositis	68 (28)	17 (28)	0.971	85 (28)
Renal disease	138 (57)	42 (69)	0.093	180 (59)
Neuropsychiatric disease	62 (26)	21 (34)	0.168	83 (27)
Hematologic manifestations	206 (85)	56 (92)	0.173	262 (86)
Leukopenia	122 (50)	36 (59)	0.229	158 (52)
Lymphocytopenia	159 (66)	37 (61)	0.461	196 (65)
Thrombocytopenia	70 (29)	20 (33)	0.555	90 (30)
Hemolytic anemia	19 (8)	6 (10)	0.615	25 (8)
Immunological manifestations	228 (94)	59 (97)	0.434	287 (95)
Anti-dsDNA-positive	178 (74)	52 (85)	0.056	230 (76)
Anti-Smith-positive	46 (19)	18 (30)	0.073	64 (21)
Anti-Ro-positive	132 (55)	35 (57)	0.691	167 (55)
Anti-La-positive	50 (21)	7 (11)	0.101	57 (19)
ANA-positive	239 (99)	60 (98)	0.386	299 (99)

SLEDAI: SLE Disease Activity Index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Table 2. Clinical features of lupus flares in the preceding year.

	No. of Episodes	Rate of Flare (per patient-yr)
All flares	72	0.24
Renal flares	28	0.09
Neuropsychiatric flares	8	0.03
Other flares		
Mucocutaneous	16	0.05
Musculoskeletal	11	0.04
Hematologic	10	0.03
Vasculitis	9	0.03
Serositis	2	0.01

(15%) had musculoskeletal flare, and 7 (13%) had hematologic flare. Eight out of 61 (12.9%) patients had multiorgan flare involving 2 to 5 organ systems (median 2).

Lupus flare and the SF-36 scales. Only in the mental health subscale and mental health summary scale were data normally distributed. Table 3 summarizes the SF-36 subscales and summary scales of the study population, cross-classified by the number of flares, severity of flares (for those with 1 flare only), number of involved organs of flares, and manifestations of flares (for those with single-organ flares only). Patients with flares in the preceding year had significantly lower scores in the areas of role limitation due to physical problems, general health, social function, and role limitation due to emotional problems compared to those without flare. Physical health summary scale was also lower in patients with flare, but there was no difference in mental health summary scale findings between these 2 groups. The number of flares, the severity of flares (mild/moderate vs severe), and the number of organs involved (single-organ vs multiorgan flare) did not influence the domains of HRQOL measured by the SF-36. For those with single-organ flares, patients with musculoskeletal flares had lower levels of physical function, bodily pain, social function, and physical health summary compared to those with other flares. However, patients with renal/NP flares did not have significantly poorer level of HRQOL measured by the SF-36.

Multivariate analysis. Results of the multivariate regression are shown in Table 4. We found no relationship between gender, education level, disease duration, severe flare, and multiorgan flare in the preceding year and HRQOL. The number of flares and SDI scores were the independent explanatory variables associated with the impairment of role limitation due to physical problems. Older age was associat-

Table 3. Mean ± standard deviation for SF-36 subscales and summary scales for the study population, cross-classified by presence of flares in the preceding year and severity or manifestations of flares.

			No. of Flares		Severity		Organ System		Manifestations		
	Without Flare, n = 242	With Flares, n = 61	One Flare, n = 50	Two Flares, n = 11	Mild/ moderate, n = 18	Severe, n = 32	Single Organ, n = 53	Multiorgan, n = 8	Renal/NP, n = 26	Musculoskeletal, n = 8	Other, n = 19
Subscales											
Physical function	73 ± 26	66 ± 30	65 ± 30	59 ± 31	64 ± 25	66 ± 32	68 ± 28	52 ± 40	68 ± 33	48 ± 26*	74 ± 14
Role limitation due to physical problems	55 ± 44	31 ± 38††	34 ± 39	20 ± 31	39 ± 40	30 ± 40	32 ± 39	25 ± 35	30 ± 39	28 ± 36	37 ± 40
Bodily pain	65 ± 25	58 ± 28	59 ± 27	53 ± 35	50 ± 28	65 ± 25	56 ± 28	70 ± 29	60 ± 27	30 ± 16*	63 ± 28
General health	41 ± 22	35 ± 20†	35 ± 21	32 ± 20	34 ± 18	36 ± 22	35 ± 21	32 ± 18	34 ± 23	27 ± 13	41 ± 19
Vitality	50 ± 20	47 ± 23	49 ± 22	38 ± 23	45 ± 22	52 ± 22	47 ± 23	49 ± 19	46 ± 26	39 ± 21	52 ± 19
Social function	73 ± 24	64 ± 26†	65 ± 26	59 ± 26	61 ± 28	68 ± 26	65 ± 26	58 ± 30	65 ± 26	44 ± 24*	74 ± 22
Role limitation due to emotional problems	59 ± 44	45 ± 45†	46 ± 46	39 ± 42	43 ± 47	48 ± 46	43 ± 45	54 ± 47	38 ± 46	25 ± 39	58 ± 46
Mental health	64 ± 19	62 ± 20	63 ± 19	55 ± 20	60 ± 21	65 ± 19	62 ± 21	63 ± 14	60 ± 22	53 ± 18	68 ± 19
Summary scales											
Physical health summary	45 ± 9	41 ± 9†	41 ± 9	40 ± 11	40 ± 9	41 ± 9	41 ± 9	38 ± 8	42 ± 10	34 ± 7*	43 ± 8
Mental health summary	44 ± 11	42 ± 12	43 ± 12	38 ± 13	41 ± 12	44 ± 13	42 ± 12	44 ± 13	43 ± 12	36 ± 9	46 ± 11

† $p < 0.05$; †† $p < 0.005$, significant differences between patients with and without flares. * $p < 0.05$, significant difference between patients with musculoskeletal flares and other flares. NP: neuropsychiatric.

Table 4. Results from final regression models showing coefficients (95% confidence interval) for independent variables associated with SF-36 subscales and summary scales. Only mental health and mental health summary were normally distributed, log 10 transformation was performed for other scales before entering the regression analysis.

	Physical Function	Role Limitation Due to Physical Problems	Bodily Pain	General Health	Physical Health Summary	Vitality	Social Function	Role Limitation Due to Emotional Problems	Mental Health	Mental Health Summary
Age (per year)	–0.37 (–0.63, –0.11)		–0.32 (–0.56, –0.07)		–0.13 (–0.22 to –0.04)					
SLEDAI score (per unit, 0–105)				–1.1 (–2.0, –0.7)						
SDI score (per unit, 0–47)	–4.8 (–7.6, –2.1)	–5.7 (–10.2, –1.2)		–2.6 (–4.8, –0.4)	–1.5 (–2.4 to –0.5)		–2.7 (–5.2, –0.1)	–5.7 (–10.3, –1.0)		
Number of flares		–19.1 (–28.6, –9.6)								
Musculoskeletal flare	–22.5 (–38.1, –6.9)		–34.2 (–49.2, –19.1)	–13.2 (–26.1, –0.3)	–9.2 (–14.6 to –3.7)	–13.0 (–25.4, –0.5)	–30.0 (–44.7, –15.4)	–32.8 (–59.5, –6.1)		–8.1 (–15.1, –1.2)
Adjusted R^2	0.097	0.069	0.078	0.056	0.114	0.014	0.065	0.038	–	0.018

ed with poorer physical function and more bodily pain. SLEDAI score was associated only with impaired general health. Disease damage measured by SDI was the independent explanatory variable associated with the impairment of 3 of the 4 physical health components (except bodily pain), poorer social function, and more role limitation due to mental problems. Musculoskeletal flare in the preceding year was independently associated with impairment of most of the subscales of the SF-36, except role limitation due to physical problems and mental health. Independent variables associated with poorer physical health summary were older age, higher level of disease damage, and musculoskeletal flare in the preceding year. The independent variable associated with poorer mental health summary score was musculoskeletal flare in the preceding year.

DISCUSSION

We previously found that there was no relationship between disease activity measured by SLEDAI and HRQOL measured by the SF-36 in a cohort of patients with SLE[22]. In our study, we found that the SLEDAI score was significantly associated only with general health measured by the SF-36. This is consistent with previous studies that also found no or only a weak relationship between disease activity measured

at a single timepoint and HRQOL in patients with SLE[6]. However, the aim of our study was to evaluate if the changes in disease activity or flares could influence HRQOL in patients with SLE. Although patients with flares in the preceding year experienced poorer HRQOL in some domains measured by the SF-36, this would probably be associated with the presence of musculoskeletal flare.

The relationship between flare and HRQOL in patients with SLE was also studied by Doria, *et al*, who found that a higher number of flares was associated with lower levels of general health and physical function measured by the SF-36[3]. They also proposed that arthritis/arthralgia was the unique clinical manifestation able to influence the HRQOL. Our results are consistent with these findings, in that we found the presence of musculoskeletal flares in the preceding year was independently associated with both physical and mental health domains of HRQOL, after adjustment for other demographic and clinical characteristics.

The definitions of flares we used in this study were adopted from the SELENA flare tool, which has been shown to be reliable and valid[23]. The limitations of using the SLEDAI alone to define flares have been discussed, including a lack of descriptors for several types of activity, such as hemolytic anemia and mononeuritis multiplex[23]. Although we incorporated disease activity index and disease activity scenarios and treatment changes that might be missed by the indices used to define flares, a few concerns should be raised. First, some clinical manifestations of disease activity scenarios were not specified in the definitions, such as acute or subacute cutaneous lupus or mild/moderate hematological abnormalities for the definitions of mild/moderate flare; or acute lupus pneumonitis, interstitial pneumonitis, pulmonary hypertension, pulmonary hemorrhage, and myocarditis for the definitions of severe flare. However, some of these manifestations might have been identified by the changes in treatments, which were individual items of the definitions. Second, anemia was defined only according to hemoglobin levels, without considering other causes, such as gastrointestinal bleeding. However, we did not observe any case with low hemoglobin due to causes other than SLE.

As a generic instrument, the SF-36 has shown construct validity and responsiveness in measuring HRQOL in patients with SLE. However, HRQOL research in patients with chronic illnesses strives to use disease-specific instruments to obtain the optimal measure of HRQOL in specific patient groups. The SF-36 is not disease-specific and therefore it may contain irrelevant items and/or lack items that are important for SLE[24]. Several SLE-specific HRQOL questionnaires have been developed recently, such as the SLE-specific quality of life instrument[25], the Lupus Quality of Life[6], and the SLE Quality of Life Questionnaire (L-QoL)[26]. However, the use of these instruments remains limited to Singaporean Chinese and British Caucasian populations[5]. Further cultural adaptation and validation have to be undertaken before they can be applied to the Chinese population in Hong Kong.

There are several limitations in our study design. An important one is the difference in the assessment timeframe between the SF-36 and lupus flare. The SF-36 assesses HRQOL in the preceding 4 weeks, but we recorded lupus flare in the preceding 12 months. Patients who last experienced a flare 13 months ago will not be considered to have had a flare. This one-year cutoff was arbitrary. However, we still found a significant correlation between the presence of flares and the deterioration in some domains of the SF-36. It is possible that the influence of flares on patients' HRQOL might last longer than the duration of flares themselves. Because we did not record information about time to the last flare, we could not determine whether a recent lupus flare would have a greater influence on HRQOL than an old flare. And it would be of great interest to investigate the perturbation of HRQOL after a lupus flare. The small number of patients with flares is a very important limitation of our study; reliable conclusions cannot be based on comparisons between such uneven groups. An investigation to replicate our findings using a larger patient group is needed. We compare demographic and clinical characteristics between patients with and without flares, using multiple univariate comparisons. Caution should be taken in interpreting these results. We used a convenience sample of patients with SLE and there may have been some selection bias or overestimation of patients' HRQOL. Finally, we did not assess fibromyalgia, which has been shown to have high prevalence in patients with SLE and as a major contributor to patients' HRQOL in SLE[27].

In summary, using the SF-36, a lower level of HRQOL in the areas of general health, social function, and role limitation due to physical/emotional problems, as well as the physical health summary, was found in patients with lupus flares compared to those without flares. The severity of flares did not influence patients' HRQOL. The low level of patients' HRQOL is probably associated with the presence of musculoskeletal flares. This implies that treatments that effectively prevent flares, especially musculoskeletal flares, in patients with SLE might improve patients' HRQOL.

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