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. (J Rheumatol First Release Feb 1 2010; doi:10.3899/jrheum.090876)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
LUPUS FLARE
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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.

REFERENCES

1. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
2. Rinaldi S, Doria A, Salaffi F, Ermani M, Iaccarino L, Ghirardello A, et al. Health-related quality of life in Italian patients with systemic lupus erythematosus. I. Relationship between physical and mental dimension and impact of age. Rheumatology 2004;43:1574-9.
3. Doria A, Rinaldi S, Ermani M, Salaffi F, Iaccarino L, Ghirardello A, et al. Health-related quality of life in Italian patients with systemic lupus erythematosus. II. Role of clinical, immunological and psychological determinants. Rheumatology 2004;43:1580-6.

4. Zheng Y, Ye DQ, Pan HF, Li WX, Li LH, Li J, et al. Influence of social support on health-related quality of life in patients with systemic lupus erythematosus. Clin Rheumatol 2009;28:265-9.
5. Lau CS, Mak A. The socioeconomic burden of SLE. Nat Rev Rheumatol 2009;5:400-4.
6. McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. Lupus 2006;15:633-43.
7. Clarke AE, Petri MA, Manzi S, Isenberg DA, Gordon C, Senecal JL, et al. An international perspective on the well being and health care costs for patients with systemic lupus erythematosus. Tri-Nation Study Group. J Rheumatol 1999;26:1500-11.
8. Gripenberg M, Helve T. Outcome of systemic lupus erythematosus. A study of 66 patients over 7 years with special reference to the predictive value of anti-DNA antibody determinations. Scand J Rheumatol 1991;20:104-9.
9. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. Systemic Lupus International Collaborative Clinics: development of a damage index in systemic lupus erythematosus. J Rheumatol 1992;19:1820-1.
10. Stoll T, Sutcliffe N, Mach J, Klaghofer R, Isenberg DA. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus — a 5-yr prospective study. Rheumatology 2004;43:1039-44.
11. Petri M. Disease activity assessment in SLE: do we have the right instruments? Ann Rheum Dis 2007;66 Suppl 3:iii61-4.
12. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142:953-62.
13. Zhu TY, Tam LS, Lee VW, Lee KK, Li EK. Systemic lupus erythematosus with neuropsychiatric manifestation incurs high disease costs: a cost-of-illness study in Hong Kong. Rheumatology 2009;48:564-8.
14. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
15. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630-40.
16. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.
17. Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. Br J Rheumatol 1996;35:248-54.
18. Ware JE Jr, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995;33 Suppl:AS264-79.
19. Lam CL, Tse EY, Gandek B, Fong DY. The SF-36 summary scales were valid, reliable, and equivalent in a Chinese population. J Clin Epidemiol 2005;58:815-22.
20. Lam CL, Li TK, Lam TP, Gandek B. Population based norming of the Chinese (HK) version of the SF-36 health survey. Hong Kong Practitioner 1999;21:460-70.
21. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599-608.
22. 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. J Rheumatol 2008;35:1038-45.
23. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus 1999;8:685-91.
24. Thumboo J, Strand V. Health-related quality of life in patients with systemic lupus erythematosus: an update. Ann Acad Med Singapore 2007;36:115-22.
25. Leong KP, Kong KO, Thong BY, Koh ET, Lian TY, Teh CL, et al. Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). Rheumatology 2005;44:1267-76.
26. Doward LC, McKenna SP, Whalley D, Tennant A, Griffiths B, Emery P, et al. The development of the L-QoL: a quality-of-life instrument specific to systemic lupus erythematosus. Ann Rheum Dis 2009;68:196-200.
27. Gladman DD, Urowitz MB, Gough J, MacKinnon A. Fibromyalgia is a major contributor to quality of life in lupus. J Rheumatol 1997;24:2145-8.