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An exploration of patient reported symptoms in systemic lupus erythematosus and the relation to health related quality of life

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Key words: Lupus Erythematosus, Systemic, patient perspective, symptom, pain, fatigue, health related quality of life.

Abbreviation

HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related Quality of Life
IQR	Interquartile Range
SF-36	Medical Outcomes Study Short-Form 36

Abstract

Objective. The aim of this study was to explore the most distressing symptoms of systemic lupus erythematosus (SLE) and determine how these relate to health-related quality of life (HRQoL), anxiety/depression, patient demographics and disease characteristics (duration, activity, organ damage).

Methods. In a cross-sectional study, patients with SLE (n=324, age 18-84 years) gave written responses regarding which SLE-related symptoms they experienced as most difficult. Their responses were categorized. Within each category, patients reporting a specific symptom were compared with non-reporters and analyzed for patient demographics, disease duration, results from the questionnaires: Medical Outcomes Study Short-Form 36, Hospital Anxiety and Depression Scale, Systemic Lupus Activity Measure, SLE disease activity index and the Systemic Lupus International Collaboration Clinics/American College of Rheumatology damage index.

Results. 23 symptom categories were identified. Fatigue (51%), Pain (50%) and Musculoskeletal distress (46%) were most frequently reported. Compared with non-reporters, only patients reporting Fatigue showed statistically significant impact on both mental and physical components of HRQoL. Patients with no present symptoms (10%) had higher HRQoL ($p<0.001$) and lower levels of depression ($p<0.001$), anxiety ($p<0.01$) and disease activity (SLAM) ($p<0.001$).

Conclusion. Fatigue, pain or musculoskeletal distress dominated the reported symptoms in approximately half of the patients. Only patients reporting Fatigue scored lower on both mental and physical aspects of HRQoL. Our results emphasize the need for further support and interventions to ease the symptom load and improve HRQoL in patients with SLE. Our findings further indicate that this need is particularly urgent for patients with symptoms of pain or fatigue.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease with individual variation of organ involvement (e.g., skin, joints, kidneys, nervous system and serous membranes) (1). Disease activity often varies over time and subjective symptoms are described as being prominent (2, 3). Both clinical care and research assessments are traditionally focused on predefined aspects of SLE (e.g., selected symptoms or aspects of disease impact) in which patients are asked to rate or assess different parameters according to chosen standards. When SLE disease activity and manifestation are assessed, the focus is often on objective signs and symptoms traditionally observed by physicians. There are however indications that several concepts of importance to patients (e.g. subjective symptoms) are not adequately captured by recommended measures of disease activity and health status (4, 5). This insight has contributed to today's recommendation to incorporate patient-reported outcomes in research (6) in an effort to cover disease activity and impact more fully. In recent years a number of studies have sought to gain a better understanding of the aspects of living with SLE by involving the patient's perspective and thus identify variations in the experience of SLE and disease-related symptoms. One example of this approach is the development of a SLE Specific Symptom Checklist (7-9), as well as other procedures used to identify disease-driven health issues identified by patients (10).

To understand the consequences of patient-reported symptoms on disease impact data from health-related quality of life (HRQoL) questionnaires can be used. HRQoL includes several dimensions, physical as well as psychological, and represents a broad perspective of the overall impact of disease. HRQoL is an important complement to measures of disease activity and damage (11-13). For instance, comparative studies have shown that patients with SLE

perceive reduced HRQoL compared with controls and in parity with several other diseases (14-19).

How the broad spectrum of SLE symptoms affects patients' experience of HRQoL is not yet well understood. Different methods, as focus-groups and Delphi studies, have been used to capture aspects of SLE that are important to the patients (4, 20). Stamm et al (4) explored if important concepts of daily functioning per se are represented in the HRQoL and Bauernfeind et al (20) how important concepts could be identified by International Classification of Function (ICF). These studies did not explore if these concepts represent differences in self-reported HRQoL.

To contribute to the understanding of patients' experience of SLE we aimed to explore the spontaneously most distressing symptoms of systemic lupus erythematosus (SLE) and to determine how these symptoms relate to HRQoL, anxiety/depression, patient characteristics (age, partner status) and disease characteristics (duration, activity and organ damage).

PATIENTS AND METHODS

The present study is part of an ongoing cohort project started in 2004 at Karolinska University Hospital Solna, where all patients with SLE have consecutively received an information letter and given the opportunity to participate. The patients gave their written consent in a reply-paid envelope. Patients included in the cohort study from January 2004 to March 2010 were consecutively and continuously included in the present study. All patients were 18 years of age or older, Swedish speaking and writing, and fulfilled the American College of Rheumatology (ACR) 1982 revised criteria for SLE (≥ 4 ACR criteria) (21). Exclusion criteria

were difficulties to read and write Swedish. The study was approved by the regional ethical review board.

At the study inclusion, the participants gave written answers to two open questions (*“What SLE-related symptoms have you experienced as most difficult during your disease?”* and *“What symptoms do you presently perceive as most difficult?”*). The patients also completed self-assessment measures of HRQoL, anxiety and depression (see below). These self-assessments were followed by a physical examination, assessment of disease manifestations, activity and organ damage, all of which were performed by a rheumatologist.

Self-assessment measures. The study used the self-assessment questionnaire Medical Outcomes Study Short-Form 36 (SF-36) to measure HRQoL (22). The SF-36 includes 36 items divided into eight dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). Each dimension is rated on a scale from 0 to 100, where high values represent better HRQoL. The eight domains can also be divided into two summary scales, the Mental Component Summary scale (MCS) and the Physical Component Summary scale (PCS). The MCS represents by VT, SF, RE and MH and the PCS by PF, RP, BP and GH. The SF-36 standard version representing health status for the past four weeks was used.

The Hospital Anxiety and Depression Scale (HADS) (23, 24) consists of 14 items, equally divided into two scales (an anxiety scale and a depression scale). The range for each scale is 0-21: the cut-off for normal values is described to be 7. According to standard protocol, the respondents were requested to answer each item based on their feelings during the past week.

Disease-specific measures. At the inclusion visit, the physicians performed all the disease-specific assessments. Two instruments were used to assess disease activity: the Systemic Lupus Activity Measure (SLAM) (25, 26) and the SLE disease activity index (SLEDAI) (27). The SLAM covers clinical symptoms during the past month, including laboratory parameters, organ manifestations and some subjective symptoms such as fatigue and headache. It is divided into nine areas (score range 0-86, with high values representing a higher level of activity). SLEDAI includes 24 items corresponding to nine organ systems (score range 0-105). We chose to use both of these two frequently used instruments due to indications that SLAM is more sensitive to changes important to patients (28) but SLEDAI is more frequently used.

To assess cumulative organ damage the Systemic Lupus International Collaboration Clinics/American College of Rheumatology (SLICC/ACR) damage index was used. This index includes 12 organ systems with scores ranging from 0 to 47 (29, 30).

Data analysis. The study used a mixed method approach representing of data from free written answers as well as standardized questionnaires. The data collection of the written answers were inspired from the free-listing methods originally used in anthropology and also used and described in oncology in the collection of patient reported symptoms from persons with e.g. lung cancer (31). The method of using an open question was applied to capture *spontaneous* answers from the respondent.

The approach to process the written answers from the open questions emanated from an inductive procedure of mixed method (31) and conducted as follows. To increase the study's validity independent researchers (LEE, ML, CM) with experience in qualitative methods in other fields than rheumatology were involved in the process to uncover patients' symptom

descriptions. Using an inductive approach, the answers from the initial 200 respondents (i.e. the number of included patients at the time) were classified by the principal author (SP) according to content similarities. The inductive process and the result of “groups of patient answers” were discussed between SP and the last author (EWH), resulting in a preliminary coding list. The preliminary coding list was tested and used by another author (LEE) as a pilot to categorize answers from the 300 first responders, followed by suggestions used to adjust and clarify distinctions between the codes. The adjusted coding list was discussed and revised by several of the authors (SP, ML and EWH). Finally, SP, ML and CM each coded 25% of the statements from the 320 consecutive respondents included in the project. Cohen’s kappa was calculated and the majority of the coding categories had good to very good agreement (from 0.74 to 1.0). In four symptom categories agreement was moderate, these were all reported by only few patients ($n \leq 6$) (32). Using the final coding list, SP coded all statements the 320 respondents and four later included patients giving the final number of 324 respondents.

The second of the two open questions referred to present time (“What symptoms do you *presently* perceive as most difficult?”). Because several parameters could possibly change over time, statements from this question were used when comparing the symptom categories with the patients’ answers from the questionnaires. Two categories were excluded from the comparative analysis: Allergy (not reported by any respondents as present at time of inclusion in the study) and Discomfort (reported by one respondent as a current problem at inclusion). The Wilcoxon Signed Ranks test was applied to compare individual responses within each symptom category between the first and second open question (symptom ever vs. present symptom).

To explore the symptom categories comparisons were conducted between *reporters* (patients with a written statement in a specific symptom category) and *non-reporters* (patients reporting any other symptom but not the specific symptom investigated) within the symptom categories using the Mann-Whitney U test.

The collected quantitative data were mostly categorical, nominal or ordinal and therefore non-parametric tests were used. Medians with interquartile ranges (IQRs) are presented for numerical data and percent is used for frequency data. The quantitative data from the questionnaires were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago IL, USA), version 15.

RESULTS

Participants.

This study included a total of 324 patients with SLE: median age 48 years (IQR 35-58), median disease duration 12 years (IQR 5-22) and median number of fulfilled SLE criteria 6 (IQR 5-7). Demographic variables are presented in Table 1 and the results from the self-assessments of health related quality of life (HRQoL), anxiety and depression are summarized in Table 2.

Patients' report of symptom distress.

Twenty-three symptom categories were identified from the respondents' answers to the open questions (Table 3). The three most frequently reported symptom categories were Fatigue, Pain and Musculoskeletal distress (Table 3). The median number of reported categories corresponding to the question of ever-present symptoms was 3 (IQR 2-4). The patients reported fewer ($p<0.001$) symptom categories as being present at the time of study inclusion (median 2, IQR 1-3) compared with symptom categories reported as ever-present. A majority of the patients ($n=255$, 78.7%) described at least one of the top three most frequently reported symptom categories (Fatigue, Pain and Musculoskeletal distress) as being an ever-present problem.

We investigated whether patients reported the same symptoms as present at the time of study inclusion and compared this with symptoms ever experienced (Table 3). In half of the symptom categories the respondents did not change their answer. In six categories (Fatigue, Pain, Psychological/emotional, Cognitive, Reproduction and Sleeping disorder) over 45% of the respondents described the complaint as both an ever-present distress and as one of the presently most distressing symptoms.

One tenth of the patients stated that they perceived no present symptom at time of inclusion in the study.

Symptom distress compared with demographic data

Present symptoms were further evaluated by comparing patients who reported a specific symptom with patients who did not report a specific symptom. The reporters in each symptom category were also compared in relation to age, disease duration and partner status. Patients reporting Cognitive distress at inclusion in the study had shorter disease duration (median 4 years, IQR 1-17, $p=0.04$) than patients reporting other symptoms (median 12 years, IQR 5-21). Only three patients reported present problems with Reproductive distress, all with a disease duration of less than 1 year. The question of present symptoms was not answered (i.e. left blank) by 16.3 % of the patients and was therefore separately analyzed. Patients who did not answer the question regarding present SLE-related symptoms ($n=53$) at inclusion had a longer disease duration (median 18 years, IQR 7.5-25.5) than patients reporting any SLE-related symptom (median 11 years, IQR 4.5-21; $p= 0.009$). There were no statistically significant differences in age or partner status within any of the symptom categories (data not shown).

Symptom distress compared with disease characteristics

The symptom categories were further analyzed for disease activity, disease duration and organ damage (Table 4). When comparing reporting patients with non-reporting patients within each symptom category (see data analysis), reporting patients in the categories Fatigue, Pain Musculoskeletal, Swelling, Psychological/emotional, Fever, Cognitive Distress and Sleeping had higher disease activity as measured by SLAM. Only patients reporting Reduced physical capacity had more extensive organ damage (SLICC/ACR, median=3, IQR 0.5-5, $p=0.008$) than those not reporting the corresponding symptom category (no reduced physical capacity: SLICC/ACR, median=1, IQR 0-2). Patients who reported no present symptoms of SLE had lower disease activity (SLAM, median=3, IQR 2-6, $p<0.001$) and organ damage (SLICC/ACR, median=0, IQR 0-1, $p<0.05$) than patients reporting any kind of symptom (SLAM, median=7, IQR 4-10; SLICC/ACR, median=1, IQR 0-2), but no differences in disease duration.

Symptom distress compared with measurements of anxiety, depression and HRQoL

Each category was subsequently compared with results from the anxiety, depression (Table 4) and HRQoL self-assessment questionnaires (Table 5 and supplementary data). Patients with present Psychological/emotional distress had the highest anxiety levels ($n=22$) (HADS anxiety median=9.5, IQR 5.75-14) compared with those without psychological/emotional distress (HADS anxiety median=6, IQR 3-9) ($p=0.005$). In comparison with the patients reporting any symptom, the no-symptom patients showed higher HRQoL, less anxiety and less depression (Tables 4 and 5). The groups did not differ in age.

The three most frequently reported symptom categories (Fatigue, Pain and Musculoskeletal distress) were associated with reduced HRQoL (Table 5). Patients with Fatigue reported

significantly lower scores (meaning worse) in both MCS and PCS and higher scores (meaning worse) on the questionnaires measuring anxiety and depression. Patients reporting Pain had lower scores on PCS and more depression but not more anxiety. Patients in the symptom category Musculoskeletal distress reported reduced PCS. Because Fatigue and Pain were symptoms that might interact, they were further analyzed as subgroups, leaving out those patients who reported both fatigue and pain. The statistically significant differences between the subgroups were detected into the dimensions of Bodily Pain and Vitality (Supplementary data). Respondents reporting Fatigue (n=65) but not Pain scored lower on Vitality ($p=0.013$), whereas respondents reporting Pain (n=45) but not Fatigue scored lower on Bodily Pain ($p=0.003$). Notable here is that lower levels on these domains indicate more or worse impact, meaning that the results from the questionnaires were congruent with the symptoms spontaneously reported by the patients.

DISCUSSION

In the responses to the open-ended questions over 75% (n=255) of the SLE patients reported Fatigue, Pain or Musculoskeletal distress as the most difficult symptoms. Only patients reporting fatigue scored lower on both mental and physical aspects of HRQoL. Other symptom categories showed statistically significant impact on either the mental or the physical components of HRQoL. Noteworthy, 10% of the patients reported that they perceived no SLE symptom at the time of study inclusion. This latter finding is consistent with the finding that these patients also had lower disease activity and higher HRQoL. In recent years there has been several improvements in the treatment of patients with SLE (33, 34), but the new therapies do not appear to have changed the fact that fatigue and pain are still perceived as the most distressing symptoms. Our results emphasize the need for further support and interventions to recognize and ease symptom load and thus improve the HRQoL

of patients with SLE. Further, the results indicate that the need is particularly urgent for patients with symptoms of pain or fatigue.

To our knowledge, this is the so far largest cohort study focusing on patients' self-report of SLE-related symptoms which provided us with data representing a heterogenic variation of patient-reported distress. The results are based on data from only one cohort, which calls for caution concerning the generalizability. However, the results from our study are strengthened by similarities to the symptoms identified in other studies (7, 20). In the study of Grootsoorten et al 89% of the patients reported fatigue, 61% painful joints and 54% painful muscles (7). Their symptom category "loss of concentration" (reported by 54%) has similarities to our category Cognitive distress (reported by 5%). Their result presented the highest scores for perceived burden of single symptoms as related to fatigue but also sensitivity to sunlight and disturbed memory. At least six of our categories were not clearly described in the lupus specific symptom checklist (7) (Kidney function, Reduced physical capacity, Fever, Infections, Treatment/examination, Forced adaptation or dependence). Stamm et al (4) used the World Health Organization's International Classification of Functioning, Disability and Health (ICF) as a framework to sort "concepts of importance" collected from persons with SLE. The authors pointed out that environmental factors are not covered by standard measures suggested for SLE (35) and specifically mentioned medication to be an environmental factor. Our symptom category distress related to Treatment/examination could be considered as such an environmental factor reported by patients as having distressing impact. In future studies it would be informative to compare patients' reports of symptoms with nursing diagnostic terms (e.g., the North American Nursing Diagnosis Association, NANDA) (www.nanda.org).

Patients reporting Fatigue and Pain in the present study scored lower than non-reporting patients on self-assessments of HRQoL. This finding is consistent with previous studies showing that pain and fatigue influenced HRQoL in patients with SLE (3, 36). Fatigue and pain are thus well-known symptoms that need more attention if we strive to improve the care of patients with SLE. It is possible that we would have obtained similar results using SLE specific instruments such as SLEQOL or LupusQoL to assess HRQoL (37, 38) but at the time for data collection they were not available in Swedish. Also, an approach using pre-defined answers would not have allowed us to explore spontaneous answers from the informants.

In clinical care as well as in research, attention must be paid to how questions are posed to patients. It was previously demonstrated that physicians only detect 62% of the most important health outcomes in SLE as reported by individual patients (39). Our approach with open questions without fixed answer alternatives reflects the patient's experiences of symptoms. This approach makes it possible to enlighten and detect problem areas neglected by physicians, but crucial to the individual patient. A potential limitation of our study is that the results are dependent on how the respondents interpret the questions. Interpretations are based on the patients' knowledge, individual perception and personal thoughts of their disease-related distress. A previous study has shown a discrepancy between patients and physicians' selection of important health and symptom outcomes (39). This discrepancy has also been illustrated in the fact that even when physicians incorporate aspects of what patients tell them, a discrepancy was found between patients and physicians assessment of disease activity (40). When evaluating disease activity, patients are influenced by their psychological and physical well-being. Physicians, on the other hand, score disease activity based on the clinical and physical signs and symptoms of lupus (41, 42). It is however important to recall that some patient reported symptoms are manifestation of active disease, and is therefore not

surprisingly significantly associated with disease activity measures. To further explore patients' experience of symptom distress, it would be interesting to give physicians the same possibility to answer an open question of the patients' most distressing symptom and compare this with the perceptions of the patients. In future studies it would also be valuable to follow symptom reports over time, using the procedure with an open question to allow detection of symptom change and distress over time, as well as to increase the possibility to uncover symptoms reported by only a few patients.

To conclude, patients with SLE reported a multitude of distressing symptoms, many of which are not covered by present measures of disease activity. The three most frequently reported symptom categories (i.e. Fatigue, Pain and Musculoskeletal distress) were associated with lower HRQoL, however only patients reporting Fatigue showed impact on both mental and physical components of HRQoL. Notably, one tenth of the patients reported that they did not perceive having present symptoms of SLE, and this group also had less disease activity and better HRQoL. We suggest that open questions should be used as a complement to standard measures of disease activity in order to facilitate communication and capture the patient's perspective of disease-related distress.

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Table 1 Characteristics of patients with SLE (n=324)

	%	median	(IQR)	range
Age (yrs)		48	(35-58)	18-84
Women	91%			
Living with partner	57 %			
Disease duration (yrs)		12	(5-22)	0-58
SLE criteria		6	(5-7)	4-10
SLAM ^a		6	(4-10)	0-27
SLEDAI ^b		2	(0-6)	0-26
SLICC ^c		1	(0-2)	0-10
Lupus manifestation				
Malar rash	54%			
Discoid rash	19%			
Photosensitivity	67%			
Oral ulcers	34%			
Arthritis	83%			
Pleuritis	36%			
Pericarditis	18%			
Nephritis	40%			
Neurology ^d	11%			
Blood manifestation ^e	69%			
Ongoing medication^f				
Chloroquine	32%			
Cyclophosphamide p.o.	2%			

Cyclophosphamide i.v.	11%
Azathioprine	19%
Methotrexate	4%
Mycofenolatmofetil	7%
Ciclosporin	2%
Rituximab (ever)	8%
Steroid dose mg, median (IQR)	3.4 (0-7.5)

^aSystemic Lupus Activity Measure (25, 26), ^bSLE disease activity index (27), ^csystemic lupus International collaboration Clinics/American College of Rheumatology (SLICC/ACR) damage index (29, 30), ^dpsychosis or seizures, ^eleukopenia, thrombocytopenia, lymphopenia or hemolytic anemia, ^fongoing treatment with disease-modifying antirheumatic drugs (DMARDs)

Table 2 Patients' self-assessment of health related quality of life ^a, anxiety ^b and depression ^b
(n=324)

	Median	IQR
Physical Functioning(PF) ^a	75	50-90
Role Physical (RP) ^a	50	0-100
Bodily Pain (BP) ^a	52	41-84
General Health (GH) ^a	42	25-62
Vitality (VT) ^a	40	25-60
Social Functioning SF) ^a	75	50-100
Role Emotional (RE) ^a	100	0-100
Mental Health (MH) ^a	72	52-84
Mental Component Summary (MCS) ^{a,c}	44	(33-53)
Physical Component Summary (PCS) ^{a,d}	39	(29-50)
HADS ^b depression	4	2-7
HADS ^b anxiety	6	3-9

^aDimension and summary component from Medical Outcomes Study Short-Form 36 (SF-36), scale 0-100 (22). ^bHospital Anxiety and Depression scale, scale 0-21, cut-off ≥ 7 (23, 24).

^cMCS represents by VT, SF, RE, MH. ^dPCS represents by PF, RP, BP, GH.

Table 3 Categories of patient-reported symptoms^a related to SLE (n=324). Symptoms reported as most difficult ever and compared with most difficult at the present time

Category name	Ever		Present		P-value ^b	
	n	(%) ^c	n	(%) ^c		% ^d
Missing/no answer	16	(4.9)	53	(16.4)		
Fatigue	165	(50.9)	124	(38.3)	0.058	64
Pain	162	(50.0)	104	(32.1)	<0.001	49
Musculoskeletal	148	(45.7)	102	(31.5)	0.017	40
Skin, hair or nails	77	(23.8)	39	(12.0)	0.001	33
Lungs	47	(14.5)	26	(8.0)	0.016	28
Eyes or mouth	38	(11.7)	23	(7.1)	0.074	40
Heart or circulation	34	(10.5)	18	(5.6)	0.194	15
Neurological distress	33	(10.2)	21	(6.5)	0.289	43
Kidney function	32	(9.9)	6	(1.9)	<0.001	16
Swelling	28	(8.6)	10	(3.1)	0.001	25
Reduced physical capacity	28	(8.6)	16	(4.9)	0.008	29
Blood (cells/vessels)	24	(7.4)	5	(1.5)	<0.001	17
Psychological/emotional distress	24	(7.4)	22	(6.8)	0.808	46
Fever	19	(5.9)	9	(2.8)	0.012	26
Infections	16	(4.9)	4	(1.2)	0.002	19
Cognitive distress	15	(4.6)	17	(5.2)	0.705	80
Treatment/examination	11	(3.4)	7	(2.2)	0.317	0
Gastro-intestinal distress	11	(3.4)	6	(1.9)	0.527	9
Forced adaptation or dependence	9	(2.8)	8	(2.5)	0.317	11

Discomfort	8	(2.5)	1	(0.3)	1.000	13
Reproduction	5	(1.5)	3	(0.9)	0.157	60
Allergy	2	(0.6)	0	-	-	0
Sleeping disorder	2	(0.6)	5	(1.8)	1.000	50

^aAnalysis of answers from the two questions: ever: *“What SLE-related symptoms have you experienced as most difficult during your disease?”* Present: *“What symptoms do you presently perceive as most difficult?”* ^bWilcoxon Signed Ranks Test for change in answer, ^cpercent of all patients, ^dpercent of patients reporting symptom distress as ever distressing as well as present distress.

Table 4 Present symptoms reported by patients with SLE (n=324) and compared with patients' self-assessment of depression ^a, anxiety ^b physicians' assessment of SLE activity^{c,d} and organ damage^e.

Category name	Depression ^a	Anxiety ^b	SLAM ^c	SLEDAI ^d	SLICC/ACR ^e
No present symptom ^f	1.5***	4**	3***	2	0*
Fatigue	5***	6.5*	7**	2	1
Pain	5**	6	7***	4**	1
Musculoskeletal	4	6	7**	3	1
Neurological	5*	7	6	2	1
Swelling	4.5	8	8.5*	7*	1
Reduced capacity	3.5	1*	7	3	3**
Blood (cells or vessels)	1*	4	10.5	3.5	0
Psychological/emotional	6.5**	9.5**	9**	2	1
Fever	5	5	14***	6*	1
Cognitive	7**	6	10**	4	2
Sleeping	13.0*	10**	15**	9*	0

Median value from patient reporting a symptom compared with non-reporters of that symptom category. Only categories with statistically significant difference are shown. **Bold** = significant difference between non-reporters and reporters with-in the category. Significance level: *** p<0.001, ** p<0.01, * p<0.05, Mann-Whitney U test. ^aDepression from Hospital Anxiety and Depression scale (23, 24), ^banxiety from Hospital Anxiety and Depression scale (23, 24), ^cSystemic Lupus Activity Measure (25, 26), ^dSLE disease activity index, (27), ^e the Systemic Lupus International Collaboration Clinics/American College of Rheumatology (SLICC/ACR) damage index (29, 30). ^fNo present symptom = patients given a clear

description of no SLE-related symptom at inclusion compared with patients reporting any symptom.

Table 5 Distress reported from patients with SLE at inclusion of study grouped by symptom category and compared with self-assessment of quality of life^a (n=324)

	MCS Median (IQR)	p-value^b	PCS Median (IQR)	p-value^b
No symptom ^c	52 (46-56)	<0.001	54 (51-57)	<0.001
Fatigue	40 (25-48)	<0.001	37 (29-46)	0.002
Pain	43 (27-52)	0.187	34 (25-41)	<0.001
Musculoskeletal	43 (30-54)	0.850	34 (26-42)	<0.001
Skin/hair/nails	45 (32-51)	0.504	43 (31-52)	0.384
Lungs	47 (30-56)	0.547	33 (24-48)	0.040
Eyes/mouth	45 (31-55)	0.583	44 (32-52)	0.334
Heart or circulation	36 (26-47)	0.106	33 (27-43)	0.065
Neurological	33 (24-49)	0.049	36 (29-41)	0.139
Kidney	54 ^d (50-60)	0.036	36 (19-49)	0.561
Swelling	27 (23-51)	0.214	35 (26-41)	0.098
Reduced physical capacity	49 (28-60)	0.219	25 (15-36)	<0.001
Blood	52 (45-57)	0.103	46 (26-52)	0.821
Psychological/emotional	37 (24-43)	0.005	33 (30-49)	0.427
Fever	40 (34-48)	0.404	26 (18-32)	0.001
Infections	39 (14-51)	0.429	35 (20-43)	0.281
Cognitive	39 (25-44)	0.033	34 (30-42)	0.156
Treatment/examination	44 (30-55)	0.872	23 (15-27)	0.009
Gastro-intestinal	41 (27-52)	0.716	38 (22-50)	0.695
Forced adaptation or dependence	31 (25-58)	0.733	36 (15-46)	0.244

Sleep	33 (18-38)	0.074	25 (14-44)	0.094
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^aSubscales of SF-36: MCS=Mental Component Scale, PCS=Physical Component Scale (22),

^bMann-Whitney U test. ^cNo symptom= patients given a clear description of no SLE-related symptom at inclusion of the study compared with patients reporting any symptom. Symptom groups excluded from this table: Discomfort (only one person), Allergy (reported by none), Reproduction (only three respondents). ^d better HRQoL than non-reporters (other categories with statistically significant difference represent worse HRQoL than non-reporters). **Bold**= significant difference between non-reporters and reporters with-in the category. Numbers of patients reporting in each symptom category see Table 3 and the column Present.

Supplementary Material: Distress reported from patients with SLE at inclusion of study
grouped by symptom category and compared with self-assessment of quality of life^a (n=324)

Category	PF	RP	BP	GH	VT	SF	RE	MH
No symptom ^b .	95***	100***	100***	77***	70***	100***	100***	84***
No answer ^c	65	50	51	40	40	62.5	100	72
Fatigue	70**	25***	47**	37***	30***	50***	50***	64***
Pain	65***	25***	41***	34***	35***	63***	67	64*
Musculoskeletal	65***	25***	41***	35**	40	63*	66.7	68
Skin/hair/nails	80	50	52	45	45	45.75	100	72
Lungs	58	25	41	33*	40	56	67	72
Eyes or mouth	85	87.5	62	45	50	75	100	72
Heart/circulation	70	0*	41*	30*	30	38**	33	60
Neurological	70	12.5*	41*	37	40	50**	0*	60
Kidney	80	33	74	17	45	88	100	84
Swelling	70	25	41*	30	40	4*	0	56
Reduced capacity	35***	0*	31**	30*	20	50	100	52
Blood	85	50	84	67	60	100	100	*92
Psychol./emotional	65	13	51	37	33	38**	33*	50**
Fever	60*	0**	31**	27*	15**	25**	67	60
Infection	63	13	48	28	35	25*	50	76
Cognitive	65	13	41	40	25**	50	33*	60*
Treatment/examin.	25**	0	31	25	40	62.5	100	64
Gastro-intestinal	60*	0	36.5	42	33	38	0	78
Forced adaptation	60	25	22*	42	23*	63	67	42

Sleep	35	12.5	0	15	10	13	0*	40*
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^a dimensions of SF-36: PF=Physical functioning, RP=Role Physical, BP=Bodily Pain, GH=General Health, VT=Vitality, SF=Social Functioning, RE=Role Emotional, MH=Mental Health (22), ^bNo symptom= patients given a clear description of no SLE-related symptom at inclusion of the study compared with patients reporting any symptom, ^cNo answer= patients did not answer the question of SLE-related symptom distress compared with patients reporting any symptom distress. Reduced capacity= Reduced physical capacity, Blood = blood cells or vessels. Psychol./emotional= Psychological or emotional distress, Cognit = Cognitive distress, Treatment/examin.= Distress related to Treatment or examination, GI= Gastro-intestinal distress, Forced adaptation = Forced adaptation or dependence, Sleep= Sleeping disorder. **Bold**= significant difference between non-reporters and reporters with-in the category. Significance level: *** p<0.001, ** p<0.01, * p<0.05, Mann-Whitney U test. Symptom groups excluded from this table: Discomfort (only one person), Allergy (reported by none), Reproduction (only three respondents).