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Quality of life among female patients with systemic lupus erythematosus in remission

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Abstract

The objective is to assess quality-of-life (QoL) parameters among Indian female systemic lupus erythematosus (SLE) patients with durable remission. Indian female SLE patients in remission determined by the European consensus criteria and age-matched female control participants were included in the study. All included participants underwent measurements of QoL [Medical Outcomes Study Short-Form-12 (SF12)], Fatigue Severity Scale, and structured interview with a clinical psychologist. The population comprised of 126 female SLE patients [median age: 27.5 years [interquartile range (IQR): 11]; median disease duration: 36 months (IQR 26)] and 110 female controls [median age 30 years (IQR 9)]. Clinical remission was seen in 65.9% (83/126) and complete remission in 34.1% (43/126). Significant fatigue was present in 18.3% (23/126). Both SF-12 physical component summary (PCS) and mental component summary (MCS) were similar between SLE patients and controls [median PCS: 50.3 (IQR: 16.2) vs. 48.6 (IQR: 11.6); median MCS: 57.2 (IQR: 4.8) vs. 57.9 (IQR: 7.6)]. In generalised linear modelling, PCS was associated with fatigue [odd's ratio (OR) 0.012, 95% confidence interval (CI) 0.006–0.025, $p < 0.001$], disease duration ≥ 5 years (OR 23.16, 95% CI 1.548–346.58, $p = 0.023$), and complete remission (OR 33.16, 95% CI 4.43–248.15, $p = 0.001$); MCS with fatigue (OR 0.53, 95% CI 0.34–0.84, $p = 0.007$) and absence of depression (OR 3.65, 95% CI 1.07–12.44, $p = 0.038$). Patients with SLE in remission report significant fatigue in 18.3% of subjects. Both PCS and MCS scores are similar to healthy controls. Better PCS was associated with less fatigue, longer disease duration, and complete remission. Better MCS was associated with less fatigue and absence of depression.

Keywords Clinical remission · Complete remission · Depression · Fatigue · Remission · Systemic lupus erythematosus · Quality of life

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease with fluctuating disease course characterized by periods of disease activity and remission [1]. Treatment of SLE targets organ-specific remission and prevention of organ damage and mortality and optimization of health-related quality of life (QoL) [2]. Health-related quality of life (QoL) is a multi-dimensional construct aimed at evaluations of different health perceptions and self-reported functional status. QoL is generally considered to be a key patient-reported outcome measure (PRO) in studies involving chronic disease. Patients with SLE in remission often perform worse on QoL measures compared to the general population [3], especially those with associated fibromyalgia or significant fatigue [4–6]. Self-reported QoL among patients with SLE is comparable to other diseases such as heart failure, end-stage airways disease, human

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immunodeficiency virus infection, and rheumatoid arthritis [7–9]. In contrast to these diseases, SLE is characterized by episodes of disease flare followed often by periods of quiescence. [10] It has been shown that non-remission of SLE is associated with more organ damage and consequent poor QoL [1, 11]. Association of poor QoL with disease activity is well known [12–15]. However, QoL parameters in lupus patients with remission are not clear. One issue may be that the varying definitions of remission taken in different studies or taking a relatively "soft" definition of remission. On the other hand, remission in a longitudinal sense, i.e., demonstrable remission over a period of time before inclusion into studies, is an important consideration that need to be addressed. Consequently, reports on QoL in lupus patients in durable remission, checked longitudinally, are relatively sparse.

As there are still no data on QoL of Indian SLE patients in remission, this study was carried out to describe quality-of-life parameters (QoL) among Indian female systemic lupus erythematosus patients in durable remission and to find out its predictors.

Patients and methods

This is a prospective study done from July, 2014 to May, 2017 and was done in the Department of Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, India. Adult female lupus patients fulfilling revised American College of Rheumatology classification criteria for SLE, 1997 (ACR 1997) were recruited [16].

Assessment of disease activity and damage

Disease activity of SLE was assessed by SLE disease activity index 2000 (SLEDAI), a validated instrument used extensively [17]. Organ damage was assessed by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR damage index) [18].

Definition of remission

Definition of remission was in line with European Consensus Criteria [19]. Clinical remission (CLR) was present when clinical SLEDAI score = 0 and physician global score < 0.5 (0–3). Complete remission (CR) was defined as clinical remission together with inactive hematological and biochemical parameters and normal lupus serology (anti-dsDNA and complements within normal range). The anti-dsDNA was measured by a commercially available ELISA kit (Euroimmun, Germany) and serum complement levels were assayed by nephelometry (Siemens, Germany).

Follow-up design and inclusion and exclusion criteria

Patients were screened at visit 0 for inclusion in the study and followed with once in 2-month visits for 3 such visits till last visit (visit 3) at 6th month. Following was a typical patient profile for screening at visit 0: currently, asymptomatic female lupus patient deemed to be in remission by the previous routine clinical visits for ≥ 6 months on stable dose of prednisolone (≤ 5 mg/day) and/or other immunosuppressive agents (methotrexate ≤ 15 mg/week or mycophenolate mofetil ≤ 1500 mg/day or azathioprine ≤ 100 mg/day). Final inclusion and classification into clinical remission (CLR) and complete remission (CR) were done at the 6th month visit (visit 3) and further assessments (vide infra) were done at that point of time. Clinical examination and serological and hematological studies were done at each visit including visits 0 and 3.

Inclusion criteria were: fulfillment of ACR 1997 criteria; female patients; appearance in all three consecutive bimonthly visits between visits 0 and 3; no change in immunosuppressive agents (prednisolone and/or other additional immunosuppressive agents limited to mycophenolate, azathioprine or methotrexate) between visits 0 and 3; attainment at least clinical remission (CLR) in visit 0; and maintenance of at least clinical remission (CLR) till visit 3.

Exclusion criteria were: not attaining at least clinical remission (CLR) between visits 0 and 3; serological or clinical flare between visits 0 and 3; any increase in prednisolone or other immunosuppressive dose between visits 0 and 3; hospitalization due to any cause during study period; pregnancy or lactation; any acute infection or chronic infection (HIV, hepatitis B or C, or tuberculosis) during the study period; presence of end-stage renal disease or renal replacement therapy; use of antiepileptic or psychiatric drugs during and up to 1 year before the onset of the study; and presence of organic brain syndromes such as active seizure disorder or psychosis; cerebrovascular accident; acute confusional state; delirium; aseptic meningitis; demyelinating syndrome; cranial neuropathy; encephalopathy; history of head trauma; hypothyroidism or diabetes mellitus; subjective memory complaints; visual problems not corrected by glasses, intellectual, or learning disability or other medical conditions unrelated to SLE that could affect cognition; and presence of any impairment/handicap or disability and SLICC/ACR damage index ≥ 1.

Control subjects

Age-matched female control subjects were recruited from healthy medical students and staff and family members

of patients and were administered the SF-12, FSS, and structured psychiatric interview. We also recorded age and years of formal education from the control subjects.

Assessments

QoL

We used the Medical Outcomes Study Short-Form-12 (SF-12), a validated, generic measure of HRQoL, to assess overall self-reported health, reported as physical (PCS) and mental (MCS) component summaries [20]. The SF-12, a shorter version of the longer SF-36, measures overall self-perceived health and 8 domains related to health status. MCS and PCS scores were calculated separately. In the general population, using norm–based methods, the mean ± standard deviation (SD) was 50 ± 10 [21]. Higher SF-12 scores indicate better QoL in both PCS and MCS domains. We used the English version of the SF-12.

Fatigue

Fatigue Severity Scale (FSS), a 9-item questionnaire, was used as primary fatigue assessment tool. FSS assesses the impact of fatigue on day-to-day functioning during the preceding couple of weeks as perceived by the patient. The maximum score is 7 and higher scores indicate worse fatigue. Scores ≥ 4 is taken as clinically relevant level of fatigue [22]. Psychometric properties of the FSS have been validated previously and FSS is a commonly used measure for this purpose in patients with SLE [22–24].

Clinical and demographic data

The following additional data were recorded: age, duration of disease, duration of remission (as determined by history and examination before visit 0), lupus-related manifestations before attainment of remission, presence or absence of hypovitaminosis D (< 20 ng/mL, in-house ELISA), and current immunosuppressive agents.

Clinical interview to rule out psychiatric disorders

The subjects were interviewed by a trained clinical psychologist in accordance with DSM IV-TR and ICD 10 DCR guidelines. Only those with mild depression were not excluded. All the other psychiatric disorders were ruled out.

Statistical analyses

Continuous variables were expressed as median [interquartile range (IQR)] as none of the variables of interest (SF-12 PCS, SF-12 MCS, and FSS) were normally distributed. Categorical variables were expressed as number (percentage). Comparisons of means were carried out using the Mann–Whitney *U* test and comparison of proportions using the Chi-squared test or Fisher's exact test as appropriate. Multivariate associations of PCS and MCS with various predictor variables among patients with lupus were tested with generalised linear modelling (GLM). All statistical analyses were done using the software package IBM SPSS v 21.

Ethical statement

All participants were informed of the study details and written informed consents were taken. The study protocol was reviewed and approved by the Institutional Ethics Committee (Memo no IPGME&R/IEC/2015/197).

Results

Baseline parameter in patients with lupus

We included 126 female SLE patients with median age 27.5 years (IQR: 11) and median duration of disease of 36 months (IQR 26). Baseline diagnoses at initiation at the rheumatology clinic are given in Table 1 along with current medications. All the patients were on hydroxychloroquine. At the time of inclusion in the study, clinical remission (CLR) was seen in 65.9% (83/126) and complete remission (CR) was seen in 34.1% (43/126). Median duration of remission was 18 months (IQR 24). Duration of remission achieved was for less than 1 year in 20 (15.9%), 1–2 years in 47 (37.3%), 2–3 years in 21 (16.7%), and > 3 years in 38 (30.2%). Hypovitaminosis D was present in 59.5% (75/126) lupus patients, which was similar in prevalence compared to control subjects (61.8%, 68/110, $p = 0.72$). Vitamin D levels were also comparable between patients with SLE and controls [respectively, median vitamin D levels were 16 (IQR: 10.63) and 15.3 (IQR: 10.86, $p = 0.44$)].

Control subjects and comparison between patients with SLE with controls

We also included 110 female controls with median age median age 30 years (IQR 9). Comparison of SLE cases with controls is given in Table 2. Control subjects were matched with SLE patients in terms of age, fatigue, and prevalence of depression. However, control subjects had higher number of years of formal education. In addition, SLE patients with depression had lower FSS compared to control subjects [median FSS (IQR): 1.59 (2.55) vs. 4.22 (2.61), $p = 0.00008$]. SLE patients without depression had comparable FSS score to control subjects without depression [median FSS (IQR): 2.55 (2.55) vs. 1.44 (1.72), $p = 0.09$].

Table 1 Baseline clinical features of patients with systemic lupus erythematosus (SLE)

Types	Manifestations	% (*n*)
Constitutional		40.5 (51)
Musculoskeletal	Arthralgia	39.7 (50)
	Myositis	25.4 (32)
Nephritis		36.5 (46)
Neuropsychiatric	Psychosis	7.9 (10)
	Seizure	3.9 (5)
Serositis	Pleuritis	20.6 (26)
	Pericarditis	11.3 (12)
Haematologic	AIHA	27.7 (35)
	Leucopenia	19.8 (25)
	Thrombocytopenia	9.5 (12)
Mucocutaneous	Alopecia	45.2 (57)
	Oral ulcer	33.3 (42)
	ALE	34.9 (44)
	SCLE	34.1 (43)
	DLE	19.8 (25)
Myocarditis		0.8 (1)
Current drugs		
Prednisolone	On prednisolone	38.1 (48)
	Dose (mg/day)	3.6 (1.6)[a]
Other immunosuppressant agents		58.7 (74)
Mycophenolate	On mycophenolate	18.3 (23)
	Dose (mg/day)	1456.5 (208)[a]
Azathioprine	On azathioprine	40.5 (51)
	Dose (mg/day)	71.5 (23)[a]

AIHA autoimmune haemolytic anaemia, *ALE* acute cutaneous lupus, *DLE* discoid lupus rash, *SCLE* subacute cutaneous lupus

[a]Mean (standard deviation)

Quality of life in patients with SLE in remission

Median SF-12 PCS among patients with SLE was 50.32 (IQR: 16.14) and median MCS was 57.16 (IQR: 4.74). PCS ≥ 50 was observed in 52.4% (66/126) and in MCS ≥ 50 was observed in 100%. Both the mean PCS and MCS scores were comparable between SLE patients and controls (Table 2).

Relationship of QoL in patients with lupus with predictor variables

Among SLE patients, PCS had a moderate inverse correlation with FSS ($r = -0.734$, $p < 0.001$) and no correlation with years of education ($r = -0.136$, $p = 0.128$) or age ($r = 0.09$, $p = 0.317$). MCS had weak inverse correlation with both FSS ($r = -0.307$, $p < 0.001$), years of education ($r = -0.249$, $p = 0.005$) and no correlation with age ($r = -0.131$, $p = 0.144$). Univariate association of PCS and MCS with various parameters is given in Table 3.

Results of multivariate GLM, in patients with SLE keeping PCS and MCS as dependent variables, are given in Tables 4 and 5.

PCS showed the following associations: FSS [odd's ratio (OR) 0.012, 95% confidence interval (CI) 0.006–0.025, $p < 0.0001$], disease duration ≤ 5 years (OR 0.042, 95% CI 0.003–0.612, $p = 0.02$), and complete remission (OR 33.16, 95% CI 4.43–248.15, $p = 0.001$).

MCS showed the following associations: FSS (OR 0.53, 95% CI 0.34–0.84, $p = 0.007$) and absence of depression (OR 3.65, 95% CI 1.07–12.44, $p = 0.038$).

Discussion

The present study showed that female patients with SLE in remission had comparable parameters of QoL, both physical and mental, compared to age-matched controls. However, among patients with SLE, those in complete remission (CR) showed significantly better PCS compared to those in only clinical remission (CLR). In multivariate modelling, PCS was negatively associated with fatigue and positively with longer disease duration and complete remission. MCS was also negatively associated with fatigue and depression.

The effect of SLE disease activity on QoL has been reported in the past [12–15]. A recent prospective international multicenter longitudinal cohort study reported that in addition to higher disease activity, disease-related damage also lowers QoL in childhood SLE patients [25]. However, assessment of QoL, a questionnaire-based technique, becomes difficult in SLE patients experiencing organ threatening or life-threatening complications. The question of "quality" of life is applicable more appropriately in functioning of day-to-day life. Current composite disease activity markers deal with parameters of specific organ involvement. When a patient is deemed in remission by these parameters such as the SLEDAI, the question of quality of life remains to be addressed.

QoL in SLE patients in remission or low disease activity state has been reported in a few previous studies only. In an uncontrolled childhood SLE study, Donnelly et al. reported that poor QoL was not uncommon and is not associated with disease activity or damage accrual [26]. In childhood SLE patients with well-controlled disease, i.e., with disease in remission, poor HRQoL was predicted by fatigue and mood disorder [26]. The presence of depression was 34% in their cohort compared to 38.1% in the present study and significant fatigue was present in 66% compared to 18% in the present study. Since comorbidity of depression with SLE is a commonly observed and reported finding, depression per se was not considered prudent to be ruled out in entirety.

Table 2 Comparison of demographics and quality-of-life parameters between patients with systemic lupus erythematosus (SLE) and controls

Parameters		Patients with SLE ($N=126$)	Control subjects ($N=110$)	p value
Age (in years)	Median (IQR)	27 (11)	30 (9)	0.159[a]
Years of formal education	Median (IQR)	10 (6.5)	11 (10)	0.028[a]
Depression	% (n)	38.1 (48)	37.3 (41)	0.89[b]
SF-12: MCS	Median (IQR)	50.3 (16.2)	48.6 (11.6)	0.074[a]
SF-12: MCS	Median (IQR)	57.2 (4.8)	57.9 (7.6)	0.442[a]
FSS	Median (IQR)	2.05 (2.5)	2.3 (2.9)	0.181[a]
FSS ≥ 4	% (n)	18.3 (23)	28.2 (31)	0.07[b]
Parameters	Patients with SLE ($N=48$)		Control subjects ($N=41$)	p value
Participants with depression				
FSS ≥ 4	% (n)	20.8 (10)	53.7 (22)	0.001[b]
Parameters	Patients with SLE $N=78$		Control subjects ($N=69$)	p value
Participants without depression				
FSS ≥ 4	% (n)	16.7 (13)	13 (9)	0.539[b]

FSS fatigue severity scale, *IQR* interquartile range, *MCS* mental component summary, *PCS* physical component summary

[a]Mann–Whitney U test

[b]Chi-squared test

Table 3 Comparison of quality-of-life parameters in patients with systemic lupus erythematosus (SLE) with demographic and disease-related parameters

SF-12 parameters	≤ Median (27 years) ($n=63$)	> Median (27 years) ($n=63$)	p value
Age			
PCS	47.9 ± 7.9	48.9 ± 8.5	0.37
MCS	58 ± 3.5	57.4 ± 3.5	0.56
SF-12 parameters	Present ($n=48$)	Absent ($n=78$)	p value
Depression			
PCS	48.4 ± 8.6	48.4 ± 7.8	0.765
MCS	58.3 ± 3.7	57.3 ± 3.3	0.062
SF-12 parameters	≤ 5 years ($n=99$)	> 5 years ($n=27$)	p value
Disease duration			
PCS	48.2 ± 8.02	49.3 ± 8.9	0.287
MCS	58.1 ± 3.3	56.2 ± 3.7	0.018
SF-12 parameters	≤ Median (18 months) ($n=65$)	> Median (18 months) ($n=61$)	p value
Duration of remission			
PCS	48.4 ± 8.3	48.4 ± 8	0.864
MCS	57.9 ± 3.4	57.5 ± 3.7	0.87
SF-12 parameters	Clinical remission ($n=83$)	Complete remission ($n=43$)	p value
Quality of remission			
PCS	46.5 ± 7.8	52.2 ± 7.7	< 0.001
MCS	57.8 ± 3.2	57.4 ± 3.9	0.85

MCS mental component summary, *PCS* physical component summary, *SD* standard deviation

All the comparisons of means were carried out using the Mann–Whitney U test

Table 4 Multivariate generalised linear model with SF-12: PCS as dependent variable

Predictors	B	SE	OR	95% CI of OR	*p* value
Age	0.07	0.06	1.07	0.95–1.21	0.26
Years of formal education	0.14	0.09	1.15	0.95–1.39	0.14
FSS	−4.39	0.35	0.012	0.006–0.025	<0.0001
Duration of disease ≥ 5 years	3.18	1.38	23.16	1.548–346.58	0.023
Duration of remission ≤ 18 months	−0.37	1.07	0.68	0.08–5.61	0.73
Complete remission	3.5	1.03	33.16	4.43–248.15	0.001

CI confidence interval, *FSS* fatigue severity scale, *MCS* mental component summary, *OR* odd's ratio, *PCS* physical component summary, *SD* standard deviation, *SE* standard error

Table 5 Multivariate generalised linear model with SF-12: MCS as dependent variable

Predictors	B	SE	OR	95% CI of OR	*p* value
Age	−0.078	0.042	0.925	0.852–1.005	0.064
Years of formal education	−0.074	0.063	0.929	0.821–1.051	0.242
FSS	−0.627	0.231	0.534	0.34–0.84	0.007
Absence of depression	1.296	0.625	3.654	1.073–12.446	0.038
Duration of disease ≥ 5 years	−1.077	0.893	0.341	0.059–1.96	0.228
Duration of remission ≤ 18 months	−1.039	0.700	0.354	0.09–1.394	0.137
Complete remission	−0.283	0.6995	0.354	0.09–1.394	0.672

CI confidence interval, *FSS* fatigue severity scale, *MCS* mental component summary, *OR* odd's ratio, *PCS* physical component summary, *SD* standard deviation, *SE* standard error

However, including moderate or severe depression was beyond the scope of this study, as it would require introducing more categorization of the sample. In healthy controls too, mild depression was, therefore, not excluded.

Mok et al. reported that SLE patients in remission ≥ 5 years had better QoL compared to patients not in remission [1]. A recent study from the Asia Pacific Lupus Collaboration reported that patients in low disease activity state (LLDAS) had better PCS ($p < 0.001$) and MCS ($p < 0.001$) scores [27]. Finally, Mishra et al. reported, from a small cohort, that SLE patients with low disease activity have worse PCS and MCS compared to controls [10]. In the Chinese study [1], no distinction was made between complete and clinical remission, cognitive assessment or assessment for depression was not done, and QoL was a secondary assessment. Significant damage accrual was observed which could adversely affect QoL assessment. In the Asia Pacific Lupus Collaboration study [27], damage was present in 35% and active renal disease at the time of assessment was present in 25.9% of participants. In fact, they reported that disease damage was negatively associated with PCS. In the small previous Indian study [10], no psychiatric assessment was done, damage accrual was not reported, low disease activity was not defined in a durable fashion, and 25% of their patients were on daily prednisolone ≥ 7.5 mg/day and mean prednisolone dose was 8.1 mg. In the present study, SLE patients were carefully selected, so that those with demonstrable durable remission were only selected and those with damage accrual were not included. In addition, a detailed psychiatric interview was conducted and those with other psychiatric issues other than depression were screened out. This ensured a relatively homogeneous population in well-controlled disease activity with relatively low dose prednisolone (mean 3.6 mg/day). It was observed that patients with SLE had similar QoL summary scales compared to healthy controls. However, in multivariate analysis, complete remission had higher odds of better PCS compared to clinical remission only. However, in the current cohort of patients with SLE without damage, those with longer disease duration showed better quality of life. One hypothesis is that longer disease duration with no damage implies better control of disease itself and consequently higher PCS. Another hypothesis could be, as disease duration increases, both duration of follow-up and possibility of complete remission also increase. Though the present study was not designed to test these hypotheses, it appears that prolonged time spent in clinical or complete remission without damage accrual affects QoL in a positive way.

Another important observation was that fatigue significantly affects both PCS and MCS in SLE patients in remission. In the present study, 18% patients with SLE had significant fatigue (FSS ≥ 4). Self-reported fatigue is not an uncommon concern among SLE patients in remission. A recent multinational European study estimated that around 15–30% of SLE patients in remission report significant fatigue [28]. Various theories have been postulated linking

widespread fatigue and systemic autoimmune diseases such as cytokine-induced "sickness behavior," which shares features with depression and anhedonia [29]. The presence of significant depressive symptoms may be associated with pro-inflammatory cytokines in a bi-directional relationship [30]. Likewise, in patients with SLE, a relationship between fatigue and mood disorders is often noted [31]. Other possible contributing factors are disease activity, use of immunosuppressant agents, vitamin D status, and thyroid status among others [29, 32]. In the present study, patients with hypothyroidism were excluded. Prevalence of hypovitaminosis D was similar to controls. Also excluded were patients with neuropsychiatric manifestations, which is another identified cause of fatigue. The presented cohort of patients with SLE was in durable remission and whether the cytokine theory holds in this subgroup is questionable. Association of fatigue with worse quality of life has been reported previously in other cohorts from the UK, Italy, and Peru [33–35]. However, population included in these studies is generally variable and includes both patients with low- and high-disease activities. SLE patients in the present study were in remission for a median duration of 18 months at the time of inclusion and additional 6 months of follow-up during the study protocol. In a cohort of childhood SLE, mostly inactive SLE patients, Donnelly et al. reported that fatigue and depressive symptoms predicted worsened QoL in a prospective study [26]. The current report shows that fatigue influences both physical and mental components QoL in SLE patients with remission.

The strengths of the present study are the relatively well-defined and homogeneous sample and presence of a control population. SLE patients with potential confounders in the assessment of QoL were thoroughly excluded and patients with damage accrual were not included.

Limitations of the study include: QoL was measured by a relatively short instrument (SF-12); lupus-specific instrument was not used; single-centre nature of the study; control subjects were taken from care givers, medical staff, and students; controls were not matched to the patients in terms of years of formal education, and Bengali version of SF-12 could not be used. However, certain points need to be highlighted. Control subjects were matched with SLE patients in terms of age, fatigue, and prevalence of depression. As the primary independent variables for analysis were fatigue and depression, our control groups did perform well in this setting. At the time of inception of this study, to the best of knowledge of the authors, no cross-culturally validated Indian translation was available for SF-12.

In conclusion, about a fifth of Indian female patients with SLE in remission had significant self-reported fatigue. Both PCS and MCS components of QoL among SLE patients in remission are similar to healthy controls. Better PCS was associated with less fatigue, longer disease duration, and complete remission. Better MCS was associated with less fatigue and absence of depression.

Author contributions RPG design of the study, acquisition, analysis, or interpretation of data, drafting the work, revising the work critically for important intellectual content, and final approval of the latest version. RC design of the study, acquisition, analysis, or interpretation of data, drafting the work, revising the work critically for important intellectual content, and final approval of the latest version. PG design of the study, acquisition of data, revising the work critically for important intellectual content, and final approval of the latest version. GS acquisition of data, revising the work critically for important intellectual content, and final approval of the latest version. AG acquisition of data, revising the work critically for important intellectual content, and final approval of the latest version. All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest The authors' declares that they have no conflict of interest.

Ethical standards The study protocol was reviewed and approved by the Institutional Ethics Committee (Memo no IPGME&R/IEC/2015/197).

Informed consent All participants were informed of the study details and written informed consents were taken.

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