LUPUS SCIENCE & MEDICINE™

Predictors of patient-reported outcomes phenotypes in SLE during remission: a cluster analysis approach

Elena Elefante ,[1] Francy Cruz-Sanabria,[2] Luca Gualtieri,[1] Chiara Stagnaro,[1] Dina Zucchi ,[1] Chiara Cardelli ,[1] Viola Signorini,[1] Linda Carli,[1] Francesco Ferro,[1] Chiara Tani,[1] Marta Mosca[1]

To cite: Elefante E, Cruz-Sanabria F, Gualtieri L, *et al*. Predictors of patient-reported outcomes phenotypes in SLE during remission: a cluster analysis approach. *Lupus Science & Medicine* 2025;**12**:e001673. doi:10.1136/lupus-2025-001673

EE and FC-S contributed equally.

Received 21 May 2025
Accepted 11 September 2025

[1]Rheumatology Unit, University of Pisa, Pisa, Italy
[2]Department of Developmental Neuroscience, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Foundation Stella Maris, Pisa, Italy

Correspondence to
Dr Marta Mosca; marta.mosca@unipi.it

ABSTRACT

Objective To identify different clusters of SLE patients in remission based on patient-reported outcomes (PROs) and clinical factors that predict cluster membership.

Methods A cross-sectional monocentric study of adult consecutive SLE outpatients in stable clinical remission. Clinical and laboratory data were collected. At enrolment, each patient completed PROs. A hierarchical clustering analysis based on PROs exploring fatigue (Functional Assessment of Chronic Illness Therapy), disease impact (Lupus Impact Tracker), mental and physical health (mental component summary and physical component summary of the Short Form 36) was performed. Logistic regression assessed predictors of cluster membership, adjusting for demographic and clinical variables.

Results 195 SLE patients were enrolled. Two distinct clusters emerged: a 'low symptom burden (LSB)' cluster, including 81/195 (41.5%) patients, and a 'high symptom burden (HSB)' cluster, including 114/195 (58.5%) patients. The HSB was characterised by worse scores in all PROs compared with the LSB. The HSB cluster exhibited older age at diagnosis (33.23±11.97 vs 27.75±11.57; p=0.002), less frequent previous renal involvement (33.3% vs 65.4%; p<0.001), more frequent previous neuropsychiatric lupus (17.2% vs 1.3%; p=0.001), more fibromyalgia (26.3% vs 5.3%; p=0.001) and ongoing glucocorticoid use (58.8% vs 37.0%; p=0.004). Fibromyalgia (OR 7.27, 95% CI 2.27 to 29.15, p=0.002) and glucocorticoid treatment (OR 3.05, 95% CI 1.43 to 6.77, p=0.005) were independently associated with higher likelihood of HSB membership; renal involvement was associated with LSB membership (OR 0.23, 95% CI 0.10 to 0.51, p≤0.001).

Conclusions Among SLE patients in remission, two distinct health-related quality of life phenotypes can be identified: an HSB and an LSB. Fibromyalgia and glucocorticoid treatment emerged as independent predictors of HSB. These findings underline the need to optimise disease management and align treatment goals with patient priorities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ SLE has a negative impact on patients' health-related quality of life (HRQoL). According to current literature, patients in stable and prolonged remission have a better physical HRQoL than patients not in remission. However, patterns of disease activity and HRQoL patterns seem to follow different trajectories.

WHAT THIS STUDY ADDS

⇒ In this study, we performed a hierarchical clustering analysis based on Patient Reported Outcomes (PROs) demonstrating that, even in a uniform and 'ideal' population of SLE patients in stable remission, two different HRQoL phenotypes can be identified: one characterised by a high symptom burden (HSB), and one characterised by a low symptom burden, in terms of fatigue, disease impact on daily living and physical and mental health. We also demonstrated that fibromyalgia and chronic glucocorticoid treatment are independent predictors of HSB.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlights that recognising the heterogeneity in patient-reported experiences is critical for optimising care. Future studies are needed to refine PROs-based stratification of SLE patients and tailored strategies to manage the disease.

INTRODUCTION

SLE is a chronic, systemic autoimmune disease characterised by a widespread range of clinical manifestations and an unpredictable course.[1]

The disease has a negative impact on patients' health-related quality of life (HRQoL), which refers to the impact that a disease and its treatment have on an individual's ability to function and his or her perceived well-being in physical, mental and social domains of life.[2] Therefore, the correlation between disease status and HRQoL is not straightforward.[3–5]

Current literature data coming from different lupus cohorts show that patients in stable and prolonged remission have a better mean HRQoL than patients not in remission, with a positive impact mostly on the physical well-being compared with mental

health-related domains.[6–9] According to a German longitudinal study on SLE patients, 60% of the physical component of the Short Form 36 (SF-36) is explained by clinical and laboratory findings and may therefore follow clinical remission, compared with only 25% of the mental component.[10] A post hoc analysis of the data from the BLISS-52 and BLISS-76 trials demonstrated that shorter time in remission than in low disease activity was required for a clinically important benefit in HRQoL, and longer time in remission for a benefit in mental compared with physical HRQoL aspects.[11]

However, the attainment of disease targets does not seem sufficient to determine a parallel improvement in patients' quality of life.[12]

Recently, Fung *et al* have examined the association between patterns of disease activity and HRQoL patterns among SLE patients followed at the Toronto Lupus Clinic. They demonstrated that disease activity and cumulative involvement of specific organ domains are not able to independently account for the long-term trajectories of physical or mental HRQoL in SLE. On the contrary, HRQoL trajectories seemed to be influenced by fibromyalgia and age at diagnosis.[13]

So, HRQoL has a multifactorial origin and factors other than disease status may influence patients' perception of their well-being.[14]

For this reason, in this study, we wanted to explore if, in an 'ideal' population of SLE patients, characterised by stable clinical remission, it is possible to identify different HRQoL profiles. So, the objectives of the study are: (1) to identify different subgroups of SLE patients in remission based on patient-reported outcomes (PROs), using a hierarchical clustering approach and (2) to identify predictors of cluster membership, using a logistic regression analysis.

METHODS

This is a cross-sectional monocentric study of adult consecutive SLE outpatients, fulfilling the 1997 American College of Rheumatology (ACR) classification criteria,[15] or 2012 SLICC classification criteria,[16] or 2019 European Alliance of Associations for Rheumatology (EULAR)/ACR classification criteria,[17] regularly followed at the Rheumatology Unit of Pisa. Patients were enrolled in this study between 2019 and 2023.

Patients were included in the study if they were in clinical remission, according to the DORIS definition,[18] for at least 6 months.

For each patient, the following data were retrieved from clinical records: demographics, disease duration, cumulative organ involvement, laboratory data, ongoing treatment and concomitant fibromyalgia. Disease activity was assessed by using the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Activity Index (SLEDAI)[19] and organ damage was assessed by using the SLICC-Damage Index (SLICC-DI).[20]

Moreover, at enrolment, each patient completed the following PROs: the SF-36 (Medical Outcomes Study SF-36) questionnaire to assess HRQoL. The survey captures the status of eight domains (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health) and the questionnaire results are then summarised into two global scores: the physical component summary (PCS) and the mental component summary (MCS). Each score ranges from 0 to 100, with higher values representing better self-perceived HRQoL[21 22]; the Lupus Impact Tracker (LIT) questionnaire to assess the impact of SLE on daily living which includes 10 questions about cognition, lupus medication, physical health, pain/fatigue impact, emotional health, body image and planning/desires/goals. This questionnaire provides a single summary score from 0 to 100, with lower scores signifying lower impact of SLE on patient life[23]; the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire to assess fatigue. The score ranges from 0 to 52, with lower scores indicating greater fatigue[24 25]; the Systemic Lupus Activity Questionnaire (SLAQ), which is a patient-reported assessment of subjective SLE disease activity. The SLAQ score includes a list of questions regarding 24 symptoms including constitutional, mucocutaneous, articular, respiratory, neuropsychiatric and gastrointestinal manifestations. Items are weighted according to their clinical importance and grouped into 17 categories; each item can be scored from 0 to 3 according to the severity of the symptom. The final SLAQ score sum can range from 0 to 47. The Italian version of the SLAQ questionnaire has been validated by Tani *et al*.[26]

Patients were not involved in the design, or conduct, or reporting of this study.

Statistical analysis

A clustering analysis, a data-driven approach allowing the identification of inherent structures within complex datasets, was used to identify different 'HRQoL profiles' based on PROs. We employed a hierarchical clustering approach, specifically Ward's method with Euclidean distance metric, chosen for its capability to handle multivariate continuous data and effectively identify distinct groups. Patient subgroups (clusters) were constructed based on multivariate standardised metrics evaluating PROs, including SF-36 PCS, SF-36 MCS, FACIT and LIT. The Clustering Process involved: (1) Standardisation of variables: All PRO variables (SF-36 PCS, SF-36 MCS, FACIT, LIT) were standardised to have a mean of 0 and an SD of 1 to ensure equal contribution to the analysis, (2) Distance calculation: We used the Euclidean distance metric to calculate the distances between each pair of standardised observations, (3) Application of Ward's method: We employed Ward's linkage method to merge clusters, minimising within-cluster variance at each step and (4) Determination of final clusters: The resulting dendrogram from the hierarchical clustering was cut at the level corresponding to two clusters, representing the

groups with low (LSB) and high symptom burden (HSB). This approach allowed us to robustly and objectively identify subgroups of SLE patients in remission, characterised by different HRQoL profiles, and facilitated subsequent analysis of factors associated with membership in each cluster.

Identified clusters were compared using parametric statistics (t-test) regarding clinical descriptors such as gender, age at evaluation, disease duration, damage (SLICC-DI score), patient-reported disease activity (SLAQ scores), cumulative organ involvement, fibromyalgia diagnosis, ongoing treatment (glucocorticoid (GC) therapy, hydroxychloroquine (HCQ), immunosuppressive (IS) therapy with conventional and biologic disease-modifying antirheumatic drugs) and variables used in the clustering process (PCS, MCS, FACIT, LIT). A logistic regression analysis explored the association between predictor variables and cluster membership, with the outcome variable being cluster membership derived from the hierarchical clustering analysis based on PROs. Participants were categorised into two clusters: Cluster 1 represented individuals with low-burden symptoms, while cluster 2 comprised individuals with high-burden symptoms. The initial full model included as predictor variables clinical descriptors: gender, age at evaluation, age at diagnosis, disease duration and damage (SLICC-DI score). Additionally, cumulative involvement in cutaneous, haematological, renal, joint and serositis manifestations of SLE was considered. Furthermore, a diagnosis of fibromyalgia and ongoing treatment regimens (GC, HCQ, IS, biologics) was included as predictor variables. To obtain a parsimonious model and minimise overfitting, we applied a stepwise model selection approach based on the Akaike information criterion (AIC), which retains predictors that contribute to overall model fit regardless of individual statistical significance. Adjusted ORs, 95% CIs and p values were reported for each retained variable. Variables achieving a significance level of $p<0.05$ were retained in further models exploring the interaction between variables as predictors of cluster membership. All statistical analyses were conducted using R V.4.3.1 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

A total of 195 SLE patients over a total of 264 consecutive outpatients evaluated at our clinic in the same period were included in the study as they met our inclusion criteria for remission. Patients were predominantly female (92.3%) with a mean age at evaluation of 47.1±13.2 years and a mean age at SLE diagnosis of 30.9±12.1 years. Unsupervised hierarchical cluster analysis, using patient-reported fatigue (measured through FACIT), disease impact (LIT), mental and physical health (PCS and MCS of SF-36), identified two distinct clusters

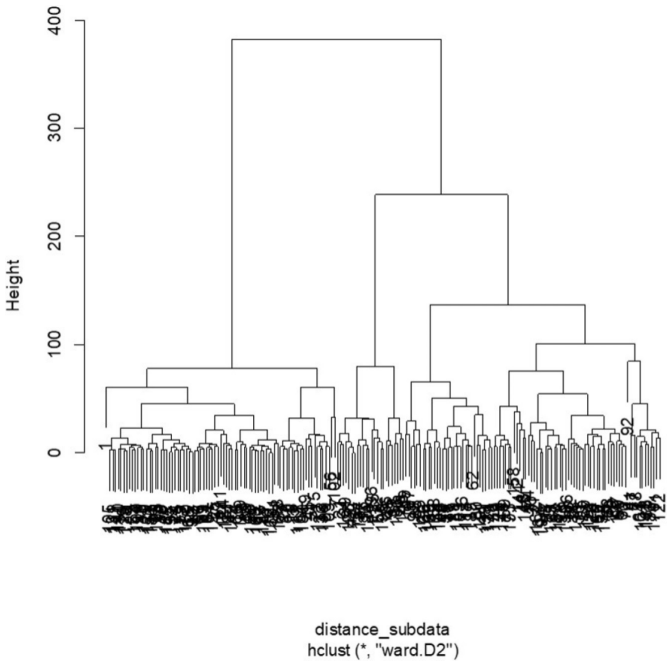

Figure 1 Cluster dendrogram. Dendrogram summarising the hierarchical clustering results based on patient-reported outcomes. Clusters were identified using Ward's method with a Euclidean distance metric, leveraging standardised metrics from the SF-36 Physical Component Summary, SF-36 Mental Component Summary, Functional Assessment of Chronic Illness Therapy and Lupus Impact Tracker. SF-36, Short Form 36.

(figure 1). Cluster 1, including 81/195 (41.5%) patients, was labelled as 'LSB', while cluster 2, including 114/195 (58.5%) patients, was labelled as 'HSB'. The HSB cluster exhibited significantly worse scores in all PROs compared with the LSB cluster, indicating a poorer HRQoL in all the aspects explored.

The identified clusters exhibited significant differences concerning age at diagnosis, prevalence of renal and neuropsychiatric past involvement, concomitant fibromyalgia and ongoing GC treatment. Specifically, the HSB cluster demonstrated older age at diagnosis (HSB=33.23±11.97 vs LSB=27.75±11.57, p=0.002), a lower proportion of past renal involvement (LSB=65.4% vs HSB=33.3%, p<0.001), a higher proportion of past neuropsychiatric SLE (NPSLE) (HSB=17.2% vs LSB=1.3%, p=0.001) and a more frequent concomitant fibromyalgia diagnosis (HSB=26.3% vs LSB=5.3%, p=0.001), as well as a higher proportion of patients being treated with a low dose of GC (HSB=58.8% vs LSB=37%, p=0.004), when compared with the LSB cluster. Interestingly, despite all patients being in remission, the HSB group also showed higher scores of the SLAQ questionnaire compared with the LSB (HSB=12.61±6.43 vs LSB=3.9±3.07, p<0.001), suggesting a worse self-perception of disease activity (table 1).

In the final logistic regression model, several variables were significantly associated with membership in the HSB cluster. The presence of fibromyalgia (OR 7.27, 95% CI

Table 1 Descriptive data of identified clusters and parametric between-group comparisons

	Low symptom burden cluster	High symptom burden cluster	P value
	N=81	N=114	
Sex=female (%)	75 (92.6)	105 (92.1)	1.000
Age at evaluation (mean (SD))	44.94 (12.98)	48.56 (13.26)	0.065
Age at diagnosis (mean (SD))	27.75 (11.57)	33.23 (11.97)	0.002*
Disease duration (mean (SD))	16.70 (11.03)	14.45 (10.91)	0.172
SLICC-DI (mean (SD))	0.63 (0.94)	1.07 (1.61)	0.038*
Cutaneous cum†=yes (%)	45 (58.4)	55 (54.5)	0.705
Haematologic cum†=yes (%)	44 (56.4)	49 (49.0)	0.406
Renal cum†=yes (%)	51 (65.4)	34 (33.3)	<0.001*
Articular cum†=yes (%)	46 (59.0)	75 (72.8)	0.072
Serositis cum†=yes (%)	11 (14.1)	23 (22.8)	0.203
Neuropsychiatric cum†=yes (%)	1 (1.3)	17 (17.2)	0.001*
Fibromyalgia=diagnosis (%)	4 (5.3)	26 (26.3)	0.001*
GC=yes (%)	30 (37.0)	67 (58.8)	0.004*
HCQ=yes (%)	67 (82.7)	88 (77.2)	0.446
IS=yes (%)	36 (44.4)	40 (35.4)	0.261
Biologic=yes (%)	7 (8.6)	17 (15.0)	0.265
PCS (mean (SD))	54.51 (6.38)	43.37 (10.71)	<0.001*
MCS (mean (SD))	52.57 (8.04)	40.17 (10.32)	<0.001*
SLAQ (mean (SD))	3.90 (3.07)	12.61 (6.43)	<0.001*
FACIT (mean (SD))	47.60 (4.91)	32.69 (9.84)	<0.001*
LIT (mean (SD))	5.90 (4.39)	38.16 (17.61)	<0.001*

Demographic, clinical, treatment-related and patient-reported outcome (PRO) characteristics are presented for patients in the low symptom burden (LSB) and high symptom burden (HSB) clusters. Categorical variables are expressed as n (%) and continuous variables as mean (standard deviation). Between-group comparisons were performed using chi-squared or Fisher's exact test for categorical variables and independent-samples t-tests for continuous variables.
*Statistically significant p-values (p<0.05).
†Cumulative organ involvement during the disease course.
FACIT, Functional Assessment of Chronic Illness Therapy; GC, glucocorticoid; HCQ, hydroxychloroquine; IS, immunosuppressive; LIT, Lupus Impact Tracker; MCS, mental component summary; PCS, physical component summary; SLAQ, Systemic Lupus Activity Questionnaire; SLICC-DI, SLICC-Damage Index.

2.27 to 29.15, p=0.002) and GC use (OR 3.05, 95% CI 1.43 to 6.77, p=0.005) were strongly associated with higher odds of belonging to the high burden group. In contrast, a history of renal involvement was associated with significantly lower odds of HSB (OR 0.23, 95% CI 0.10 to 0.51, p<0.001). HCQ use showed a non-significant trend toward reduced odds (OR 0.41, 95% CI 0.14 to 1.14, p=0.094), and age at diagnosis showed a borderline association (OR 1.03, 95% CI 1.00 to 1.06, p=0.079). Likewise, a history of neuropsychiatric symptoms (NPSLE) showed a trend toward association with HSB (OR 8.35, 95% CI 1.31 to 167.79, p=0.061), though this did not reach statistical significance (see table 2). Variables that did not reach conventional statistical significance (p<0.05) were retained in the model as part of the stepwise AIC-based selection process, which accounts for their contribution to overall model performance and prioritises overall model fit rather than individual p values. Finally, to assess potential synergistic effects between significant predictors, we tested pairwise interaction terms (fibromyalgia×GC, fibromyalgia×renal involvement, GC×renal involvement) in separate logistic regression models. None of the interactions significantly improved model fit compared with the final main effects model, as evaluated by likelihood ratio tests. Thus, interaction terms were not retained in the final model.

DISCUSSION

In this study, we performed a cluster analysis among SLE patients to identify different patients' subgroups based on PROs. We included only patients in stable remission that could represent a uniform and ideal cohort of patients who are supposed to behave similarly with respect to HRQoL.

Conversely, the study results show that a heterogeneity exists as far as HRQoL is concerned among individuals with well-controlled SLE. In fact, starting from the PROs results, we were able to identify two different phenotypes of remitted patients with SLE: one characterised by an HSB, and one characterised by an LSB, in terms of fatigue, disease impact on daily living and physical and

Table 2 Logistic regression model predicting high symptom burden cluster membership

Variable	OR	CI_lower	CI_upper	P value
(Intercept)	0.996	0.231	4.333	0.996
Age at diagnosis	1.03	1.00	1.06	0.079
Fibromyalgia diagnosis (yes vs no)	7.27	2.27	29.15	0.002
Renal cumulative (yes vs no)	0.23	0.10	0.51	<0.001
NPSLE cumulative (yes vs no)	8.35	1.31	167.79	0.061
Glucocorticoid use (yes vs no)	3.05	1.43	6.77	0.005
Hydroxychloroquine use (yes vs no)	0.41	0.14	1.14	0.094

Logistic regression model showing the association between clinical and treatment-related variables and the likelihood of belonging to the high symptom burden cluster among patients with Systemic Lupus Erythematosus (SLE) in clinical remission. The model was selected using a stepwise AIC-based approach.
Odds ratios (OR), 95% confidence intervals (CI) and p-values are reported. Binary predictors coded as 0 = no and 1 = yes; odds ratios represent the odds of being in the high symptom burden cluster for "yes" vs "no" categories.
NPSLE, neuropsychiatric SLE.

mental health, confirming that the relationship between HRQoL and disease activity measures is controversial.

In a recent study by Touma *et al*, in a large cohort of SLE patients, four different clusters were identified starting from signs and symptoms of disease activity (very mild, mild, moderate and severe). PROs across the clusters showed some differences for fatigue and anxiety/depression only between the 'extreme' clusters (very mild and severe), while patients in the 'intermediate' clusters (mild and moderate) did not present significant differences in HRQoL.[27]

More recently, among patients attending the Toronto Lupus Clinic, Gupta *et al* described three distinct clusters based on patient-reported symptoms (perceived cognitive deficits, anxiety, depression, fatigue, HRQoL); The three clusters presented a growing symptom burden (mild, moderate and severe) but symptom severity did not correlate with disease activity.[28]

Margiotta *et al* performed a study in two Italian cohorts of SLE patients, identifying three clusters based on HRQoL, fatigue, pain and depression: one was characterised by good physical and mental HRQoL, low fatigue and depression; one presented reduced mental but preserved physical HRQoL and the last one was characterised by reduced both mental and physical HRQoL, with particularly high levels of bodily pain and a higher prevalence of fibromyalgia. Interestingly, SLEDAI scores did not differ significantly among these three clusters, but patients in the third cluster presented a lower prevalence of prolonged remission.[29]

In our cohort of remitted patients, we were able to identify only two subgroups of patients that differ markedly in all the aspects of HRQoL considered, both mental and physical, suggesting that among patients who perceive their HRQoL and health status as poor, all aspects are affected equally. Moreover, patients in the HSB cluster presented higher SLAQ scores compared with those in the LSB cluster, indicating that a poorer HRQoL is accompanied by a tendency to overestimate disease activity by the patients, potentially leading to a patient-physician discordance in the evaluation of disease status and patient dissatisfaction.[30]

In a large study among patients with primary Sjögren's syndrome, patient-reported symptoms were used to identify four subgroups of patients which also presented distinct clinical and biological profiles, suggesting that these are true endotypes, and these patients are likely to differ in their response to targeted therapies.[31] So, we can speculate that different PROs-based phenotypes among SLE patients too may identify two different 'pathobiological' endotypes of remission in SLE.

The complexity and heterogeneity of SLE has led to diverse proposed approaches to identify phenotypes of SLE manifestations.[28] Among these ones, Pisetsky *et al*[32] proposed a model according to which SLE manifestations may be divided into two categories: Type 1 SLE includes the classical symptoms of 'active inflammatory' disease, while type 2 SLE includes symptoms such as fatigue, widespread body pain, depression, anxiety, cognitive dysfunction and sleep disturbance that are often unrelated to periods of disease activity as conventionally defined and do not respond to therapy with GC and immunosuppressants. Therefore, a better understanding of the underlying mechanisms of type 2 SLE is needed, and it may be difficult to clearly distinguish between type 2 lupus and lupus in remission with dominant symptoms of fibromyalgia.

Our findings regarding predictors of cluster membership provide further insights into factors influencing HRQoL in SLE remission. A comorbid fibromyalgia and ongoing GC treatment emerged as significant and independent predictors of belonging to the HSB cluster, indicating their potential role in exacerbating symptom burden and impacting HRQoL outcomes.

It is well-known from the literature that fibromyalgia is one of the main determinants of poor HRQoL in SLE.[13 33] Actually, the persistence of symptoms like pain and fatigue, even in a condition of remission, represents an important unmet need in the management of SLE from the patient perspective,[34 35] and these symptoms are reported as the most burdensome symptoms for patients, impairing their

ability to perform daily activities[36 37]; moreover, they are often the drivers for patients seeking medical help and using healthcare resources.[31]

It is interesting to underline that GC treatment, even at the low dosage allowed by the definition of remission, in our cohort predicts an HSB from the patient perspective. A growing attention in the literature[38] and in the latest EULAR recommendations[39] is given to the withdrawal of GC in patients with SLE, considering the importance of preventing GC-related damage accrual and comorbidities. Our results suggest that withdrawal GC is an element to be considered in the management of patients with SLE, also to improve patients' HRQoL.

Cumulative renal involvement in our study was associated with a higher likelihood of belonging to the LSB cluster, suggesting a potential protective effect on HRQoL. This observation aligns with existing evidence indicating that renal involvement tends to have a lesser impact on HRQoL compared with milder organ manifestations, as patients often do not perceive symptoms related to renal dysfunction.[40] Notably, in our cohort, patients with past renal involvement also exhibited less frequent articular involvement, a manifestation commonly associated with worse HRQoL. This interplay between organ involvement and perceived quality of life warrants further investigation to clarify these associations.

Past NPSLE was more frequent in the HSB cluster, highlighting its role as a severe organ involvement and its potential to impact patients' HRQoL, even many years after the acute manifestations. In our study, when analysing the entire cohort, patients with past NPSLE showed significantly lower MCS scores compared with those without NPSLE, while no significant differences were observed in other PROs. Supporting these findings, a large Chinese cohort study identified a link between a history of neuropsychiatric events and impaired general health subscale scores, with cognitive impairment specifically associated with lower mental health subscale scores.[41] Similarly, a study of SLE patients from a tertiary clinic in Leiden, referred for neuropsychiatric symptoms, reported significantly reduced mean MCS scores. Notably, improvements in HRQoL over time were observed only in patients whose neuropsychiatric symptoms were not related to SLE.[42] Taken together, these findings align with our results, underscoring the enduring impact of NPSLE on mental health domains of HRQoL and the importance of addressing these issues even in remission.

The limitations of this study include: first, the relatively small sample size that limited the possibility of performing sub-analyses within each cluster or examining the impact of specific past disease manifestations, such as neuropsychiatric involvement; second, the cross-sectional design of the study that precludes an evaluation of temporal changes and causality between factors influencing HRQoL; third, the study does not account for all potential variables that may affect HRQoL, including depression and anxiety symptoms at the moment of the evaluation, which are highly prevalent in this clinical population and can be associated with worse PROs. Future longitudinal studies are needed to investigate the dynamic changes in PROs over time, even among remitted patients, to better identify factors influencing HRQoL.

However, we believe that our study offers the opportunity to analyse an ideal population of SLE patients in remission and with low organ damage, through complete clinical and PRO data.

Overall, our findings confirm the importance of considering HRQoL as an independent disease outcome in SLE. In particular, this study underscores the importance of considering patient-reported symptoms-based stratification, particularly during periods of remission, as a clinically meaningful approach for identifying different patients' profiles and developing targeted interventions to optimise SLE outcomes from the patient perspective. However, further research is warranted to address the heterogeneity of patient experience and explore other stratification strategies and additional factors influencing HRQoL in SLE.

In conclusion, this study used cluster analysis to identify subgroups among SLE patients in remission based on PROs. Despite the uniform condition of remission, our findings identified two distinct HRQoL phenotypes: an HSB group and an LSB group, differing in fatigue, disease impact, physical and mental health, and self-perception of disease activity. This highlights the complexity of the relationship between HRQoL and disease activity. Recognising and addressing the heterogeneity in patient-reported experiences is critical for optimising care and aligning treatment goals with patient priorities. Further research is warranted to refine PROs-based stratification strategies and explore additional determinants of HRQoL in SLE, paving the way for more personalised and effective management approaches.

Contributors EE and FC-S contributed to the conception and design of the study and to the acquisition of data, to the analysis and interpretation of data and were in charge of writing the manuscript. LG, CS, DZ, CC, VS, LC and FF actively contributed to the acquisition of data and drafting of the manuscript. CT and MM contributed to the conception and design of the study, to the analysis and the interpretation of data and contributed to write the manuscript, supervising all the work. All the authors have read and approved the final version of the article. MM is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involved human participants and was approved by the ethics committee 'Comitato Etico di Area Vasta Nord Ovest' (CEAVNO), reference number 14478. All participants provided informed consent before taking part in the study

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs
Elena Elefante http://orcid.org/0000-0003-0657-485X
Dina Zucchi http://orcid.org/0000-0002-2161-2562
Chiara Cardelli http://orcid.org/0000-0001-6407-6213

REFERENCES

1 Fava A, Petri M. Systemic lupus erythematosus: Diagnosis and clinical management. *J Autoimmun* 2019;96:1–13.
2 Panopalis P, Clarke AE. Quality of life in systemic lupus erythematosus. *Clin Dev Immunol* 2006;13:321–4.
3 Schmeding A, Schneider M. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2013;27:363–75.
4 Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? *J Rheumatol* 2005;32:1706–8.
5 Alarcón GS, McGwin G Jr, Brooks K, *et al*. Systemic lupus erythematosus in three ethnic groups. XI. Sources of discrepancy in perception of disease activity: a comparison of physician and patient visual analog scale scores. *Arthritis Rheum* 2002;47:408–13.
6 Tsang-A-Sjoe MWP, Bultink IEM, Heslinga M, *et al*. The relationship between remission and health-related quality of life in a cohort of SLE patients. *Rheumatology (Sunnyvale)* 2019;58:628–35.
7 Mok CC, Ho LY, Tse SM, *et al*. Prevalence of remission and its effect on damage and quality of life in Chinese patients with systemic lupus erythematosus. *Ann Rheum Dis* 2017;76:1420–5.
8 Ugarte-Gil MF, Gamboa-Cárdenas R, Reátegui-Sokolova C, *et al*. Low Disease ActivityState/Remission Predicts a Better Health-Related Quality of Life in Systemic LupusErythematosus Patients. *Arthritis Care Res* 2019.
9 Shi Y, Li M, Liu L, *et al*. Relationship between disease activity, organ damage and health-related quality of life in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmun Rev* 2021;20:102691.
10 Vordenbäumen S, Brinks R, Sander O, *et al*. Determinants of health-related quality of life in systemic lupus erythematosus: a monocentric, retrospective long-term observational study in Germany. *Z Rheumatol* 2019;78:813–9.
11 Emamikia S, Oon S, Gomez A, *et al*. Impact of remission and low disease activity on health-related quality of life in patients with systemic lupus erythematosus. *Rheumatology (Sunnyvale)* 2022;61:4752–62.
12 Hanly JG. Disease activity, cumulative damage and quality of life in systematic lupus erythematosus: results of a cross-sectional study. *Lupus (Los Angel)* 1997;6:243–7.
13 Fung W, Lim LSH, Tomlinson G, *et al*. Joint trajectories of disease activity, and physical and mental health-related quality of life in an inception lupus cohort. *Rheumatology (Sunnyvale)* 2020;59:3032–41.
14 Tamayo T, Fischer-Betz R, Beer S, *et al*. Factors influencing the health related quality of life in patients with systemic lupus erythematosus: long-term results (2001--2005) of patients in the German Lupus Erythematosus Self-Help Organization (LULA Study). *Lupus (Los Angel)* 2010;19:1606–13.
15 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
16 Petri M, Orbai A-M, Alarcón GS, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
17 Aringer M, Costenbader K, Daikh D, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Ann Rheum Dis* 2019;78:1151–9.
18 van Vollenhoven R, Voskuyl A, Bertsias G, *et al*. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76:554–61.
19 Griffiths B, Mosca M, Gordon C. Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. *Best Pract Res Clin Rheumatol* 2005;19:685–708.
20 Gladman DD, Goldsmith CH, Urowitz MB, *et al*. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. *J Rheumatol* 2000;27:373–6.
21 Stoll T, Gordon C, Seifert B, *et al*. Consistency and validity of patient administered assessment of quality of life by the MOS SF-36; its association with disease activity and damage in patients with systemic lupus erythematosus. *J Rheumatol* 1997;24:1608–14.
22 Gladman D, Urowitz M, Fortin P, *et al*. Systemic Lupus International Collaborating Clinics conference on assessment of lupus flare and quality of life measures in SLE. Systemic Lupus International Collaborating Clinics Group. *J Rheumatol* 1996;23:1953–5.
23 Jolly M, Garris CP, Mikolaitis RA, *et al*. Development and Validation of the Lupus Impact Tracker: A Patient-Completed Tool for Clinical Practice to Assess and Monitor the Impact of Systemic Lupus Erythematosus. *Arthritis Care & Research* 2014;66:1542–50.
24 Lai JS, Beaumont JL, Ogale S, *et al*. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. *J Rheumatol* 2011;38:672–9.
25 Goligher EC, Pouchot J, Brant R, *et al*. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. *J Rheumatol* 2008;35:635–42.
26 Tani C, Vagelli R, Stagnaro C, *et al*. Translation, cultural adaptation and validation of the Systemic Lupus Erythematosus Activity Questionnaire (SLAQ) in a cohort of Italian systemic lupus erythematosus patients. *Lupus (Los Angel)* 2018;27:1735–41.
27 Touma Z, Hoskin B, Atkinson C, *et al*. Systemic Lupus Erythematosus Symptom Clusters and Their Association With Patient-Reported Outcomes and Treatment: Analysis of Real-World Data. *Arthritis Care & Research* 2022;74:1079–88.
28 Gupta A, Johnson S, Barraclough M, *et al*. Outcome clusters and their stability over 1 year in patients with SLE: self-reported and performance-based cognitive function, disease activity, mood and health-related quality of life. *Lupus Sci Med* 2024;11:e001006.
29 Margiotta DPE, Fasano S, Basta F, *et al*. Clinical features of patients with systemic lupus erythematosus according to health-related quality of life, entity of pain, fatigue and depression: a cluster analysis. *Clin Exp Rheumatol* 2019;37:535–9.
30 Elefante E, Tani C, Stagnaro C, *et al*. Articular involvement, steroid treatment and fibromyalgia are the main determinants of patient-physician discordance in systemic lupus erythematosus. *Arthritis Res Ther* 2020;22:241.
31 Tarn JR, Howard-Tripp N, Lendrem DW, *et al*. Symptom-based stratification of patients with primary Sjögren's syndrome: multi-dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. *The Lancet Rheumatology* 2019;1:e85–94.
32 Pisetsky DS, Clowse MEB, Criscione-Schreiber LG, *et al*. A Novel System to Categorize the Symptoms of Systemic Lupus Erythematosus. *Arthritis Care & Research* 2019;71:735–41.
33 Ceccarelli F, Ciancarella C, Pirone C, *et al*. Fibromyalgia, mood disorders and chronic damage are the main determinants of worse quality of life in systemic lupus erythematosus patients: Results from a cross-sectional analysis. *Lupus (Los Angel)* 2024;33:1584–93.
34 Tamirou F, Arnaud L, Talarico R, *et al*. Systemic lupus erythematosus: state of the art on clinical practice guidelines. *RMD Open* 2018;4:e000793.
35 Cornet A, Andersen J, Myllys K, *et al*. Living with systemic lupus erythematosus in 2020: a European patient survey. *Lupus Sci Med* 2021;8:e000469.
36 Golder V, Ooi JJY, Antony AS, *et al*. Discordance of patient and physician health status concerns in systemic lupus erythematosus. *Lupus (Los Angel)* 2018;27:501–6.
37 Morgan C, Bland AR, Maker C, *et al*. Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. *Lupus (Los Angel)* 2018;27:681–7.
38 Zucchi D, Cardelli C, Elefante E, *et al*. Treat-to-Target in Systemic Lupus Erythematosus: Reality or Pipe Dream. *J Clin Med* 2023;12:3348.
39 Fanouriakis A, Kostopoulou M, Andersen J, *et al*. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. *Ann Rheum Dis* 2024;83:15–29.
40 Appenzeller S, Clarke AE, Panopalis P, *et al*. The relationship between renal activity and quality of life in systemic lupus erythematosus. *J Rheumatol* 2009;36:947–52.
41 Tam L-S, Wong A, Mok VCT, *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.
42 Monahan RC, Beaart-van de Voorde LJJ, Steup-Beekman GM, *et al*. Neuropsychiatric symptoms in systemic lupus erythematosus: impact on quality of life. *Lupus (Los Angel)* 2017;26:1252–9.