

Health-related quality of life, fatigue and health utilities in lupus nephritis: A systematic literature review

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease characterized by abnormal B-cell activation and the presence of autoantibodies, which can result in organ damage. Lupus nephritis (LN) is the most common severe organ manifestation of SLE and may result in impaired kidney function. However, there is limited research on the health-related quality of life (HRQoL) burden amongst patients with LN. The objective of this systematic literature review was to assess the HRQoL, fatigue and health utilities associated with LN.

Methods: A structured literature search (GSK Study 212980) of the MEDLINE and Embase databases was conducted in July 2019 and updated September 2021. Relevant international congress abstracts from 2016 to 2021 were searched, and gray literature searches and keyword-based searches in PubMed, Google, and Google Scholar were also conducted. Results were screened according to predefined criteria and data on the outcomes of interest were extracted. A quantitative analysis was conducted to supplement the narrative review, to provide 36-item Short Form survey (SF-36) estimates, and to determine variation by prognostic factors.

Results: Of 1155 articles identified, 26 studies for a total of 3440 patients were included. Patients with LN showed poorer HRQoL and more fatigue than healthy controls/the general population, although these were similar between patients with SLE with and without LN. HRQoL was worse in patients with LN Class III/IV or with active disease. Fatigue was generally reported as the most burdensome symptom and was associated with lower HRQoL and increased treatment dissatisfaction. During induction treatment, HRQoL and fatigue were improved with mycophenolate mofetil versus cyclophosphamide. HRQoL improved over time with treatment amongst patients with active LN. Very limited data were identified assigning utilities to health states for cost-effectiveness analysis. Nine studies were considered for quantitative analysis of baseline SF-36 scores. The analysis suggested that LN has a significant impact across all SF-36 domains, with the lowest scores in the general health perceptions and role-physical domains and physical component summary.

Conclusions: There is a large HRQoL burden in patients with LN, in particular regarding symptoms of fatigue. Future research should focus on investigating fatigue severity and health utilities in LN.

Keywords

Lupus erythematosus, systemic, lupus nephritis, health-related quality of life, fatigue, health utilities

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Introduction

Systemic lupus erythematosus (SLE) is a multifaceted, chronic, autoimmune disease that primarily affects women of childbearing age.¹ It is characterized by abnormal B-cell activation and the presence of autoantibodies, resulting in systemic or organ-specific manifestations that can affect the skin, joints, blood cells and kidneys.^{2,3} Patients with SLE carry a high disease burden, including a significant reduction in health-related quality of life (HRQoL). Fatigue in

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particular, but also depression and pain, contribute to the substantial humanistic burden of this disease.⁴

Lupus nephritis (LN) is a form of glomerulonephritis that results in impaired kidney function and is the most common severe organ manifestation of SLE.^{3,5} Approximately 30%–40% of patients with SLE will develop clinically diagnosed LN over the course of the disease, with increased prevalence in non-Caucasian populations.^{5–10} Furthermore, approximately 20% of patients with LN progress to end-stage kidney disease (ESKD) within 10 years of diagnosis,^{5,11} requiring dialysis or renal transplant, and having a significant impact on all aspects of patients' lives.¹²

Symptoms of LN arising from chronic kidney disease (CKD) commonly include foamy urine, edema of the face, hands and legs, and high blood pressure.¹³ Importantly, patients with LN carry the additional symptom burden associated with nonrenal SLE, including joint pain and fatigue.^{13,14} Fatigue is also one of the most common symptoms reported by people with CKD.¹⁵

Previous literature reviews have assessed the substantial effect of SLE on HRQoL, socioeconomic burden and work disability, which include potentially modifiable contributors such as controlling disease activity and preventing or minimizing organ damage.^{4,16,17} However, there is limited research in these areas focusing specifically on the HRQoL burden amongst the subgroup of patients with SLE and LN.

As new therapies emerge for the treatment of LN, patients, physicians, and payers will seek to understand the relevance of the drugs' clinical efficacy and tolerability profile for the patient. In many countries, cost-effectiveness analyses estimating the cost per quality-adjusted life-year (QALY) gained by new treatments for LN will inform reimbursement decisions. This emphasizes the need for robust utility estimates, representing the strength of an individual's preference for specific outcomes that are required by the cost per QALY approach.

In light of these factors, this systematic literature review (SLR; GSK Study 212980) was designed to assess the impact of LN on HRQoL, fatigue, and health utilities, to understand how they may change over time and how they may vary with LN class, disease activity, treatment, and other factors. Specifically, this SLR presents the impact of LN on HRQoL using 36-item Short Form survey (SF-36) domain and summary scores, as well as other measures including the Lupus Patient-Reported Outcome (LupusPRO) tool, Pediatric Quality of Life Inventory (PedsQL) and Pediatric Quality of Life Inventory-Rheumatology Module (PedsQL-RM) survey scores. Additionally, the impact of LN on fatigue is presented using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale, Fatigue Scale for Motor and Cognitive functions (FSMC), Fatigue Visual Analog Scale (VAS), total Krupp Fatigue Severity Scale (FSS), and SLE Symptom Checklist (SSC) scores.

Materials and methods

Study design

A structured search of the literature was performed using the search strategy presented in [Supplementary Table 1](#) on 15 July 2019 with no limit on the publication date, using the Medical Literature Analysis and Retrieval System Online (MEDLINE) and the Excerpta Medica Database (Embase). The searches were updated on 2 September 2021.

The structured search was complemented by gray keyword-based literature searches (Google, Google Scholar, and PubMed) and back-referencing of studies published from 2016 onward ([Supplementary Table 2](#) provides the keyword-based search terms). Relevant international congress abstracts were also searched, covering the American College of Rheumatology (ACR)/Association of Rheumatology Professionals (ARP) Annual Meeting 2016–2021; the European League Against Rheumatism (EULAR) Annual European Congress of Rheumatology 2017–2021; the European Lupus Meeting 2016, 2018, and 2020; and the LUPUS International Congress on SLE 2017, 2019, and 2021.

Eligibility criteria

The parameters used to identify relevant publications were study type, population, intervention, comparators, outcomes, and language. The study types eligible for inclusion in the SLR were: observational studies (prospective cohort, retrospective cohort, case-control, and cross-sectional studies) and clinical trials (randomized control trials [RCTs], non-RCTs, and single-arm trials). Economic evaluations were reviewed and included when direct utility elicitation was reported. Case series, case reports, systematic reviews, and narrative reviews were excluded; however, systematic and narrative reviews published since 2016 were considered for bibliographic searches.

Only studies conducted in humans were included. Patients in the studies were required to have a diagnosis of LN (any class; with or without confirmation of biopsy) and comprised all age groups (i.e., both adult and pediatric populations). Any SLE study was included, regardless of intervention. The study outcomes of interest were: HRQoL, fatigue, health status, and utility values. Studies reporting only clinical parameters, economic outcomes, other patient-reported outcomes (PROs) or other humanistic burden parameters were excluded. The study outcomes of interest were not required to be the primary objective of the study to be included in the SLR.

Generally, only studies in the English language were included. Studies in other languages were included if their abstract was in English; information was extracted from the abstract.

Selection and data extraction

The results were screened by title and abstract and full-text copies of all publications of interest were obtained and reviewed for eligibility. Data were extracted from the publications that met the predefined inclusion criteria. The chosen studies were also assessed for quality.

Screening, data extraction and quality assessment of all studies were conducted by two independent reviewers, and any differences in opinion were resolved by a third reviewer. Quality assessments were made using a relevant tool selected according to the study type. RCTs were assessed using the National Institute for Health and Care Excellence (NICE) manufacturer's template, non-RCTs and single-arm trials were assessed using the Quality Assessment Tool developed by the Agency for Healthcare Research Quality (AHRQ), and observational studies (cohort/case-control/cross-sectional) were assessed with the Newcastle–Ottawa Scale (NOS).

The following information was extracted from each article and summarized in tabular format: study title and reference; study details: countries, study design, study population, LN diagnosis criteria, number of patients, data collection period, follow-up duration (mean/median follow-up); key baseline characteristics (including LN class); treatment groups; outcome: cross-sectional HRQoL (using generic and disease-specific scales), change in HRQoL over time, HRQoL by LN classes/by different treatments, cross-sectional fatigue (using generic and disease-specific scales), change in fatigue over time, fatigue by LN classes/by different treatments, cross-sectional health status/utilities, change in health status/utilities over time, health status by LN classes/by different treatments, predictors/associated factors for HRQoL, fatigue, and health utilities.

Data analysis

A quantitative analysis of baseline SF-36 domain and summary scores was conducted to provide estimates for the population of patients with LN. Given the substantial heterogeneity between studies (e.g., mix of study designs, interventions, and participants), the statistical analysis focused on studies and arms where baseline values for SF-36 domains and summary scores were reported. Data points were pooled and weighted by the square root of the sample size to calculate average scores across each of the SF-36 domains and summary scores, with between-study heterogeneity measured by the I^2 statistic. To determine whether prognostic factors could predict variation in SF-36 scores, a series of univariate linear regressions were conducted for those factors and domains with sufficient data points, regressing each of the SF-36 domain and summary scores against potential prognostic factors. However, as statistically significant associations do not take multiple testing into account, a Bonferroni correction was applied

based on the number of tests conducted. Pairwise meta-analysis of treatment versus control was considered inappropriate due to the heterogeneity within the intervention and control groups. Quantitative analyses were not conducted for other measures or outcomes. All analyses were conducted in Stata 17.

Results

Included studies

Of 1155 articles identified from the literature searches, a total of 26 relevant studies met the inclusion criteria for this SLR. [Figure 1](#) provides a flowchart of the study selection procedure, showing the number of studies included and excluded at each stage of the process. There were 1125 studies excluded that did not meet the inclusion criteria for the following reasons: focus of review not of interest ($n = 420$), outcome analyzed ($n = 296$), study design ($n = 230$), disease ($n = 133$), duplicate publication ($n = 21$), animal/in vitro ($n = 22$), and non-English ($n = 3$). A further study was excluded since it reported data derived from a study already included in this review.¹⁸

Study characteristics

Patient characteristics ($N = 3440$ across all studies) and an overview of the included studies are shown in [Table 1](#). As expected, the studies included a majority of female patients (73.5%–95%; data not shown) and adults, with three studies reporting data for a pediatric population.^{19–21}

Of the 26 included studies, 20 were reported in peer-reviewed journal articles, five were conference abstracts, and one was identified through ClinicalTrials.gov. Twenty-two reported data for HRQoL, nine for fatigue, and two for health utilities (some studies reported data for multiple outcomes and thus have been counted more than once). Most were observational studies (65% of the total; cross-sectional, $n = 10$; prospective cohort, $n = 4$; retrospective cohort, $n = 2$; case-control, $n = 1$), followed by clinical trials (31%; RCTs, $n = 6$; single-arm trial, $n = 1$; non-RCT, $n = 1$). One economic evaluation reporting utility data from direct elicitation was included. The most commonly used instrument was SF-36 (18 studies) with the majority using the Medical Outcomes Study (MOS) SF-36 version (9 studies).

Nine of the studies were designed to compare outcomes across two or more interventions (including placebo), and 12 were designed to compare outcomes across two populations (e.g., LN vs healthy controls/general population, LN vs SLE non-LN, LN vs other glomerular CKDs, and induction phase vs maintenance phase). The remaining five studies were not comparative in design (i.e., they either assessed the impact of a single treatment regimen or assessed outcomes of interest only among patients with LN).

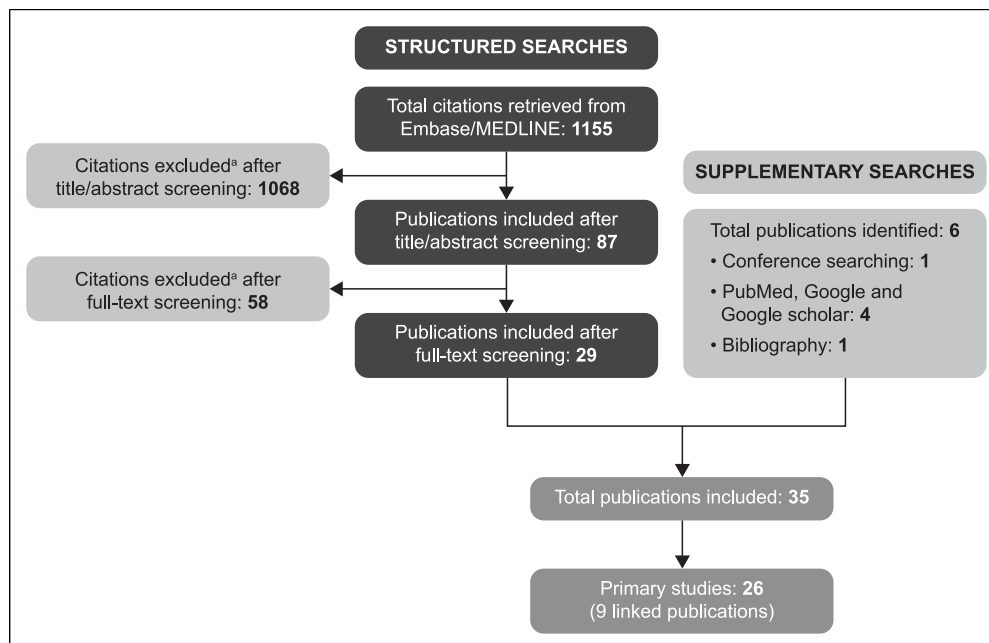


Figure 1. Flowchart of study selection.

^a 1125 studies were excluded that did not meet the inclusion criteria for the following reasons: focus of review not of interest ($n = 420$), outcome analyzed ($n = 296$), study design ($n = 230$), disease ($n = 133$), duplicate publication ($n = 21$), animal/in vitro ($n = 22$) and non-English ($n = 3$). A further study was excluded since it reported data derived from a study already included in this review.

The sample size of patients with LN ranged from 12 to 700. Approximately 65% of the studies ($n = 17$) recruited fewer than 100 patients, while two studies included more than 500 patients.

Most studies were conducted in Asia ($n = 7$), followed by the United States of America (USA; $n = 5$) and Europe ($n = 5$). Seven studies were conducted across multiple countries, two studies were conducted in Canada, and one in Egypt.

Impact of LN on HRQoL: SF-36

The overall quality scores for the HRQoL studies, based on the NOS scoring system, were 6–9, out of a maximum of 9 (i.e., moderate to high quality). Across multiple studies, HRQoL in patients with LN, as measured by the SF-36, was significantly worse (most with a p -value < 0.01) than that in healthy controls (Figure 2(a)). One study included age- and gender-matched healthy controls,²² while another study used SF-36 data from a non-matched general population reference group as a comparator group.²³ Patients with LN scored lower than healthy controls/general population on all individual domains of the SF-36.^{22,23} In Dalebout et al.²³, significantly lower SF-36 scores were observed in the general health perceptions, physical functioning, role-physical, social functioning, and role-emotional domains ($p < 0.01$). Overall, SF-36 scores (range: 0–100 with higher numbers associated with better quality of life [QoL]) were mostly in the range of 40–60 compared with corresponding

scores of 70–80 in healthy controls/general population comparator groups (in SLE, the mean minimally important differences [MIDs] for improvement in SF-36 range from 2.8 to 10.9 points for domain scores, and from 2.1 to 2.4 for summary scores²⁴). This difference in SF-36 scores between patients with LN and healthy controls/general population was noted regardless of the disease state or whether LN was proliferative.^{22,23}

A large study by Hanly et al.⁸ reported adjusted analyses (adjusted for age, gender, ethnicity, country and years after LN diagnosis) in which SF-36 scores were not significantly different between patients with SLE, with or without LN, but with some differences in individual SF-36 domains. In this study, subscale scores for pain and vitality domains were higher in patients with LN than in those without.⁸ In two smaller studies reporting unadjusted analyses, SF-36 score were worse in patients with SLE with LN than those without LN. Aghdassi et al.²⁵ reported significantly greater impairment in physical component summary (PCS) scores of the SF-36 in patients with LN versus without LN ($p = 0.03$). Kim et al.²⁶ reported a significant difference in SF-36 scores in physical activity between patients with SLE with and without LN ($p = 0.01$) (Figure 2(a)).²⁶

Several other studies reported HRQoL, as assessed by SF-36, in patients with LN but did not include comparisons with healthy controls/the general population. However, the SF-36 data reported were consistent with those in the LN

Table 1. Overview of studies.

Study name	Study design	Country	Sample size (LN)	LN population	Comparison(s)	Evidence
Aghdassi et al. ²⁵	CS	Canada	62	Adults with LN	SLE with versus without renal involvement Active ^a versus inactive SLE	MOS SF-36
Arends et al. ^{38,b}	Single-arm trial	Netherlands	71	Adults with proliferative LN treated with CYC IV, MMF and AZA	NA	MOS SF-36, SSC
Askanase et al. ²⁹ (ACCESS trial)	RCT	USA, Mexico	134	Adults with active LN class III/IV ± V	ABA versus placebo	MOS SF-36
Bantornwan et al. ^{39,b}	Non-RCT	Thailand	30	Adults with SLE and CKD stage 1–5 attending the nephrology clinic	Meditation versus no meditation	Thai SF-36
Bland et al. ³⁶ (PRO-LUPUS Study)	PC	EU5	100	Adults with LN ISN grade II–V	NA	FSMC, SF-36v2, LupusQoL
Cader et al. ³⁰	CS	Malaysia ^c	194	Adults with LN	NA	SF-36 (version not stated)
Cooper et al. ²⁰	PC	USA ^c	41	Children with new-onset proliferative LN initiating MMF or ivCYC	NA	CHQ
Daleboudt et al. ²³	RC	Netherlands	32	Adults with proliferative LN	LN versus general population reference group	RAND-36 ^d , SSC
Furie et al. ³²	RCT	Multiple ^e	298	Adults with active LN class III or IV (±V)	ABA versus placebo	SF-36 (version not stated), fatigue VAS, FSS
Galbraith et al. ³³	Pilot RCT	Canada	15	Adults with SLE and history of class III/IV ± V LN with at least PR	Prednisone continuation versus prednisone withdrawal	EQ-5D-3L, RAND-36
Grootsholten et al. ²⁷	PC	Netherlands	17	Adults with proliferative LN receiving ivCYC	NA	SSC, MOS SF-36

(continued)

Table 1. (continued)

Study name	Study design	Country	Sample size (LN)	LN population	Comparison(s)	Evidence
Grootscholten et al. ²⁸	RCT	Netherlands	87 ^f	Patients with proliferative LN with active nephritis and/or worsening renal function	ivCYC versus AZA	Health status VAS, MOS SF-36, SSC
Hanly et al. ⁸	PC	Multiple ^g	700	Adults with LN by ACR classification criteria or biopsy (any class)	SLE with versus without LN Patients with LN by health states defined by eGFR and by ePrU	MOS SF-36
Jolly et al. ¹	CS	Multiple ^h	539	Adults with LN defined by presence of I renal/ACR classification criteria at any time	SLE with versus without LN ⁱ Active LN versus not active LN	LupusPRO
Kim et al. ²⁶	CS	Korea	93	Adults with LN (67% proliferative)	SLE with versus without LN	MOS SF-36
Knight et al. ¹⁹	CS	USA	34	Children with LN and eGFR 30–90 mL/min/1.73 ²	LN versus other gCKDs	PedsQL
Mohara et al. ⁴²	CEA ^j	Thailand	18 ^k	Adults with LN	LN by disease state (CR, PR, active LN, renal failure, major infection)	EQ-5D
Mozaffarian et al. ⁴⁰	CS	USA	206	Adults with LN	SLE with versus without LN	FACIT-fatigue
Muhammed et al. ⁴³	CS	India	33	Adults with LN	SLE with versus without LN versus NPSLE	EQ-5D-3L, ^l Global health VAS
NCT00377637 ³⁴	RCT	Multiple ^m	370	Adults with active LN class III/IV±V or V	ivCYC versus MMF	SF-36 (version not stated)
Putera et al. ²¹	CS	Indonesia	62	Children with LN	Induction versus maintenance phase	PedsQL-RM
Rogers et al. ⁴¹	CS	USA	67	Adults with LN	SLE with versus without LN	SSS
Rovin et al. ³⁵ (LUNAR trial)	RCT	Multiple ^h	144	Active LN class III/IV	RTX versus placebo	MOS SF-36
Sliem et al. ²²	Case-control study	Egypt	59	Adults with LN (77.9% proliferative; 54.2% active LN)	LN versus healthy controls	MOS SF-36

(continued)

Table 1. (continued)

Study name	Study design	Country	Sample size (LN)	LN population	Comparison(s)	Evidence
Tse et al. ³⁷	RC	Hong Kong	12	Adults who had received two or more episodes of proliferative LN	MMF-based induction versus iCYC based induction	WHOQoL, Chinese SF-36 ^b
Vu and Escalante ³¹	CS	USA	22	Adults with LN (history of 1 renal ACR classification criteria) and ESKD receiving long term dialysis	LN with ESKD versus SLE with preserved renal function	SF-36 (version not stated)

Notes. CHQ: This is a generic person-reported outcomes measure to assess HRQoL for children and adolescents; score ranges from 0 to 100 (0 is the worst possible health state and 100 the best possible health state). EQ-5D-3L: Comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has three levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state. FACIT-Fatigue: This scale records patient-reported measure of fatigue; score ranges from 0 to 52 (lower scores indicate more fatigue)FSMC: This scale assesses cognitive and motor fatigue; score ranges from 20 to 100 (20 represents "no fatigue at all" and 100 is "severest grade of fatigue")FSS: This scale measures the severity of fatigue and its effect on a person's activities and lifestyle and consists of nine items; score ranges from 1 to 7 (higher the score, the more severe the fatigue).LupusPRO: This is a disease-targeted quality of life tool with both HRQoL and non-HRQoL constructs, contains 43 items; score ranges from 0 to 100 (higher scores denote better quality of life).PedsQL-4.0: This scale contains 23 items encompassing physical functioning, emotional functioning, social functioning, and school functioning; score ranges from 0 to 100 (higher scores indicate better HRQoL).SF-36: It consists of eight domains and two summary scores; score ranges from 0 to 100 (higher scores indicate better HRQoL). Domain scores were not normalized in the study.SSC: It is a disease-specific scale to measure treatment burden and comprised of total distress level (score range: 0–152) and number of complaints (score range: 0–38). A lower score denotes better quality of life.VAS: This scale measures subjective characteristics or attitudes of patients; score ranges from 0 to 10 (higher score represents a higher degree of general wellbeing).WHOQoL: Generic HRQoL scale, contains 26 items grouped into four domains; score ranges from 0 to 100 (higher scores indicate better HRQoL). ABA: abatacept; ACR: American College of Rheumatology; AZA: azathioprine; CEA: cost-effectiveness analysis; CHQ: Child Health Questionnaire; CKD: chronic kidney disease; CR: complete remission; CS: cross-sectional study; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; eP-U: estimated proteinuria; ESKD: end-stage kidney disease; EQ-5D: EuroQol 5D; EU5: France, Germany, Italy, Spain, and the UK; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FSMC: Fatigue Scale for Motor and Cognitive functions; FSS: Fatigue Severity Scale; gCKD: glomerular chronic kidney diseases; HRQoL: health-related quality of life; ISN: International Society of Nephrology; IV: intravenous; LN: lupus nephritis; LupusPRO: Lupus Patient-Reported Outcome; LupusQoL: Lupus Quality of Life; MMF: mycophenolate mofetil; MOS: Medical Outcomes Study; NA: not applicable; NIH: National Institutes of Health; NPSLE: non-proliferative systemic lupus erythematosus; PBO: placebo; PC: prospective cohort study; PedsQL: Pediatric Quality of Life Inventory; PR: partial remission; PedsQL-RM: Pediatric Quality of Life Inventory-Rheumatology Module; QALY: quality-adjusted life-year; RC: retrospective cohort study; RCT: randomized control trial; RTX: rituximab; SF-36: 36-item Short Form survey; SF-36v2: 36-item Short Form version two; SLE: systemic lupus erythematosus; SSC: SLE Symptom Checklist; SSS: Symptom Severity Score; VAS: Visual Analog Scale; WHOQoL: World Health Organization Quality of Life.

^aPercentage of active LN calculated from number of patients.

^bData reported from figure using Digitizer software.

^cBased on author's country.

^dThe authors stated that the questions about mood were excluded because memory for emotions had been shown to be especially subjective to bias from subsequent experiences. As a result, two of the nine scales (i.e., vitality and mental health) of the SF-36 were not included in the study.

^eNorth America, Europe, South America, Asia (including India and Turkey), and in the rest of the world (Australia and South Africa).

^fOnly 47 with complete HRQoL data.

^gUSA, EU, Canada, Mexico, and Asia.

^hUSA, Canada, Mexico, Argentina, Europe, Turkey, Philippines, and China.

ⁱRenal biopsy results were available for 184 of 304 patients with LN.

^jUtility elicitation from patients is reported in the paper.

^kUtility elicitation was conducted on 18 patients over time for 216 observations.

^lScores are not reported only the proportion of patients reporting each level of the EQ-5D items.

^mUSA, Argentina, Australia, Belgium, Brazil, Canada, China, EU5, Czech Republic, Greece, Hungary, Mexico, and Portugal.

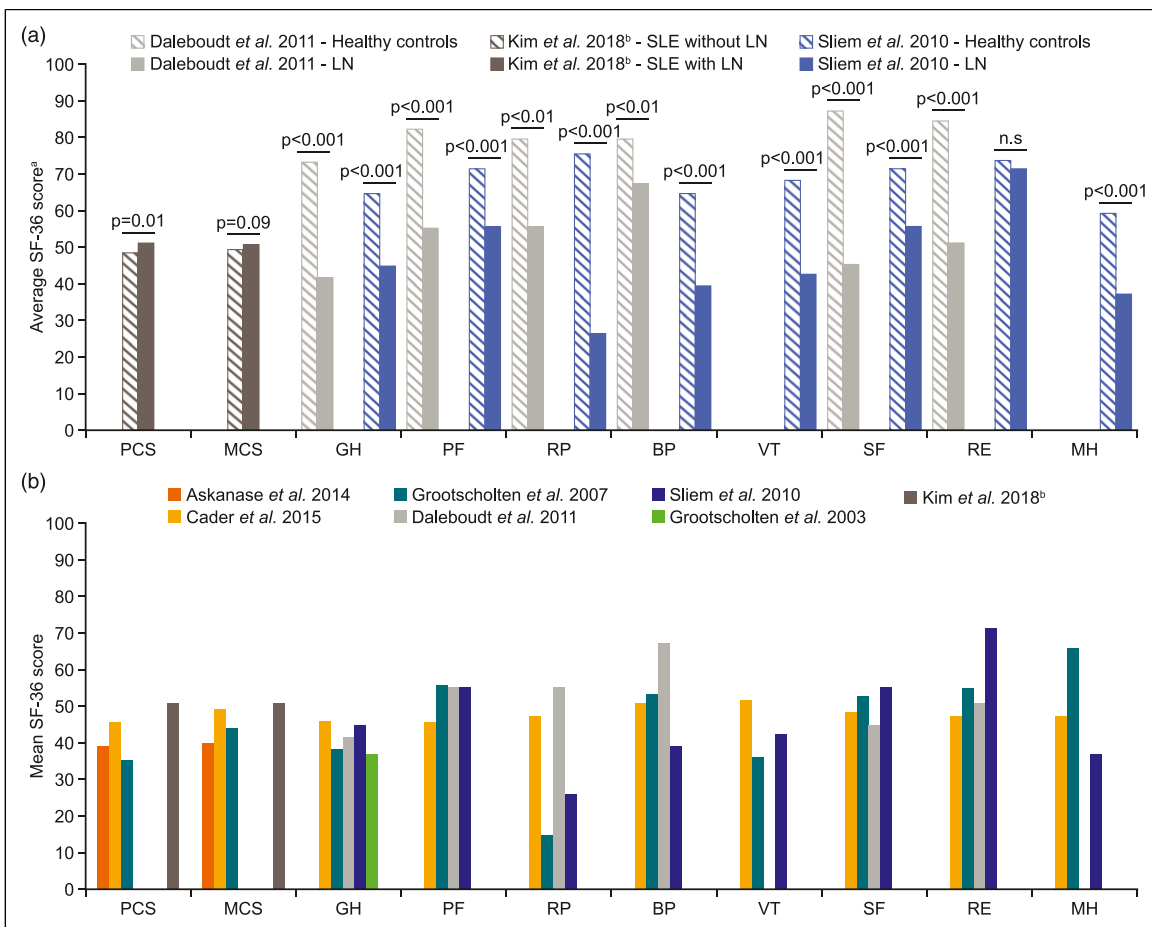


Figure 2. The impact of LN on SF-36 scores in patients with LN versus healthy controls or patients with SLE without LN (A) and in patients with LN with no comparator (B).

^aDaleboudt et al.²³ and Sliem et al.²² present the mean SF-36 scores. Kim et al.²⁶ present the median SF-36 scores.

BP: bodily pain; GH: general health perceptions; LN: lupus nephritis; MH: mental health; MCS: mental component summary; n.s: not significant; PCS: physical component summary; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; SF-36: 36-item Short Form survey; SLE: Systemic lupus erythematosus; VT: vitality.

studies that contained such comparisons, with domain scores ranging from 15 to 70 (Figure 2(b)).^{8,22,23,26-30}

Only one small case-control study assessed the association between LN class and HRQoL. This single study found a consistent downward trend in SF-36 scores from LN Class I-II (minimal, mesangial) to Class IV-V (diffuse, membranous; using the International Society of Nephrology/Renal Pathology Society [ISN/RPS] criteria). Differences were seen across all SF-36 domains except physical functioning.²²

Active disease was generally associated with lower SF-36 scores in LN, as shown in four studies.^{22,23,25,29,30} Several additional factors also showed association with lower SF-36 scores at baseline in patients with LN. Daleboudt et al.²³ found that higher social functioning in particular was associated with higher serum C4 levels, a marker of low SLE disease activity. Compared with those with higher estimated glomerular filtration rate (eGFR), patients with eGFR <30 mL/min at baseline reported poorer HRQoL

as assessed by baseline PCS, physical function, role-physical, and bodily pain domain scores.⁸ In a separate study, being on dialysis itself was associated with lower general health perceptions and physical functioning, but higher mental health scores, in patients with LN compared with patients with SLE and preserved renal function.³¹ Other factors that were associated with lower SF-36 scores were impaired cognitive function,¹⁹ higher proteinuria,²³ and longer disease duration.²⁵

Of the 18 studies that provided quantitative data on the SF-36 scores,^{8,22,23,25-39} a total of nine studies were eligible for inclusion in the statistical analysis.^{22,26-31,38,39} The highest weighted SF-36 scores (>50) for patients with LN were observed for the physical functioning and mental health domains, as shown in Table 2. In contrast, the lowest weighted SF-36 scores (<40) for patients with LN were observed in the role-physical and general health perceptions domains, and the PCS. This suggests that LN has a significant

Table 2. Unweighted and weighted SF-36 domain scores.

Domain/summary score (0–100) ^a	Number of data points (studies or arms)	Unweighted mean (SD) SF-36 score	Weighted mean SF-36 score	Between-study heterogeneity (I ²)
Physical component summary	10	36.81 (8.19)	39.43	91.25
Mental component summary	10	39.03 (10.54)	41.85	88.86
General health perceptions	7	33.59 (13.44)	37.91	92.77
Physical functioning	4	54.36 (6.11)	52.97	93.78
Role-physical	3	29.47 (16.29)	33.77	97.46
Bodily pain	4	48.77 (6.47)	49.06	71.20
Vitality	6	34.06 (15.96)	40.00	96.42
Social functioning	6	42.62 (14.28)	46.43	89.89
Role-emotional	5	48.74 (15.05)	48.15	95.90
Mental health	6	48.71 (22.27)	51.70	96.91

SD: standard deviation; SF-36: 36-item Short Form survey.

^aEach domain and summary scale ranges from zero (worst possible health) to 100 (best possible health).

impact across all SF-36 domains and summary scores. The considerable heterogeneity (71%–97%) observed between data points suggests this applies across different LN populations (Table 2).

Age and gender were the most consistently reported prognostic factors across the studies, other factors reported included ethnicity, LN class, SLE disease activity index (SLEDAI) score, disease duration, and eGFR.^{22,26,28–30,38,39} The linear regressions of SF-36 by these potential prognostic factors reported across studies found five statistically significant results (Supplementary Table 3). However, after a Bonferroni correction was applied based on the number of tests conducted, none of the statistically significant results were maintained.

Impact of LN on HRQoL: Other measures

Several studies used other alternative methods to the SF-36 to report the impact of LN on HRQoL. Jolly et al.¹ reported lower HRQoL on multiple LupusPRO domains in patients with LN with active SLE disease compared with those without active SLE disease. Additionally, a regression model of overall HRQoL and LupusPRO individual HRQoL domains (lupus symptoms, lupus medications, procreation, emotional health, and body image) demonstrated worse HRQoL among patients with active LN than in those without active SLE ($p < 0.05$). One study, assessing the HRQoL of pediatric patients with LN using the PedsQL survey, found that children with LN had significantly better executive function with an equivalent parent-reported HRQoL score, compared with children with other glomerular CKDs ($p = 0.03$).¹⁹ In another study, using the PedsQL-RM, all the patients in induction phase had poor QoL (score < 70), while 97.8%

of the patients in maintenance phase had good QoL (score ≥ 70).²¹

Impact of LN on fatigue

Nine studies reported fatigue data based on a fatigue-specific instrument. Mozaffarian et al.⁴⁰ evaluated fatigue using the validated FACIT-Fatigue, Bland et al.³⁶ included the FSMC and Furie et al.³² included the Fatigue VAS and total Krupp FSS. However, the most commonly reported tool was the SSC, which is a disease-specific scale designed to assess the presence and burden of 38 disease- and treatment-related symptoms.^{23,27,28,38} Data for individual domains of the SF-36 and the Lupus Quality of Life (LupusQoL) measurement are reported when these were relevant to fatigue.^{22,36} The overall quality scores for the studies reporting fatigue, based on the NOS scoring system, were 5–7, out of a maximum of 9 (i.e., low to moderate quality).

Fatigue was generally reported as the most burdensome symptom of LN.^{23,28,38} Overall, patients with LN had significantly worse fatigue than healthy controls ($p < 0.001$). A single case-control study in Egypt reported that SF-36 energy/vitality domain scores in patients with LN were significantly lower ($p < 0.001$), indicating a higher fatigue burden, than in age- and gender-matched healthy controls.²² In three studies in patients with active proliferative LN,^{23,28,38} more than 90% of patients with LN (range: 92%–97%) reported fatigue on the SSC at baseline evaluation.

Furthermore, the frequency of fatigue in patients with LN appeared to be equal to or lower than in patients with SLE without LN. In a large US study, the frequency of fatigue was similar in patients with SLE with and without LN (32% vs 36%, respectively; $p = 0.427$).⁴⁰ Another US study reported that the frequency of moderate or severe fatigue was

significantly lower in patients with SLE and with LN (47% in active LN and 52% in LN in remission) compared with patients with SLE without LN (64%; $p < 0.05$).^{36,41} The authors discussed the possibility that poor HRQoL in patients with LN may be driven by factors other than fibromyalgia and fatigue.

In one small case-control study, fatigue severity was significantly worse in patients with Class III–V LN (focal, diffuse, membranous) than with Class I–II LN ($p < 0.001$).²²

The frequency of fatigue was similar between patients with active LN and patients without active LN.³⁶ While one small study reported that higher fatigue levels were associated with low C4 levels,²³ two larger studies found no such association.^{36,41}

In two studies using cross-sectional univariate analyses, higher fatigue severity (assessed by the SSC and the FACIT-Fatigue) was associated with other PROs including lower HRQoL, increased treatment dissatisfaction and higher impact of disease on daily activities.^{23,40} In Bland et al.³⁶, both cognitive and motor aspects of fatigue were significantly and negatively correlated with HRQoL ($p < 0.01$) (i.e., reduction in fatigue was associated with improvement in QoL).³⁶

Effect of treatment on HRQoL and fatigue

Data on HRQoL and fatigue according to SLE/LN treatment were limited; the real-world studies involved small sample sizes ($n = 32$ in Dalebout et al.²³; $n = 12$ in Tse et al.³⁷) and had significant methodological limitations such as the

completion of HRQoL scales by patients based on their recollection of prior treatments.^{23,37}

The comparative effects of cyclophosphamide (CYC) and mycophenolate mofetil (MMF) on HRQoL in induction treatment in LN were evaluated in three studies.^{23,34,37} In two studies, better HRQoL, as assessed by the SF-36 physical functioning and social functioning domains, was reported for patients receiving MMF alone or in combination with low-dose CYC, compared with CYC alone.^{23,37} Tse et al.³⁷ retrospectively collected data on 12 patients' experiences with treatment. All patients had received treatment with CYC and MMF at different times in their treatment history and reported higher SF-36 scores (indicating better HRQoL) with MMF. Induction treatment with MMF was associated with significantly lower fatigue than treatment with CYC (mean scores of SF-36 energy/vitality domain were 52.2 vs 38.6, respectively; $p = 0.019$).³⁷ The authors attributed this to lower side effects in patients during MMF treatment compared with CYC treatment.

Furthermore, Dalebout et al.²³ found moderate improvements in physical functioning, social functioning, change in health and role-emotional domains between treatments, favoring MMF. In contrast, a large unpublished RCT (ClinicalTrials.gov identifier: NCT00377637) did not appear to find any difference in HRQoL between patients on MMF and those receiving CYC; change in HRQoL score of 370 patients across SF-36 domains appeared mostly similar over 6 months (Figure 3), although statistical significance results were not provided.³⁴

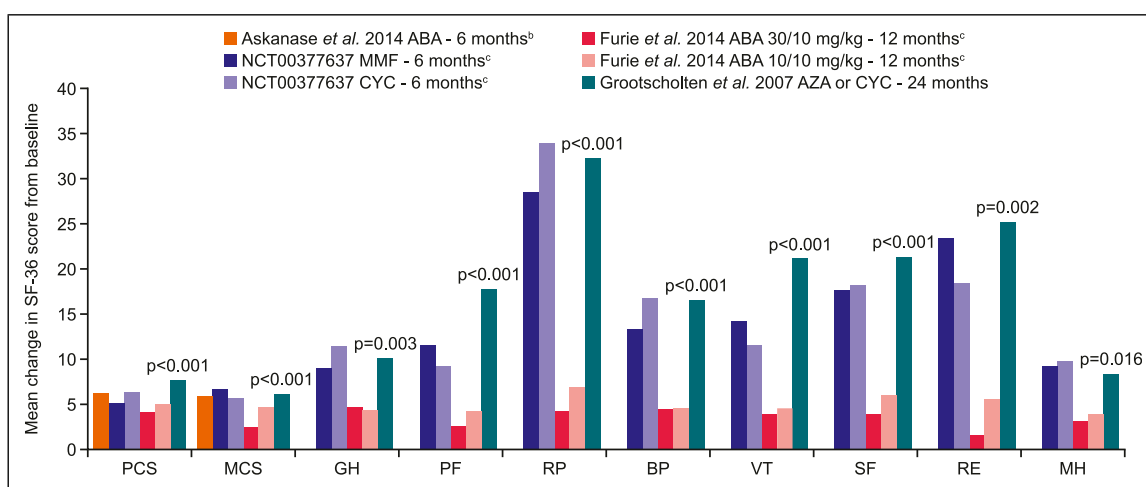


Figure 3. Change from baseline^a in SF-36 domain scores with different treatment regimens.

^aMean change from baseline was calculated from mean SF-36 values before and after treatment for Askanase et al.²⁹ and Grootsholten et al.²⁸

^bNot significant.

^cp-values not reported.

ABA: abatacept; AZA: azathioprine; BP: bodily pain; CYC: cyclophosphamide; GH: general health perceptions; HRQoL: health-related quality of life; MH: mental health; MMF: mycophenolate mofetil; MCS: mental component summary; PCS: physical component summary; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; SF-36: 36-item Short Form survey; VT: vitality.

Note: Studies are ordered by length of follow-up. Lower SF-36 scores indicate lower HRQoL.

Grootscholten et al.²⁸ found no significant differences for any SF-36 domain in patients with LN receiving CYC compared with those receiving azathioprine (AZA), except in the mental component summary (MCS) score, in which patients on AZA showed a significantly greater improvement (p -value not reported), suggesting a better impact on mental functioning. The authors noted that these differences might not be clinically relevant due to the observed ceiling effect. In addition, Grootscholten et al.²⁷ found that patients with LN receiving CYC experienced an improvement in the SF-36 general health perceptions domain score after 1 year of treatment. Askanase et al.²⁹ reported that no significant difference was observed in the SF-36 scores between patients receiving treatment with abatacept (ABA) compared with those receiving placebo for 6 months. Rovin et al.³⁵ also reported no significant difference in the SF-36 physical function domain score between patients receiving rituximab treatment for 12 months compared with those receiving placebo.

A pilot trial among a small cohort of patients with LN in partial remission showed that continuation of glucocorticoid therapy (maintained on 5–7.5 mg/day) did not have a significant impact on SF-36 scores or the severity of fatigue compared with patients who were withdrawn from therapy.³³

Finally, in a prospective pilot study on the effect of meditation on the QoL of patients with LN, summary scores of the physical and mental components improved significantly compared with the control group ($p = 0.02$ and $p < 0.01$ for physical and mental components, respectively).³⁹

An overview of the mean change in SF-36 scores across four studies with different treatment periods (6–24 months) showed that all scores were positive, indicating an improvement from baseline in all SF-36 domains (Figure 3).^{28,29,32,34} Only small treatment differences were identified in mean SF-36 PCS and MCS scores.

There was a trend towards an increased magnitude of improvement over time in two single-arm studies reporting data across multiple time points.^{28,38} Arends et al.³⁸ found that six out of the eight SF-36 domain scores (physical functioning, role-physical, bodily pain, social functioning, role-emotional, and mental health), as well as the PCS, improved significantly (all $p < 0.05$) over 4 years, with mean improvements ranging from 10 to 30 points for most domains in patients treated with intravenous CYC and oral prednisolone. In Grootscholten et al.²⁸, both generic (patient's VAS; SF-36; Profile of Mood States [POMS]) and disease-specific (SSC) HRQoL outcomes improved during treatment over 24 months with CYC or AZA, particularly during the first year, in patients with proliferative LN.

In the same two studies, the rate and severity of fatigue (measured by the SSC and POMS) decreased with treatment (CYC, MMF, and AZA) over 1–4 years of follow-up, although the magnitude of change was relatively small.^{28,38}

Another study reported that placebo treatment (with standard therapy) resulted in changes in individual SF-36

domain scores (improvements of 3–5 points) and measures of fatigue (the fatigue VAS and FSS) over 1 year, similar to the improvements in scores for patients in the active treatment group who were receiving ABA with standard therapy.³²

Health utilities

As only two studies reported health utilities data in LN, the limited data available do not constitute a robust evidence base.^{42,43} In Mohara et al.⁴², using the EQ-5D (it was not reported whether it was -3L or -5L), health utility weights in which values ranged from 0 (death) to 1 (full health) for calculating QALY were obtained from 216 observations of patients (18 patients for 12 visits each, on average) in four tertiary care hospitals in Thailand. The health states related to the QoL of patients with LN included: complete remission, partial remission, active disease, renal failure and major infection. The highest disutility score was reported for major infection, with the mean overall health utility scores ranging from 0.22 for major infection to 0.94 for complete remission.

Muhammed et al.⁴³ found that a significantly higher proportion of patients with LN reported problems in the EQ-5D-3L domains of self-care ($p < 0.001$), mobility ($p = 0.009$), pain ($p = 0.003$), and anxiety/depression ($p = 0.009$) compared with patients with SLE without LN.

Differences by treatment were reported only in terms of QALYs, rather than health utility values. CYC was more expensive and resulted in lower QoL (i.e., less cost-effective) than both MMF and AZA in maintenance treatment.⁴²

Discussion

Patients with SLE carry a high disease burden, including a significant effect on HRQoL, which has been demonstrated in several previous SLRs.^{4,16,17} The most common severe organ manifestation of SLE is LN, a form of glomerulonephritis that causes impaired kidney function.^{3,5} Despite this, SLRs reporting the impact of LN on HRQoL, fatigue, and health utilities are limited. Although some SLRs have focused on the management and economic burden of LN,^{44–47} there is a need for more SLRs that are focused on the humanistic burden. Therefore, this SLR was carried out to assess the impact of LN on HRQoL, fatigue, and health utilities in this specific subpopulation of patients with SLE. With the results found, we were able to adequately summarize the data on the HRQoL burden in patients with LN; however, data were limited for fatigue severity and health utilities in these patients.

HRQoL

The available studies demonstrate that LN has a substantial and negative impact on HRQoL compared with healthy

controls/general population; this impact was seen across all domains of the SF-36 scale, when observed differences of approximately 2–50 points were greater than the corresponding MID of 2.8–10.9 points across domains.²⁴

HRQoL was mostly similar in patients with SLE with and without LN as shown in two large studies using adjusted analyses.^{1,8} However, a smaller unadjusted analysis comparing proportions of patients instead of mean/median values reported significantly worse physical activity in patients with LN compared with those without LN.²⁵ This suggests that the type of analysis may impact results when comparing patients with and without LN, and this is important to consider when interpreting study results. Nevertheless, LN is one of the more severe manifestations of SLE and as such, patients with LN, especially those in Class III–V, are likely to have higher disease activity with associated worsened HRQoL.

In line with clinical expectations, HRQoL was consistently worse in proliferative (III/IV) and membranous (V) LN classes, in patients with other renal factors (including lower eGFR, higher proteinuria and being on dialysis), as well as in those with active SLE/LN disease compared with those without.^{1,8,22,23,25,30,31} Patients with eGFR <30 mL/min at baseline reported poorer SF-36 domain scores.⁸ This is to be expected as an eGFR <30 mL/min represents significant impairment in kidney function.⁴⁸

Studies on the effect of treatment on HRQoL were mainly limited to CYC compared with MMF or AZA. Treatment with CYC was generally associated with worse HRQoL compared with other treatments, and this differential impact appeared to be driven by tolerability issues with CYC, which highlights the impact of treatment toxicity on HRQoL.^{23,28,34,37} Furthermore, some of the treatment studies included CYC administered through a maintenance period, which is no longer reflective of best practice.⁴⁹ Whilst only small treatment differences were identified in SF-36 PCS and MCS scores, the changes from baseline could be considered meaningful based on previous work to establish an MID in SLE (domain scores: 2.8–10.9; summary scores: 2.1–2.4).²⁴

In patients with active LN disease, HRQoL improved over time, consistent with corresponding clinical improvements; the magnitude of improvement was approximately 10–30 points for most SF-36 domains.

Results from the quantitative analysis of SF-36 domain and summary scores suggest that LN has a significant impact on health across all domains. This is supported by Gu et al.⁵⁰, a meta-analysis to evaluate the impact of SLE on HRQoL assessed by SF-36. The pooled mean scores for all SF-36 domains were higher (reflecting better HRQoL) than those we observed for patients with LN in our meta-analysis. Gu et al.⁵⁰ also compared SF-36 domain scores for patients with SLE with those of the general population and found that patients with SLE had lower SF-36 domain

scores versus the general population from multiple countries (UK, Norway, France and USA), which suggests that the SF-36 domain scores observed for patients with LN in our study are also lower than those for the general population. Given the substantive heterogeneity in our meta-analysis, the statistical analysis focused upon studies and arms where baseline values for SF-36 domains and summary scores were reported and resulted in a sample size of nine studies. In the univariate linear regression analysis, LN Class IV–V, White ethnicity, and mean SLEDAI score were negatively associated with different SF-36 domains. However, these statistically significant associations failed to take account of multiple testing and after a Bonferroni correction was applied based on the number of tests conducted, none of the statistically significant results were maintained. Furthermore, these findings are qualified by the small number of data points available, which led to a lack of predictive ability and precluded multivariate analysis.

Fatigue

The limited available data on fatigue are generally consistent with those seen for HRQoL (i.e., fatigue was significantly worse in patients with LN compared with healthy controls). In three studies, fatigue was generally reported as the most burdensome symptom of LN.^{23,28,38} Two of these studies had no comparator group,^{28,38} but it appears the magnitude of fatigue reported could be clinically relevant. There was no evidence to suggest that fatigue was worse in patients with SLE with LN versus those without LN,⁴⁰ indicating that fatigue may not be related to renal symptoms, but rather is a burden of SLE in general. However, the data to inform this are extremely limited and should be confirmed through further research, particularly since studies ranged from finding no association between LN disease activity and fatigue to higher fatigue being associated with higher disease activity.^{22,23,28,36,38} Fatigue is unlikely to be related only to renal activity, which emphasizes the need to manage patients with LN holistically (i.e., by treating both renal and extra-renal manifestations).

Longitudinal datasets showed only a small change in fatigue with treatment over time using the SSC, indicating that fatigue may be a relatively treatment-resistant symptom in patients with LN.³⁸ However, an RCT showed a substantial change from 3.2 points (ABA 10 mg/kg followed by 10 mg/kg) to 4.8 points (placebo) using the FSS (in which an MID for improvement is 0.08–0.4),^{32,51} indicating that the FSS may be a more sensitive measure than the SSC for assessing the impact of treatment on fatigue in LN. The FACIT-Fatigue has proven to be a valid measure in SLE and is commonly used to assess the severity of this symptom in SLE.^{52,53} However, only one study was identified that used the FACIT-Fatigue in patients with LN; it found that the

frequency of fatigue was similar in patients with SLE with and without LN.⁴⁰

Health utilities

Overall, the data on health utilities are very limited. In the single study that elicited preference-based utility weights for disease states in LN directly from patients with LN, these were broadly along expected lines based on LN disease severity.⁴² In alignment with the treatment data on HRQoL, QALYs (as an indirect measure of health utilities) suggested that CYC induction treatment was inferior to MMF in improving HRQoL.⁵⁴ This was related to direct assumptions around worse HRQoL of CYC-treated patients and to higher infection rates versus MMF. Maintenance treatment with MMF appeared to be superior to AZA with respect to QALYs.¹⁸ However, a study by Kim et al.⁵⁵ suggested that tacrolimus as induction and maintenance therapy was the most effective (in terms of remission rates) and cost-effective treatment for LN when compared with CYC, MMF, and AZA. Since there are limited health utility data in LN, these three studies relied on QALYs and data from other studies and other diseases.^{18,54,55} Therefore these studies were excluded from this analysis.

Gaps and limitations of the literature

This SLR identified 26 relevant studies; however, only 22 had a specific focus on HRQoL, nine on fatigue and two on health utilities, resulting in limited data on fatigue and health utilities. The identified studies did not always report sufficient data characterizing the study populations; for example, only approximately three-quarters of the studies reported whether biopsies were used for LN diagnosis or provided data on disease activity or LN class.

Overall, there are adequate data for HRQoL in patients with LN and the quality scores for most of the studies (6–9 out of a maximum possible score of 9, based on the NOS scoring system) indicate they were of a moderate to high quality. There are, however, limited data for fatigue in patients with LN and the quality scores for most of the studies (5–7) indicate they were of a low to moderate quality. Furthermore, fatigue is multifactorial and not always due to SLE or active LN.¹⁵

There are a number of specific data gaps and limitations. For HRQoL, no longitudinal data were available reflecting the progression of HRQoL in patients with renal response receiving maintenance therapy, as opposed to patients with active LN who were initiating induction treatment. There were also limited data on the clinical characteristics associated with HRQoL and the differences in HRQoL by treatment; although some evidence was available for comparisons between MMF and CYC, data for comparisons between MMF and AZA were scarce. For fatigue, few

studies reporting comparative data were identified and the studies were not robust enough to inform definitive conclusions.

In addition, many of the studies used generic measures of HRQoL (i.e., SF-36), despite this not being fully validated for use in an LN population to our knowledge. Whilst generic measures are useful for comparison between diseases and therefore informative for health policy decision-makers, including payers, they may not be entirely relevant to the patient population being studied. Disease-specific measures and, more specifically, measures developed with appropriate input from patients experiencing the condition, are needed to fully capture the impact of a disease on HRQoL and the potential for treatments to have patient-relevant benefits. Furthermore, the few interventional studies that were identified may not be representative of the overall LN population, as the patients required urgent control of renal activity. More SLE-specific data to inform our understanding in this regard are expected from the ongoing PRO-Lupus study.³⁶

A limitation of the quantitative analysis on SF-36 was the small number of data points available for prognostic factors, which precluded multivariate analysis and led to a lack of predictive ability. Furthermore, the pooled SF-36 scores suffer from substantial heterogeneity given the disparate study designs and included populations of the contributing studies.

Measures of fatigue were more disparate than for HRQoL (i.e., varied outcome measures), very few explored fatigue severity with a valid instrument and many reported estimates relied on a single item from a broader PRO. Further research is important considering fatigue was also reported in most patients with active proliferative disease and was rated the most burdensome symptom.^{23,28,38}

Overall, there are very limited data for health utilities in patients with LN. This has implications for future decision-making, health technology assessment, and reimbursement in this disease area. There is increasing need for this type of data for payers in light of the availability of emerging therapies for LN (e.g., belimumab and voclosporin).^{56,57} Whilst standard therapies do improve HRQoL, these new treatments offer improved efficacy that may result in an improved HRQoL for patients with LN.^{58,59}

The indirect estimates used were very limited as they were derived from nonstandard scales for health utilities (VAS) or applied generic preference scores to LN health states. Finally, only two studies reported HRQoL in patients with LN on dialysis. Given the high cost of renal dialysis, the prevention of ESKD in patients with LN is likely to be cost-saving. However, in cost-effectiveness studies, the utility associated with dialysis is usually derived from studies of patients with general CKD, which is another area of unmet need in LN. A pairwise meta-analysis was not performed in this study due to the heterogeneity across

interventions, which consisted of non-pharmaceutical interventions, dose ranging studies, placebo-controlled studies, and active comparator studies (Table 1). A meta-analysis conducted by Gu et al.⁵⁰ in SLE had narrower exclusion criteria than the current review, and lacked quality assessment. However, the broader range of study designs and interventions across the included studies in this review resulted in a more difficult interpretation.⁵⁰

Conclusions

In conclusion, the results of this SLR suggest that there is a large HRQoL burden in patients with LN. This is supported by the quantitative analysis on SF-36 scores, which suggests that LN has a significant impact on health across all domains. Fatigue remains as prevalent and burdensome in the broader SLE population, but robust data in patients with LN are more limited.

Patients with active LN had considerably worse HRQoL than those without active disease and HRQoL was found to improve over time with treatment amongst patients with active LN; however, data describing the magnitude of HRQoL change with a renal response was not available. Furthermore, the treatment tolerability profile influences HRQoL in LN. As reflected in SLE guidelines, improved HRQoL should be a key treatment goal.⁶⁰

More research is needed to understand fatigue severity in LN and to elicit health utilities for use in cost-effectiveness analyses of treatments for LN. A more detailed understanding of the influence of renal response, extra-renal symptoms, and fatigue on overall HRQoL is needed to inform holistic assessments of the patient-relevant benefit of LN treatments.

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Data availability statement

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Supplemental Material

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