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Patient-reported outcomes and healthcare resource utilization in systemic lupus erythematosus: impact of disease activity

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Abstract

Background Limited real-world data exists on clinical outcomes in systemic lupus erythematosus (SLE) patients by SLE Disease Activity Index 2000 (SLEDAI-2 K), hereafter, SLEDAI. We aimed to examine the association between SLEDAI score and clinical, patient-reported and economic outcomes in patients with SLE.

Methods Rheumatologists from the United States of America and Europe provided real-world demographic, clinical, and healthcare resource utilization (HCRU) data for SLE patients. Patients provided self-reported outcome data, capturing their general health status using the EuroQol 5-dimension 3-level questionnaire (EQ-5D-3 L), health-related quality of life using the Functional Assessment of Chronic Illness Therapy (FACIT) and work productivity using the Work Productivity and Activity Impairment questionnaire (WPAI). Low disease activity was defined as SLEDAI score ≤ 4 and ≤ 7.5 mg/day glucocorticoids; patients not meeting these criteria were considered to have "higher" active disease. Data were compared between patients with low and higher disease activity. Logistic regression estimated a propensity score for SLE based on demographic and clinical characteristics. Propensity score matched analyses compared HCRU, patient-reported outcomes, income loss and treatment satisfaction in patients with low disease activity versus higher active disease.

Results Data from 296 physicians reporting on 730 patients (46 low disease activity, 684 higher active disease), and from 377 patients' self-reported questionnaires (24 low disease activity, 353 higher active disease) were analyzed. Flaring in the previous 12 months was 2.6-fold more common among patients with higher versus low active disease. Equation 5D-3 L utility index was 0.79 and 0.88 and FACIT-Fatigue scores were 34.78 and 39.79 in low versus higher active disease patients, respectively, indicating better health and less fatigue, among patients with low versus higher active disease. Absenteeism, presenteeism, overall work impairment, and total activity impairment were 47.0-, 2.0-, 2.6- and 1.5-fold greater in patients with higher versus low disease activity. In the previous 12 months there were 28% more healthcare consultations and 3.4-fold more patients hospitalized in patients with higher versus low disease activity.

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Conclusion Compared to SLE patients with higher active disease, patients with low disease activity experienced better health status, lower HCRU, less fatigue, and lower work productivity impairment, with work absenteeism being substantially lower in these patients.

Keywords Disease activity, Healthcare resource utilization, Patient-reported outcomes, Real world systemic lupus erythematosus

Introduction

Assessments of disease activity and response to therapy in systemic lupus erythematosus (SLE) have to take into account the complex, multi-organ manifestations of SLE [1], and the course of the disease over time, including the possibility of disease flares [2]. Several measures have been developed and validated to assess SLE disease activity in an appropriate and reproducible manner, including the British Isles Lupus Assessment Group (BILAG) index [3, 4], the Systemic Lupus Activity Measure (SLAM) [4, 5], and the Systemic Lupus Activity Questionnaire (SLAQ) [6]. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) assesses disease activity in the past 30 days using 24 weighted clinical and laboratory descriptors across nine organs/systems [7–9]. Modified versions of the SLEDAI include the SLEDAI-2000 (SLE-DAI-2 K) [8, 9] and a version developed for use in the Safety of Estrogens in Lupus National Assessment study, the SELENA-SLEDAI [10]. We use the SLEDAI-2 K in this study, hereafter referred to as just SLEDAI.

Achieving good disease control, as evidenced via a disease activity measure, would be expected to improve a patient's outcomes and result in lower healthcare resource utilization (HCRU) [11, 12]. European clinical guidelines recommend treatment goals in SLE of remission or low disease activity [13], and a definition of a Lupus Low Disease Activity State (LLDAS) that includes a SLEDAI score of ≤4 and prednisone≤7.5 mg/d has been developed by an international panel of SLE experts [14–16]. As both the SLEDAI and the LLDAS have been employed primarily in clinical trials and longitudinal observational studies, [17, 18], exploring the relationship of SLEDAI scores and low disease activity with real-world patient outcomes is of interest.

The objective of the current study, therefore, was to quantify the effect of achieving low disease activity in a real-world patient cohort on the clinical, patient and economic impact of SLE. To achieve this, we compared flaring, patient-reported outcomes (PRO), HCRU, and income loss in SLE patients between those with low disease activity and higher active disease.

Methods

Study design and data collection

This was an analysis of data from the Adelphi Real World Lupus Disease Specific Programme™ (DSP), collected in the United States of America (USA) and Europe in 2010, 2013 and 2015, these data did not follow the same patients, but rather were comprised of three separate cohorts. Data from these three years were then aggregated for analyses in this study. The Lupus DSP is a real-world, non-interventional, point-in-time survey of rheumatologists and their patients with SLE; the full DSP methodology has been published previously [19].

Rheumatologists from a broad geographical area in the USA and five European countries (France, Germany, Spain, Italy and the United Kingdom [UK]) were identified from publicly available lists and invited to participate in the DSP if they were actively managing patients with SLE and saw≥5 patients with SLE in a typical month. A total of 754 participating rheumatologists completed a patient record form for the next 5 consecutively consulting patients with SLE aged≥18 years. Data recorded on the form included patient demographic and clinical characteristics, physician-defined current disease severity (mild, moderate or severe), most recent SLEDAI score, SLE management history, flaring, healthcare professional (HCP) consultations and hospitalizations during the 12 months prior to data collection.

Patients for whom a patient record form had been completed were invited to complete a patient self-completion form. The self-completion form included PRO questionnaires assessing health status, flare, fatigue and its impact, and productivity.

The definition of flare in SLE has not yet been universally decided or accepted [20], therefore, flare was defined in this study based on the clinical judgement of managing physicians. We collected data on the number of flares patients had experienced in the last 12 months as well as whether the patient was experiencing a flare at the time of consultation. As with flares, disease severity was based on the clinical opinion of the managing rheumatologist, thus a physician global assessment. Data on which classification criteria rheumatologists used to make their judgement of disease severity were not collected during this study.

Patient-reported outcome questionnaires

The EuroQoL 5D-3 L (EQ-5D-3 L), a widely used generic measure of health status [21, 22], consists of two parts: the descriptive system, which assesses health in five dimensions (Mobility, Self-care, Usual Activities, Pain / Discomfort, and Anxiety / Depression), each of which has three levels of response (no problems, some problems,

extreme problems / unable to do), and the EQ-VAS, a 20 cm visual analog scale (VAS) on which the patient rates their perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). Application of country-specific scoring algorithms to the scores of the five domains provides a single health utility index, with a value of 1 indicating perfect health, a value of 0 indicating death, and a value of <0 indicating a health state worse than death [23, 24].

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale assesses fatigue and its impact on daily activities and functioning in chronic disease [25, 26]. The questionnaire includes 13 items such as tiredness, weakness, listlessness, lack of energy, and the impact of these feelings on daily functioning (e.g., sleeping, and social activities). Each item is scored between 0 and 5, and all items contribute equally to the sum score, with 0 being the worst possible sum score and 52 being the best possible score, indicating no fatigue. The content validity and psychometric properties of the FACIT-Fatigue scale have been established in numerous chronic conditions, including SLE [27–29].

The Work Productivity and Activity Impairment-Lupus questionnaire (WPAI-Lupus) assesses the impact of SLE on work productivity and activity impairment over the past 7 days [30]. The questionnaire comprises 6 items, and results in the generation of scores for absenteeism, presenteeism, overall work impairment, and total activity impairment, each expressed as a percentage of work time missed or percentage impairment.

Statistical analyses
LLDAS is defined as a SLEDAI score≤4 (with no activity in renal, central nervous, gastrointestinal, or cardiopulmonary systems, and no vasculitis, fever, or hemolytic anemia), a SELENA-SLEDAI physician global assessment≤1, receiving≤7.5 mg/day glucocorticoid, immunosuppressant or approved biologics only at well-tolerated standard maintenance doses, and demonstrating no new lupus disease activity compared with the previous assessment [14, 15]. In our analysis, a variation of the LLDAS, low disease activity, was defined as a SLEDAI score of ≤4 and a glucocorticoid dose of ≤7.5 mg/day. This definition of low disease activity was used to reflect the LLDAS as closely as possible, given that not all data included in the published definition were available. By contrast, higher active disease was defined as a SLEDAI score of >4 or a glucocorticoid at a dose of >7.5 mg/day. Patients were compared based on this objective assessment of disease activity, rather than subjective physician-reported disease severity.

Descriptive analyses of patient demographics and clinical characteristics were performed for the total study population and stratified by whether they had low disease activity or not. Means and standard deviations were calculated for continuous variables, and frequency counts and percentages for categorical variables. Results were compared using chi-squared tests for categorical variables, Fisher's exact test for 2-by-2 categorical variables, and Mann-Whitney tests or t-tests for numeric variables.

To calculate the impact of disease activity on income, patient's reported incomes were converted to US dollars for consistency, taking into account country, age and/or sex (where appropriate) [31–36]. Loss of income was calculated for each patient as the product of salary and WPAI absenteeism, presenteeism, and overall work impairment. Mean income loss was then compared in those with and without low disease activity.

- Due to the observational nature of the data, any observed significant difference in an outcome using a bivariate test between two groups (e.g., a t-test) may be due to confounding factors. Propensity score matching is a statistical matching technique that attempts to balance pre-specified covariates between patient groups through the use of the propensity score (a measure of how likely a patient is to belong to either group, based on the covariates used) [37]. Therefore, analyses to compare HCRU, PRO scores and income loss in patients with low disease activity versus higher active disease were conducted utilizing propensity score matching. Low disease activity and higher active disease patient groups were matched on age, sex and ethnicity. Propensity scores were estimated using a logistic regression model. Patients in the low disease activity group were matched 1:1, with replacement and allowing for ties, to patients in the higher active disease group. A caliper was not applied. The balance in covariates between groups, following propensity score matching, was assessed by calculating standardized mean differences (SMDs), with an SMD between – 0.1 and 0.1 (not inclusive) taken to be indicative of adequate balance [38]. The treatment effect, or difference in outcomes between groups, was computed by taking the average of the difference between the outcomes in matched patients. The Abadie-Imbens standard error and the corresponding test statistic and associated p-value were also calculated [39]. Propensity score matching was repeated three times, for analyses of the following groups of variables: (1) physician-reported HCRU outcomes; (2) patient-reported EQ-5D-3 L utility index, FACIT-Fatigue scores and WPAI total activity impairment; (3) patient-reported (when employed) WPAI absenteeism, presenteeism, and overall work impairment (with their dollar adjusted equivalents).

Sensitivity analyses

To further investigate the definition of disease activity levels, patients were grouped according to the criteria for classifying them as having active disease. As glucocorticoids are used to manage short-term increases in disease activity (flares), patients receiving high dose glucocorticoids might not be considered to have higher active disease in general. The base case analyses were therefore re-run excluding patients classified as having active disease because they were receiving >7.5 mg/day of glucocorticoid, rather than due to their SLEDAI score. All analyses were conducted in Stata v16.0 [40].

Results

Patients

Complete patient record forms were provided by 296 physicians for a total of 730 patients: 166 from the USA and 564 from Europe (France, n=132; Germany, n=96; Spain, n=99; Italy, n=113; UK, n=124). Of these patients, 46 had low disease activity and 684 had higher active disease.

Patients with low disease activity and higher active disease were comparable for age, proportions of each sex, and time since diagnosis (Table 1). The proportion of non-White patients was numerically higher in the group with active disease than the group with low disease activity, although this difference was not statistically significant. Although disease severity as defined subjectively by physicians indicated greater severity in patients with higher active disease than those with low disease activity (p<0.05), more than half of patients classified as having higher active disease were considered by their physicians to have mild SLE, and just over 20% of patients classified with low disease activity were assessed subjectively by their physicians to have moderate or severe SLE. In total, 94% of patients with higher active disease were receiving steroids at the time of data collection compared with 37% of patients with low disease activity, and more than two thirds of all patients had received steroids at some point in their treatment history. Overall, 4.1% of patients were receiving biologics, with a higher percentage of patients with low disease activity (6.5%) compared with higher active disease (3.9%) receiving these. Of these, 10 (1.4%) patients were receiving belimumab, with no significant difference in belimumab prescription between low and higher active disease groups (p=0.4806).

Flaring

The likelihood of having a flare and the mean number of flares in the 12 months prior to data collection were both 2.6-fold higher in patients with higher active disease than those with low disease activity (Fig. 1a and b; both p<0.01).

Patient-reported outcomes and loss of income

Of those patients with data available to assess their disease activity, 377 (51.6% of total) completed a patient self-completion form, 88 from the USA and 289 from Europe (France, n=78; Germany, n=78; Spain, n=48; Italy, n=46; UK, n=39). Of these 377 patients, 24 had low disease activity and 353 had higher active disease.

Propensity score matching for EQ-5D-3 L utility index, FACIT-Fatigue sum score and WPAI total activity impairment achieved balance for potential confounding variables (Additional file 2). Propensity score matching for WPAI absenteeism, presenteeism, overall work impairment, and lost income due to these achieved balance for age; however, propensity score matching was unable to balance groups for proportions of males and females and ethnicity, with SMDs of 18.1% and 14.8%, respectively, for these variables (Additional file 3). Post-matching compared with pre-matching, in the group with active disease, mean patient age was lower and there were higher proportions of male patients and White patients (Additional files 2 and 3).

The mean EQ-5D-3 L utility index score in patients with low disease activity was 0.88 compared with 0.79 in patients with higher active disease, indicating better health status in patients with low disease activity compared to those with higher active disease (Fig. 2a; p<0.05). Patients with low disease activity also reported lower levels of fatigue, with mean FACIT-Fatigue sum score of 39.79 compared with 34.78 in patients with higher active disease (Fig. 2b; p<0.05). Patients with higher active disease also had 47-fold greater mean percentage absenteeism (Fig. 2c; p<0.05), 2-fold greater mean percentage presenteeism (Fig. 2c; p<0.001), 2.6-fold greater mean percentage overall work impairment (Fig. 2c; p<0.001), and 1.5-fold greater mean percentage total activity impairment (Fig. 2c; p=0.072) compared with patients with low disease activity.

Additionally, those patients with higher active disease had 37-fold, 1.9-fold and 2.1-fold higher annual loss of income associated with absenteeism (Fig. 2d; p<0.05), presenteeism (Fig. 2d; p<0.05) and overall work impairment (Fig. 2d; p<0.01), compared to those with low disease activity.

Healthcare resource utilization

Propensity score matching for HCP consultations and hospitalizations achieved balance for all variables, with an SMD in the range of -10–10% (Additional file 1). In the previous 12 months, the numbers of consultations with HCPs was 28% lower in patients with low disease activity compared with patients with higher active disease (Fig. 3; p<0.01) and the percentage of patients hospitalized at least once was 3.4-fold higher in patients with

Table 1 Patient demographics and clinical characteristics reported by physicians

	Total (N = 730)	Low disease activity (N = 46)	Higher active disease (N = 684)	p-value
Age, years				
n	730	46	684	0.3068
Mean (SD)	39.9 (12.6)	38.1 (13.5)	40.0 (12.5)	
Range	17–80	20–74	17–80	
Sex, n (%)				
n	730	46	684	1.0000
Female	646 (88.5)	41 (89.1)	605 (88.5)	
Male	84 (11.5)	5 (10.9)	79 (11.5)	
Ethnicity, n (%)				
n	730	46	684	0.4179
White	496 (67.9)	34 (73.9)	462 (67.5)	
Non-White	234 (32.1)	12 (26.1)	222 (32.5)	
Time since diagnosis, years				
n	719	44	675	0.5169
Mean (SD)	5.0 (5.6)	5.5 (5.8)	4.9 (5.6)	
Range	0.0–31.0	0.5–30.9	0.0–31.0	
Current disease severity, n (%)				
n	725	45	680	0.0291
Mild	427 (58.9)	35 (77.8)	392 (57.6)	
Moderate	265 (36.6)	9 (20.0)	256 (37.6)	
Severe	33 (4.6)	1 (2.2)	32 (4.7)	
Current treatment, n (%)				
n	730	46	684	
Steroid	690 (94.5)	17 (37.0)	673 (98.4)	< 0.0001
Immunosuppressant	413 (56.6)	20 (43.5)	393 (57.5)	0.0671
Anti-malarial	482 (66.0)	32 (69.6)	450 (65.8)	0.7480
Biologic	30 (4.1)	3 (6.5)	27 (3.9)	0.4277
Patients receiving belimumab	10 (1.4)	1 (2.2)	9 (1.3)	0.4806
Other	140 (19.2)	12 (26.1)	128 (18.7)	0.2444
Treatment ever received				
n	730	46	684	684
Steroid	713 (97.7)	33 (71.7)	680 (99.4)	< 0.0001
Immunosuppressant	477 (65.3)	27 (58.7)	450 (65.8)	0.3397
Anti-malarial	566 (77.5)	37 (80.4)	529 (77.3)	0.7177
Biologic	58 (7.9)	5 (10.9)	53 (7.7)	0.4009
Other	202 (27.7)	14 (30.4)	188 (27.5)	0.7335
Current treatment line				
n	730	46	684	0.4917
1	223 (30.5)	11 (23.9)	212 (31.0)	
2	285 (39.0)	21 (45.7)	264 (38.6)	
3	129 (17.7)	7 (15.2)	122 (17.8)	
4	58 (7.9)	4 (8.7)	54 (7.9)	
5	25 (3.4)	3 (6.5)	22 (3.2)	
6	10 (1.4)	0 (0.0)	10 (1.5)	

SD, standard deviation

Patients were considered to have low disease activity if they had a SLEDAI score of ≤4 and were receiving a glucocorticoid dose of ≤7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of >4 or were receiving a glucocorticoid at a dose of >7.5 mg/day

Current SLE disease severity is based on physician response to the question "What is the current level of disease severity for this patient? Response options were Mild, Moderate and Severe"
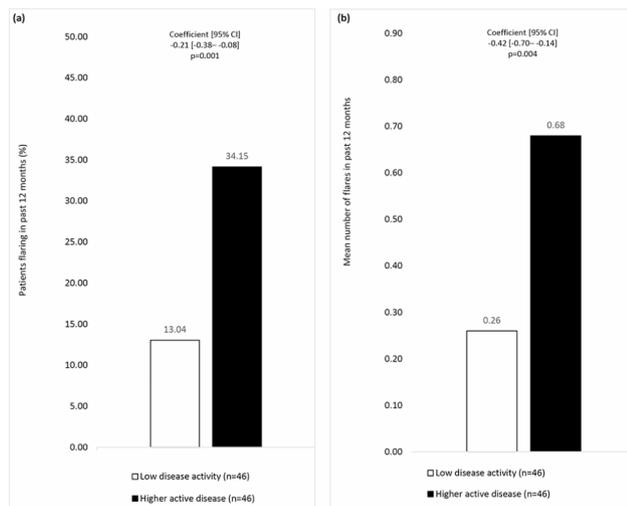
Fig. 1 Disease activity in patients that flared in the past 12 months. Association of disease activity with (**a**) Patients flaring in past 12 months (**b**) Number of flares in past 12 months. Patients were considered to have low disease activity if they had a SLEDAI score of ≤4 and were receiving a glucocorticoid dose of ≤7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of >4 or were receiving a glucocorticoid at a dose of >7.5 mg/day. CI, confidence interval; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

higher active disease compared with patients with low disease activity (Fig. 3; p<0.01).

Sensitivity analyses

Excluding patients who were classified as having higher active disease solely due to receiving >7.5 mg/day of glucocorticoid reduced the number of patients in the higher active disease group from 684 to 453. Results of the sensitivity analyses were broadly in line with those from the main analyses. The likelihood of having a flare and mean number of flares in the previous 12 months were 2.8-fold and 3.5-fold lower, respectively, in patients with low disease activity than those with higher active disease. In patients with low disease activity, the mean EQ-5D-3 L utility index score was 0.88 and the mean FACIT-Fatigue sum score 39.79 compared with 0.79 and 34.78, respectively, in patients with higher active disease, indicating better health status and lower fatigue levels in patients with low disease activity compared with patients with higher active disease. The mean percentages of absenteeism, presenteeism, overall work impairment, and total activity impairment were 25-fold, 2-fold, 2.2-fold and 1.6-fold lower, respectively, in patients with low disease activity versus higher active disease. A 27-fold, 1.7-fold and 1.8-fold lower annual loss of income was associated with absenteeism, presenteeism, and overall work impairment, respectively, in patients with low disease activity than those with higher active disease. The numbers of consultations with HCPs and the percentage of patients hospitalized in the previous 12 months were 1.4-fold and

5.7-fold lower, respectively, in patients with low disease activity compared with patients with higher active disease. All statistically significant differences between low disease activity and higher active disease groups found in the main analyses were reflected in the sensitivity analyses, except for absenteeism, for which there was no significant difference.

Discussion

We analyzed real-word data from a large cohort of patients with SLE, collected from both the patients and their managing physicians, in the USA and Europe. Our findings demonstrated that patients achieving a low disease activity at a given point in time had lower previous flaring rates, fatigue, productivity impairment (in particular, lower levels of absenteeism), income loss and HCRU, and better health status, compared with patients who had higher active disease or had not achieved low disease activity during the same time.

Our finding that low disease activity was associated with lower levels of flaring over the last 12 months has been previously reported in a prospective cohort study across 13 centers in eight Asia Pacific countries, in which low disease activity was defined via the LLDAS [15].

We showed low disease activity to be associated with better health status, as assessed with the EQ-5D-3 L. The mean EQ-5D-3 L utility index of 0.79 that we observed among those with higher active disease was below population norms reported for females from Europe (0.89) and the USA (0.85), indicating that our analysis cohort (which consisted of almost 90% females) had poorer health status than the general population. The mean EQ-5D-3 L health utility index of 0.88 for patients with low disease activity suggests health status on a par with the general population [24]. Our finding that patients with low disease reported an average EQ-5D-3 L score 0.09 points higher than patients with higher disease suggests there is likely to be an observable difference in health-related quality of life (HRQoL) in these patients as this difference is higher than 0.07, the minimal clinically important difference (MCID) for this measure in SLE [41]. While few studies have examined EQ-5D-3 L scores in relation to disease activity in SLE, there are two studies that found an association of overall health status with disease activity. In the first study they reported modest correlations between SLEDAI score and EQ-5D-3 L VAS in Canada [42], and similar findings were reported in a second study in China between SLEDAI score and EQ-5D-3 L utility index [43]. A Swedish study also reported a significant association of EQ-5D-3 L utility index and disease activity, although in that study disease activity was measured using the patient-reported SLAQ and glucocorticoid dose [44].
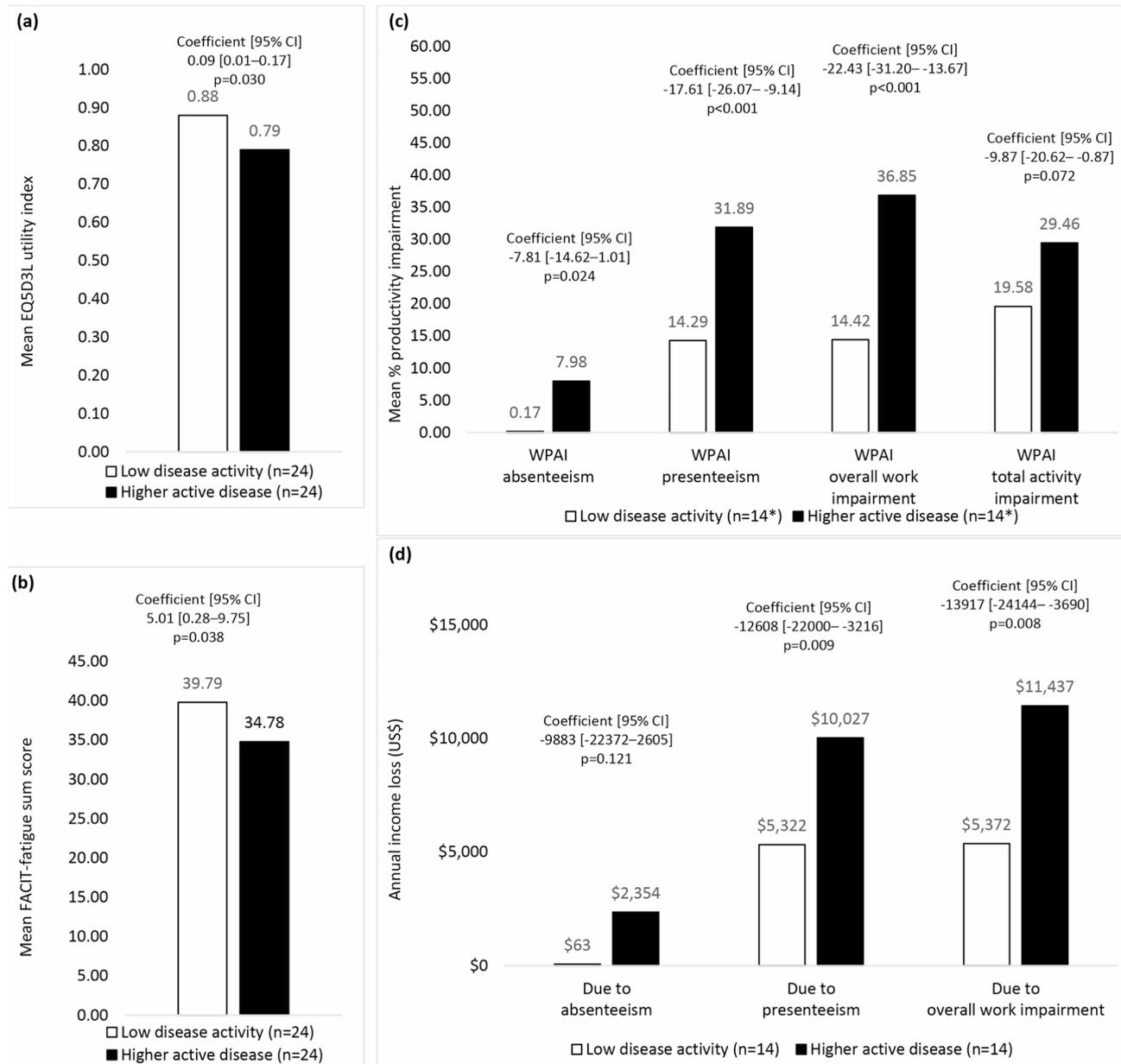
Fig. 2 Patient-reported outcomes by disease activity. Association of disease activity with PROs and income (**a**) EuroQoL-5D-3 L,[a] (**b**) Functional Assessment of Chronic Illness Therapy-Fatigue,[b] (**c**) Work Productivity and Activity Impairment-Lupus questionnaire, (**d**) Annual loss of income. [a] Higher scores on the EuroQoL-5D-3 L indicate better health status. [b] Higher scores on the Functional Assessment of Chronic Illness Therapy-Fatigue indicate lower levels of fatigue. *WPAI total activity impairment: Low disease activity (N = 24); Active disease (N = 24). Patients were considered to have low disease activity if they had a SLEDAI score of ≤ 4 and were receiving a glucocorticoid dose of ≤ 7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of > 4 or were receiving a glucocorticoid at a dose of > 7.5 mg/day. CI, confidence interval; EQ-5D-3 L, EuroQoL-5D-3 L; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; WPAI, Work Productivity and Activity Impairment questionnaire

Irreversible damage (as assessed by Systemic Lupus International Collaborating Clinics [SLICC] score/ American College of Rheumatology [ACR] damage index) is widely recognized to be associated with poorer quality of life, with the type of organ involvement potentially affecting disability and work ability differently [45, 46]. For example, a past study found that organ damage, specifically musculoskeletal damage, was negatively correlated with HRQoL, particularly the physical and social aspects [46]. A second study reported similar findings, with skin and joint involvement leading to a higher proportion of the patients experiencing activity impairment [45], indicating that patients with this type of organ
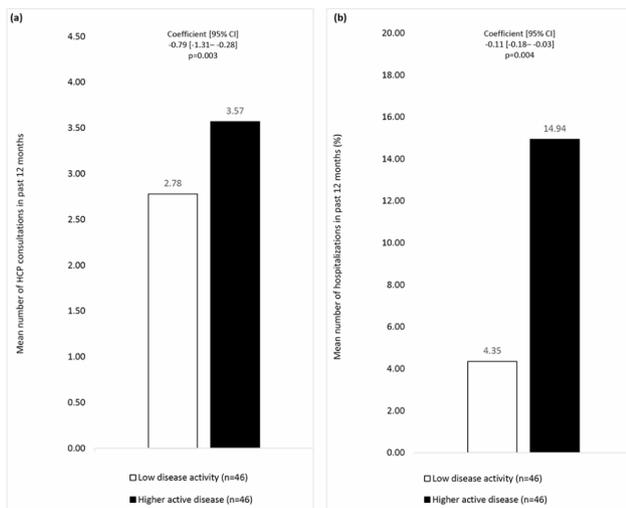
Fig. 3 Healthcare resource utilization in past 12 months by disease activity. Patients were considered to have low disease activity if they had a SLE-DAI score of ≤ 4 and were receiving a glucocorticoid dose of ≤ 7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of > 4 or were receiving a glucocorticoid at a dose of > 7.5 mg/day. CI, confidence interval; HCP, healthcare professional; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

damage should be examined and monitored closely in clinical practice [46].

Other PROs have been utilized in studies investigating the relationship of disease activity in SLE with HRQoL. A cross-sectional Brazilian study showed higher disease activity as assessed via the SLEDAI in women with SLE to be associated with poorer HRQoL assessed with the World Health Organization Quality of Life Group (WHOQOL-100) assessment instrument [47]. A Swiss cohort study reported similar findings, with increases in disease activity assessed by the SELENA-SLEDAI negatively correlated with the physical and mental component summaries of the SF-36, signifying reduced HRQoL [48].

We observed a mean FACIT-Fatigue sum score of 39.79 in patients with low disease activity and a mean sum score of 34.78 among those with higher active disease, these were both lower than the mean of 43.6 reported for > 1,000 and > 2,400 members of the general population in the US and Germany [25, 49]. This indicates that fatigue in both groups of SLE patients is worse than in the general population. Findings in the literature on the association between SLE disease activity and fatigue severity are mixed, with two published US studies reporting no significant association of disease activity with fatigue assessed [50, 51] while two studies observed similar findings as we reported here, with fatigue being worse in patients with more severe disease [52, 53]. One study exploring MCIDs in SLE reported that FACIT-F scores among patients experiencing "much more fatigue" differed from those feeling "somewhat more fatigued" by 15.0 points which is larger than the difference we found

between patients with low and higher disease activity [54] suggesting that this difference in score may not have an impact on patient HRQoL.

We saw a much lower impact on productivity, and consequently on income, in patients with low disease activity. Absenteeism was only 0.17%, with a consequent income loss of $63/year, in patients with low disease activity, but in patients with higher active disease these were close to 8% and more than $2,300/year. When presenteeism was also considered, the difference between patients with low disease activity and higher active disease was even more marked: overall work impairment and annual income loss were 14% and $5,400 in patients with low disease activity but more than doubled to 37% and $11,400 in patients with higher active disease.

In an analysis of data from a large population-based US SLE cohort, overall work impairment assessed with the WPAI was correlated with disease activity assessed with the SLAQ [55]. Higher self-reported disease severity was also directly associated with higher levels of absenteeism and presenteeism in a survey of patients with SLE in the USA [56]. An analysis of a large cohort of US SLE patients reported that disease activity, assessed via the SLAQ, was a significant predictor of reduced work productivity [57]. Similarly, a study based in Germany found that high levels of disease activity as well as fatigue, pain and poor mental health and physical functioning were associated with impairment in work productivity and daily activities [58]. However, findings on the effect of disease activity on fatigue are mixed: a study of patients in Italy experiencing remission (no disease activity) for at least five years reported improvements in many of the physical components of HRQoL, including physical functioning and bodily pain, compared with those who had had shorter remission periods or were unremitted, but no differences in fatigue levels between these groups [59]. Published studies have also shown the indirect costs of SLE, including lost earnings, to be related to disease activity [57, 60]. Collectively, these data underscore the importance of disease activity in the burden of illness in SLE from the patient perspective.

In our study, patients with low disease activity had 28% fewer HCP consultations in the 12 months prior to data collection, compared with patients with higher active disease. In the 12 previous months, only 4% of patients with low disease activity were hospitalized, compared with 15% of those with higher active disease. The lower HCRU that we observed in patients with low disease activity is consistent with previous published studies. Reductions in disease activity assessed with the SLEDAI were associated with reductions in HCRU and healthcare costs in a retrospective longitudinal study of SLE patients in the USA [61]. Analysis of a cohort of SLE patients from various regions of Sweden reported indirect and

direct healthcare costs (which relate to HCRU) around 50% higher in patients with a SLEDAI score≥4 compared with patients with SLEDAI score<4 [62]. In an SLE patient cohort from a single tertiary hospital in Australia, patients in LLDAS for ≥50% of the observation period incurred significantly lower (by 26%) annual direct healthcare costs than those in LLDAS for <50% of the time [12]. A retrospective, observational cohort study of patients with SLE from the Japan Medical Data Center claims database identified increasing HCRU and cost with increasing disease severity, with disease severity defined based on an algorithm that included SLEDAI score with a number of other parameters [63].

We observed discrepancies between subjective physician-reported disease severity and objectively defined disease activity, with 58% of patients classified as having higher active disease being considered by their physicians to have mild SLE. Excluding patients defined as having higher active disease on the basis of receiving glucocorticoid at a dose of >7.5 mg/day reduced the patients classified as having higher active disease but considered by their physicians to have mild SLE to 48%, but this is still a marked misalignment of these means of assessing SLE. The lack of clear alignment of subjective physician-reported disease severity with the disease activity groups defined for the purposes of this analysis highlighted the challenges of assessing disease activity in SLE. One possible explanation for this misalignment, and a limitation of the SLEDAI, is that the presence of laboratory features alone, which could be chronic and not necessarily require treatment, may give patients a high disease activity score. The differences demonstrated in flaring, PROs and HCRU between patients with low disease activity and higher active disease even when including patients that physicians considered to have mild SLE in the active disease group indicated that the criteria used in defining disease activity, including SLEDAI score and receipt of high-dose glucocorticoid, are associated with the patient-reported and economic burden of SLE.

This study found an association between low disease activity and improved patient outcomes, functionality and HCRU. Although the clinical real-world effectiveness of biologic therapy fell outside the current scope, past studies have reported an association between advanced therapies, and improved patient outcomes. For example, treatment with belimumab has been shown to have a positive impact on HRQoL by improving physical functioning and fatigue [64]. In general, biologic agents have shown positive effects on HRQoL in randomized clinical trials [65]. However, of the total cohort, just 10 patients were receiving belimumab in our study.

There were potential limitations to our study. Despite the large number of study participants, missing data (particularly PRO data) resulted in small sample sizes being available for some analyses. Data were included for the next five consecutively consulting patients; the study sample was therefore pseudo-random, rather than truly random, and the study population could include a high proportion of patients who consult their physician more frequently than is typical in SLE, and who may be atypical in other ways. The point-in-time nature of the survey allowed assessment of the association between factors but precluded assessment of causality. Our methodology relied on accurate recall and reporting by physicians and patients, and missing data were expected but may have influenced results—always a challenge in this type of study. While the mean age and preponderance of females in our dataset reflected published demographics for SLE, our study population included a high proportion of White patients, although globally SLE has a higher prevalence in other ethnic groups. As non-White SLE patients have a higher likelihood of developing severe disease with poor outcomes [66, 67] caution should be exercised in extrapolation of these findings to a broader population.

Our data source did not include some of the data used to define low disease activity in the published definition of LLDAS [14, 15], and we were therefore not able to classify patients based exactly on that definition. However, patients that we defined as having higher active disease had a SLEDAI score≥4 and/or were receiving≥7.5 mg/day glucocorticoid, and therefore would be excluded from the LLDAS group based on the published definition. A total of 23 patients that we classified as having low disease activity were receiving an immunosuppressant or biologic, but insufficient data were available to ascertain whether all of these therapies were at well-tolerated standard maintenance doses, as required in the published definition of LLDAS.

As the definition of a flare in SLE has not yet been universally accepted, we defined flare in this study based on the clinical judgement of managing physicians, this may mean that different physicians classified the presence or absence of a flare using different criteria. Similarly, the classification criteria physicians used to make their judgement on whether a patient was experiencing a flare were not collected during this study. Because we collected data on both the number of flares patients had experienced in the last 12 months and whether the patient was experiencing a flare at the time of consultation, the outcome of a flare was, in part, retrospective, flares experienced in the last 12 months could have impacted the SLEDAI score at the time of evaluation. Similarly, disease severity was physician-defined based on their subjective assessment of the consulting patient and therefore there may be some variation in how physicians classify severity of SLE in this study.Finally, we recorded the most recent SLEDAI score recorded by the physician for each patient,

this may have been collected up to six months prior to the day of the consultation.

Despite the limitations, real-world studies play an important role in exploring areas of concern that cannot be addressed in randomized clinical trials. Patients included in clinical trials represent only a small proportion of the consulting population as a result of the stringent eligibility criteria that patients are required to meet to be involved, for example, patients tend to be younger and without comorbidities [68]. Similarly, patients treated in the real-world setting may be less likely to be adherent to medication than those included in clinical trials and therefore better reflect outcomes of patients in the real world [69] As a result, data from real-world studies can complement clinical trials and provide insight into the effective of interventions in patients commonly seen in clinical practice.

Our analysis of a large real-world patient cohort from multiple countries and two continents provided insight into the association of clinical, patient-reported and economic outcomes with disease activity in SLE. Our findings indicated that patients with low disease activity experienced significantly better health status, less fatigue, and lower levels of productivity impairment, and were less burdensome to the healthcare system than those with higher active disease. We are hopeful that with an established definition of low SLE disease activity in place, there will be a useful guide for treatment goals and an aid to assess drugs in development and their potential to improve patient outcomes and reduce HCRU.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41927-023-00355-6.

Additional file 1. Patient characteristics before and after propensity score matching for physician-reported outcomes. Patients were considered to have low disease activity if they had a SLEDAI score of ≤ 4 and were receiving a glucocorticoid dose of ≤ 7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of > 4 or were receiving a glucocorticoid at a dose of > 7.5 mg/day. SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SMD, standardized mean difference.

Additional file 2. Patient characteristics before and after propensity score matching for general health status and fatigue. Domains included: EQ-5D-3 L utility index, FACIT-fatigue sum score and WPAI total activity impairment. Patients were considered to have low disease activity if they had a SLEDAI score of ≤ 4 and were receiving a glucocorticoid dose of ≤ 7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of > 4 or were receiving a glucocorticoid at a dose of > 7.5 mg/day. EQ-5D-3 L, EuroQoL-5D-3 L; FACIT-fatigue, Functional Assessment of Chronic Illness Therapy-fatigue; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SMD, standardized mean difference; WPAI, Work Productivity and Activity Impairment questionnaire

Additional file 3. Patient characteristics before and after propensity score matching for work productivity and activity. Domains include: WPAI absenteeism, WPAI presenteeism, WPAI overall work impairment, lost income due to absenteeism, presenteeism, and overall work impairment. Patients were considered to have low disease activity if they had a SLEDAI score of ≤ 4 and were receiving a glucocorticoid dose of ≤ 7.5 mg/day; patients were considered to have active disease if they had a SLEDAI score of > 4

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or were receiving a glucocorticoid at a dose of > 7.5 mg/day. EQ-5D-3 L, EuroQoL-5D-3 L; FACIT-fatigue, Functional Assessment of Chronic Illness Therapy-fatigue; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SMD, standardized mean difference; WPAI, Work Productivity and Activity Impairment questionnaire.

Data Availability

All data that support the findings of this study are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Ben Hoskin at ben.hoskin@adelphigroup.com.

Declarations

Ethics approval and consent to participate

Data collection was undertaken in line with European Pharmaceutical Marketing Research Association [70] guidelines and as such it does not require ethics committee approval. Each survey was performed in full accordance with relevant legislation at the time of data collection, including the US Health Insurance Portability and Accountability Act 1996 [71], and Health Information Technology for Economic and Clinical Health Act legislation. [72]. All patients gave written informed consent before any study-related procedures were performed.

Consent for publication

Not applicable.

Competing interests

Zahi Touma collaborated with Janssen employees on this study, has acted as a consultant for AstraZeneca, Biogen IDEC, EMD Serono, Pfizer Inc., GlaxoSmithKline, Janssen Inc., UCB, Eli Lilly and Sarkana Pharma. Karen Costenbader collaborated with Janssen employees on this study, has acted as a consultant for AstraZeneca and Neutrolis, and has research collaborations with Glaxo Smith Kline, Lilly, Exagen Diagnostics, Gilead, Amgen and Merck. Ben Hoskin, Christian Atkinson, David Bell, and James Pike are employed by Adelphi Real World. Chetan Karyekar is an employee and shareholder of Janssen pharmaceuticals. Pamela Berry is an employee and shareholder of Janssen pharmaceuticals.

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