Clinical Rheumatology (2019) 38:1857–1864
https://doi.org/10.1007/s10067-019-04485-6

ORIGINAL ARTICLE

Health-related quality of life in patients with systemic lupus erythematosus: a Spanish study based on patient reports

J. A. Román Ivorra[1] · N. Fernández-Llanio-Comella[2] · A. San-Martín-Álvarez[3] · P. Vela-Casasempere[4] · I. Saurí-Ferrer[5] · S. González-de-Julián[6] · D. Vivas-Consuelo[6,7]

Received: 30 November 2018 / Revised: 13 February 2019 / Accepted: 17 February 2019 / Published online: 28 February 2019

Abstract

Introduction and objectives Systemic lupus erythematosus (SLE) is a disease that significantly affects the quality of life and welfare of patients. SLE patients can be classified into multimorbidity levels using Clinical Risk Groups (CRGs) to help to incorporate predictive models of health needs. The goal of this study was to correlate CRGs with health-related quality of life (HR-QoL) and costs in SLE patients.

Methods A questionnaire was administered to SLE patients in four hospital centers of the Valencian Community (Spain) between October 2015 and March 2016. The factors studied included HR-QoL (EQ-5D-5L and VAS), disease activity (SLAI/SELENA), damage (SLICC/ACR), and severity (IGK).

Results The patients ($N = 190$, 92.06% female, age (mean ± SD) 47.23 ± 13.43 years) were sorted according to health status in nine CRGs. We found that most SLE patients (> 70%) were in CRGs 5 and 6. The main HR-QoL issues in these patients were related to mobility, ability to perform usual activities, and pain/discomfort. The scores (mean ± SD) for EQ-5D-5L and VAS were 0.74 ± 0.25 and 65.67 ± 23.52, respectively. We found that the age of the patients negatively affected their HR-QoL ($r = -0.266$). SLE direct costs per patient increased with each CRG group, representing 71.92% of the total costs, while indirect costs were highly variable. The average cost per patient with SLE amounted to €8432.85 (year 2014).

Conclusions Patients' quality of life is related with age, disease activity, damage, and severity. Age was the parameter which most affects HR-QoL. Most costs of SLE are concentrated in two CRGs in which the HR-QoL deteriorates sharply.

Keywords Health-related quality of life · Patient costs · Patient-reported outcomes · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic, heterogeneous, inflammatory, and multisystem autoimmune disease characterized by periods of exacerbations and a variable course [1]. The estimated prevalence of SLE in Europe is 0.09%, affecting mostly women (> 90%) of working age (mean age at diagnosis, 33 years) [2]. The recent 2016 EPISER study of rheumatic diseases in the adult population of Spain showed a markedly higher prevalence of 0.2% (95% CI, 0.1–0.4) [3].

SLE causes an important financial and social burden on the patients and on society as a whole [4]. SLE leads to significant morbidity and mortality through effects on multiple organ systems, including mucocutaneous, musculoskeletal, renal, hematologic, neurologic, and cardiovascular systems [2]. SLE is a complex chronic disease, and although there is no cure, the life expectancy of patients with SLE has been

✉ D. Vivas-Consuelo
dvivas@upv.es

1 Hospital Universitario y Politécnico La Fe, Valencia, Spain

2 Hospital Arnau de Vilanova, Valencia, Spain

3 Hospital General Universitario de Elda, Alicante, Spain

4 Hospital General Universitario de Alicante, Alicante, Spain

5 Instituto de Investigación Sanitaria (INCLIVA), Valencia, Spain

6 Centro de Ingeniería Económica (INECO), Universitat Politècnica de València (UPV), Valencia, Spain

7 INECO. Department of Economics and Social Sciences, Universitat Politècnica de València, Edificio 7J. Oficina 3.24, Cn de Vera s/n, 46022 Valencia, Spain

improving substantially over the last 50 years [5]. However, patients often suffer lifelong symptoms and have a long-term need for medical attention. Patients with SLE experience poor health-related quality of life (HR-QoL), which can be worse than in groups with other chronic diseases, such as congestive cardiac failure, myocardial infarction, and diabetes [6]. Pain can remain a significant burden in up to a quarter of SLE patients over long periods of time, which correlates with worsening HR-QoL [7].

Several studies have been focused on evaluating the quality of life of patients with SLE. Some of them used tools created specifically to evaluate the welfare of patients with SLE, as in the case of *Systemic Lupus Activity Questionnaire* (SLAQ) [8], LupusQoL [9], LupusPRO [10], L-QOL [11], and SLEQOL [12]. Others made use of generic questionnaires of quality of life, such as SF-36 or EQ-5D [4, 9, 13, 14]. On this basis, it is possible to calculate the quality adjusted life years (QALYs), which complement the economic evaluation and are widely recognized tools that allow establishing comparisons with other pathologies. However, their disadvantage is that they present deficiencies in measuring specific aspects of the disease with great impact in SLE. In recent years, ad hoc questionnaires have been developed to evaluate factors, such as fatigue [15], pain [16], depression, and work activity [17] that could be appropriate for their use in SLE.

The Clinical Risk Groups (CRGs) can be used as a measure of multimorbidity [18]. This system classifies individuals into mutually exclusive categories, using medical contact or consultation data. Each patient is assigned to a severity level according to his/her chronic health conditions. CRGs classify the individual and all the medical services used over a predetermined period. There are 1079 basic CRGs, all of which can be classified into the CRG core health status that maintain clinical significance and consider future medical attention needs and the clinical similarities of the individuals assigned to the CRGs. The CRG core health status are (1) healthy, (2) significant acute disease, (3) single or multiple minor chronic disease, (4) moderate chronic diseases, (5) dominant chronic diseases, (6) chronic disease in two or more organ systems, (7) multiple dominant chronic diseases, (8) metastatic malignancies, and (9) catastrophic conditions. These basic groups can be aggregated into three levels (ACRG) with each successive level maintaining the health states and severity, while reducing the number of groups and, if necessary, adjusting the severity level. This grouping system gives a morbidity population pattern [18, 19].

The objectives of this study were to classify SLE patients into multimorbidity levels using CRGs, correlate CRG health main levels with HR-QoL, and correlate direct and indirect cost with SLE multimorbidity health status.

Patients and methods

Records of all patients diagnosed with SLE in the Valencian Community (Spain) were retrieved electronically from the Assistance Information System using the CIE-9 (code 710.0—systemic lupus erythematosus). The patients were classified by health status and associated comorbidities using the records of the Valencian Community Patient Classification System (SCP-CV), which is based on CRG and the Outpatient Care Information System (SIA).

Patient-reported outcomes

A questionnaire was administered to 190 consecutive patients with SLE in four hospital centers of the Valencian Community (Hospital Arnau de Vilanova, Hospital General Universitario de Elda, Hospital Universitario y Politécnico La Fe, and Hospital Universitario General de Alicante) between October 2015 and March 2016.

Information related to HR-QoL was collected using the EQ-5D-5L and the visual analog scale (VAS) [20].

The EQ-5D-5L questionnaire collects information on five dimensions that affect patient health as a result of the disease: mobility, self-care, usual activities (work, study, housework, family, or leisure activities), pain/discomfort, and anxiety/depression. In this questionnaire, each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient had to indicate his/her health state by choosing the most appropriate statement in each of the five dimensions. The EQ-5D-5L final score ranges from − 0.654 (bad QoL) to 1 (good QoL).

The VAS measured the patient's self-rated health on a vertical scale, where the endpoints were "The best health you can imagine" and "The worst health you can imagine." This index could be used as a quantitative measure of health based on the patient's own judgment [21]. The VAS score ranged from 0 (bad quality of life) to 100 (good quality of life).

Clinician-rated measurements of disease activity, damage, and severity

Disease activity was quantified by the clinicians at the four hospital centers of the Valencian Community by considering flare episodes suffered by SLE patients during a certain period. A flare was defined as a measurable increase in disease activity in one or more organs involving new or worse clinical signs or symptoms and/or laboratory measurements, which would be considered clinically significant and prompt increase or initiation of treatment [22]. Disease activity was evaluated by the Systemic Lupus Erythematosus Disease Activity Index (SLAI/SELENA) that provides a general measure of the activity with its 24 descriptors. The total score of

SLAI/SELENA ranges from 0 (no activity) to 105 (maximum activity) [2, 23].

In SLE, permanent end-organ damage can be caused by the disease itself, its treatment, or a co-morbidity. This damage can have a major impact on patient morbidity and mortality. Disease impairment was quantified by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI), which measures long-term organ damage [24]. This index score ranges from 0 to 47, where 0 = absence of damage.

Finally, disease severity was determined by the Katz severity Index or IGK [17]. This index is the most suitable instrument to assess functional status as a measurement of ability to perform activities of daily living independently. This index is computed using seven components (hematocrit, creatine, number of ACR criteria met, history of proteinuria, cerebritis or pulmonary disease, diffuse proliferative glomerulonephritis). Each component is assigned 1 or 2 "points" that are then added, with score ranging from 1 to 13.

Cost analysis

The reference year for costs was 2014. Indirect costs were computed only from patients who were self-employed or employed workers. We considered labor costs related to sick leave and loss of labor productivity. Costs related to sick leave were calculated according to the temporary disability benefits regulated by the Government of Spain (the costs represent 60% of their wages from day 4 of sick leave to 20 days inclusive and 75% from 21 onwards). Wages were estimated according to the rank of the Individual Health Card (SIP) awarded, which depends on the worker's income.

Costs relating to the loss of labor productivity were obtained by calculating proportional wages to the time of a working day in which worker productivity was affected due to illness. The degree of involvement of productivity and activity was reported by patients in the questionnaire Work Productivity and Activity Impairment (WPAI: Lupus) [9].

Statistical analysis

An analysis of descriptive statistics was presented for all the variables. The continuous variables were summarized by *N*, mean, and standard deviation (SD). The categorical variables were described by *N* and percentage of each category. Bivariate correlation analyses were conducted to identify parameters significantly affecting patients' quality of life. The Pearson correlation analysis was used cross-sectional data to assess the relationships between age, VAS, HR-QoL summary scores (EQ-5D-5L), and SLE disease measurements (SLAI/SELENA, SLICC/ACR, and IGK).

Results

SLE in the Valencia Autonomous Community

In 2014, there were 4422 cases of SLE in the Valencian Community (population = 5,032,126), and therefore, the prevalence of this disease was 0.09%. The patients were mostly female (84.92%) and the mean age (± SD) was 50.40 ± 15.76 years. The mortality rate of SLE patients in the Valencia Community in this period was 1.04%.

The classification of the 4422 SLE patients according to CRG is shown in Table 1. We found that most patients (> 70%) had a health status of 5 or 6 (dominant chronic disease or chronic disease in two or more organ systems, respectively).

Patient- and physician-reported outcomes

SLE patients ($N = 190$) from four hospitals participating in the study were randomly selected to determine patient and physician reported outcomes. All patients were ≥ 17 years of age, and 92.06% were female. The mean (± SD) age of the patients was 47.23 ± 13.43 years, age at diagnosis was 34.19 ± 13.82 years, and years since diagnosis was 13.28 ± 9.95. Most patients were classified in CRG health status 5 (71 patients, 38.59%) or 6 (96 patients, 52.17%).

The mean ± SD scores for the EQ-5D-5L instrument and a VAS were 0.74 ± 0.25 and 65.67 ± 23.52, respectively. When the mean EQ-5D-5L scores were sorted according to CRG status, we found that they were stable until CRG 5 and then declined sharply (Fig. 1). Table 2 summarizes the results of the EQ-5D-5L questionnaire when the patients are classified by CRG, including the information about the five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and their severity). Most of the SLE patients experimented one or more of the difficulties measured in this questionnaire. The main issues were related to mobility (38.1% show slight to moderate problems), usual activity (42.4% suffer slight to moderate problems), and pain/discomfort (53.8% reflect slight to moderate problems). The prevalence of moderate or severe problems was lowest for self-care and anxiety/depression.

The mean ± SD SLAI/SELENA, SLAI/SELENA2, and SLICC/ACR scores were 0.99 ± 0.73, 6.02 ± 6.02, and 1.22 ± 1.76, respectively. For disease severity, the mean ± SD IGK score was 2.74 ± 1.96. These scores suggested low disease activity, no or little end-organ damage, and low severity (good functional status) in these patients.

Since a chronic disease, such as SLE, tends to have significant implications for the physical, social, and psychological aspects of patients' life that can become worse with age, we then attempted to determine if there was a

Table 1 Classification of all SLE patients in 2014 according to CRG and severity ($N = 4422$)

CRG health status		Severity								
		0	1	2	3	4	5	6	Unclassified	Total
1 Healthy	Population	110	44	7		1	92			254
	Male	36	13				19			68
	Female	74	31	7		1	73			186
	Mean age	38.50	44.77	33.00		38.00	40.96			40.32
2 Significant acute disease	Population	23		170		1	26			220
	Male	5					6			11
	Female	18		170		1	20			209
	Mean age	41.30		37.58		36.00	42.15			38.50
3 Single minor chronic disease	Population		128	6						134
	Male		28							28
	Female		100	6						106
	Mean age		47.30	42.17						47.07
4 Minor chronic disease in multiple organ systems	Population		39	17	16	7				79
	Male		4	6		1				11
	Female		35	11	16	6				68
	Mean age		48.00	61.82	57.75	57.86				53.82
5 Single moderate dominant or chronic disease	Population		206	1111	74		3	1		1395
	Male		48	115	15		1	1		180
	Female		158	996	59		2			1215
	Mean age		50.56	44.69	44.39		59.33	43.00		45.58
6 Significant chronic disease in multiple organ systems	Population		835	425	243	160	68	6		1737
	Male		105	70	38	27	7	1		248
	Female		730	355	205	133	61	5		1489
	Mean age		53.80	55.39	57.89	57.54	57.21	51.17		55.23
7 Dominant chronic disease in three or more organ systems	Population		58	59	106	23	9	15		270
	Male		10	19	25	5	3	5		67
	Female		48	40	81	18	6	10		203
	Mean age		61.36	58.07	63.96	67.65	70.11	67.00		62.80
8 Dominant neoplasms, metastases and complications	Population		2	7	11	11	6			37
	Male			2	2	1	2			7
	Female		2	5	9	10	4			30
	Mean age		65.50	61.14	54.82	64.64	55.83			59.68
9 Severe diseases or extreme health care needs	Population		3	4	7	9	2	27		52
	Male			1	1	3		5		10
	Female		3	3	6	6	2	22		42
	Mean age		51.33	42.25	47.14	52.22	65.00	50.44		50.29
Total	Population	133	1315	1806	457	212	206	49	244	4422
	Male	41	208	213	81	37	38	12		630
	Female	92	1107	1593	376	175	168	37		3548
	Mean age	38.98	52.53	47.14	56.87	58.59	48.68	55.45		50.40

correlation between age and the measurements derived from the patient- or physician-reported outcomes. The results, summarized in Table 3, show that the age of the patients negatively affected their quality of life ($r = -0.266$). Disease activity and damage are negatively correlated with EQ-5D-5L ($r = -0.239$ and $r = -0.255$, respectively). These parameters are also significantly correlated with severity ($r = 0.179$ and $r = 0.291$, respectively). The EQ-5D-5L instrument and VAS were highly correlated ($r = 0.699$).

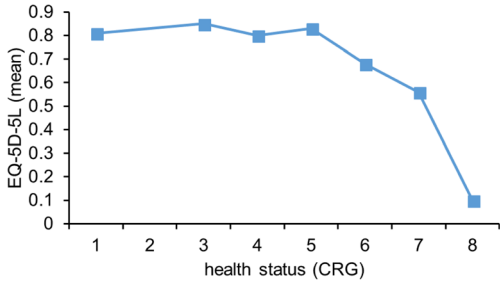

Fig. 1 EQ-5D-5L scores (mean) by CRG health status for SLE patients

Cost per patient with SLE

The direct and indirect costs of patients with SLE are summarized in Table 4. Direct costs included primary care, hospital admissions, and outpatient pharmacy costs. We considered all types of medication currently used to treat SLE, which included selective biologic immunosuppressants (rituximab, belimumab), aminoquinolines, corticosteroids, AINES, and analgesics. Most SLE patients (70.22%) did not use prednisolone to treat SLE, but 20.44% used prednisolone at a dose of < 5 mg/day and 9.34% of the patients used prednisolone at a dose of > 10 mg/day.

The results show that direct costs per patient increased as the CRG increased, representing 71.92% of the total costs. The direct cost distribution according to morbidity and clinic risk was mainly allocated to CRG 6 (€8193 per patient per year) and CRG 7 (€10,165 per patient per year). However, patients classified in CRG 8 presented the highest result with €12,243 per year, possibly due to their special needs.

We found that indirect costs were highly variable, with an average cost per patient of €4787.58 per year. The number of

Table 2 EQ-5D-5L results by CRG

	Total ($n = 184$) *n* (%)	CRG 1 ($n = 4$) *n* (%)	CRG 3 ($n = 1$) *n* (%)	CRG 4 ($n = 1$) *n* (%)	CRG 5 ($n = 71$) *n* (%)	CRG 6 ($n = 96$) *n* (%)	CRG 7 ($n = 10$) *n* (%)	CRG 8 ($n = 1$) *n* (%)
Mobility								
No problem	107 (58.2)	3 (75.0)	1 (100.0)	0 (0.0)	56 (78.9)	43 (44.8)	4 (40.0)	0 (0.0)
Slight problem	41 (22.3)	1 (25.0)	0 (0.0)	1 (100.0)	9 (12.7)	28 (29.2)	1 (10.0)	1 (100.0)
Moderate problem	29 (15.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (7.0)	22 (22.9)	2 (20.0)	0 (0.0)
Severe problem	7 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	3 (3.1)	3 (30.0)	0 (0.0)
Unable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Self-care								
No problem	130 (70.7)	3 (75.0)	1 (100.0)	1 (100.0)	59 (83.1)	61 (63.5)	5 (50.0)	0 (0.0)
Slight problem	32 (17.4)	1 (25.0)	0 (0.0)	0 (0.0)	7 (9.9)	22 (22.9)	2 (20.0)	0 (0.0)
Moderate problem	21 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (7.0)	13 (13.5)	2 (20.0)	1 (100.0)
Severe problem	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(10.0)	0 (0.0)
Unable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Usual activity								
No problem	92 (50.0)	2 (50.0)	0 (0.0)	1 (100.0)	42 (59.2)	43 (44.8)	4 (40.0)	0 (0.0)
Slight problem	41 (22.3)	2 (50.0)	1 (100.0)	0 (0.0)	16 (22.5)	22 (22.9)	0 (0.0)	0 (0.0)
Moderate problem	37 (20.1)	0 (0.0)	0 (0.0)	0 (0.0)	11 (15.5)	22 (22.9)	4 (40.0)	0 (0.0)
Severe problem	12 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	8 (8.3)	2 (20.0)	0 (0.0)
Unable	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (100.0)
Pain/discomfort								
No problem	57 (31.0)	0 (0.0)	0 (0.0)	0 (0.0)	31 (43.7)	23 (24.0)	3 (30.0)	0 (0.0)
Slight problem	53 (28.8)	3 (75.0)	1 (100.0)	0 (0.0)	20 (28.2)	28 (29.2)	1 (10.0)	0 (0.0)
Moderate problem	46 (25.0)	1 (25.0)	0 (0.0)	1 (100.0)	13 (18.3)	27 (28.1)	3 (30.0)	1 (100.0)
Severe problem	25 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (9.9)	16 (16.7)	2 (20.0)	0 (0.0)
Unable	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	1 (10.0)	0 (0.0)
Anxiety/depression								
No problem	103 (56.0)	3 (75.0)	1 (100.0)	1 (100.0)	51 (71.8)	45 (46.9)	2 (20.0)	0 (0.0)
Slight problem	46 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	15 (21.1)	26 (27.1)	4 (40.0)	0 (0.0)
Moderate problem	18 (9.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	14 (14.6)	2 (20.0)	0 (0.0)
Severe problem	15 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)	9 (9.4)	2 (20.0)	1 (100.0)
Unable	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.1)	0 (0.0)	0 (0.0)

Table 3 Correlation (Pearson's) between age and HR-QoL outcomes

	Pearson's correlation, *N*	AGE	EQ5D5L	VAS	SLAI/ SELENA	SLAI/ SELENA2	SLICC/ ACR	IGK
AGE	*r*	1.000	− 0.266**	− 0.328**	− 0.101	− 0.224**	0.364**	− 0.123
	N	189	185	189	154	188	189	189
EQ5D5L	*r*		1.000	0.699**	− 0.516**	− 0.239**	− 0.255**	− 0.053
	N		186	186	151	185	186	186
VAS	*r*			1.000	− 0.444**	− 0.190**	− 0.174*	0.041
	N			190	155	189	190	190
SLAI/SELENA	*r*				1.000	0.400**	0.033	− 0.014
	N				155	154	155	155
SLAI/SELENA2	*r*					1.000	− 0.056	0.179*
	N					189	189	189
SLICC/ACR	*r*						1.000	0.291**
	N						190	190
IGK	*r*							1.000
	N							190

**$p < 0.01$

*$p < 0.05$

comorbidities and the occurrence of flare-ups related to the disease probably explain this wide variability in costs.

The average cost per patient with SLE amounted to €8432.85 per year.

Discussion

In this study, we examined HR-QoL and modifiable factors that can impair HR-QoL in a sample of 190 SLE patients from the Valencian Community in Spain. We found that most SLE patients (> 70%) can be classified as CRGs 5 (single moderate dominant or chronic disease) and 6 (significant chronic disease in multiple organ systems). We found that SLE patients score highly in HR-QoL, as measured by the EQ-5D-5L instrument, until they reach CRG 5. Patients classified in higher CRGs, which are the majority in our study, present progressively deteriorating EQ-5D-5L scores. The patients reported that the HR-QoL aspects that were most affected were related to mobility, ability to perform usual activities, and pain/discomfort. A recent study of American patients, using different PRO instruments, also reported that disease severity correlated with HR-QoL, especially in the domains of fatigue, pain, cognition, physical function, and psychosocial illness, with pain being an important independent contributor [25]. Additionally, our study showed that disease activity and damage presented a weak correlation with EQ-5D-5L, as has been observed before [26].

Age is the parameter that best correlates with the patients' HR-QoL. This effect is likely to derive from the fact that disease activity, damage, and severity usually increase over time and also as a result of added comorbidities. A previous longitudinal study showed a correlation between higher morbidity health status with age [27]. It is likely, however, that the

Table 4 Direct and indirect costs (€) per patient sorted by CRG

Health status (CRG)	*N*	Mean direct costs per patient	Number of patients with a job	Mean indirect costs per patient	Mean total costs per patient
1 Healthy	4	1228.37	2	3074.32	2765.54
3 Single minor chronic disease	1	440.61	0	–	440.61
4 Minor chronic disease in multiple organ systems	1	697.05	1	7027.03	7724.08
5 Single moderate dominant or chronic disease	74	3019.87	52	4259.71	6013.18
6 Significant chronic disease in multiple organ systems	96	8193.21	36	5605.02	10,295.09
7 Dominant chronic disease in three or more organ systems	11	10,165.31	2	4391.89	10,963.84
8 Dominant neoplasms, metastases and complications	1	12,243.07	0	–	12,243.07
TOTAL	188	6064.53	93	4787.58	8432.85

introduction of more effective and less toxic immunosuppressive drugs, together with a better control of comorbidities and lesser use of corticoids, will improve the management of SLE in aging patients.

Published studies report that SLE is a disease that undermines patients' quality of life, affecting their daily life and having a major economic impact. In our study, direct costs represented a high proportion of the total costs of SLE patients. The quantification of direct and indirect costs revealed a concentration of health expenditure in SLE patients in CRGs 6 and 7. Reported annual direct cost per patient related to SLE management in Spain have been estimated previously between €3604 and €5968 for non-severe and severe patients, respectively [4]. In our study, the average direct costs are considerably higher and range between €8193 and €10,165 for patients in CRGs 6 and 7, respectively. Direct costs related to hospitalizations, pharmacological treatment, visits to specialists, and laboratory tests were higher for patients with severe disease and reached €12,243 for very severe patients (CRG8). The direct costs associated with SLE are clearly higher for severe SLE patients. It has been proposed that this effect is due to insufficient control of the disease activity, resulting in an increase in flares and increased costs in hospitalization [4]. A study of medical costs of managing SLE patients in five European countries showed that while severe flares are the major cost predictor (each flare increasing annual total cost by about €1002), medical treatments were the main cost drivers [28]. This study also concluded that medication, specially immunosuppressants and recently introduced biologicals, represented up to 53% of the total costs of severe patients. Similarly, a study on Swedish patients showed that disease activity, fatigue, and corticosteroids were significant drivers of costs [8]. Future research will need to focus on the cost-effectiveness of emerging SLE therapies and the best strategies to mitigate escalating costs generated by longer survival times.

Our study suffers from some methodological limitations. CRGs categorize individual behaviors with respect to the use of health services, which probably are a good approximation to the health status of the individuals. However, as health transitions and their associated costs are largely unpredictable, costs could have predictive value only when averaged over many individuals. Despite this limitation, we believe that the classification of SLE patients into multimorbidity levels using CRGs, along with the use of the new information and communication technologies, could potentially help to develop predictive models of health needs [19]. The classification according to different health status (CRG) suggests that a model can be built to predict the specific CRG of new patients. This in turn could allow the development of models of future costs and resource utilization. Our work aimed to provide knowledge, which can support clinicians' decisions as well as improve the resources allocation devoted to SLE. In the case of SLE patients, early intervention has been shown to be a potentially useful approach to mitigate costs [29]. Further, the CRG-based patient categorization could allow more efficient and accurate comparison of different diseases. For example, a preliminary categorization into CRGs of rheumatoid arthritis patients in the Valencian Community found that they also be mostly allocated to CRGs 5 and 6 (37.5 and 44.8%, respectively).

In conclusion, our study found that most SLE patients could be classified as CRG health status 5 and 6, a point at which HR-QoL deteriorates. SLE clearly disrupted the patients' HR-QoL, and disease severity was associated with problems of mobility, ability to perform usual activities, and pain/discomfort, effects that are more pronounced in older patients. The reported deficits in HR-QoL should help monitor and evaluate patients in routine clinical practice. Most direct costs of SLE were concentrated in two CRGs (6 and 7), reflective of the high costs of biological drugs. Direct costs associated with SLE were higher for severe SLE patients, while indirect costs were highly variable among patients.

Acknowledgements The authors thank Francisco López de Saro (Trialance SCCL) for medical writing support.

Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest.

References

1. Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, Ruiz-Irastorza G, Hughes G (2016) Systemic lupus erythematosus. Nat Rev Dis Prim 2:16039. https://doi.org/10.1038/nrdp.2016.39
2. Cervera R, Doria A, Amoura Z, Khamashta M, Schneider M, Guillemin F, Maurel F, Garofano A, Roset M, Perna A, Murray M, Schmitt C, Boucot I (2014) Patterns of systemic lupus erythematosus expression in Europe. Autoimmun Rev 13:621–629
3. Seoane-Mato D, Sánchez-Piedra C, Díaz-González F, Bustabad S (2018) Prevalence of rheumatic diseases in the adult population in Spain. EPISER 2016 study. Ann Rheum Dis 77:535–536
4. Cervera R, Rúa-Figueroa I, Gil-Aguado A, Sabio JM, Pallarés L, Hernández-Pastor LJ, Iglesias M (2013) Direct cost of management and treatment of active systemic lupus erythematosus and its flares in Spain: the LUCIE study. Rev Clínica Española 213:127–137. https://doi.org/10.1016/j.rce.2012.11.018
5. Chambers SA, Allen E, Rahman A, Isenberg D (2009) Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. Rheumatology 48:673–675. https://doi.org/10.1093/rheumatology/kep062
6. Golder V, Hoi A (2017) Systemic lupus erythematosus: an update. Med J Aust 206:215–220. https://doi.org/10.5694/mja16.01229

7. Waldheim E, Ajeganova S, Bergman S, Frostegård J, Welin E (2018) Variation in pain related to systemic lupus erythematosus (SLE): a 7-year follow-up study. Clin Rheumatol 37:1825–1834. https://doi.org/10.1007/s10067-018-4079-1
8. Bexelius C, Wachtmeister K, Skare P, Jönsson L, Vollenhoven R (2013) Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. Lupus 22:793–801. https://doi.org/10.1177/0961203313491849
9. Holloway L, Humphrey L, Heron L, Pilling C, Kitchen H, Højbjerre L, Strandberg-Larsen M, Hansen BB (2014) Patient-reported outcome measures for systemic lupus erythematosus clinical trials: a review of content validity, face validity and psychometric performance. Health Qual Life Outcomes 12:116. https://doi.org/10.1186/s12955-014-0116-1
10. Jolly M, Pickard AS, Block JA, Kumar RB, Mikolaitis RA, Wilke CT, Rodby RA, Fogg L, Sequeira W, Utset TO, Cash TF, Moldovan I, Katsaros E, Nicassio P, Ishimori ML, Kosinsky M, Merrill JT, Weisman MH, Wallace DJ (2012) Disease-specific patient reported outcome tools for systemic lupus erythematosus. YSARH 42:56–65. https://doi.org/10.1016/j.semarthrit.2011.12.005
11. Doward LC, McKenna SP, Whalley D et al (2009) The development of the L-QoL: a quality-of-life instrument specific to systemic lupus erythematosus. Ann Rheum Dis 68:196–200. https://doi.org/10.1136/ard.2007.086009
12. Yazdany J (2011) Health-related quality of life measurement in adult systemic lupus erythematosus: Lupus Quality of Life (LupusQoL), Systemic Lupus Erythematosus-Specific Quality of Life Questionnaire (SLEQOL), and Systemic Lupus Erythematosus Quality of Life Questionnaire. Arthritis Care Res (Hoboken) 63:S413–S419. https://doi.org/10.1002/acr.20636
13. Cho JH, Chang SH, Shin NH, Choi BY, Oh HJ, Yoon MJ, Lee EY, Lee EB, Lee TJ, Song YW (2014) Costs of illness and quality of life in patients with systemic lupus erythematosus in South Korea. Lupus 23:949–957. https://doi.org/10.1177/0961203314524849
14. Jones JT, Cunningham N, Kashikar-Zuck S, Brunner HI (2016) Pain, fatigue, and psychological impact on health-related quality of life in childhood-onset lupus. Arthritis Care Res 68:73–80. https://doi.org/10.1002/acr.22650
15. Schmeding A, Schneider M (2013) Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. Best Pract Res Clin Rheumatol 27:363–375. https://doi.org/10.1016/j.berh.2013.07.009
16. Roche PA, Klestov AC, Heim HM (2003) Description of stable pain in rheumatoid arthritis: a 6-year study. J Rheumatol 30:1733–1738
17. Katz JD, Senecal JL, Rivest C et al (1993) A simple severity of disease index for systemic lupus erythematosus. Lupus 2:119–123. https://doi.org/10.1177/096120339300200210
18. Hughes J, Verill R, Eisenhandler J et al (2004) Clinical risk groups (CRGs): a classification system for risk-adjusted capitation-based payment and health care management. Med Care 42:81–90
19. Vivas-Consuelo D, Usó-Talamantes R, Guadalajara-Olmeda N, Trillo-Mata JL, Sancho-Mestre C, Buigues-Pastor L (2014) Pharmaceutical cost management in an ambulatory setting using a risk adjustment tool. BMC Health Serv Res 14:462. https://doi.org/10.1186/1472-6963-14-462
20. EuroQol Group (1990) EuroQol—a new facility for the measurement of health-related quality of life. Health Policy:10109801
21. EuroQol Research (2015) EQ-5D-5L user guide. Basic Inf how to use EQ-5D-5L Instrum 28. doi: 1–25
22. Isenberg DA, Allen E, Farewell V, D'Cruz D, Alarcon GS, Aranow C, Bruce IN, Dooley MA, Fortin PR, Ginzler EM, Gladman DD, Hanly JG, Inanc M, Kalunian K, Khamashta M, Merrill JT, Nived O, Petri M, Ramsey-Goldman R, Sturfelt G, Urowitz M, Wallace DJ, Gordon C, Rahman A (2011) An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis 70:54–59. https://doi.org/10.1136/ard.2010.132068
23. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, Austin A, Bell A, Bloch DA, Corey PN, Decker JL, Esdaile J, Fries JF, Ginzler EM, Goldsmith CH, Hochberg MC, Jones JV, Riche NGHL, Liang MH, Lockshin MD, Muenz LR, Sackett DL, Schur PH (1992) Derivation of the sledai. A disease activity index for lupus patients. Arthritis Rheum 35:630–640. https://doi.org/10.1002/art.1780350606
24. Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, Gordon C, Hanly JG, Isenberg DA, Petri M, Nived O, Snaith M, Sturfelt G (2000) The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for systemic lupus erythematosus international comparison. J Rheumatol 27:373–376
25. Lai JS, Beaumont JL, Jensen SE, Kaiser K, van Brunt DL, Kao AH, Chen SY (2017) An evaluation of health-related quality of life in patients with systemic lupus erythematosus using PROMIS and Neuro-QoL. Clin Rheumatol 36:555–562. https://doi.org/10.1007/s10067-016-3476-6
26. Aggarwal R, Wilke CT, Pickard AS et al (2009) Psychometric properties of the EuroQol-5D and short form-6D in patients with systemic lupus erythematosus. J Rheumatol 36:1209–1216. https://doi.org/10.3899/jrheum.081022
27. Carreras M, Ibern P, Coderch J, Sánchez I, Inoriza JM (2013) Estimating lifetime healthcare costs with morbidity data. BMC Health Serv Res 13:440. https://doi.org/10.1186/1472-6963-13-440
28. Doria A, Amoura Z, Cervera R, Khamastha MA, Schneider M, Richter J, Guillemin F, Kobelt G, Maurel F, Garofano A, Perna A, Murray M, Schmitt C, Boucot I (2014) Annual direct medical cost of active systemic lupus erythematosus in five European countries. Ann Rheum Dis 73:154–160. https://doi.org/10.1136/annrheumdis-2012-202443
29. Khamashta MA, Bruce IN, Gordon C, Isenberg DA, Ateka-Barrutia O, Gayed M, Donatti C, Guillermin AL, Foo J, Perna A (2014) The cost of care of systemic lupus erythematosus (SLE) in the UK: annual direct costs for adult SLE patients with active autoantibody-positive disease. Lupus 23:273–283. https://doi.org/10.1177/0961203313517407