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LUPUS AROUND THE WORLD

Clinical and financial burden of active lupus in Greece: a nationwide study

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Analyses of the medical and economic burden of chronic disorders such as systemic lupus erythematosus (SLE) are valuable for clinical and health policy decisions. We performed a chart-based review of 215 adult SLE patients with active autoantibody-positive disease at the predefined ratio of 30% severe (involvement of major organs requiring treatment) and 70% non-severe, followed at seven hospital centres in Greece. We reviewed 318 patients consecutively registered over three months (sub-study). Disease activity, organ damage, flares and healthcare resource utilization were recorded. Costs were assessed from the third-party payer perspective. Severe SLE patients had chronic active disease more frequently (22.4% vs 4.7%), higher average SLE disease activity index (SLEDAI) (10.5 vs 6.1) and systemic lupus international collaborating clinics (SLICC) damage index (1.1 vs 0.6) than non-severe patients. The mean annual direct medical cost was €3741 for severe vs €1225 for non-severe patients. Severe flares, active renal disease and organ damage were independent cost predictors. In the sub-study, 19% of unselected patients were classified as severe SLE, and 30% of them had chronic active disease. In conclusion, this is the first study to demonstrate the significant clinical and financial burden of Greek SLE patients with active major organ disease. Among them, 30% display chronic activity, in spite of standard care, which represents a significant unmet medical need. *Lupus* (2016) **0,** 1–10.

Key words: Lupus nephritis; disease activity; organ damage; biologics; laboratory tests; hospitalization

Introduction

Systemic lupus erythematosus (SLE) is the prototype systemic autoimmune disease affecting a variety of organs and resulting in pleomorphic clinical manifestations.[1] SLE patients are usually treated with a combination of medications, including glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, immunosuppressants or cytotoxic drugs and also biological agents in refractory cases or when other treatments are not tolerated.[1–3]

As a result of chronic, persisting, disease activity and cumulative drug exposure, a considerable proportion of SLE patients can develop irreversible organ damage and/or comorbidities, which adversely impact on survival.[4,5] Despite progress over the past decades in diagnosis and treatment, SLE patients still have almost three-fold increased mortality compared to the general population,[6] and their life expectancy was recently shown to be

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reduced by an average of 12 years.[7] Studies performed in North America,[8–17] Europe[18–22] and Asia[23,24] have illustrated the substantial societal and economic burden of SLE, with high direct and indirect costs. Utilization of healthcare resources and associated medical costs correlate with underlying disease activity and flares, particularly involvement of the renal and neurological domains.[9,12,14,20–23,25,26]

The economic crisis that occurred since 2008 has imposed significant challenges on public health policies. This is more evident in Southern European countries, where policy makers are under pressure to cut public spending on health and/or re-allocate resources within the health system, sparing funds for innovative drugs covering unmet needs of conventional therapy.[27] Comprehensive analyses appraising both the medical and economic burden of chronic, complex disorders, such as SLE, are particularly valuable for clinical and health policy decisions. Such data are not available for Greece. Moreover, existing analyses[8–16,18–24] are either out-of-date, or they have been derived from single centres, and are thus not entirely representative at the country level. Furthermore, these studies do not provide estimates at the national level of the prevalence of severe forms of SLE, the clinical and financial burden and the unmet needs of standard-of-care therapy. To this end, we undertook a multicentre study to evaluate the clinical characteristics and direct medical costs per annum for adult Greek patients with SLE.

Methods

Study design and population (see also Supplementary Methods)

The Systemic Lupus Erythematosus Cost of Care in Greece Study (LyCoS) is a one-year, retrospective prevalence study conducted in seven hospital centres spanning the entire country. The study followed the local legal requirements and was approved by the local ethics committees in all participating centres. All patients were adults and fulfilled ≥4 of the revised American College of Rheumatology (ACR) criteria.[28] Investigators identified potentially eligible patients from the consecutive routine visits register. Starting with the most recent visit, patients with consecutive visits (backwards in time) were screened.

For the main study, patients' notes were reviewed from January to September 2011 (Supplementary Figure S1A) to identify the first visit that fulfilled the inclusion criteria: (a) being on medication for SLE; (b) having active disease. The latter was defined by either or both of the following criteria.

1. A change in treatment related to SLE activity (increase in dose and/or new lupus medication(s)), and/or a new manifestation and/or worsening of clinical symptoms of SLE.
2. The presence of at least one biomarker of SLE activity (anti-dsDNA antibodies and/or C3 or C4 below normal) and at least one clinical and/or haematological SLE feature.

In addition, patients should have had autoantibody positive disease (an ANA and/or anti-dsDNA positive test at least once during the study period), be regularly followed-up, not be involved in a clinical trial and not be pregnant during the study period. The main study was designed to include 30% severe and 70% non-severe patients in order to assess direct medical costs stratified by disease severity. Severe patients were defined as having at least one major domain (renal, neurological, cardiovascular or respiratory) actively involved at inclusion and required glucocorticoids (prednisone equivalent >7.5 mg/day) and/or immunosuppressants.

In a sub-study to evaluate the disease patterns and severity of the overall SLE population, investigators captured all consecutive patients followed-up in the centres over a three-month period (April – June 2011) (Supplementary Figure S1B). (Review of patient chart data; Supplementary Methods and Supplementary Table 1).

Assessment of disease profile and description of flares

Disease activity and damage were assessed using the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI[29,30] and the SLICC/ACR damage index (SDI),[31] respectively. Active involvement of major organs was determined by the SELENA-SLEDAI and/or the presence of biological or symptomatic/clinical activity according to physician judgment. The activity profile that most closely represented each patient was based on the investigators' clinical judgment as follows: long quiescent (absence of disease activity for ≥1 year), relapsing–remitting (periods of disease activity interposed with periods of inactivity), chronic active (persistent active disease for ≥1 year).

A flare was identified by a physician statement and/or by intensification in lupus treatment due to disease activity and/or hospitalization for SLE, and was classified as mild/moderate or severe, based on the modified SELENA-SLEDAI flare index[30]

(Supplementary Table 2). The end of a flare was set at six months after its start, or at the date of the follow-up visit when NSAIDs were removed (if initiated for a flare) or glucocorticoids dose was reduced by ≥50% of the increase that identified the flare.

Healthcare resource evaluation and cost calculation

Information on medications, laboratory tests, biopsies, imaging tests, specialist visits and hospitalizations was collected from the medical records. The direct medical cost per annum was calculated, taking into account resources used and unit costs from the third party payer perspective (social insurance) (2013 prices). Cost of medicines was taken from the official Price Bulletin and is net of patient's co-payments (if applicable). The costs of inpatient stays were calculated according to the Greek DRG system. The cost of biopsies, laboratory tests, day hospitalization and visits to specialists is based on official tariffs. Corresponding tariffs on physicians' visits were assigned, depending on the site that the visit took place (hospital outpatient department versus office-based practice). The official 2013 list prices were used for all cost estimates. (Estimation of 20-year direct medical cost – see Supplementary Methods.)

Statistical analyses

Statistical analysis was performed using the SAS system version 9.3 (SAS Institute Inc., Cary, USA). Inter-individual comparisons were performed using the two-sample *t*-test or Mann–Whitney test for quantitative variables and the χ^2 test or the Fisher exact test for qualitative variables. Comparisons between multiple groups were performed using analysis of variance (ANOVA) or the Kruskal–Wallis test. Major cost drivers were identified by multivariate adjusted models. The statistical significance of the independent variables was first examined by univariate ordinary least squares (OLS) regression analysis, and variables with marginal statistical significance ($p < 0.1$) were included in a stepwise multivariate OLS model. Log-transformation was used for modelling the annual medical costs.

Results

Baseline characteristics of the main study sample

A total of 67 severe and 148 non-severe patients were included in the main study (Table 1). The mean (SD) follow-up duration was 9.0 (2.8) months for non-severe and 9.4 (2.7) months for severe SLE patients ($p = 0.206$). Biomarkers of SLE activity were more frequently abnormal in severe than non-severe SLE

Table 1 Baseline demographic, serological and clinical characteristics of the main study sample stratified according to SLE severity

	Non-severe SLE (n = *148*)	*Severe SLE* (n = *67*)	P *value*
Age (years)	43.5 (14.6)	42.6 (14.2)	0.643
Gender (female)	94.4	87.9	0.096
Ethnicity (Greek Caucasian)	95.9	100.0	0.240
SLE duration (years)	8.7 (7.5)	8.9 (7.3)	0.715
Serology			
ANA (positive)	96.9	96.4	0.717
Anti-dsDNA (positive/increased)	55.6	74.5	0.019
ENA (positive)	66.2	66.7	0.964
Antiphospholipid antibodies (positive)	20.0	29.2	0.559
Low C3	27.0	55.4	<0.001
Low C4	41.0	59.6	0.001
Disease activity			
SELENA-SLEDAI score	6.1 (3.3)	10.5 (5.5)	<0.001
SELENA-SLEDAI ≥ 10	10.8	49.3	<0.001
Disease activity pattern			
Long quiescent	0.0	0.0	–
Relapsing–remitting	83.1	62.7	<0.001
Chronic active	4.7	22.4	0.002
Unknown	12.2	14.9	0.662
Domains[a] with activity			
General/constitutional	28.4	40.3	0.083
Mucocutaneous	52.7	41.8	0.138
Neurological	3.4	11.9	0.015
Musculoskeletal	52.0	29.9	0.002
Cardiorespiratory	3.4	20.9	<0.001
Vasculitis (gastrointestinal/skin)	0.0	4.5	0.010
Renal	2.7	43.3	<0.001
Haematology	18.9	28.4	0.121
≥3 domains with activity	17.6	38.8	0.001
Organ damage			
SDI score	0.6 (1.0)	1.1 (1.2)	<0.001
SDI ≥ 2	14.2	23.9	<0.001
Domains[b] with damage			
Cardiovascular	4.7	9.0	0.229
Diabetes	0.0	3.0	0.035
Gastrointestinal	0.0	0.0	–
Malignancy	1.4	4.5	0.159
Musculoskeletal	9.5	10.4	0.821
Neurological	8.1	23.9	0.001
Ocular	6.8	7.5	0.851
Peripheral vascular	5.4	1.5	0.185
Premature gonadal failure	0.7	0.0	0.500
Pulmonary	4.7	13.4	0.024
Renal	0.0	20.9	<0.001
Skin	5.4	4.5	0.775
≥2 domains with damage	8.8	19.4	0.047
Flare at inclusion visit	81.8	88.1	0.246
Severe flare	15.7	91.5	<0.001

[a]Modified BILAG domains.
[b]Based on SDI.

patients. At inclusion, high disease activity (SELENA-SLEDAI ≥ 10) was almost five times more prevalent in severe than non-severe SLE patients (49.3% vs 10.8%, $p < 0.001$). Organ damage was present in 67.2% of severe vs 35.8% of non-severe patients ($p < 0.001$). More frequently damaged organ systems in severe SLE were the neurological ($p = 0.001$), pulmonary ($p = 0.024$) and renal ($p < 0.001$) ones. At least one comorbidity was present in 80.6% of severe and 50.7% of non-severe patients ($p < 0.001$) (Supplementary Table 3).

Flares of SLE

Mild/moderate flares were defined most frequently by new/worsening clinical manifestation (93.5%), and to a lesser extent by increase in dosage of glucocorticoids (56.1%) and initiation of NSAIDs or hydroxychloroquine (19.6%). Likewise, severe flares (34.0% of the study sample) were most frequently defined based on the clinical criterion (new/worsening of clinical manifestation, 63.0%), especially in severe SLE patients (75.9% vs 26.3% in non-severe, $p < 0.001$), followed by initiation of immunosuppressants/cytotoxic treatment (42.5%), hospitalization due to SLE (41.1%), increase in glucocorticoids dosage (31.5%) and initiation of biologic treatment (rituximab, intravenous immunoglobulin (IVIG)) (2.7%). The treatment of flares included primarily glucocorticoids (62.8%), immunosuppressants (30.6%) and antimalarials (23.3%).

Over the study period, 89.8% of patients experienced at least one flare, with a mean (SD) of 1.1 (0.6) flares per patient. Excluding the flare at inclusion visit, significantly more patients with severe disease experienced flare during follow-up (82.1% vs 57.4% in non-severe patients, $p < 0.001$).

Use of healthcare resources at study entry and during follow-up

At inclusion visit, 91.6% of SLE patients underwent laboratory tests including testing for serum autoantibodies and C3/C4 in 88.4% and 73.0%, respectively (data not shown). Proteinuria was assessed by means of 24-h urine collection or spot urine sample twice as frequently in severe than non-severe SLE patients. Imaging tests were done in 14 (20.9%) severe and 18 (12.2%) non-severe patients ($p = 0.096$). Glucocorticoids were most frequently prescribed (88.4%), followed by antimalarials (70.2%), immunosuppressants (53.5%), anti-osteoporotic (49.8%), NSAIDs (4.2%) and biologic agents (3.7%).

During follow-up, 96.3% of SLE patients underwent at least one laboratory test (Table 2). The average number of tests performed was 48.3 in severe vs 25.7 in non-severe patients ($p = 0.006$). Severe patients had a higher average number of biopsies and imaging tests than their non-severe counterparts (0.3 vs 0.1, $p = 0.002$, and 1.3 vs 0.8, $p = 0.041$, respectively). Glucocorticoids, antimalarials, immunosuppressants and anti-osteoporosis drugs were each given to more than half of the patients. The proportion of severe patients taking antimalarials was lower than that of non-severe (58.2% vs 81.1%, $p < 0.001$), whereas it was higher for immunosuppressants (88.1% vs 53.4%, $p < 0.001$). From the nine patients (4.2%) that were prescribed biological drugs, seven (10.4%) had severe SLE and only two (1.4%) non-severe ($p = 0.002$).

The mean number of specialist visits over the follow-up period was 4.5 for severe patients compared to 3.2 for non-severe ($p < 0.001$) (Table 2). All patients consulted a rheumatologist, with an average number of visits of 3.6 for severe and 2.6 for non-severe patients ($p < 0.001$). Other specialties consulted included ophthalmologists (13.5%), cardiologists (6.0%) and nephrologists (5.1%). The latter were 9.5 times more likely to be consulted by severe patients (13.4% vs 1.4%, $p < 0.001$). A significantly greater percentage of severe patients were hospitalized at some point during follow-up than non-severe patients (day hospitalization/day surgery: 37.3% vs 7.4%, inpatient stays: 32.8% vs 12.2%, $p < 0.001$).

Results from the sub-study and predictors for severe SLE

Over a three-month period, a total of 381 SLE patients were consecutively registered at the outpatient clinics of the participating centres. Sub-study patients had comparable demographic characteristics to the main study population (Table 3). 19.0% of the sub-study patients were classified as having severe SLE based on: (a) active involvement of renal, neurological, cardiovascular or respiratory organs over the last six months; (b) intake of glucocorticoids at a dosage of prednisone equivalent >7.5 mg/day and/or immunosuppressants/biologic agent(s). Renal involvement was present in 19.7% (7.1% with active, 12.6% with inactive nephritis). Compared with non-severe patients, severe patients were more likely to have the chronic active pattern of SLE (30.0% vs 6.7%, $p < 0.001$).

By combining data from the main study and the sub-study, classification tree analysis was performed to identify clinical factors predictive for severe SLE. Renal involvement had the highest

Table 2 Healthcare resources utilization in the follow-up period stratified according to SLE severity

	Non-severe SLE (n = 148)		*Severe SLE (n = 67)*		P *value*[a]	P *value*[b]
	Use (%)	*Mean (SD)*[c]	*Use (%)*	*Mean (SD)*		
Laboratory test						
Any laboratory test	96.6	25.7 (25.2)	95.5	48.3 (67.3)	0.693	0.006
Blood chemistry tests	95.9	20.3 (24.2)	94.0	37.7 (58.3)	0.537	0.084
Haematology tests	95.3	3.2 (2.7)	92.5	6.7 (12.1)	0.419	<0.001
Immunological tests	32.4	1.1 (2.1)	44.8	1.4 (2.1)	0.081	0.142
Other biological fluid tests	49.3	1.1 (1.5)	73.1	2.4 (2.2)	0.001	<0.001
Biopsies	7.4	0.1 (0.3)	22.4	0.3 (0.5)	0.002	0.002
Imaging tests	29.7	0.8 (2.0)	43.3	1.3 (2.4)	0.052	0.041
Medications						
Any medication	97.3	8.2 (7.0)	98.5	14.1 (9.6)	0.586	<0.001
Anti-osteoporosis drugs	45.9	2.0 (3.2)	62.7	4.0 (4.5)	0.023	0.002
Antimalarials	81.1	2.0 (1.8)	58.2	2.1 (2.3)	<0.001	0.673
Biological drugs	1.4	0.0 (0.2)	10.4	0.3 (1.1)	0.002	0.002
Rituximab	1.4	0.0 (0.2)	4.5	0.1 (0.7)	0.159	0.152
IVIG	0.0	0.0 (0.0)	3.0	0.1 (0.9)	0.035	0.035
Bosentan	0.0	0.0 (0.0)	3.0	0.0 (0.3)	0.035	0.035
Corticosteroids	87.2	2.6 (2.3)	91.0	4.3 (3.3)	0.411	<0.001
Immunosuppressants	53.4	1.4 (2.0)	88.1	3.3 (2.4)	<0.001	<0.001
Azathioprine	20.3	0.4 (0.9)	41.8	1.2 (1.8)	0.001	<0.001
Cyclophosphamide	2.0	0.1 (0.7)	19.4	0.9 (2.0)	<0.001	<0.001
Cyclosporine	2.0	0.1 (0.4)	0.0	0.0 (0.0)	0.241	0.242
Leflunomide	4.7	0.1 (0.5)	0.0	0.0 (0.0)	0.070	0.071
Mycophenolate mofetil	12.2	0.3 (0.9)	35.8	1.0 (1.6)	<0.001	<0.001
Methotrexate	20.9	0.5 (1.1)	10.4	0.2 (0.8)	0.062	0.060
Thalidomide	1.4	0.0 (0.3)	0.0	0.0 (0.0)	0.339	0.340
NSAIDs	7.4	0.1 (0.5)	6.0	0.1 (0.4)	0.697	0.682
Specialists visits						
Any specialist	100.0	3.2 (2.4)	100.0	4.5 (2.5)	–	<0.001
Cardiologist	6.8	0.1 (0.4)	4.5	0.1 (0.5)	0.516	0.528
Dermatologist	3.4	0.1 (0.6)	1.5	0.0 (0.1)	0.437	0.431
Internist	0.7	0.0 (0.1)	0.0	0.0 (0.0)	0.500	0.501
Nephrologist	1.4	0.0 (0.2)	13.4	0.3 (0.9)	<0.001	<0.001
Neurologist	2.7	0.0 (0.2)	6.0	0.1 (0.5)	0.241	0.235
Ophthalmologist	16.2	0.2 (0.5)	7.5	0.1 (0.3)	0.082	0.076
Psychiatrist	2.7	0.0 (0.2)	1.5	0.1 (0.6)	0.586	0.599
Pulmonologist	0.7	0.0 (0.1)	4.5	0.1 (0.3)	0.056	0.056
Rheumatologist	100.0	2.6 (1.7)	100.0	3.6 (2.1)	–	<0.001
Surgeon	2.7	0.0 (0.3)	0.0	0.0 (0.0)	0.174	0.175
Other specialist	10.1	0.1 (0.5)	13.4	0.2 (0.6)	0.477	0.474
Hospitalizations						
Day Hospitalization/surgery	7.4	0.1 (0.5)	37.3	1.0 (1.8)	<0.001	<0.001
Inpatient stays	12.2	0.2 (0.7)	32.8	0.7 (1.7)	<0.001	<0.001

[a]Comparison of prevalence of use.
[b]Comparison of average number of times used.
[c]Calculated amongst all patients (both users and non-users of each item).

discrimination power, followed by neurological involvement, cardiovascular or respiratory involvement and SDI score ≥2 (Figure 1).

Direct medical cost

The mean direct medical cost per annum for adult SLE patients with active autoantibody-positive disease and on medication for SLE was €2009 (SD 3768) (median: €633) (Table 4). The cost was three times higher in severe than non-severe patients (€3741 versus €1225, $p < 0.001$). Medications, inpatient stays, laboratory investigations, day hospitalizations, biopsies-imaging tests and specialist visits represented 51.7%, 33.8%, 7.9%, 2.7%, 2.6% and 1.2%, respectively, of the

Table 3 Disease patterns and treatment in 381 unselected SLE patients in the sub-study

Gender (female)	91%
Age (years) (mean ± SD)	47.3 ± 15.2
Disease severity	
Non-severe	81.0%
Severe	19.0%
Lupus nephritis	19.7%
Active nephritis[a]	7.1%
Disease activity pattern	
Long quiescent	24.7%
Relapsing–remitting	60.6%
Chronic active	11.6%
Unknown	3.2%
Use of SLE medications[b]	
Corticosteroids	66%
>7.5 mg/day	22%
Antimalarials	99%
Immunosuppressants/DMARDs	97%

[a]Active nephritis was defined as proteinuria >0.5 g/24 h (or protein-to-creatinine ratio >0.5) with or without a reduction in glomerular filtration rate (GFR); inactive nephritis was defined as proteinuria ≤0.5 g/24 h (or protein-to-creatinine ratio ≤0.5) with normal or near-normal (±10%) GFR.
[b]During a period of three months.

Table 4 Direct medical cost (€) per annum of active SLE stratified by disease severity

	Non-severe SLE (n = 148)	*Severe SLE (n = 67)*	*P value*
Total medical cost			
Mean (SD)	1225 (2044)	3741 (5684)	<0.001
Q1	239	680	
Median	434	1951	
Q3	1196	3687	
Minimum–maximum	95–12,629	57–30,015	
Per category, mean (SD)			
Laboratory tests	142 (72)	198 (104)	<0.001
Blood chemistry tests	66 (54)	91 (74)	0.019
Haematology tests	7.8 (6.3)	10.2 (6.9)	0.001
Immunological tests	52 (39)	53 (38)	0.661
Other biological fluids tests	17 (27)	44 (38)	<0.001
Biopsies and imaging tests	39 (95)	80 (177)	0.001
Day hospitalizations	29 (91)	111 (184)	<0.001
Inpatient stays	380 (1347)	1342 (3206)	<0.001
Medications	613 (1456)	1982 (4437)	<0.001
Anti-osteoporosis drugs	110 (319)	142 (223)	0.002
Antimalarials	50 (33)	37 (37)	0.010
Biological drugs	55 (643)	1201 (4807)	0.006
Corticosteroids	36 (78)	73 (156)	<0.001
Immunosuppressants	378 (1302)	650 (1037)	<0.001
NSAIDs	3.7 (26.5)	0.4 (3.1)	0.181
Specialists visits	22 (13)	28 (13)	<0.001

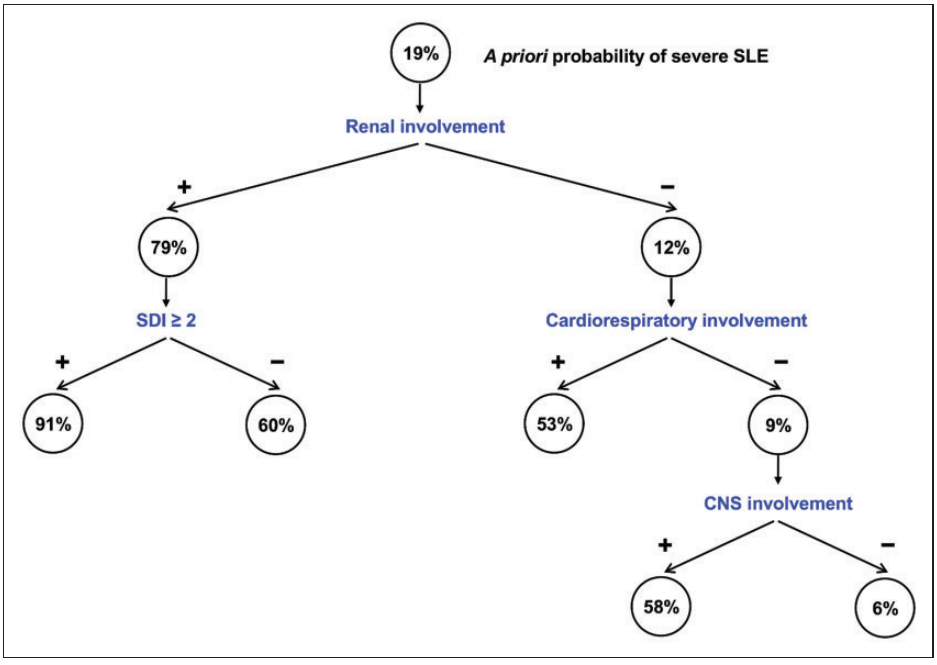

Figure 1 Classification tree analysis for the identification of the subgroup of severe SLE patients associated with high disease burden and direct medical costs. Percentages in circles represent the probability of severe SLE in the presence/absence of selected clinical manifestations/characteristics. Based on the results of the sub-study, the a priori probability for severe SLE among unselected patients was 19%.

total medical cost. In all previous categories, the average cost was higher in severe vs non-severe patients by 1.3 to 3.9 times. The mean cost per annum of glucocorticoids and immunosuppressants was increased in severe patients ($p < 0.001$ for both). The mean cost of immunosuppressants and biologics represented 44.5% and 39.7% of the total medications cost, respectively, with mycophenolate mofetil, rituximab and bosentan accounting for the greatest costs. The mean cost of inpatient stays was €1342 in severe vs €380 in non-severe patients ($p < 0.001$).

To estimate the weighted mean cost, the percentages of severe (19.02%) and non-severe (80.98%) patients as found in the sub-study were applied as weights. The direct medical cost per annum of active SLE, weighted by disease severity, was estimated at €1703.5.

Predictors of direct medical costs

Table 5 shows the results of the multivariate regression used to identify independent predictors of cost per annum in the main study sample. There is an additional cost of €343 for patients with SDI score of 1 ($p < 0.001$) and €862 for patients with SDI score of ≥2 ($p < 0.001$), compared to those with SDI = 0. A severe flare at inclusion visit ($p < 0.001$) increases the cost per annum by €541 and renal system involvement by €256 ($p = 0.066$), while a 10-year increase in age ($p = 0.047$) reduces the cost per annum by €44. Weighting the regression model by the proportion of severe/non-severe patients from the sub-study resulted in comparable results (Supplementary Table 4). In univariate analysis, the average direct medical cost per annum correlated positively with the number of flares experienced by SLE patients during follow-up, and was significantly increased in patients with ≥2 flares (€3131 (SD 5744)) and with one flare (€2271 (3159)) compared to those with no flare (€1061 (2939)) ($p < 0.001$ for both pairwise comparisons) (Supplementary Figure S2).

Using the results of the multivariate regression and the demographic and clinical characteristics of the patients included in the LyCoS main study and sub-study, we estimated the direct medical cost for active SLE to increase by 45.95% over a period of 20 years, therefore resulting in average cumulative cost per patient of €43,488 (Supplementary Figure S3).

Table 5 Predictors of direct cost per annum in active SLE patients

Variable	*Coefficient*	*Standard error*	P *value*	*Percent increase in cost*	*Amount (€)*
Intercept	6.080	0.460	<0.0001	–	437
Age (per 10 years)	−0.010	0.005	0.0474	−10.0	−44
SDI					
Score = 1	0.580	0.172	0.0009	78.5	343
Score ≥ 2	1.090	0.207	<0.0001	197.3	862
Severe flare at baseline	0.806	0.215	0.0002	123.9	541
Renal system involved	0.461	0.249	0.0660	58.6	256

Multivariate stepwise OLS regression (log-transformed costs). The r^2 for the full model was 39%.
SDI: SLICC/ACR damage index.

Discussion

The LyCoS study describes the impact of active, autoantibody-positive SLE on disease outcomes, healthcare resources utilization and direct medical cost per annum in Greece. Moreover, the sub-study provides an update on the disease activity pattern and severity in Greek SLE patients.[32–34] Together, the results suggest that approximately one in five SLE patients display active major organ disease associated with significant disease burden, increased use of healthcare resources and higher direct medical costs.

The outcome of SLE is determined by the degree and severity of the inflammatory disease and the development of irreversible organ damage as a consequence of the disease itself, comorbidities and applied treatments.[35] We found that almost one-quarter (23%) of active, autoantibody-positive SLE patients (30% with severe major organ disease) had high disease activity (SELENA-SLEDAI ≥ 10) at inclusion. Active involvement of multiple (≥3) organ domains occurred in 24%, and it was more than twice as prevalent in severe than in non-severe SLE patients. After average disease duration of 8.7 years, organ damage was already present in 67% of severe and 36% of non-severe patients. These figures are compatible with those obtained from large cohorts showing that 40%–50% of SLE patients accrue damage within the first five years after disease diagnosis.[5,35,36] Organ damage is a powerful predictor of future damage development and mortality in SLE,[5,37,38] and prevention of damage accrual has been recognized as a therapeutic target.[39]

Observational studies have reported significant association between SLE flares and adverse clinical outcomes, such as organ damage development and mortality.[40–43] Owing to the inclusion criteria,

nearly 84% of patients enrolled in the LyCoS main study met the SFI modified definition of flare. Severe flares occurred in the majority (91.5%) of patients with severe SLE and often resulted in treatment with high-dose glucocorticoids (31.5%), initiation or intensification of immunosuppressants/cytotoxic or biologic therapy (43.9%) or hospitalization (41.4%). Furthermore, severe SLE patients were more likely to experience a flare during the follow-up period. These findings illustrate significant disease burden in active, autoantibody-positive Greek SLE patients, especially among severe patients with major organ disease who demonstrate involvement from multiple organ domains, increased rates of organ damage and severe flares.

To our knowledge, this is the first report of healthcare utilization and direct costs of SLE care in Greece. Previous studies have assessed the cost-of-illness for SLE patients in North America, Europe and Asia.[44–46] The LUCIE study estimated direct medical costs of SLE management in Germany, the United Kingdom, France, Italy and Spain.[21,22] The weighted average annual direct medical cost per patient in Greece was €1704, which is less than half of the average cost reported in the LUCIE (€3483)[21] and two earlier European (range €3421–€3636)[18,19] studies. Cost differences between the LyCoS and the aforementioned studies could be explained by variation in study design, study period, characteristics of included patients, differences in resource utilization and unit costs. Thus, lower cost estimates in our study can be attributed to: (1) lower prices for pharmaceuticals, (2) lower tariffs for inpatient care, laboratory tests and physician or allied health professional consultations[17] and (3) lower wage levels in Greece as compared to other European countries and the US (OECD, https://stats.oecd.org/Index.aspx?DataSetCode=AV_AN_WAGE (accessed 15 April 2015)).

The cost of SLE care in Greece was significantly (three-fold) higher in patients with active major organ involvement compared to patients with non-severe disease. This difference was largely due to increased cost of medications, especially immunosuppressants and biologics, and of inpatient stays in the former group. Medications accounted for more than half (51.7%) and inpatient stays for approximately one-third (33.8%) of the total direct cost. These figures are comparable to those described in the LUCIE study (50.9% and 26.6%, respectively).[21] Notably, the costs of medications in the LyCoS and the LUCIE studies are considerably higher than those reported in two earlier European studies, where they accounted for 17.3%[18] and 26.6%[19] of the total cost. This discrepancy can be explained by differences in study methodology and in the proportions of enrolled patients with active severe SLE, who consume more healthcare resources. Moreover, in recent years, novel immunosuppressants (such as mycophenolate) and biological agents (including rituximab), which are more expensive than traditional immunosuppressants/cytotoxic agents, have been introduced in the medical care of SLE.

Organ damage, severe flare at inclusion and renal system involvement were identified as independent predictors of higher direct cost of care. Our results agree with those of previous studies conducted in Europe and worldwide, which have described high disease activity,[18] flares[21,22,26] and damage (especially in major organs, such as the renal[9,12–14,21,22,47] and neurological[21,23]) as significant cost predictors. These findings support the development and implementation of therapeutic strategies in SLE that will adequately control disease activity and prevent organ damage,[39] therefore reducing both the clinical and economic burden.

A number of novel biological therapies are currently being developed in SLE.[3] While these therapies represent important advancements in SLE care, they are considerably more expensive than traditional immunosuppressants, and will need to be evaluated on the basis of their clinical and cost effectiveness.[44] Pending such analyses, it is useful to define the 'target' patient population who may be candidates for novel lupus treatments. To this end, we used data from the LyCoS sub-study, which captured all consecutive SLE patients followed-up in the participating centres over a three-month period. We found that 19% of unselected patients had severe disease on standard medication for SLE, and 30% of them had chronic active disease during the past year. By extrapolation, approximately 5.7% of SLE patients suffered from active severe disease refractory to current treatment(s), which represents an important unmet medical need. Confirmation of these findings in larger patient cohorts with longitudinal follow-up will be required. Notably, the patients included in the sub-study used antimalarials more frequently than their main study littermates (99% vs 74%, respectively). This could be explained by the lower prevalence of active severe disease in the sub-study, and accords with the reported underutilization of antimalarials in active or severe SLE,[48,49] as well as with the increased rates of non-adherence to medical treatment among SLE patients with high disease activity.[50]

Our study has a number of limitations, such as the lack of longitudinal data on disease activity/severity and the effectiveness of administered treatments. Due to the retrospective design it was not feasible to use validated instruments such as the BILAG to define active involvement of major organs, and the definition of severe SLE used was not validated up-front. The one-year study duration did not allow organ damage accrual to be captured. The severity of flares was determined only at baseline and not during follow-up. Likewise, assessment of the disease burden in the sub-study was cross-sectional. Although it can be argued that the sample size was relatively small ($n = 381$), nonetheless it was derived from seven centres spanning the entire country. The cost estimates from this selected sample of patients may not be representative of SLE patients seen at other centres or with milder forms of disease. Finally, the study may have underestimated certain components of the direct cost (e.g. non-medical costs) and it did not include indirect costs.[20,44]

In conclusion, the LyCoS study provides for the first time cost-of-illness data for active SLE in Greece. Our results show increased consumption of healthcare resources, especially off-label medications and inpatient stays that are major drivers of increased medical costs, in patients with active major organ disease. Importantly, the study quantifies at a single-country level the prevalence of active major organ disease in SLE, which is associated with significant clinical and economic burden and represents an important unmet need.

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Research material

Research material can be accessed by contacting GlaxoSmithKline, Greece (Dr D Psomali, 266 Kifissias Avenue, 15232 Halandri, Athens, Greece).

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