Determinant Factors of Morbidity in Patients with Systemic Lupus Erythematosus

Fatores Determinantes de Morbilidade nos Doentes com Lúpus Eritematoso Sistémico

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ABSTRACT

Introduction: Severity in systemic lupus erythematosus may vary from mild to even fatal consequences. There are no biomarkers to predict the disease's prognosis. The Systemic Lupus International Collaborating Clinics/ Systemic Damage Index defines systemic lupus erythematosus disease severity and is found to predict prognosis.

Objective: To test damage determinants in a single-centre systemic lupus erythematosus cohort.

Material and Methods: Retrospectively followed systemic lupus erythematosus female patients (defined by the identification of at least four systemic lupus erythematosus American College of Rheumatology criteria – fulfillment 100%, n = 76) over the past five years. Age of onset, ethnicity, disease duration, number of American College of Rheumatology criteria at the end of follow-up, cumulative: renal, neuropsychiatric and articular phenotypes, hypertension, dyslipidaemia, smoking and Systemic Lupus Erythematosus Disease Activity Index 2K were correlated to the presence and degree of irreversible damage (Systemic Lupus International Collaborating Clinics Damage Index). Accumulation of American College of Rheumatology criteria was measured in a sub-group of patients followed from disease onset (within a year of the first symptom ascribed to systemic lupus erythematosus) (n = 39 – 51%); Systemic Lupus Erythematosus Disease Activity Index and Systemic Lupus International Collaborating Clinics Damage Index were performed. Statistical analysis was performed using Chi-square, Wilcoxon Mann-Whitney tests and Spearman correlation rho (Sig. 2-tailed $p < 0.05$).

Results: Systemic Lupus International Collaborating Clinics/Systemic Damage Index > 0 was present in 56.6% and significantly associated to a longer duration, a higher number of American College of Rheumatology criteria and a neuropsychiatric phenotype when compared with those with no damage. The final number of American College of Rheumatology criteria accrued was positively correlated to a higher disease activity over the past five years of follow-up (Spearman´s rho 0.02 and $p < 0.05$). There was no effect from other features.

Discussion and Conclusion: Disease duration and number of American College of Rheumatology criteria predict Systemic Lupus International Collaborating Clinics/ Systemic Damage Index. neuropsychiatric disease has an impact on damage accrual.

Keywords: Activities of Daily Living; Health Status Indicators; Lupus Erythematosus, Systemic; Morbidity; Portugal; Quality of Life

RESUMO

Introdução: O lúpus eritematoso sistémico pode apresentar uma gravidade variável. Contudo, não existem biomarcadores que preveem o curso da doença. O dano é medido pelo índice *Systemic Lupus International Collaborating Clinics/Systemic Damage Index* que define a gravidade e prevê o seu prognóstico.

Objetivo: Avaliação dos fatores que determinam dano nos doentes com lúpus eritematoso sistémico.

Material e Métodos: Estudo retrospetivo, monocêntrico, em doentes com lúpus eritematoso sistémico (≥ 4 critérios do American College of Rheumatology – 100% dos doentes, n = 76), do sexo feminino, seguidos por um período ≥ 5 anos. Início da doença, etnia, duração, número de critérios American College of Rheumatology no final do seguimento, fenótipo renal, neuropsiquiátrico (e articular, co-morbilidades e *Systemic Lupus Erythematosus Disease Activity Index* -2K foram correlacionados com a presença e grau de dano medido pelo índice *Systemic Lupus International Collaborating Clinics/Systemic Damage Index*. A acumulação de critérios American College of Rheumatology foi objetivada num sub-grupo de doentes seguidos desde o início. A análise estatística utilizou o qui-quadrado, Wilcoxon Mann-Whitney e a correlação de Spearman ($p < 0,05$).

Resultados: O *Systemic Lupus International Collaborating Clinics Index* era superior a 0 em 56,5% dos doentes. Estes doentes tinham um maior tempo de doença, um maior número de critérios American College of Rheumatology e um fenótipo neuropsiquiátrico, quando comparados com doentes sem dano ($p < 0,05$). Verificou-se uma correlação positiva entre o valor numérico de critérios American College of Rheumatology acumulados no final do seguimento e a atividade da doença nos últimos cinco anos (Spearman *rho* 0,02 e $p < 0,05$). Não se verificaram diferenças em relação às outras variáveis.

Discussão e Conclusão: A duração da doença e o número de critérios do American College of Rheumatology acumulados conseguem prever a presença de dano. A doença neuropsiquiátrica teve impacto na morbilidade dos doentes com lúpus eritematoso sistémico, identificando um subgrupo em risco.

Palavras-chave: Actividades da Vida Diária; Indicadores de Saúde; Lupus Eritematoso Sistémico; Morbilidade; Portugal; Qualidade de Vida

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a wide-ranging multi-systemic autoimmune disease affecting almost all systems with a severity ranging from mild to lethal. An estimated prevalence of 100-200/100,000 people has been found in Portugal,[1] higher when compared to the remaining Southern European countries with a prevalence of 34-91/100,000 people.[2] Women are predominantly affected, with a 9:1 ratio and childbearing-aged women correspond to over 80% of the patients. The disease runs an undulating course of exacerbations and remissions with a variable outcome[3] even in patients under therapy. A reduction in mortality has been found over the past few decades and a long-term progressive remission has been described; thrombotic events are the most frequent cause of death.[4] Therefore, the presence of cardiovascular comorbidities (high blood pressure, smoking and dyslipidaemia) has a relevant role in the assessment of patients with SLE.

The disease may be approached from two dimensions: (i) lupus disease activity and (ii) the cumulative target organ damage. A standardized, validated, reliable, feasible instrument and sensitive to changes in disease activity should be used in clinical follow-up, in order to be applied during medical appointments. Even though different validated lupus activity indices have been developed, the *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI)[5] modified by SLEDAI-2K[6] has been mostly used and validated for retrospective use.[7] This is a quantitative index within a 0-105 score range used for the assessment of clinical and laboratory manifestations of lupus at the time of clinical evaluation and for a 10-day window. The presence of active disease has been defined with a score ≥3.[8] Target organ damage has been assessed by the *Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index* (SLICC/ACR)[9] for the quantification of cumulative damage upon the diagnosis of SLE, present for at least six months, not aiming at the definition of any etiologic relationship with the disease. A 0-49 score range and 12-domain assessment is used; the presence of any nonreversible damage was defined as a score of 1. In case of repeat episodes occurring at least 6 months apart [stroke, acute myocardial infarction (AMI), avascular necrosis, malignancy, for instance], a separate score is assigned to each event. Three was the maximum score within the renal domain in case of end-stage kidney failure. A SLICC score can only increase over time meaning that organ damage is always accounted for, even when corrective measures have been carried out (cataract surgery or arthroplasty of the joint affected by avascular necrosis, for instance). Baseline followed by annual assessment is recommended. SLICC validity remains when retrospectively used, as with the SLEDAI.[10]

There are still no biomarkers of lupus progression. Cumulative target organ damage assessed by SLICC / *Systemic Damage Index* (SDI) has been the single measure used in the clinical practice for the definition of disease's severity, as it has been clearly associated with further damage and with mortality.[11-15] Bad outcome factors have been identified by different studies and have been globally recognised: juvenile disease onset, patient's gender, social and economic status, pattern of affected organs and serological findings. Determinants of morbidity and mortality in patients with SLE have been defined by different authors, mainly including (i) disease activity (arthritis, malar erythema, active lupus nephritis, fever, neurological involvement, Raynaud's phenomenon, serositis, thrombocytopenia and thrombosis), (ii) infections, (iii) high blood pressure, (iv) dyslipidaemia, (v) smoking, (vi) osteoporosis, (vii) medication-induced cytopenia and (viii) malignancy.[16-18]

Patients with at least four ACR classification criteria for SLE are usually involved in observational studies[19] cumulatively fulfilled throughout clinical follow-up, with no defined duration. Up to this moment, no index has been developed allowing for the relationship between disease's global form of presentation and outcome. A demographic and clinical characterisation of the patients with SLE has been carried out in this study, together with the factors potentially related to the presence of damage, even though not included into the SLICC/SDI, such as patient's ethnicity, the number of cumulative ACR classification criteria present over six months upon disease onset, presence of high blood pressure, dyslipidaemia and smoking.

MATERIAL AND METHODS

This was a retrospective study involving female patients attending the Autoimmune Disease Outpatient Clinic at the *Hospital Curry Cabral*, *Centro Hospitalar Lisboa Central* from 1 Jan 2009 to 31 Dec 2014 having attended at least once throughout 2014. All the patients had been diagnosed with SLE according to 1997 American College of Rheumatology (ACR) classification criteria and met at least 4 out of 11 criteria (n = 76, 100%). The variables considered for the study included: patient's age at disease onset, patient's ethnicity, disease duration, number of cumulative ACR criteria present over six months upon disease onset and at the end of the follow-up, high blood pressure, dyslipidaemia and smoking. Patients have been classified according to the main clinical phenotype: neuropsychiatric (NP), renal or articular.[20,21]

Lupus activity has been retrospectively assessed at least every six months using a modified SLEDAI, the SLEDAI-2K. The SLICC/ACR has been used for the quantification of cumulative damage upon disease onset and was annually assessed. Patients were divided according to the presence of organ damage (SLICC = 0, no damage; SLICC > 0, damage) and the correlation with the variables in each group has been analysed.

All data have been obtained from patient paper-based and electronic (using SCLINICO software) clinical records. The *Statistical Product and Service Solutions* (SPSS) software has been used in statistical analysis: chi-square and Wilcoxon-Mann-Whitney test for non-parametric

Table 1 – Clinical characteristics of the patients with systemic lupus erythematosus

Clinical and demographic characteristics	
Age at disease onset (mean ± standard deviation)	32 ± 12
Non-Caucasian patients (n, %)	9 (11.8)
Disease duration (years) (mean ± standard deviation)	17 ± 7.9
High blood pressure (n, %)	44 (57.9)
Dyslipidaemia (n, %)	35 (46.1)
Smoking (n, %)	16 (21.1)
Malignancy (n, %)	5 (6.6)
Infection (n, %)	41 (53.9)
Neuropsychiatric disorders (n, %)	16 (21.1)
Kidney disorders (n, %)	31 (40.8)
Articular disorders (n, %)	56 (73.7)
ANA (n, %)	76 (100)
Anti-dsDNA (n, %)	58 (76.3)
Mean SLEDAI score (half-year assessment for 5 years)	3.1 ± 0.5
Cumulative ACR criteria - final	5.4 ± 1.3

distribution data and Spearman's Rho for the association test between linear variables.

RESULTS

In total, 101 patients diagnosed with SLE according to ACR criteria attended our unit during the study period (93 female and 84 attended the outpatient clinic at least from 2009 onwards). From these, a 76-patient sample has been included in the study, meeting the following four criteria: SLE diagnosis according to ACR criteria, female gender, patients diagnosed from at least 2009 onwards and having attended the unit at least once throughout 2014. Demographic and clinical data are shown in Table 1 [mean age of 32 years at the time of SLE diagnosis with a standard deviation of 12 (range 11-66); mean age of 49 years with a standard deviation of 13 (range 23-79) at the time of the study; 17-year disease duration (σ = 7.92; range 5-36 years) and 12.62 average follow-up (σ = 4.86; range 5-22 years)]. Approximately one third of the patients were single (28 patients, 36.84%). Nine non-Caucasian patients (11.8%) were included, predominantly of African origin. At the end of the follow-up, mean cumulative ACR score was 5.37 (σ = 1.32, range 4-10). Organ damage (SLICC > 0) has been found in 43 (56.58%) patients. Mean disease activity (SLEDAI 2-K ≥ 3) within a five-year window (Table 2) did not correlate with the damage found at the end of clinical follow-up, not even when the analysis was made according to disease duration (17 patients with 10-year disease duration; 32 patients with 10-19 years and 27 patients with >20-year duration). The presence of organ damage showed statistically significant association with longer disease duration, higher number of ACR criteria and NP phenotype (Table 3) and showed no relationship with the remaining demographic and clinical characteristics. The highest final number of cumulative ACR criteria was positively correlated to lupus activity over the last five years

Table 2 – Retrospective SLEDAI assessment (half-year value)

Assessment year	SLEDAI 1st semester	SLEDAI 2nd semester
2010	4.36	3.24
2011	3.48	3.49
2012	3.02	2.28
2013	2.54	2.71

Table 3 – Comparison between patients with organ damage vs. no damage (according to SLICC/SDI)

Characteristics	SLICC = 0 (n = 43)	SLICC ≥ 1 (n = 33)	*p* (Sig*)	Statistical test
Age at disease onset (mean ± standard deviation)	32 ± 11	31 ± 13	0.653	MW
Non-Caucasian patients (n, %)	4 (44.4)	5 (55.6)	0.610	PCS
Disease duration (years) (mean ± standard deviation)	14 ± 7	19 ± 8	0.007*	MW
High blood pressure (n, %)	16 (36.4)	27 (61.4)	0.338	PCS
Dyslipidaemia (n, %)	12 (34.3)	22 (62.9)	0.201	PCS
Smoking (n, %)	7 (43.8)	9 (56.2)	1.000	PCS
Malignancy (n, %)	0 (0)	6 (100)	0.111	PCS
Infection (n, %)	16 (39)	24 (58.5)	0.809	PCS
Neuropsychiatric disorders (n, %)	2 (11.1)	16 (88.9)	0.004*	PCS
Kidney disorders (n, %)	13 (41.9)	17 (54.8)	0.614	PCS
Articular disorders (n, %)	22 (39.3)	33 (58.9)	0.631	PCS
ANA (n, %)	32 (42.1)	43 (56.6)	1.000	PCS
Anti-dsDNA (n, %)	24 (41.4)	33 (56.9)	1.000	PCS
Mean SLEDAI (half-year assessment for 5 years)	2.2 ± 2.0	3.6 ± 2.9	0.054	MW
Cumulative ACR criteria – over six months upon disease onset (available n)	4.1 ± 1.3 (n = 21)	3.7 ± 1.5 (n = 18)	0.280	MW
Cumulative ACR criteria – final	5.0 ± 1.1	5.6 ± 1.4	0.046*	MW

MW: Mann-Whitney; PCS: Pearson's chi-square

of follow-up (Spearman's Rho = 0.02).

DISCUSSON AND CONCLUSION

This group of patients had been also involved in a previous study[22] and results were in line with the Iberian record of SLE patients.[23] A similar organ damage frequency has been found in our group of patients, even though showing higher SLICC score[24] predominantly related to neurological manifestations.

In our group of patients, a similar mean age at the time of diagnosis and similar percentage of non-Caucasian patients has been found in both subgroups (with and with no damage), instead of what would have been expected as late-onset diagnosis and non-Caucasian ethnicity seem to have a modifier effect on disease's outcome.[14,25] Previous kidney involvement was not associated with organ damage in our group of patients, in line with the SLICC record.[14] Surprisingly, instead what would have been expected, the presence of cardiovascular risk factors including dyslipidaemia, smoking and high blood pressure, as well as the presence of malignancy and infections, were not associated with higher morbidity. No relationship has been found between cumulative ACR criteria over six months upon disease onset, even though we should mention that these data were only available for about half of the patients from each subgroup (with and with no damage). Significantly higher percentage of patients with organ damage and more severe damage has been found in patients with longer disease duration and higher number of cumulative ACR criteria in our group of patients, in line with previous studies.[14]

This was a monocentric, observational and retrospective study from which eight male patients have been excluded and these were the limitations of the study; a higher number of patients would have brought statistical power to the correlation between mean SLEDAI over the past five years and the presence of organ damage, showing a value that was close to statistical significance.

This study allowed for the conclusion that patients with higher morbidity and with organ damage (SLICC > 0) had longer disease duration, neuropsychiatric phenotype and higher number of cumulative ACR criteria at the end of clinical follow-up. Therapeutic strategies aimed at reducing clinical manifestations and at disease control will lead to the reduction of morbidity and mortality that are still found in patients with this disease.

OBSERVATIONS

This manuscript has been presented as a Poster at the 2015 Meeting of the American College of Rheumatology (ACR/ARPH) and has been published in 29 Sep 2015 in the abstract book.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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