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Concise report

Identification of clinical predictors of flare in systemic lupus erythematosus patients: a 24-month prospective cohort study

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Abstract

Objective. SLE has a relapsing–remitting course with disease activity flares over time. This study aims to identify clinical predictors of SLE flares.

Methods. This prospective cohort study over 24 months included all SLE patients on follow-up at one academic lupus clinic. Flare was defined as an increase in SLEDAI-2K score $\geqslant 4$ points. Baseline clinical and demographic parameters were compared using survival analysis for time-to-flare outcome with univariate log-rank tests. Variables with significant differences were further evaluated as predictors with multivariate Cox regression models adjusting for potential confounding or contributing factors and hazard ratio (HR) calculation.

Results. A total of 202 SLE patients were included. Over the follow-up period, 1083 visits were documented and 16.8% of patients presented with flares. In multivariate analysis, the following parameters emerged as flare predictors: SLE diagnosis up to 25 years of age (HR = 2.14, $P = 0.03$), lupus nephritis previous to baseline visit (HR = 4.78, $P < 0.0001$) and immunosuppressor treatment for severe SLE (HR = 3.22, $P < 0.001$). Baseline disease activity, disease duration and treatment with prednisone or HCQ were not predictive factors.

Conclusion. Patients with an SLE diagnosis before age 25 years, lupus nephritis or immunosuppressor treatment for severe SLE present greater HRs for flares, suggesting the need for tighter clinical monitoring. Current immunosuppressive strategies seem to be inefficient in providing flare prevention.

Key words: systemic lupus erythematosus, outcomes research, cohort study, prospective study, prognosis.

Introduction

SLE has a relapsing–remitting course, with patients experiencing disease activity flares over time [1]. Aiming at flare reduction, HCQ is the standard treatment for most SLE patients during the entire disease course and conventional immunosuppressors are given to those with severe organ involvement [2, 3]. New biologic agents might further

reduce flares but pose challenges regarding appropriate case selection [4]. In clinical practice, the ability to identify patients at risk of flares in the next few months is crucial to optimize monitoring and preventive treatment. However, previous research efforts have not been successful in identifying clinical or biomarker predictors of flares that are reliable enough for use in clinical practice [5–7]. This study aims to identify clinical predictors of SLE flares. Eventually most SLE patients will develop a flare, therefore the more relevant question is not whether, but how soon, it may occur. Thus we applied survival analysis to identify predictors of flare.

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Methods

All patients fulfilling the ACR classification criteria for SLE on regular follow-up at a single academic lupus clinic were included [8]. This specialized clinic was established in

2005 at the University Hospital of Coimbra Rheumatology Department. Referrals come in equal parts from primary care units and other departments from this and other hospitals from a geographic area of one-third of the country and with a population of ∼2 million. This is an ethnically homogeneous population with >90% native Caucasian. The lupus clinic is the main care provider for SLE patients managed in long-term follow-up. Patients gave written informed consent according to the Declaration of Helsinki and the hospital's ethics committee (Comissão de ética para a saúde dos Hospitais da Universidade de Coimbra) approved the study. Regular follow-up was defined as at least two visits 2–6 months apart and no absence from the clinic >12 consecutive months during the study period, from 1 June 2009 to 31 January 2012.

The study design was a prospective cohort study with outcome defined as the time to first flare from baseline up to the 24-month follow-up. Patients were included at their first visit to the clinic after study start (baseline), with new participants allowed to enter at any time during the study period. All patients were assessed by the same rheumatologist at each visit (every 1–6 months), disease activity being scored according to SLEDAI-2K [9]. Flare was defined as an increase in SLEDAI-2K $\geqslant 4$ points from inclusion [9, 10]. At baseline, demographic data, cumulative SLE organ involvement and medication were registered. Immunosuppressive treatment at baseline was assumed as the intent-to-treat marker for severe SLE. As a summary measure of disease activity over time, we calculated the time-adjusted mean SLEDAI-2K (AMS) over follow-up for each patient [11].

Statistical analysis

Clinical and demographic parameters at study entry were evaluated as potential predictors for flare outcome in survival analysis. For each patient, the time (in months) from study entry to the first flare event was determined, and in those without flares during follow-up, observation was censored at the time of the last visit up to 24 months after baseline. The duration of observation period was variable, as participants could be added or lost to follow-up over the study period. Analysis was carried out in two steps. First, we applied univariate analysis with Kaplan–Meyer curves and log-rank tests to assess differences between groups defined by predictor. The factors tested in univariate analysis were (i) gender, (ii) age at SLE diagnosis (categorized as juvenile or young adult if diagnosed at $\leqslant 25$ or >25 years age, respectively), (iii) severe disease (defined as the use of immunosuppressors, except steroids, at baseline) (yes/no), (iv) previous biopsy-proven LN (yes/no), (v) baseline SLEDAI-2K score (categorized as low/mild activity with a score <4 and moderate/high with a score $\geqslant 4$), (vi) time since SLE diagnosis (categorized in up to or more than 2, 5 and 10 years), (vii) HCQ user status at baseline and (viii) steroid user status at study entry. In the second step, variables with significant differences were further evaluated as predictors in multivariate Cox proportional hazards models. Each significant predictor identified in the univariate

analysis was entered in a Cox multivariate model with variables we considered to be potential confounders. Non-significant covariates were excluded from the models with backward stepwise procedures in order to calculate adjusted hazard ratios (HRs) for flare. Proportional hazard assumption was verified with log-minus-log plots.

The AMS was compared between those with and without flares with a two-tailed independent samples *t*-test after a Kolmogorov–Smirnov test for normal distribution. Chi-squared tests were used to compare the distribution of categorical variables across two groups. All tests were two-sided with an α risk at 5%. Statistical analyses were performed using IBM SPSS Statistics version 19.

Results

Baseline characteristics of the 202 patients included are presented in Table 1. These accounted for 94% of the SLE patients attending the lupus clinic during the study period. An additional 12 patients attended the clinic just once or otherwise were not on regular follow-up and were excluded. Previous biopsy-proven LN was the most frequent major organ involvement at baseline, affecting 45.7% of patients [World Health Organisation (WHO) class III–V 82.4%]. At baseline, 85.1% of patients were on HCQ treatment, 49% on glucocorticoids (median dose 5 mg/day) and 32.7% on immunosuppressive drugs for SLE, mostly as maintenance treatment for nephritis, severe arthritis or haematological involvement. At study entry, 55.4% of patients presented low/mild disease activity as defined by a SLEDAI-2K score <4, and 11.4% were serologically inactive as defined by normal C3 and C4 complement and anti-dsDNA levels.

A total of 1083 visits to the lupus clinic from these 202 patients were registered over a median [interquartile range (IQR)] follow-up of 24 (10) months. The mean interval between visits was 3.8 months. Flares were observed in 16.8% of patients. All but one flare occurred in patients with serological activity at baseline. All flares included increased activity in one or more organs and not purely serological activity. Organ involvement at the time of the first flare during follow-up included nephritis (in 60.0% of

TABLE 1 Baseline characteristics of the study population (*n* = 202)

Age, mean (S.D.), years	41.9 (14.5)
Female gender, %	86.6
Caucasian, %	97.5
Age at SLE diagnosis, mean (S.D.), years	31.9 (13.5)
Time since SLE diagnosis, mean (S.D.), years	9.9 (7.8)
SLEDAI-2K score, mean (S.D.)	4.3 (3.6)
Medication, % current users	
Prednisolone, [median daily dose, mg (IQR)]	49 [5.0 (5.0)]
HCQ	85.1
Immunosuppressors[a]	32.7

[a]Immunosuppressors: AZA, MMF, calcineurin inhibitors, MTX, CYC and rituximab.

cases), arthritis (13.3%), mucocutaneous (13.3%), haematological (11.1%) and vasculitis (2.2%). The average AMS over the follow-up time was higher for patients who experienced flares [6.3 (3.4)] than in those without flares [3.1 (2.0)] ($P < 0.0001$, 95% CI 2.4, 4.1).

The predictors of SLE flare identified by univariate analysis with Kaplan–Meyer curves and log-rank tests were SLE diagnosis at a younger age ($\leqslant 25$ years old) ($P = 0.023$), severe disease defined as use of immunosuppressors at baseline ($P < 0.001$) or previous LN ($P < 0.0001$). Other factors were not predictors: gender, baseline SLEDAI-2K score, time since SLE diagnosis or HCQ or steroid user status. Steroid use was not a significant predictor when evaluated either as current vs nonuser, or as daily dose >5 mg vs up to 5 mg.

Groups defined according to the presence of each of the three flare predictors found to be significant in univariate analysis were compared. Patients with SLE diagnosis at $\leqslant 25$ years of age were more likely to have nephritis at baseline (61.1% vs 36.7%, $P < 0.001$), and those with previous nephritis were more frequently taking immunosuppressors ($P < 0.0001$).

Multivariate analysis confirmed as predictors for flare outcome a younger age at SLE diagnosis ($\leqslant 25$ years) (HR = 2.14, 95% CI 1.09, 4.19, $P = 0.03$) (Fig. 1), previous LN at baseline (HR = 4.78, 95% CI 2.08, 10.98, $P < 0.0001$) and baseline immunosuppressor treatment (HR = 3.22, 95% CI 1.63, 6.37, $P < 0.001$) (supplementary Fig. S1, available as supplementary data at *Rheumatology* Online). Due to multicollinearity concerns, the predictors were analysed in three separate, alternative models. The following covariates were included in the multivariate-adjusted analysis: (i) (for younger age at SLE diagnosis) gender and time since diagnosis (continuous variable) and
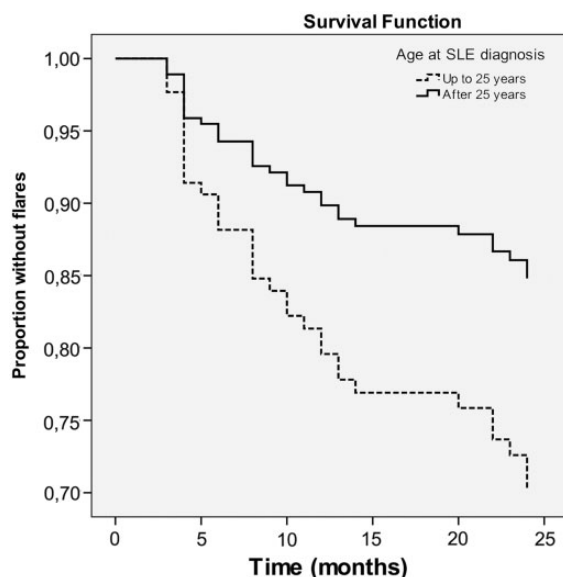
(ii) (for previous LN and for baseline immunosuppressor use) gender, younger age at diagnosis, time since diagnosis (continuous variable), baseline SLEDAI-2K (continuous variable) and baseline use of HCQ and steroids. In all models the covariates did not have a significant effect and were eliminated in the stepwise analysis.

Discussion

This study identified the following as clinical predictors for increased flare hazard: a younger age at SLE diagnosis ($\leqslant 25$ years), previous LN and baseline immunosuppressor treatment for severe SLE. Specifically, at any time point up to the 24-month follow-up, the risk of flare was more than 2-fold, 4-fold and 3-fold higher for patients with an SLE diagnosis at $\leqslant 25$ years of age, previous LN or immunosuppressor treatment, respectively. It found no evidence for a lower flare hazard associated with baseline low disease activity or longer SLE duration.

Flare is an important outcome in SLE, both in clinical practice and clinical trials, but it is challenging to measure. Existing instruments have different profiles of strengths and weaknesses, with an overall moderate to good agreement to detect flares [12]. We applied SLEDAI-2K, a simple, sensitive-to-change index and used a flare definition previously shown to represent a clinically meaningful increase in disease activity [9, 10]. The outcome event in this study was time to first flare. The time to first flare and difference in SLEDAI score were equally counted from the study baseline. Patients may progressively develop an increase in disease activity, e.g. a new malar rash (SLEDAI score of 2) in the second observation month and a new pericarditis (SLEDAI score of 2) with ongoing rash at the fourth observation month. If we looked at SLEDAI as a change over time, this same case would be classified variably as presenting a flare or not at the fourth month, depending on the absence or occurrence of an intermediate visit at the second month, respectively. Accounting for the SLEDAI change from baseline avoids this potential source of bias. Importantly, and different from previous studies, we used a time-to-event flare outcome. In the setting of person-time data, with varying risk periods derived from a dynamic open cohort such as in this study, survival analysis methods are most appropriate [13–15]. This use of Cox's proportional hazards regression model, a powerful statistical tool, offers a better opportunity to identify clinically relevant flare predictors. A similar approach was previously employed by Houssiau *et al.* [16] to evaluate the time to renal flare in the MAINTAIN trial. The same approach has been used in prospective cohort studies to evaluate the risk of SLE organ damage and mortality [17, 18]. We found a relatively low proportion of patients suffering flares as compared with other cohort studies [1, 5, 19]. It is likely that the use of a more sensitive flare instrument, such as the BILAG, or a lower cut-off for the SLEDAI-2K increase would identify a greater number of milder flares [10, 12]. The systematic treatment with HCQ in this study's cohort may also have contributed to the low flare rate and explain why we did not find a lower flare HR with HCQ [2]. Patients with and without flares

Fɪɢ. 1 Survival curve showing the flare-free proportion of patients according to categories of age at the time of SLE diagnosis (HR = 2.14).

differed significantly in the AMS over the follow-up time, which is a prognostic marker for irreversible damage accrual, coronary artery disease and mortality [11].

An important contributor to flare hazard with an SLE diagnosis at a younger age was the higher prevalence of LN in this subset of patients [19–22]. The use of immuno-suppressive treatment is a marker of severe disease. However, the fact that standard-of-care immunosuppressive medication is associated with a greater flare hazard confirms that these drugs are not effective in suppressing flares to the level of non-severe patients [13, 19].

The limitations of this study include that it is single-centre based and the fact that there is no consensus definition of flare. Observational cohorts may differ systematically with regard to variables related to exposure or outcome, which questions the generalizability of our results and increases the need for confirmatory studies in other settings and different ethnic backgrounds. Another concern was the multicollinearity between clinical predictors. We addressed this problem by developing three separate models. We think this option makes the most clinical sense, as the three identified clinical predictors should be regarded as alternatives, using one or another depending on the individual case: a patient presenting early with SLE is at increased risk of flare; if further on in the disease course the patient develops nephritis or another organ involvement requiring immunosuppressors, any one of those will be the dominant clinical predictor for flare. The primary strength is the application of survival analysis, a powerful statistical method that allowed this novel demonstration of clinical predictors of flare. In summary, our work suggests that SLE patients with a diagnosis at up to 25 years of age or previous LN or severe disease requiring immunosuppressors present a greater flare hazard and might need tighter clinical monitoring and treatment.

Rheumatology key messages

- The SLE flare hazard is higher in patients diagnosed up to 25 years of age.
- The SLE flare hazard is higher with severe disease requiring immunosuppressors or previous lupus nephritis.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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