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Review

Development and validation of a risk calculator to differentiate flares from infections in systemic lupus erythematosus patients with fever☆

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ABSTRACT

Objective: To develop and validate a predictive risk calculator algorithm that assesses the probability of flare versus infection in febrile patients with systemic lupus erythematosus (SLE).
Methods: We evaluated SLE patients admitted because of fever in the Department of Autoimmune Diseases of our Hospital between January 2000 and February 2013. Included patients were those with final diagnosis of infection, SLE flare or both. Data on clinical manifestations, treatment and laboratory results were collected. Variables considered clinically relevant were used to build up all possible logistic regression models to differentiate flares from infections. Best predictive variables for SLE relapses based on their higher area under the receiver operating characteristic (ROC) curve (AUC) were selected to be included in the calculator. The algorithm was developed in a random sample of 60% the cohort and validated in the remaining 40%.
Results: One hundred and thirty SLE patients presented 210 episodes of fever. Fever was attributed to SLE activity and to infection in 45% and 48% of the cases, respectively. Three independent variables for prediction of flares were consistently selected by multivariate analysis: days of fever, anti-dsDNA antibody titres and C-reactive protein levels. Combination of these variables resulted in an algorithm with calculated AUC of 0.92 (95% CI: 0.87 to 0.97). The AUC for the validation cohort was of 0.79 (95% CI: 0.68 to 0.91).
Conclusion: The proposed flare risk predictive calculator could be a useful diagnostic tool for differentiation between flares and infections in febrile SLE patients.

Contents

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1. Introduction

Systemic lupus erythematosus (SLE) is a relapsing multisystem autoimmune disorder that may affect almost any organ [1]. Clinical presentation is broad and heterogeneous and non-specific constitutional symptoms are common in these patients [2]. Fever has been reported as part of SLE initial manifestations in 28–36% of patients and in 52–60% during disease course [3,4]. Importantly, fever has been reported as one of the main causes leading to admission in this disease [5,6].

In SLE, fever can reflect an ongoing infection apart from being a manifestation of recurrences. Based on two retrospective series of hospitalized patients with this disorder, the estimated frequency of fever episodes that are of infectious origin or secondary to SLE activity is about 23–54% and 42–60%, respectively [7,8].

In clinical practice, differentiation between SLE flares and infections can be extremely difficult. On one side and despite current therapeutic regimes, relapses are still observed in 25–35% of lupus patients [9]. On the other side, immunosuppressive therapy used in moderate–severe cases increases the risk and severity of infections [10,11]. Infections are reported in 10–40% of SLE patients and are the main cause of death in 25–30% in large study cohorts [12,13]. To increase the complexity of this problem, systemic infections may also trigger SLE recurrences [14–16].

Based on these data, accurate discrimination of activity or infection in SLE patients presenting with a febrile episode is crucial, as treatment options are completely different. In this regard, several candidates have been evaluated as potential biomarkers for differentiation of SLE flares and infections: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), and the newer molecules pentraxin 3, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and neutrophil CD64 + [14,17–22].

The aim of this study was to develop and validate a predictive risk calculator algorithm that could assist daily clinical decision-making to differentiate flares from infections in SLE patients presenting with fever.

2. Patients and methods

2.1. Patients

A retrospective cohort study was conducted by reviewing the medical records of adult patients with SLE admitted because of fever at the Department of Autoimmune Diseases of Hospital Clínic, between January 2000 and February 2013. Patients with final diagnosis of a SLE flare and/or an infection were included. Drug-induced lupus patients and overlapping autoimmune syndromes were excluded. Fever episodes on a same patient were recorded independently. This study was approved by the local ethics committee, and was conducted in compliance with the protocol for Good Clinical Practices and Declaration of Helsinki principles.

Using an electronic case report, data encompassing more than 140 variables were collected according to a standardized protocol. SLE was established when 4 of the 11 revised criteria classification of the American College of Rheumatology were met [23]. Data of previous organ involvement was recorded in addition to number and type of immunosuppressive drugs received in the six months preceding the fever episode. Also, prednisone (PDN) dose used in the last three months and during admission episode was retrieved. Disease activity was measured with the SLE Disease Activity Index (SLEDAI 2000) [24]. On the basis of a computer-generated randomized list of febrile episodes, cohort was divided into 2 sets. The first set (60% of all episodes) was used to develop the score. The other set of episodes (40%) was used to validate the score.

2.2. Definitions

Fever was defined as an axillary temperature greater than 37.5 °C [25,26]. International consensus guidelines were used for the diagnosis of *specific infectious disorders*. When guidelines were not available, definition was similar to that described in previous studies [27]. The concept of *flare* was based on an international consensus for description of recurrences in SLE patients [28] and in the European League Against Rheumatism (EULAR) recommendations [29]. This was defined as a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. The terms flare, relapse, recurrence or exacerbation was used indistinctly. Definition of relapses affecting *specific organs* was based on previous studies [30–37], including the British Isles Lupus Assessment Group (BILAG-2004 index) [38]. Of note, in order to assess the utility of anti-double-stranded DNA antibodies (dsDNA-Ab) and complement levels to differentiate between flares and infections, our definition of flare did not include an increased dsDNA-Ab titre or low complement levels per se. Definitions used for infections and relapses affecting specific organs are included in the Appendix A.

Coexistence of flare and infection was considered only in a reduced number of patients. In these patients, promptly resolution of symptoms was observed after the start of both antimicrobial therapy and an increase in PDN dose.

2.3. Laboratory data

Levels of the following laboratory results performed in the first 3 days of admission were obtained: ESR (normal value <20 mm/h), CRP (<1 mg/dL), hemoglobin (Hb, 12–17 mg/L), ferritin (18–160 ng/mL), lactic dehydrogenase (250–450 UI/L), complement C3 (0.82–1.87 g/L) and C4 (0.11–0.44 g/L) levels, white blood cell (WBC, 4–11 $\times$ 10^6/L) with differential count and urinalysis. In addition, dsDNA-Ab levels obtained in the current admission or in the nearest date within three months were recorded (reference value <14.9 U/mL).

2.4. Statistical analysis

Patients were categorized into three groups: SLE flares (group 1), infections (group 2) or both (group 3). First, main clinical and laboratory characteristics of the 3 groups are described. Continuous variables are presented as mean (SD) and categorical data as percentages. Association between selected covariates was analyzed using student's *T* test or ANOVA for quantitative variables. Fisher's exact test or χ^2 test was used for categorical variables, depending on the validity of the underlying assumptions test for categorical data.

Based on the data of groups 1 and 2, the identification of predictive variables for SLE relapses or infections was done using logistic regression analysis. Clinically relevant variables were considered for the multivariate approach. On the basis of previous literature [39–41], pre-defined potential predictors for differentiation of infections and flares were included (age at SLE diagnosis, previous history of lupus