Time-dependent analyses of clinical manifestations of systemic lupus erythematosus identify patients at high risk of incident proteinuria

Andersen, Martin; Stockmarr, Anders; Leffers, Henrik; Troldborg, Anne Margrethe; Voss, Anne; Kristensen, Salome; Deleuran, Bent Winding; Dreyer, Lene; Johnsen, Laura Øllegaard; Colic, Ada

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Martin Andersen*[1], Anders Stockmarr[2], Henrik Leffers[1], Anne Troldborg[3], Anne Voss[4], Salome Kristensen[5], Bent Deleuran[3], Lene Dreyer[5], Laura Johnsen[6], Ada Colic[7], Søren Jacobsen[1]

[1]Copenhagen University Hospital Rigshospitalet, Center for Rhematology and Spine Diseases, Copenhagen, Denmark, *[2]Technical University of Denmark , Department of Applied Mathematics and Computer Science, Lyngby, Denmark*, *[3]Department of Biomedicine, Aarhus University, Department of Rheumatology, Aarhus, Denmark*, *[4]Odense University Hospital, Department of Rheumatology, Odense, Denmark*, *[5]Aalborg University Hospital, Department of Rheumatology, Aalborg, Denmark*, *[6]Copenhagen University Hospital Rigshospitalet, Center for Rhematology and Spine Diseases, Gentofte, Denmark*, *[7]Zealand University Hospital Køge , Department of Rheumatology , Køge, Denmark*

Background:

Nephritis (LN) in systemic lupus erythematosus (SLE) is still a major determinant of poor prognosis[1].
The vast majority of LN occurs in proximity to the SLE diagnosis[2]. Identification of individuals at high risk, especially early onset SLE, is therefore warranted. Inclusion of risk factors prior to the SLE diagnosis may thus be of importance to enable sufficient risk factor profiling. SLE-patients seem to cluster according to clinical and serological phenotypes suggesting distinct disease trajectories[3-5].

Objectives:

To determine if incident proteinuria associated with the debut age of non-renal SLE characteristics.

Methods:

Data of SLE patients from six Danish centers were obtained from the Danbio-database from 2017 – 2020. The occurrence and timing of proteinuria was compared with first time onset of any non-renal manifestations as defined by the 1997 American College of Rheumatology Classification Criteria. Cox-regression models were used to identify risk factors for incident proteinuria. Time from first occurring non-renal manifestation to incident proteinuria or censoring defined time at risk. Covariates were eliminated if $p > 0.01$ in a 'backwards' manner. After the model reduction process p-values <0.05 were considered statistically significant.

Results:

586 SLE patients, mainly white (94%) women (88%), mean age at inclusion of 34.6 years (standard deviation, SD = 0.6 years) and observed for a mean of 14.9 years (SD =0.5 years), were recruited. The cumulative prevalence of proteinuria was 40%. Male gender hazard ratio, HR = 1.35 (range 0.77-2.35), p=0.009, lymphopenia HR = 1.77 (range 1.24-2.52), p=0.005 were associated with incident proteinuria. In contrast, patients with discoid rash had lower risk of incident proteinuria HR 0.42 (range 0.21-0.83), p=0.01. Male patients with lymphopenia had the highest risk of proteinuria with a one-, 5- and 10-year risk of proteinuria ranging from 9-27%, 34-75% and 51-89 %, depending on the age at presentation (debut at 20, 30, 40 or 50 years). The corresponding risk-profiles for women with lymphopenia were 3-9%, 8-34% and 12-58%, respectively, as illustrated in Fig. 1.

Conclusion:

The occurrences of lymphopenia and discoid rash were oppositely associated with risk of incident proteinuria and the risk effects varied according to gender and patient age at onset of these manifestations. Thus, the risk of proteinuria may not be constant but could vary according to presentation of non-renal manifestations that may call for a differentiated clinical follow-up. Based on these findings, we suggest that the debut age of known prognostic factors, even prior to the SLE diagnosis should be considered when designing prognostic statistical models.

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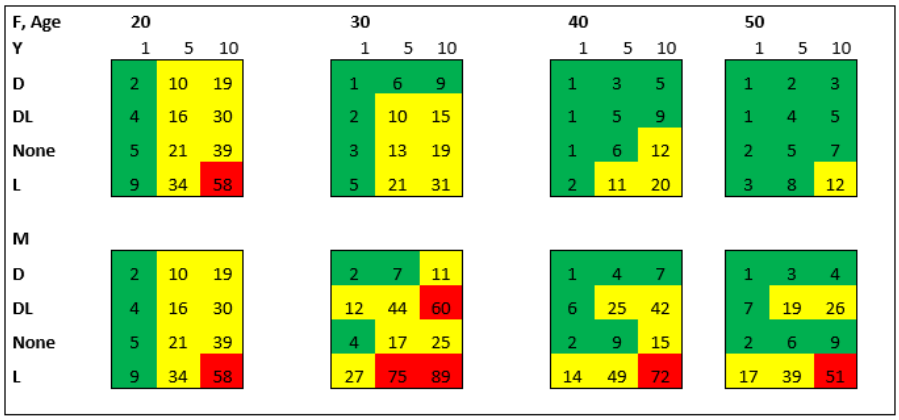
Fig. 1. One-, 5- and 10-year (Y) risk of incident proteinuria in 586 patients with SLE by gender (M,F) and age at onset of discoid rash (D) and/or lymphopenia (L) that all emerged as predictors of incident proteinuria in a time-dependent Cox regression model. Abbreviations: Age = age at debut; F = female; M= Male, None = absence of Discoid rash and Lymphopenia.



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