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Absolute risk estimation of new-onset proteinuria in patients with systemic lupus erythematosus – a Danish nationwide cohort study

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Abstract

Background

Kidney involvement in systemic lupus erythematosus (SLE) affects approximately 40% of patients and is associated with increased mortality and morbidity.

The risk of renal involvement has primarily been reported as hazard ratios (HR) which may be challenging to interpret on a patient level. Additional data reporting such as absolute risk estimates may strengthen risk stratification and compliance.

This study provides absolute risk estimations of risk of new-onset proteinuria among SLE patients.

Methods

Danish SLE-centres provided clinical data on first time observations of proteinuria and other clinical parameters listed in the 1997 American College of Rheumatology Classification Criteria for SLE. Time from first occurring non-renal manifestation to new-onset proteinuria or censoring defined time at risk. Cox-regression models were used to identify risk factors for new-onset proteinuria and to calculate risk of proteinuria stratified by risk factor debut age, duration and sex. Models were reduced using a backwards elimination process for $p > 0.01$. Potentially relevant interaction covariate terms were added to the model in a forward selection procedure using $p < 0.01$.

Results

Patient population consisted of 586 patients with SLE, mainly Caucasian (94%) women (88%), mean age at inclusion of 34.6 years (standard deviation, SD = 14.4 years), observed for a mean of 14.9 years (SD = 11.2 years). The cumulative prevalence of proteinuria was 40%. Male sex, HR = 1.35 ($p = 0.009$), lymphopenia HR = 1.77 ($p = 0.005$) were associated with new-onset proteinuria. Male patients with lymphopenia had the highest predictive risks of proteinuria with a 1-, 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.

Conclusions

Large differences in absolute risk estimates for new-onset proteinuria were identified. The differences may aid risk stratification and patient compliance among high-risk individuals.

Introduction

Systemic lupus erythematosus (SLE) is a systemic inflammatory autoimmune disease that presents through a plethora of diverse clinical and immunological manifestations as reflected by the heterogeneity of items listed in current and previous classification criteria for SLE (1). The course of SLE may be characterized by accumulation of disease manifestations over time, but immunological perturbations

have been detected years before clinical onset (2). Despite the clinical heterogeneity of SLE, it is of interest that the disease seems to evolve within distinct clusters of skin or renal disease. This supports the notion of SLE being a construct of various subgroups with particular disease trajectories calling for further investigation of the temporality of disease manifestations in SLE as potential markers of prognosis(3, 4).

Renal involvement in the form of lupus nephritis (LN) occurs in about 40% of SLE patients, frequently as part of the initial presentation and later in around 20–25% (5, 6) LN has a significant impact on mortality, morbidity, and healthcare costs (7, 8) Among Danish SLE patients, the standardized risk of cardiovascular mortality was five-fold increased by the occurrence of LN (9).Furthermore, diagnostic delay of LN has been shown to increase the risk of end-stage renal disease and increased awareness of LN risk factors might be of value in this context(10).

Established risk factors for LN comprise young age at disease onset, African ancestry, male sex, certain autoantibodies, lymphopenia and low complement levels(11, 12). Unfortunately, these risk factors have not allowed strong stratification of SLE patients as to risk of LN in clinical practice (13).

Risk factors are mainly identified through regression models reported as hazard ratios or odds ratios. The clinical significance of these statistical outcome variables can be difficult for laypeople and less statistically trained clinicians to understand.

The failure of grasping the significance of these risk factors may affect compliance and lead to potentially life threatening complications. A recent study among 1700 SLE patients reported that the reason for discontinuation of Hydroxychloroquine (HCQ), the first-line drug in SLE, could not be accounted for in 80% of cases suggesting a significant lack of compliance among SLE patients(14). The 'Strengthening the reporting of observational studies in epidemiology' (STROBE) recommendations suggest that reporting of relative risks, if relevant should be translated into absolute risk for a meaningful time period (15).

This STROBE recommendation has received recent attention within the rheumatologic research field exemplified by calculations of 5–10-year risk of cardiovascular disease in ANCA-associated vasculitis, pulmonary hypertension in SLE and risk of malignancy in sarcoidosis(16–18).

In contrast, absolute risk estimates of proteinuria have, to our knowledge, not previously been reported.

By providing absolute risk predictions of proteinuria among SLE patients at 1, 5 and 10 years we hope that the additional information may optimize patient risk stratification, strengthen compliance and thereby potentially reduce renal involvement in SLE.

Patients And Methods

Study population

The patient population consisted of SLE patients recruited to the SLEDAN network 2017–2020, fulfilling the American College of Rheumatology (ACR) 1997 SLE criteria, as previously published(19) Briefly, the SLEDAN network consists of Danish rheumatologic centres and was initiated in 2017 with the scope of strengthening research in SLE. Demographics and SLE specific data such as ACR 1997 classification criteria (20) was collected in DANBIO, a nationwide clinical rheumatological database(21)

All patients included had given written, informed consent based on protocol information approved by the Regional Ethics Committees for medical research (H17024413) and the Danish Data Protection Agency (P-2019-747).

Clinical variables and outcomes

The occurrence and date of new-onset proteinuria was compared with time of first occurrence of any non-renal manifestations as defined by the 1997 American College of Rheumatology Classification Criteria (ACR1997)(20). New-onset proteinuria was defined as a registration of 'persistent proteinuria'- ACR1997 criterium in the Danbio-registry. Patients were excluded from analysis if no dates of ACR1997 criteria items were registered.

Fine cellular casts which were not routinely performed in the clinics were not included in the data extraction. Auto-antibody measurements were carried out at certified laboratories affiliated with the hospitals either by enzyme-linked immune-sorbent assays or by indirect immune-fluorescence as previously described(22)

Statistical analyses

Cox regression models were used to identify risk factors for new-onset proteinuria. Time from first occurring non-renal manifestation to new-onset proteinuria or censoring (age at data-extraction December 2020) defined time at risk. Risk factors were identified from a pre-defined list of candidates consisting of the individual items in the ACR1997, age at SLE diagnosis, sex, ethnicity, and time to reach four ACR1997 criteria. The ACR1997 were included as time-dependent covariates, where subjects entered a (potential) new risk state from the time of occurrence of the individual ACR1997. Candidates were eliminated from a Cox regression model one variable at a time by a stepwise backwards procedure, excluding the variable with the highest p-value. To reduce the risk of type I errors variables with $p > 0.01$ were excluded. A confirmatory forward selection procedure was then applied, and subsequently possible interactions among covariates in the final model were analysed. The model was further adjusted for possible regional differences among the centres. Model control was performed on Schoenfeld residuals.

The predicted mean percentages of new-onset proteinuria were calculated from the identified hazard ratios, duration (1,5, 10 years) and age at risk factor debut.

Analyses were performed by R version 4.02(23).

Results

Data from 719 SLE patients were extracted from the DANBIO registry. 133 patients were excluded due to lack of ACR1997 dates. The included patients primarily consisted of Caucasian (94%) females (88%) observed for a mean of 14.9 years, (standard deviation, SD = 11.2 years) with an average age at diagnosis of 34.6 years (SD = 14.4). Proteinuria was prevalent among 236 (40%). Proteinuria occurred prior, at or after the SLE diagnosis in 56 (24%), 78 (33%) and 102 (43%) patients, respectively.

Table 1 provides an overview of the ACR 1997 classification criteria items with their temporal occurrence in relation to the SLE diagnose.

Table 1

Overview of patient demographics and systemic lupus erythematosus disease manifestations.

Patient characteristics			
Participants, N (%)	586 (100)		
Sex, female, N (%)	517 (88)		
Age at SLE onset, years, mean (SD)	34.6 (14.4)		
Observation time, years, mean (SD)	14.9 (11.2)		
Ethnicity, N (%)			
- Caucasian	551 (94)		
- Asian	26 (4)		
- African/Caribbean	6 (1)		
- Hispanic	1 (0)		
ACR-1997 classification criteria characteristics			
	N (%)	mean age at presentation, years (SD)	temporal relation to SLE-diagnose, years (SD)
Skin			
- Photosensitivity	275 (47)	33.5 (14.4)	-1.3 (5.6)
- Malar rash	284 (48)	30.3 (13.3)	-0.9 (5.4)
- Discoid rash	69 (12)	37.5 (15.5)	-3.9 (12.0)
- Oral ulcers	159 (27)	33.3 (13.3)	1.0 (5.1)
Musculoskeletal			
- Arthritis	411 (70)	33.3 (14.2)	-1.2 (5.4)
Serositis			
- Pericarditis	96 (16)	36.0 (15.2)	1.3 (7.9)
- Pleuritis	162 (28)	36.0 (14.2)	0.7 (5.2)
Renal			

Patient characteristics			
- Proteinuria	236 (40)	32.1 (13.1)	1.0 (7.0)
Neurologic			
- Seizures	33 (6)	31.2 (13.4)	0.3 (12.4)
- Psychosis	12 (2)	31.3 (7.0)	0.3 (5.5)
Hematology			
- Leucopenia	192 (33)	34.1 (14.0)	1.5 (6.0)
- Lymphopenia	273 (47)	35.9 (14.5)	1.9 (5.8)
- Thrombocytopenia	138 (24)	32.6 (14.0)	1.2(6.4)
- Haemolytic anaemia	48 (8)	31.2 (13.4)	1.3 (4.4)
Auto-antibodies			
- ANA	542 (92)	34.3(14.4)	-0.6 (4.9)
- Anti-dsDNA	437 (75)	34.3 (13.9)	0.2 (4.9)
- Anti-Smith	69 (12)	35.7 (13.4)	3.7 (7.9)
Phospholipid-antibodies			
- Abnormal IgG or IgM	203 (35)	35.2 (13.8)	2.5 (6.9)
- Lupus anticoagulant	95 (16)	33.6 (13.9)	2.65 (7.9)

Table 1. Disease manifestations present prior to the SLE diagnosis are reported as negative.

Abbreviations: ACR = American College of Rheumatology; Anti-dsDNA = Anti-double stranded DNA; ANA = Anti-nuclear antibodies; N= Number; IgM = Immunoglobulin M; IgG = Immunoglobulin G; SD = Standard deviation; SLE = Systemic lupus erythematosus.

The analyses identified two factors that were associated with new-onset proteinuria: lymphopenia, hazard ratio (HR) 1.77, (95% confidence limits, CL95 = 1.24–2.52), $p = 0.005$ and discoid rash HR 0.42 (CL95 = 0.21–0.83), $p = 0.01$. Male gender in the age-range 30–59 years showed a statistically significant interaction with lymphopenia, HR: 4.30 (CL95 = 1.8–10.3), $p = 0.009$. No other interactions were identified.

Lymphopenia occurred in 273 patients (47%) and among 138 of the 236 patients (58%) who developed proteinuria. In the latter case lymphopenia preceded proteinuria in 57 patients (24%) and occurred simultaneously in 47 (20%) and after proteinuria in 34 cases (14%), respectively. Lymphopenia preceded (median = 17.0 months, IQR = 40.9 months) proteinuria in 46 (45%) out of the 102 patients who developed proteinuria after the SLE diagnose.

Figure 1 provides an overview of proteinuria risk sorted by gender, age of debut and risk factor profile. Discoid rash was present in 69 patients (12%) and occurred in 16 cases among the patients who developed proteinuria (7%). Discoid rash preceded proteinuria in 9/16 (56%).

Lymphopenia among males in the age range at 30–59 years posed the highest risk of new-onset proteinuria, with 1-year risk of proteinuria ranging from 17–27% or 39–75% within 5 years and 51–89% at 10 years exposure. In contrast, patients above 30 years of age with discoid rash had the lowest risk of new-onset proteinuria with an overall risk at 1, 5 and 10 years of 1%, 2–6% and 3–9%, respectively. Patients with a debut of lymphopenia at the age of 20 had a 9%, 34% and 58% risk of proteinuria at 1,5 and 10 years of exposure. SLE patients with absence of lymphopenia or discoid rash at age 30, 40 or 50 years had an overall risk of proteinuria at 1,5,10 years of 1–4%, 5–17% and 7–25%, respectively.

Discussion

Lymphopenia among men and younger women was associated with a significant increased risk of new-onset proteinuria, with up to 89% at 10 years. Thereby showing promise as a marker of later development of LN. Indeed, it preceded proteinuria in 44% among all proteinuria cases and in 45% of the proteinuria cases that occurred after the SLE diagnosis.

As a novelty, we calculated individualized prospective risk of new-onset proteinuria based on risk factor status at different ages. The results revealed large differences in proteinuria-risk and may be a promising approach with regards to a more individualized risk factor profiling, better compliance and optimization of healthcare resources.

In contrast to high-risk individuals, the 10-year new-onset proteinuria risk was 9% among SLE patients > 50 years with absence of lymphopenia or even lower in the presence of discoid rash - a reassuring finding.

The high number of patients at a national level and long follow up should minimize referral bias, false negative proteinuria-cases and thereby account for a high degree of generalizability. The limitations of this study include the predominantly Caucasian patient population. We did, however, not identify a significant effect of ethnicity with regards to onset of proteinuria. This could in part be explained by a lack in difference with regards to prevalence in lymphopenia, but also caused by a type II error due to low patient numbers, since other ethnicities only accounted for 10% of the patient population.

For this study, we did not have access to co-morbidities, detailed medication-history or disease activity scores. The degree of confounding from other conditions of proteinuria such as hypertension and diabetes can therefore not be assessed. We however expect the degree of proteinuria from other causes than LN to be negligible since the study focused on the debut of proteinuria and 85% of patients with proteinuria had biopsy proven LN. Therapy-induced lymphopenia should not be a significant source of bias either since 66% of the lymphopenia cases occurred at or prior to the diagnosis of SLE.

The identification of lymphopenia as a risk factor of proteinuria is in line with previous publications. Anti-double-stranded DNA (anti-DNA) and anti-Smith (anti-Sm) were significantly associated with LN in the multifactorial model but became insignificant during the cofactor elimination process. The lack of significance in the reduced model may be due to sampling bias, since these tests in clinical practice often are taken in relation to the SLE diagnose, even though present years before symptoms develop. We did not have records of the degree, duration nor the characteristics of the lymphopenia which could have improved risk stratification further(24, 25). The prevalence of lymphopenia is highly variable with reports ranging from 15–82% (26). A prevalence of 47% is comparable to a recent study of 2000 SLE patients which recorded lymphopenia in 37% during a significantly shorter observation period (average 2.3 years vs. 14.9 years in our study(27).

Our findings highlight that SLE disease manifestations occurring prior to the clinical diagnosis should be considered when investigating prognostic factors.

In conclusion, we provide absolute risk estimates of new-onset proteinuria among SLE patients.

Sex, age at exposure and duration of risk factor profile (none, lymphopenia and or discoid rash) revealed large differences in risk of new-onset proteinuria.

Status of these easily obtainable variables may prove valuable in the clinical assessment of a disease known to be highly unpredictable. The results show promise with regards to better patient stratification and counselling, but further studies are needed to assess the generalizability of these findings.

Abbreviations

American College of Rheumatology

ACR	
ANCA	Anti-neutrophil cytoplasm antibodies
CL95	95% confidence limits
D	Discoid rash
DANBIO	Danish rheumatology database
DL	Presence of both lymphopenia and discoid rash
DNA	Deoxyribonucleic Acid
F	Female
HCQ	Hydroxychloroquine
HR	Hazard ratio
L	Lymphopenia
LN	Lupus nephritis
M	Male
N	None
P	Probability
SLE	Systemic lupus erythematosus
SLEDAN	Network of Danish rheumatologic centres
Sm	Smith
STROBE	Strengthening the reporting of observational studies in epidemiology
Y	Risk factor exposure, years
%	Percentage

Declarations

Ethics approval and consent to participate

All patients included had given written, informed consent based on protocol information approved by the Regional Ethics Committees for medical research (H17024413) and the Danish Data Protection Agency (P-2019-747).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

MA: Responsible for drafting the main manuscript.

AS: Responsible for statistical calculation, critical review of the manuscript.

MA and remaining authors were all involved in conceptualization of the manuscript, patient recruitment and critical review of the manuscript.

All authors read and approved the final manuscript.

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Figures

Figure 1

		Age			20 years			30 years			40 years			50 years			
Female	Years		1	5	10		1	5	10		1	5	10		1	5	10
	D		2	10	19		1	6	9		1	3	5		1	2	3
	DL		4	16	30		2	10	15		1	5	9		1	4	5
	None		5	21	39		3	13	19		1	6	12		2	5	7
	L		9	34	58		5	21	31		2	11	20		3	8	12
Male	Years		1	5	10		1	5	10		1	5	10		1	5	10
	D		2	10	19		2	7	11		1	4	7		1	3	4
	DL		4	16	30		12	44	60		6	25	42		7	19	26
	None		5	21	39		4	17	25		2	9	15		2	6	9
	L		9	34	58		27	75	89		14	49	72		17	39	51

Figure 1

One-, 5- and 10-year risk reported as predicted percentages of new-onset proteinuria in 586 SLE patients. Discoid rash and/or lymphopenia emerged as predictors of new-onset proteinuria in a time-dependent Cox regression model. Green, yellow, and red backgrounds reflect risk of proteinuria below 10%, 11-20% and 50% or more, respectively. Abbreviations: Age = age at debut of risk factor, D= Discoid rash; DL= Presence of both lymphopenia and discoid rash; F= Female, L= Lymphopenia; M= Male, None = absence of discoid rash and lymphopenia, Y= risk factor exposure, years; % = Percentage.