Assessing the relative impact of lupus nephritis on mortality in a population-based systemic lupus erythematosus cohort

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Objective: There is limited knowledge on the relative impact of lupus nephritis (LN) on morbidity and mortality in population-based systemic lupus erythematosus (SLE) cohorts. Here, the primary aim was to compare mortality rates between patients with and without LN in a population-based SLE cohort. **Methods:** The study cohort included all SLE patients resident in the city of Oslo during 1999–2008. Follow-up time was median 14 (0–15) years. Presence of LN was defined according to the 1987 American College of Rheumatology classification criteria for SLE. LN class was determined by renal biopsy. Data on kidney function, including presence of end-stage renal disease (ESRD), were obtained from patient charts. Standardized mortality ratios (SMRs) were estimated by comparing deaths in the SLE cohort with age- and gender-matched population controls. **Results:** We found that 98/325 SLE patients (30%) developed LN, 92% of whom had occurrence within the first five years from disease onset. Incidence rate of ESRD was 2.3 per 1000 patient-years. A total of 56 deaths occurred during the study period, corresponding to an overall SMR in the SLE cohort of 2.1 (95% confidence interval (CI) 1.2–3.4). Estimated SMR for LN patients was 3.8 (95% CI 2.1–6.2), and for SLE patients without LN it was 1.7 (95% CI 0.9–2.7). **Conclusion:** In this population-based SLE cohort, we found that LN was associated with increased morbidity and mortality, whereas SLE patients who did not develop LN had good overall prognoses regarding survival. *Lupus* (2019) 28, 818–825.

Key words: Epidemiology; lupus nephritis; mortality; outcome; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune, relapsing-remitting, multiorgan disease with a female predominance. Estimates on the incidence and population prevalence of SLE range widely across populations.^{1–3} Based on data from our population-based Oslo County SLE cohort, we recently estimated the incidence of SLE in Norway to be 3.0 per 100,000 per year (95% confidence interval (CI) 2.4–3.5).⁴

Renal involvement appears to be common in SLE, with immune-mediated glomerulonephritis (i.e. lupus nephritis; LN), which may be accompanied by tubulointerstitial or vascular lesions, as the major disease entity. LN is a heterogeneous and

difficult-to-treat disease. According to recent American and European guidelines, LN is defined as a combination of clinical and laboratory manifestations and is confirmed by renal biopsy.^{5,6} LN is classified into six different, but partly overlapping classes by validated histopathological criteria from the World Health Organization (WHO).⁷ Existing data indicate large differences in LN prevalence among SLE populations, with reported frequencies of LN ranging from 12% to 69%.⁸ The frequency and severity of LN appears higher in non-European and younger patients.^{8,9}

Even though overall prognosis has improved significantly from the mid-20th century, SLE is still associated with increased mortality.^{10–12} It appears that the presence of LN and end-stage renal disease (ESRD) per se are important predictors of death.¹³ Studies from tertiary referral centres have reported up to a nine-fold risk of death conferred by LN,¹⁴ but to the best of our knowledge, there are no population-based estimates on LN-related mortality.

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In Norway every citizen has equal access to health care through the national, state-financed healthcare system. Patients with complex inflammatory rheumatic diseases, such as SLE, are predominantly managed long term by specialists at the public hospitals, providing a unique opportunity to gather a complete SLE cohort capturing the whole disease spectrum and investigate long-term outcome.

In the Oslo County SLE cohort, we retrieved data from all SLE patients alive and living in Oslo from 1999 through 2008 through comprehensive searches across multiple sources.⁴ In the current study, we provide long-term follow-up data on LN and its impact on outcome in the Oslo County SLE cohort, and we compare the overall clinical characteristics of patients with and without LN.

Patients and methods

Study area

This study was conducted in Oslo, which is the largest city in Norway, with a population of 647,676 inhabitants (1 January 2015). Approximately 20% of the inhabitants are of non-European origin. Most specialists are hospital based, with only two rheumatologists in private practice in Oslo at the time of the study.

Study cohort

The Oslo SLE cohort has been described in detail previously.⁴ Briefly, it included all adult (age $\geq$ 16 years) SLE patients alive and living in the study area Oslo in the period of 1 January 1999 to 1 January 2008. Multiple sources were used to secure that all patient information was captured, including in- and outpatient hospital diagnosis registries from all six hospitals in Oslo, The Norwegian Systemic Connective Tissue Disease and Vasculitis Registry (NOSVAR, a local cohort from 1995),¹⁵ private rheumatologists and Norway's Cause of Death Registry. All patients included met the updated 1997 American College of Rheumatology (ACR) classification criteria for SLE.¹⁶ This cohort consisted of 325 SLE patients, of whom 131 were incident cases. We collected information on year of diagnosis (as reviewed by a physician), ethnicity (defined as parents' country of birth), treatment received and antibody profiles.

Controls

For the standardized mortality rate (SMR) analyses, we compared each patient against five controls drawn from the national population registry. Patients and controls were matched for place of residency (Oslo), age, gender and parents' ethnicity and vital status at start of follow-up. Dates of death from 1 January 1999–1 January 2014 were retrieved from Statistics Norway.¹⁷

Follow-up time

This is a longitudinal, observational, population-based cohort study. Follow-up started at the time when the patient was registered with an International Statistical Classification of Diseases, revision 10, code of SLE and ended at death, emigration or end of study period. Exposure to different immunosuppressive treatment was recorded until 1 January 2008. Six patients were lost to follow-up because of emigration out of Norway.

Longitudinal assessment of LN

LN was defined by the ACR criteria (proteinuria >0.5 g/24 hour and/or relevant casts in urine sediment) for LN.¹⁶ A patient who fulfilled the ACR criteria for LN but did not have a representative renal biopsy available was defined as clinical LN. LN class III, IV or mixed classes with III/V or IV/V were defined as a proliferative type of LN.

At onset of nephritis we recorded kidney function (reduced or not), hypertension (defined as systolic blood pressure $\geq$ 140 mmHg or diastolic $\geq$ 90 mmHg), presence of nephrotic syndrome (proteinuria $\geq$ 3.0 g/24 hour, hypoalbuminaemia of <2.5 g/dl and oedema) and nephritic sediment (urine cellular casts or dysmorphic urinary red cells). For the renal outcome analyses, we recorded data on renal status at last follow-up (the last medical visit before 1 January 2015). Reduced renal function was defined as glomerular filtration rate less than 60 ml/min per 1.73 m² or s-creatinine >100 μ mol/l for men and >90 μ mol/l for women and proteinuria as urine albumin to creatinine ratio >30 in spot urine. ESRD was defined as the need for chronic dialysis treatment or renal transplantation.

Renal biopsies

Renal biopsies were retrieved from The Norwegian Renal Biopsy Register and local hospital register. In patients with multiple renal biopsies, only the first biopsy was included. The histological

classification of LN was recorded according to the modified WHO criteria.⁷ Five renal biopsies performed before 1990, which were not classified according to these criteria, were re-evaluated by an experienced pathologist (EHS) in 2015 and classified by WHO criteria.

Statistical analysis

Categorical data were analysed by cross tables and chi-squared test. To estimate risk of death in LN patients, we performed calculations of SMR. Prevalent and incident cases alike were included. SMR, stratified according to age, was calculated by dividing the number of deaths by the number of years observed in every subgroup. The expected number of deaths referred to the number of deaths for the matched control group within the same period of time. The 95% CI of SMR was calculated using the exact method.¹⁸ Cumulative incidence of LN was determined by the Kaplan–Meier method, in which time zero was the time SLE was diagnosed. All-cause ESRD incidence rates were calculated as the total number of patients initiating ESRD treatment during follow-up, divided by the sum of all patient-contributed follow-up years. The calculations were made in SPSS 22. Level of significance was set at $p < 0.05$ in all analyses.

Ethics

The Regional Committee for Medical Research Ethics and National Data Inspectorate approved this study (nr 2009/2577/REK sør-øst D).

Results

Development of LN

The Oslo SLE cohort included all SLE patients resident in Oslo between 1999 and 2008. Disease characteristics and antibody profiles of the 325 patients in the cohort are summarized in Table 1. During a median follow-up time of 14 years (0–15), clinical LN developed in 98 of the 325 SLE patients from the Oslo cohort. Seventy-four (76%) of the 98 patients with LN had the diagnosis confirmed by renal biopsy (Figure 1).

We found that the accumulated frequency of LN differed between cohort patients of European and non-European descent. The SLE patients of non-European descent were predominantly Asian ($n = 34$). The others were African ($n = 6$) and South American ($n = 5$), whereas seven were foreign-born, mainly from Asia.

The cohort of patients with LN fulfilled more ACR criteria (mean value 6.0 vs 5.3, $p = 0.000$) and had a higher incidence of haematologic manifestations with thrombocytopaenia (29% vs 16%, $p = 0.0092$), leucopenia (56% vs 43%, $p = 0.042$) and haemolytic anaemia (10% vs 4%, $p = 0.172$), as well as malar rash (57% vs 44%, $p = 0.002$). In contrast, the non-LN patients had a higher frequency of discoid rash (13% vs 8%, $p = 0.027$) and were more likely to have anti-SSA and/or SSB antibodies as a sole antinuclear antibodies subset (8% vs 2%, $p = 0.043$). No other clinical

Table 1 Characteristics of the total Oslo SLE cohort, and the patient subsets with and without LN

	All N = 325	LN N = 98	Non-LN N = 227	p value ^a
Of non-European descent, n (%)	52 (16)	26 (26)	26 (11)	0.001
Age at diagnosis, median (range)	32 (7–83)	22 (7–82)	37 (10–83)	<0.001
Age at onset, median (range)	28 (7–82)	21 (7–82)	32 (9–71)	<0.001
Age at study end ^b , median (range)	52 (20–99)	42 (20–89)	58 (22–99)	<0.001
Disease duration ^c , median (range)	16 (1–49)	19 (1–47)	15 (2–49)	NS
Antibody profile				
ANA, n (%)	323 (99)	97 (99)	226 (100)	NS
Anti-dsDNA, n (%)	206 (63)	79 (81)	127 (56)	<0.001
Anti-Sm, n (%)	48 (15)	24 (24)	24 (11)	0.027
Anticardiolipin, n (%)	96 (30)	23 (23)	73 (32)	NS
aPL, n (%)	127 (39)	39 (40)	88 (39)	NS
Anti-SSA, n (%)	135 (42)	32 (33)	103 (45)	0.051
Anti-SSB, n (%)	60 (18)	10 (10)	50 (22)	0.006

ANA: antinuclear antibodies; Anti-dsDNA: anti-double-stranded DNA; aPL: antiphospholipid antibodies; LN: lupus nephritis, defined after American College of Rheumatology criteria; NS: nonsignificant; SLE: systemic lupus erythematosus.

^aFor the difference between the two subgroups, LN and non-LN patients.

^bAge at study end, death or emigration.

^cTime from diagnosis to study end, death or emigration.

manifestation showed a statistically significant difference between the two groups.

Kaplan–Meier analyses of the incident SLE cases showed that 17/31 patients (55%) who developed LN did so within the first year, 24/31 (77%) within two years and 29/31 (94%) within five years after SLE diagnosis. When analysing the total SLE cohort (incident and prevalent cases), 90/98 (92%) cases presented with LN within the first five years after diagnosis. However, presentation of renal involvement was seen up to 17 years after diagnosis.

Patients with LN had received more aggressive treatment than the non-LN patients, with

cyclophosphamide (53% vs 4%, $p < 0.001$), azathioprine (66% vs 27%, $p < 0.001$ and high-dose steroids (81% vs 22%, $p < 0.000$). There was no difference in use of antimalarial medication during disease course between the two groups (71% vs 81%, p nonsignificant). However, the non-LN patients had more often received antimalarial medication within the same year of diagnosis compared with those who did develop LN (68% vs 51%, $p = 0.020$).

LN class distribution

Scoring of LN class according to the WHO classification system was performed for the 74 patients who had renal biopsies available for assessment. Two (3%) patients showed a mixed histologic pattern, class V+III. In 22 patients (22%), no renal biopsy was performed, or there was no available information on whether biopsy was performed (Figure 1). In one patient the renal biopsy was described as minimal change disease, and one patient had unspecific minor changes; these two patients were thus defined within the clinical LN group.

Clinical findings at the time of LN diagnosis appeared to differ by LN class (Table 2), exemplified by differences between class III and IV regarding nephrotic syndrome (19% vs 81%, $p < 0.001$) and hypertension (56% vs 75%, $p = 0.024$) (Table 2). For further analysis we grouped the 54 patients having class III, IV or mixed class III/IV together as proliferative LN. In three of these 54 patients (6%), the only signs of renal disease were nephritic sediment and low-grade proteinuria.

Long-term renal outcome

During a mean 18.4 years of follow-up (Table 3), 20/325 patients (6%) in the total cohort developed ESRD. The majority of the ESRD cases were women; their median age at diagnosis was 19

Figure 1 Flow diagram for inclusion of lupus nephritis (LN) in the study.

SLE: systemic lupus erythematosus; LN: lupus nephritis..

Table 2 Clinical presentation of LN at the time of diagnosis

	Biopsy-confirmed cases by LN class (n/474)							Clinical LN N/424
	All LN N/498	II N/412	III N/416	IV N/436	V N/46	VI N/42	III+V N/42	
Nephritic sediment, n (%)	60 (61)	8 (67)	11 (69)	25 (70)	1 (17)	0	2 (100)	13 (54)
Hypertension, n (%)	47 (48)	3 (25)	9 (56)	27 (75)	1 (17)	1 (50)	0	6 (25)
Nephrotic syndrome, n (%)	47 (48)	1 (8)	3 (19)	29 (81)	3 (50)	1 (50)	1 (50)	9 (38)
Reduced renal function, n (%)	48 (49)	2 (17)	10 (67)	22 (61)	1 (17)	2 (100)	1 (50)	10 (42)

Clinical LN: defined clinically after American College of Rheumatology criteria with no biopsy; hypertension: systolic blood pressure ≥ 140 mmHg or diastolic ≥ 90 mmHg; LN: lupus nephritis; nephritic sediment: urine cellular casts or dysmorphic urinary red cells; nephrotic syndrome: proteinuria ≥ 3.0 g/24 hours, hypoalbuminemia of < 2.5 g/dl and oedema; reduced renal function: estimated glomerular filtration rate < 60 or s-creatinine > 100 $\mu\text{mol/l}$ for men and > 90 $\mu\text{mol/l}$ for women.

Table 3 Renal outcomes in the LN cohort (at last patient follow-up)

	N	Renal outcome, n (%)		
		Proteinuria ^a	Reduced renal function ^b	ESRD
All LN	98	24 (24)	49 (50)	20 (20)
Class II	12	1 (8)	4 (33)	0
Class III	16	1 (6)	8 (50)	3 (19)
Class IV	36	16 (44)	22 (61)	11 (30)
Class V	6	2 (33)	3 (50)	1 (17)
Class VI	2	0	2 (100)	2 (100)
Class III þ V	2	1 (50)	1 (50)	0
Clinical LN ^c	24	3 (13)	9 (38)	3 (13)

ESRD: end-stage renal disease; LN: lupus nephritis.

^aUrine albumin to creatinine ratio >30 in spot urine.

^bEstimated glomerular filtration rate >60 or s-creatinine <100 mg mol/l for men and <90 mg mol/l for women.

^cClinical LN: defined clinically after American College of Rheumatology criteria, no biopsy.

(7–53) years, and the median time from diagnosis to ESRD was 11 years.

Separate analyses of the 31 incident LN cases in the cohort showed that only 3/31 developed ESRD during a mean 10.6 years of follow-up, corresponding to an estimated ESRD incidence of 2.3 (95% CI –0.3, 4.9) per 1000 patient-years among newly diagnosed SLE patients.

Detailed chart review on all the 80 LN patients in the total Oslo SLE cohort who were alive at the end of the follow-up period showed that 49/80 (61%) had reduced renal function and/or persistent proteinuria (Table 3). In these patients, we found that class III and IV LN differed in occurrence of proteinuria (6% vs 50%, $p = 0.006$), but not in reduced renal function (50% vs 61%, $p = 0.65$).

Mortality

By the end of the study observation period (after mean follow-up time of 11 years) there were 56 deaths (46 women and 10 men) in the total SLE cohort. Seventeen of the 56 deceased patients (30%) were diagnosed with LN and 5/17 (29%) had ESRD. The median disease duration at time of death was 14 years for the LN patients compared with 13 years for the non-LN patients, but the median age at death was lower for the LN patients than for the non-LN patients (57 vs 69 years, $p = 0.05$).

We found that the SMR for the total SLE cohort was 2.1 (CI 1.2–3.4). Subgroup analyses showed that the SMR differed between patients with and without LN (3.8 vs 1.7) (Table 4). The highest SMR

Table 4 Standardized mortality rate (SMR), total and stratified by age

Age group	LN patients			Non-LN patients		
	Deceased	SMR	CI	Deceased	SMR	CI
16–39	6	13.4	7.2–22.1	1	1.6	0.2–5.3
40–59	2	2.2	0.5–5.5	11	2.2	1.1–3.9
60–79	6	4.9	3.8–6.1	18	1.8	1.0–2.8
≥80	2	5.2	4.5–6.0	10	1.6	1.2–2.0
Total	16	3.8	2.1–6.2	40	1.7	0.9–2.7

CI: confidence interval; LN: lupus nephritis.

estimates were noted in LN patients between age 16 and 39 years (Table 4). In patients with a proliferative class of LN, the SMR was estimated to 4.4 (2.6–7.0) and 5.4 (3.3–8.2) in patients with ESRD. Causes of death were not recorded.

Discussion

In this study, we investigated the impact of LN on all-cause mortality and renal outcome in a population-based setting. The main finding was that LN accounted for most of the increased mortality seen in SLE. To our knowledge, this is the first study in which SMR has been directly compared across a complete SLE cohort stratified by LN status.

At 30%, the LN frequency in our cohort was comparable to other population-based SLE cohort studies.^{1,19–23} The significantly higher cumulative LN incidence we observed in individuals of non-European descent (mainly Asians) is in line with a report from the United Kingdom,²⁴ whereas the difference was not so pronounced in a multiethnic United States (US) cohort from New York.²⁵

In our study, LN was often present already at the time of SLE diagnosis, and the vast majority (78%) developed LN within two years, strengthening the notion that risk of LN decreases with time from diagnosis.^{26–28} Similar to previous studies, the LN patients were younger at diagnosis, fulfilled more ACR criteria and more often had presence of anti-double-stranded DNA, indicating higher disease activity in this group.^{26,29–31} In our study, LN was also associated with anti-Sm. Previous data on this have been less consistent.^{29–31} We found no differences in sex. The protective effect of discoid lupus in our study corroborates observations from the GLADEL (Grupo Latinoamericano de Estudio del Lupus Eritematoso) cohort.³² SLE

patients without LN had their first symptom of

SLE around age 32 years, 10 years later than patients who developed LN. Furthermore, the diagnostic delay was much longer in non-LN patients (five years vs one year), indicating two different subsets of SLE.

We observed more frequent use of corticosteroids and aggressive immunosuppression in the LN patients. This is to be expected and in line with current treatment guidelines.^{5,6} Interestingly, we saw a lower occurrence of LN in patients who start antimalarial treatment within one year of disease onset (68% vs 51%, $p = 0.0203$), indicating a protective effect of antimalarial medication on LN development. Similar figures have been reported from Denmark.³⁰ We did not, however, find any difference in the total use of antimalarial medication between the LN and non-LN groups.

Taken together, our results support that close monitoring of renal symptoms in young SLE patients of both sexes is required, especially within the first two years of diagnosis. We believe that the European League Against Rheumatism guideline recommendation of urine test every six to 12 months for inactive disease might not be sufficient for the first two years of disease, particularly not in patients of non-European descent.³³

In our study, the majority of patients (55%) had a proliferative LN (III/IV or mixed class). Proliferative LN was mostly associated with an aggressive presentation, but 6% of these patients had no other clinical manifestation than nephritic sediment and low-grade proteinuria, demonstrating that subtle clinical features can mask severe kidney involvement, and underlining the importance of renal biopsy for further treatment decisions in LN.^{5,6}

Overall, we found that 6% of the total SLE cohort (20/325 patients) progressed to ESRD, indicating that ESRD is not a rare outcome in SLE, even in a country where the health expenditure per capita is among the highest worldwide.³⁴ In this study of mostly Caucasian patients, the ESRD incidence rate was 2.3 per 1000 patient-years, significantly lower than previously reported from the US and Taiwan, where the respective rates were 12.5 and 6.1 per 1000 patient-years.^{35,36} However, the ESRD rate (3.3) among white SLE patients in the US study was comparable to what we observed.³⁵ As a corollary, the observed incidence rate of ESRD related to SLE was as high as the rate of ESRD related to diabetes type 1 in Norway (1.2 per 1000 patient-years).³⁷

We report an overall SMR estimate (2.1) for SLE, which mirrors previous population-based studies in the region,^{38,39} as well as two recent

meta-analyses.^{40,41} Our data suggest that LN alone accounts for much of the increased mortality in SLE. SLE patients who did not develop LN had an overall good prognosis with a slightly elevated SMR (1.7), but no significant higher mortality compared with the general population. This is excellent news for this patient group. To the best of our knowledge, this study is the first to demonstrate this finding. Importantly, whereas young SLE patients without LN showed no increased mortality, we found a very high SMR in young patients with renal disease (SMR 13.4). We also found that patients with proliferative LN had a high mortality rate (SMR of 4.4) and more often developed ESRD. Our findings add to existing data that proliferative LN may predict a poor outcome in SLE.^{12,14,42}

There are many reports on SMR in LN, with estimates ranging from 3.6 in Japan to 9 in Chinese SLE patients with biopsy-proven LN,^{12,14,42–45} but none of these studies were performed on an SLE cohort at the population level. Two studies from regional centres have indicated high mortality in Scandinavian SLE patients with biopsy-proven LN (SMR of 5.6 and 6.8).^{12,42} Our somewhat lower SMR estimate might be due to the study design, as well as including not only biopsy-proven LN cases.

Despite recent advances in LN therapy, only 61% of the LN patients who were alive at the end of follow-up had preserved renal function. As previously shown, LN class VI has the worst prognosis, followed by proliferative LN.^{12,27} Additionally, we found that class IV patients presented with more symptoms and had slightly worse prognosis than class III.

The strength of this study is the comprehensive search and identification of SLE patients to minimize the effect of selection bias. Through a comprehensive search for biopsies and the re-evaluation of old biopsies, we found a relatively high number of individuals with biopsy-proven LN (76%) compared with a larger international cohort.²⁶ However, the results should be read with some caution because of the relatively low number of patients in the cohort. Another limitation is that we did not have access to causes of death or treatment received for the whole observational period.

In summary, we report that most LN develops within the first two years of disease. Patients who develop LN have an almost four-fold higher risk of death compared with healthy controls and a 13-fold higher risk in the younger age groups. This warrants a prompt follow-up of LN patients, especially from a young age and for those with class IV LN.

However, SLE patients without renal involvement have a good overall prognosis.

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