RHEUMATOLOGY

Rheumatology 2016;55:252–262
doi:10.1093/rheumatology/kev311
Advance Access publication 5 September 2015

Original article

The frequency and outcome of lupus nephritis: results from an international inception cohort study

John G. Hanly[1], Aidan G. O'Keeffe[2], Li Su[3], Murray B. Urowitz[4], Juanita Romero-Diaz[5], Caroline Gordon[6], Sang-Cheol Bae[7], Sasha Bernatsky[8], Ann E. Clarke[9], Daniel J. Wallace[10], Joan T. Merrill[11], David A. Isenberg[12], Anisur Rahman[12], Ellen M. Ginzler[13], Paul Fortin[14], Dafna D. Gladman[4], Jorge Sanchez-Guerrero[4], Michelle Petri[15], Ian N. Bruce[16,17], Mary Anne Dooley[18], Rosalind Ramsey-Goldman[19], Cynthia Aranow[20], Graciela S. Alarcón[21], Barri J. Fessler[21], Kristjan Steinsson[22], Ola Nived[23], Gunnar K. Sturfelt[23], Susan Manzi[24], Munther A. Khamashta[25], Ronald F. van Vollenhoven[26], Asad A. Zoma[27], Manuel Ramos-Casals[28], Guillermo Ruiz-Irastorza[29], S. Sam Lim[30], Thomas Stoll[31], Murat Inanc[32], Kenneth C. Kalunian[33], Diane L. Kamen[34], Peter Maddison[35], Christine A. Peschken[36], Soren Jacobsen[37], Anca Askanase[38], Chris Theriault[39], Kara Thompson[39] and Vernon Farewell[3]

Abstract

Objective. To determine nephritis outcomes in a prospective multi-ethnic/racial SLE inception cohort.

Methods. Patients in the Systemic Lupus International Collaborating Clinics inception cohort (⩽15 months of SLE diagnosis) were assessed annually for estimated glomerular filtration rate (eGFR), proteinuria and end-stage renal disease (ESRD). Health-related quality of life was measured by the Short Form (36 questions) health survey questionnaire (SF-36) subscales, mental and physical component summary scores.

[1]Division of Rheumatology, Department of Medicine and Department of Pathology, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada, [2]Department of Statistical Science, University College London, London, [3]MRC Biostatistics Unit, Institute of Public Health, University Forvie Site, Cambridge, UK, [4]Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [5]Instituto Nacional de Ciencias Medicas y Nutrición, Mexico City, Mexico, [6]Rheumatology Research Group, School of Immunity and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK, [7]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, [8]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, [9]Division of Rheumatology, University of Calgary, Alberta, Canada, [10]Cedars-Sinai/David Geffen School of Medicine at UCLA, Los Angeles, CA, [11]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, USA, [12]Centre for Rheumatology, Department of Medicine, University College London, UK, [13]Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, USA, [14]Division of Rheumatology, Centre Hospitalier Universitaire de Québec et Université Laval, Quebec City, Canada, [15]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, [16]Arthritis Research UK Epidemiology Unit, Institute of Inflammation and Repair, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, UK, [17]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK, [18]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, [19]Northwestern University and Feinberg School of Medicine, Chicago, IL, [20]Feinstein Institute for Medical Research, Manhasset, NY, [21]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA, [22]Center for Rheumatology Research, Landspitali University Hospital, Reykjavik, Iceland, [23]Department of Rheumatology, University Hospital Lund, Lund, Sweden, [24]Division of Rheumatology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [25]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, King's College London School of Medicine, London, UK, [26]Unit for Clinical Therapy Research, Karolinska Institute, Stockholm, Sweden, [27]Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride, Scotland, UK, [28]Josep Font Autoimmune Diseases Laboratory, IDIBAPS, Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Spain, [29]Autoimmune Diseases Research Unit, Department of Internal Medicine, BioCruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain, [30]Emory University School of Medicine, Division of Rheumatology, Atlanta, Georgia, USA, [31]Kantonsspital Geissbergstr, Schaffhausen, Switzerland, [32]Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, [33]UCSD School of Medicine, La Jolla, CA, [34]Medical University of South Carolina, Charleston, SC, USA, [35]Ysbyty Gwynedd Bangor, Gwynedd, North Wales, UK, [36]University of Manitoba, Winnipeg, Manitoba, Canada, [37]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [38]Hospital for Joint Diseases, NYU, Seligman Centre for Advanced Therapeutics, New York, NY, USA and [39]Department of Medicine, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, Canada

Submitted 8 July 2014; revised version accepted 28 July 2015

Correspondence to: John G. Hanly, Division of Rheumatology, Nova Scotia Rehabilitation Center, 1341 Summer Street, Halifax, Nova Scotia B3H 4K4, Canada. E-mail: john.hanly@cdha.nshealth.ca

CLINICAL SCIENCE

Results. There were 1827 patients, 89% females, mean (S.D.) age 35.1 (13.3) years. The mean (S.D.) SLE duration at enrolment was 0.5 (0.3) years and follow-up 4.6 (3.4) years. LN occurred in 700 (38.3%) patients: 566/700 (80.9%) at enrolment and 134/700 (19.1%) during follow-up. Patients with nephritis were younger, more frequently men and of African, Asian and Hispanic race/ethnicity. The estimated overall 10-year incidence of ESRD was 4.3% (95% CI: 2.8%, 5.8%), and with nephritis was 10.1% (95% CI: 6.6%, 13.6%). Patients with nephritis had a higher risk of death (HR = 2.98, 95% CI: 1.48, 5.99; $P = 0.002$) and those with eGFR <30 ml/min at diagnosis had lower SF-36 physical component summary scores ($P < 0.01$) and lower Physical function, Physical role and Bodily pain scores. Over time, patients with abnormal eGFR and proteinuria had lower SF-36 mental component summary ($P \leqslant 0.02$) scores compared to patients with normal values.

Conclusion. LN occurred in 38.3% of SLE patients, frequently as the initial presentation, in a large multi-ethnic inception cohort. Despite current standard of care, nephritis was associated with ESRD and death, and renal insufficiency was linked to lower health-related quality of life. Further advances are required for the optimal treatment of LN.

Key words: systemic lupus erythematosus, lupus, nephritis, inception cohort, outcomes research.

Rheumatology key messages

- Lupus nephritis is associated with a substantial risk of end-stage renal disease and death.
- New treatment strategies are required to improve the outcome of lupus nephritis.

Introduction

Renal disease affects 38% of patients with SLE, with a range of 12–69% [1]. The frequency and severity is increased in patients with African, Hispanic and Asian ancestry [1]. Although a common early manifestation, it can occur at any time in the disease course [2]. The presentation varies from subclinical laboratory abnormalities to overt nephritis and nephrotic syndrome. Despite recent advances, some studies report progression to end-stage renal disease (ESRD) and mortality has not declined in the last decade [3, 4].

Improved outcomes of nephritis result from better treatment of both primary pathogenetic mechanisms and secondary co-morbidities. Administration of i.v. CYC [5, 6] and oral MMF are effective for induction [7–9] or maintenance therapy [10, 11]. Open-label studies of targeted B-cell depletion therapies have been positive [12, 13], although unconfirmed in controlled studies [14]. These immunomodulatory strategies and treatment of co-morbidities have been incorporated into recent treatment guidelines [15, 16]. The value of future treatment strategies will be determined by comparison with current standard of care.

Between 1999 and 2012 the Systemic Lupus International Collaborating Clinics (SLICC) established the SLICC inception cohort for the long-term study of clinical outcomes in SLE. The objective of the current study was to evaluate the short-term outcomes, as reflected by health-related quality of life (HRQoL), ESRD and death in patients with LN receiving standard of care in this international multi-ethnic/racial observational cohort of newly diagnosed SLE patients.

Patients and methods

Research study network

The study was conducted by members of the SLICC network [17]. Data were collected per protocol at enrolment and annually (±6 months) thereafter and entered into a centralized database. Each of the participating centre's institutional research ethics review boards approved the SLICC inception cohort study, including this present analysis.

Patients

Patients fulfilled the ACR classification criteria for SLE [18] and provided written informed consent for the SLICC inception cohort. Enrolment occurred up to 15 months following diagnosis. Demographic variables included age, gender, race/ethnicity and education. Medication history and lupus-related variables, such as the SLEDAI-2K [19] and SLICC/ACR damage index (SDI), were also recorded [20]. Laboratory testing included haematology, chemistry and immunology required for SLEDAI-2K and SDI scores. Patient self-reported HRQoL was measured by the subscale and summary scores of the Short Form (36 questions) health survey questionnaire (SF-36) [21].

LN

Nephritis was identified by the renal disorder variable of the ACR classification criteria [18, 22] and/or biopsy evidence of nephritis as per the International Society of Nephrology and Renal Pathology Society (ISN/RPS) criteria [23].

Renal variables and data collection

The SLICC inception cohort was not initially established for the study of renal disease. Thus, some renal data was garnered retrospectively by chart review. The ISN/RPS classification [23] and activity/chronicity scores of Austin *et al.* [24] were derived from renal biopsy reports. The National Kidney Foundation (NKF) classification of chronic kidney disease (CKD) [25] and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease equation [26] were determined at each assessment. Estimated proteinuria (ePrU) was measured by either 24-h urine collection or spot urine total protein:creatinine ratio [27, 28]. ESRD was determined from the SDI renal variable [29].

At each assessment, patients were assigned to one of three eGFR and ePrU states. For eGFR: state 1 (eGFR: >60 ml/min); state 2 (eGFR: 30–60 ml/min); and state 3 (eGFR: <30 ml/min). For ePrU: state 1 (ePrU: <0.25 g/day); state 2 (ePrU: 0.25–3.0 g/day); and state 3 (ePrU: >3.0 g/day).

Statistical analyses

Descriptive statistics were used to summarize enrolment data, and Chi-square tests and *t*-tests were performed as appropriate. A simple ordinal regression based on generalized estimating equation (GEE) methods was used to assess the trends of eGFR and ePrU states as well as NKF classification of CKD over time after LN diagnosis. Non-parametric estimates of the cumulative incidence function for the time until ESRD and death were calculated using Kaplan–Meier-like methodology [30]. A Cox regression with a time-varying covariate was also used to examine the effect of LN diagnosis on the competing risks of ESRD and death. Analyses of HRQoL outcomes at enrolment or at diagnosis of LN were based on simple linear regression models. For analyses of the HRQoL longitudinal outcomes, linear regression models with GEE were used to take into account the correlation between multiple observations within patients. Hypothesis tests for the significance of regression parameters were performed using Wald tests (Cox regression) and score tests (GEE analyses), and 95% CIs were calculated.

Results

Patients

A total of 1827 patients were recruited between October 1999 and December 2012 from SLICC centres in the USA [*n* = 528 (28.9%)], Europe [*n* = 486 (26.6%)], Canada [*n* = 421 (23.0%)], Mexico [*n* = 223 (12.2%)] and Asia [*n* = 169 (9.3%)]. Of these, 89% were female, and at enrolment the mean (S.D.) age of the cohort was 35.1 (13.3) years with a varied racial/ethnic mix, although predominantly Caucasian (Table 1).

At enrolment, the mean (S.D.) disease duration was 0.5 (0.3) years and patients had low SLEDAI-2K and SDI scores while receiving a range of lupus medications. Annual assessments varied from 1 to 13, with a mean follow-up of 4.6 (3.4) years. Eighty patients (4.4%) were lost to follow-up for reasons that included relocation, living excessive distance from the clinic, referral to a non-participating site, voluntary withdrawal and change in insurance status.

Onset and characteristics of patients with LN

LN occurred in 700 (38.3%) patients: 566/700 (80.9%) at the enrolment visit and 134/700 (19.1%) during follow-up (Fig. 1). Renal biopsies were performed on 395/700 (56.4%) patients, the majority (86.6%) when nephritis was first suspected; in 377/395 (95.4%) these were of sufficient quality to identify ISN/RPS classes (%): I: 9 (2.4), II: 36 (9.5), III: 101 (26.8), IV: 163 (43.2), V: 120 (31.8) and VI: 3 (0.8). Twenty-one and 34 biopsies were class III/V and IV/V, respectively. Of the 101 class III biopsies, 72 were active (A), 19 were active and chronic (A/C), and 10 were chronic (C). Among the 163 class IV biopsies, additional information was available on 127: 50 were class IV-S (27 A, 16 A/C and 7 C) and 77 were Class IV-G (50 A, 15 A/C and 12 C). For all of the 377 biopsies, the mean (S.D.) activity index was 4.3 (3.3) and the mean (S.D.) chronicity index was 2.7 (2.6).

There were 547/566 (96.6%) patients with nephritis who had renal disorder at enrolment. The 19 patients diagnosed only by renal biopsy had the following ISN/RPS class: I: 4 (21.1), II: 2(10.5), III: 6 (31.6), IV: 5 (26.3), V: 5 (26.3) and VI: 0 (0). There were two and one biopsies with class III/V and IV/V, respectively. Of the 134 patients who were diagnosed with LN subsequent to the enrolment visit, there were 128/134 (94.8%) who had renal disorder. The six patients diagnosed only by renal biopsy had the following ISN/RSP classes: I: 1, II: 1, III: 1, IV: 3, V: 0 and VI: 0.

Patients with LN at enrolment were younger and more frequently men and of African, Asian and Hispanic race/ethnicity (Table 1). Nephritis patients had a higher frequency of ACR classification criteria [18] for serositis, neurological disorder and immunological disorder and a lower frequency of mucocutaneous disease, arthritis and ANA. The higher mean total SLEDAI-2K in patients with nephritis was due to the inclusion of renal variables in the index score. Both the mean total and similarly adjusted SDI score was higher in patients with LN. Corticosteroids and immunosuppressive drugs were used more frequently and antimalarials less frequently (49.1%) in the nephritis group at enrolment, although antimalarial use increased to 72% over the study. Hypertension was more frequent in patients with nephritis.

Of the 1827 patients at the enrolment visit, 96 (5.3%) were ANA negative. There were no statistically significant differences in ACR classification criteria between ANA-positive and ANA-negative nephritis patients, with the exception of a higher frequency of immunological disorder in the ANA-positive group (88.4% *vs* 47.5%, $P < 0.001$). Twenty-seven (8/40 ANA-negative nephritis group and 19/56 in non-nephritis group) of the 96 patients who were ANA negative at enrolment became ANA positive during the study.

Table 1 Demographic and clinical manifestations of SLE patients with and without LN at enrolment

	LN patients	Non-LN patients	*P*-value	All patients
No. of patients	566	1261		1827
Age, mean (S.D.), years	31.3 (11.9)	36.9 (13.6)	<0.001	35.1 (13.3)
Gender, *n* (%)				
Female	477 (84.3)	1149 (91.1)	<0.001	1626 (89.0)
Male	89 (15.7)	112 (8.9)		201 (11.0)
Race/ethnicity, *n* (%)				
Caucasian	182 (32.2)	716 (56.9)	<0.001	898 (49.2)
Hispanic	138 (24.4)	142 (11.3)		280 (15.4)
Asian	100 (17.7)	172 (13.7)		272 (14.9)
African	121 (21.4)	182 (14.5)		303 (16.6)
Other	24 (4.2)	47 (3.7)		71 (3.9)
Disease duration, mean (S.D.), years	0.5 (0.3)	0.5 (0.4)	0.353	0.5 (0.3)
ACR classification criteria, *n* (%)				
Malar rash	202 (35.7)	463 (36.7)	0.712	665 (36.4)
Discoid rash	48 (8.5)	179 (14.2)	<0.001	227 (12.4)
Photosensitivity	140 (24.7)	514 (40.8)	<0.001	654 (35.8)
Oral/nasopharyngeal ulcers	178 (31.5)	500 (39.7)	<0.001	678 (37.1)
Serositis	179 (31.6)	318 (25.2)	0.005	497 (27.2)
Arthritis	380 (67.1)	989 (78.4)	<0.001	1369 (74.9)
Renal disorder	547 (96.6)	0 (0)		547 (29.9)
Neurological disorder	39 (6.9)	49 (3.9)	0.008	88 (4.8)
Haematologic disorder	366 (64.7)	760 (60.3)	0.083	1126 (61.6)
Immunologic disorder	484 (85.5)	912 (72.3)	<0.001	1396 (76.4)
ANA	526 (92.9)	1205 (95.6)	0.027	1731 (94.7)
SLEDAI, mean (S.D.)	8.5 (6.7)	4.0 (4.0)	<0.001	5.4 (5.4)
SLEDAI without renal, mean	3.6 (3.8)	3.8 (3.7)	0.393	3.7 (3.7)
SDI score, mean (S.D.)	0.5 (0.9)	0.2 (0.6)	<0.001	0.3 (0.7)
SDI score without renal, mean (S.D.)	0.4 (0.7)	0.2 (0.6)	0.008	0.3 (0.7)
Medications, *n* (%)				
Corticosteroids	515 (91.6)	750 (60.3)	<0.001	1265 (70.0)
Antimalarials	277 (49.1)	954 (76.0)	<0.001	1231 (67.6)
Immunosuppressants	397 (70.5)	331 (26.4)	<0.001	728 (40.0)
Co-morbidities/lifestyle				
Diabetes, *n* (%)	27 (4.8)	37 (3.0)	0.070	64 (3.5)
Hypertension, *n* (%)	330 (58.3)	205 (16.3)	<0.001	535 (29.3)
Current smoker, *n* (%)	63 (11.2)	210 (16.7)	0.003	273 (15.0)
Alcohol, mean (S.D.)	0.6 (1.9)	1.2 (3.4)	<0.001	1.0 (3.0)
BMI, mean (S.D.)	25.0 (5.9)	25.4 (5.9)	0.129	25.3 (5.9)
Duration of follow-up				
Years, mean (S.D.)	5.0 (3.6)	4.5 (3.3)	0.008	4.6 (3.4)

Outcome of LN

Adjusting for gender, age at enrolment and race/ethnicity, a Cox regression analysis on the competing risks of ESRD and death, with the diagnosis of LN used to define a time-dependent covariate, indicated that once patients were diagnosed with LN, they had higher risks of developing ESRD [hazard ratio (HR) = 44.7, 95% CI: 6.1, 329.7; $P < 0.001$] and death (HR = 3.2, 95% CI: 1.6, 6.5; $P = 0.002$).

The estimated cumulative incidence of ESRD (as defined by the SDI) for the entire cohort at 10 years following enrolment was 4.3% (95% CI: 2.8%, 5.8%) (Fig. 2a). For all patients with LN, the cumulative incidence of ESRD at 10 years after the diagnosis of LN was 10.1% (95% CI: 6.6%, 13.6%) (Fig. 2b). Excluding patients who ever developed LN, the estimated cumulative incidence of ESRD was 0.5% (95% CI: 0%, 1.4%) (Fig. 2c), albeit that this is an *ad hoc* analysis because some patients are excluded on the basis of developing LN following the enrolment visit.

The estimated cumulative incidence of death from all causes for the entire cohort at 10 years after enrolment was 4.4% (95% CI: 2.7%, 6.1%) (Fig. 2a). Patients with LN at enrolment and those who never developed LN had a cumulative incidence of death at 10 years of 5.0% (95% CI: 2.3%, 7.6%) (Fig. 2d) and 3.6% (95% CI: 0.9%, 6.2%) (Fig. 2d), respectively. In light of the very significant association between time-dependent LN status and death in the Cox regression, these overlapping confidence intervals are likely due to the limited data available to estimate cumulative incidences at single time points late in the follow-up period. An overall test of a difference in these curves using the log-rank test of no difference is significant ($P = 0.03$). The number of patients at the time points

Fig. 1 Onset of lupus nephritis following enrolment into the SLICC cohort

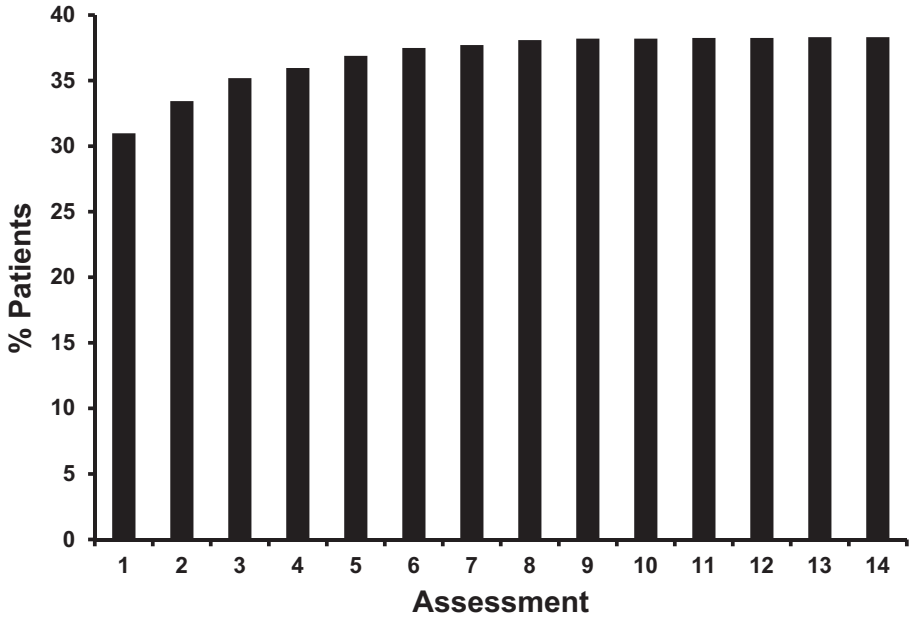
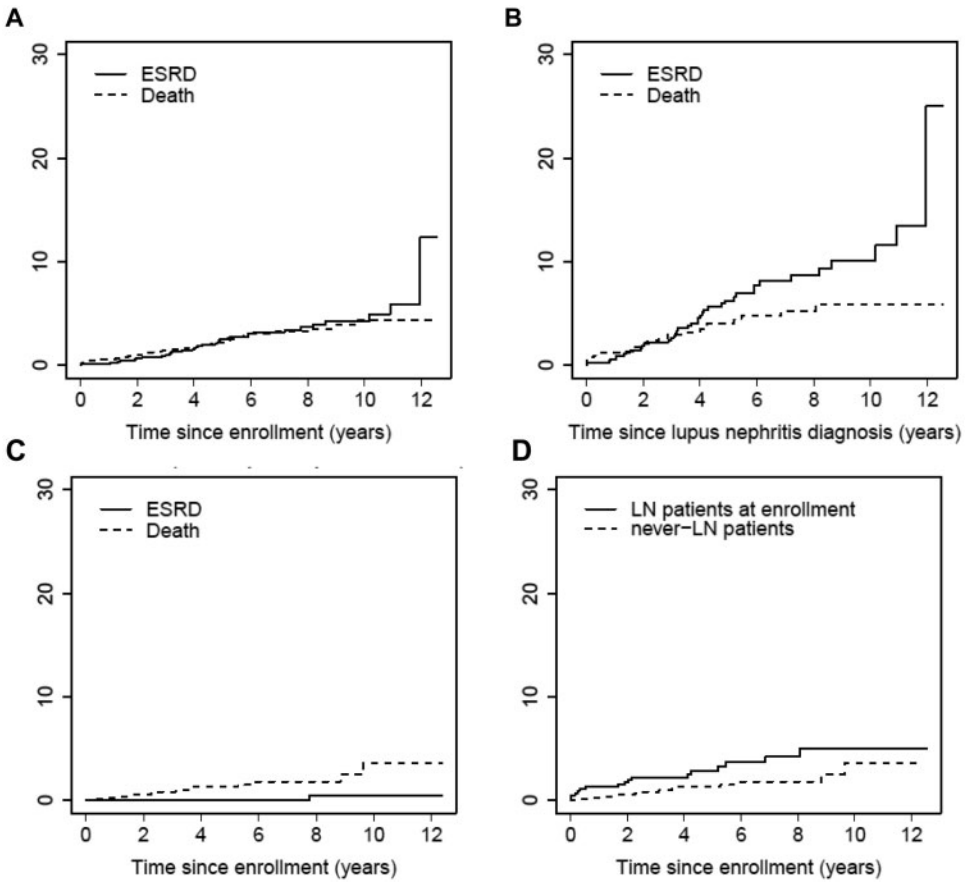


Fig. 2 Estimated cumulative incidence of end-stage renal disease and death



End-stage renal disease (all causes) in the total SLICC cohort (**A**) and in those with (**B**) and without (**C**) LN. The estimated cumulative incidence of death (all causes) for those with LN at enrolment and those who never developed nephritis (**D**). ESRD: end stage renal disease.

TABLE 2 The number (%) of patients in eGFR and ePrU states 1–3 and in 0–6 stages of chronic kidney disease at diagnosis of LN, 3 and 5 years later

	Diagnosis	3 years after diagnosis	5 years after diagnosis	*P*-value
eGFR, *n* (%)				0.443
State 1 (eGFR: >60 ml/min)	583 (86.6)	350 (85.2)	248 (87.6)	
State 2 (eGFR: 30–60 ml/min	70 (10.4)	44 (10.7)	20 (7.1)	
State 3 (eGFR: <30 ml/min)	20 (3.0)	17 (4.1)	15 (5.3)	
Total	673	411	283	
ePrU, *n* (%)				<0.001
State 1 (ePrU: <0.25 g/day)	252 (39.5)	252 (62.2)	173 (62.2)	
State 2 (ePrU: 0.25–3.0 g/day)	286 (44.8)	134 (33.1)	93 (33.5)	
State 3 (ePrU: >3.0 g/day)	100 (15.7)	19 (4.7)	12 (4.3)	
Total	638	405	278	
NKF classification of CKD, *n* (%)				0.147
Stage 0	451 (69.2)	301 (74.5)	196 (70.8)	
Stage 1	99 (15.2)	36 (8.9)	33 (11.9)	
Stage 2	60 (9.2)	34 (8.4)	26 (9.4)	
Stage 3	29 (4.5)	20 (5.0)	12 (4.3)	
Stage 4	4 (0.6)	4 (1.0)	1 (0.4)	
Stage 5	9 (1.4)	9 (2.2)	9 (3.3)	
Total	652	404	277	

Stage 0: no CKD; Stage 1: kidney damage with normal or increased eGFR ($\geqslant$90 ml/min/1.73 m^2); Stage 2: kidney damage with mild decrease in eGFR (60–89 ml/min/1.73 m^2); Stage 3: moderate decrease in eGFR (30–59 ml/min/1.73 m^2); Stage 4: severe decrease in eGFR (15–29 ml/min/1.73 m^2); Stage 5: kidney failure (<15 ml/min/1.73 m^2 or dialysis). The discrepancy between the number of patients in eGFR states and CKD classification stages is due to methodological differences for making these determinations: eGFR is measured at a specific time point, whereas CKD classification reflects a persistent abnormality in eGFR for $\geqslant$3 months and sometimes requires a determination of proteinuria or renal imaging. eGFR: estimated glomerular filtration rate; ePrU: estimated proteinuria; NKF: National Kidney Foundation; CKD: chronic kidney disease.

for curves in Fig. 2 are provided in a supplementary Table S1, available at *Rheumatology* Online. For patients with LN, the cumulative incidence of death at 10 years following the diagnosis of LN was 5.9% (95%CI: 3.3%, 8.4%) (Fig. 2b). Of the 39 patients who died, only 1 was due to ESRD. The others were attributed primarily to cardiorespiratory causes (18), infection (8), neurological disease (6), malignancy (2) and miscellaneous causes (4).

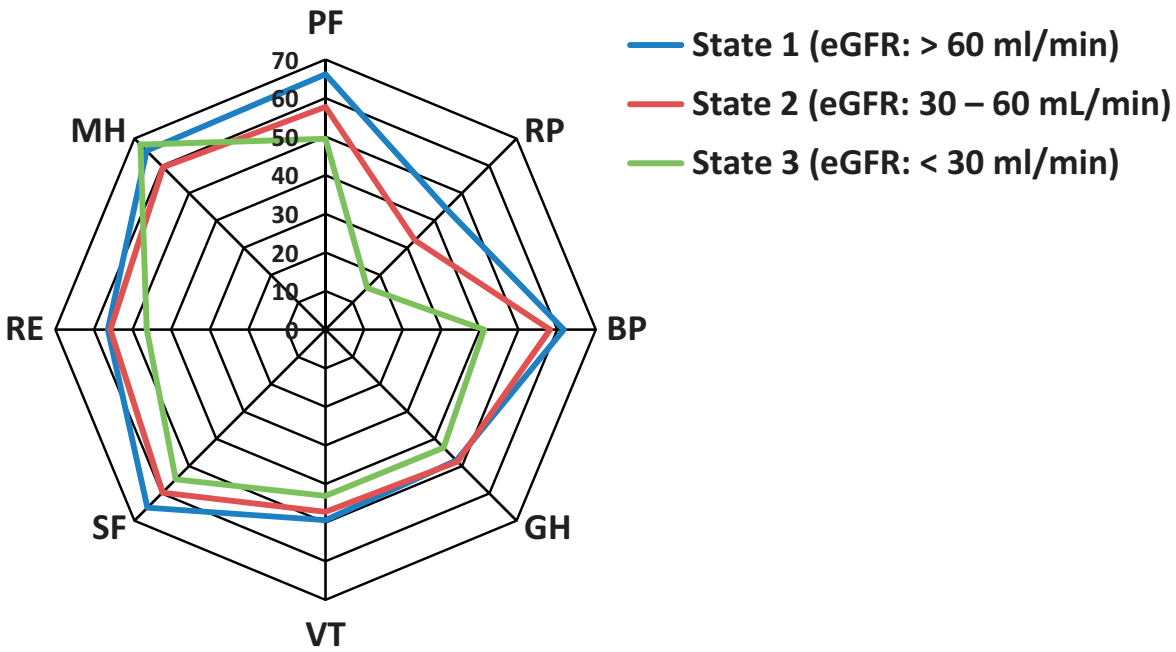
Additional analyses were performed in which the use of antimalarials at enrolment was added to the Cox regression analyses [details are provided in a supplementary Table S2, available at *Rheumatology* Online]. Controlling for gender, age at enrolment, race/ethnicity and the diagnosis of LN, antimalarial use at enrolment was not associated with the risk of ESRD (HR = 0.888, 95% CI: 0.473, 1.667; $P = 0.711$), but patients taking antimalarials at enrolment had longer survival [HR (for death) = 0.34, 95% CI: 0.15, 0.63; $P = 0.001$]. Controlling for gender, age at enrolment, antimalarial use at enrolment and at the diagnosis of LN, Hispanic patients had shorter survival than other races/ethnicities [HR (for death) = 2.60 (*vs* Caucasian), 95% CI: 1.12, 6.03]. We also examined the effect of ISN/RPS class on ESRD ($n = 16$) and death ($n = 8$). The global tests on the impact of all ISN/RPS classes on development of ESRD ($P = 0.35$) and survival ($P = 0.37$) were not statistically significant. However, univariate analyses revealed a statistically significant association between ISN/RPS Class IV LN (*vs* other ISN/RPS classes) and the development of ESRD (HR = 2.99, 95% CI: 1.04, 8.62; $P = 0.04$).

The number and proportion of patients in each of the three eGFR and ePrU states and CKD stage at LN diagnosis and at the third and fifth annual follow-up assessment after LN diagnosis is summarized in Table 2. There was no demonstrable change in the distribution of eGFR states, but there was a markedly lower frequency of ePrU state 3 over time ($P < 0.001$). There was no significant overall change in the proportion of patients with the six stages of CKD.

LN and HRQoL at enrolment and follow-up

SF-36 subscale and summary scores were not significantly lower in patients with LN at enrolment compared with the enrolment values for patients who never developed nephritis. However, the subscale scores for Bodily pain and Vitality scores were lower in non-LN patients (data not shown). Patients with LN and eGFR state 3 at diagnosis had significantly lower scores in three subscales (Physical function, Role physical and Bodily pain) (Fig. 3) and in the Physical component summary score of the SF-36 ($P < 0.01$). These findings were similar when adjustment was made for age at SLE diagnosis, gender, location, race/ethnicity, SLEDAI (without renal variables) and medication. No adjustment could be made for SDI

Fig. 3 Spidergram of SF-36 subscale scores at diagnosis of lupus nephritis in three eGFR states



PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; eGFR: estimated glomerular filtration rate.

scores due to the short disease duration at enrollment, which precluded determining an SDI score in many patients. For ePrU states at the same assessments, the Role physical scores were lower in ePrU state 3 [28.6 (40.5)] compared with ePrU state 1 [46.8 (42.7)] and state 2 [42.0 (42.8)] (unadjusted global $P = 0.008$ and $P = 0.08$ when adjusted for potential confounders).

Adjusting for years after LN diagnosis, there were statistically significant but relatively small declines in SF-36 physical component summary and mental component summary values for patients in eGFR or ePrU states 2 and 3 over time (Table 3). After adjustment for gender, age at SLE diagnosis, race/ethnicity, SLEDAI (without renal variables), medication and SLICC damage score (without renal variables), all but the relationship between physical component summary and ePrU states remained significant (Table 3). There was no statistical evidence for the dependence of these relationships on time.

Discussion

Since Merrell and Shulman [31] reported a 50% 4-year survival in the 1950s, renal and overall survival in patients with LN have steadily improved [32, 33]. This is attributed to multiple factors, including earlier diagnosis and access to health care, advances in therapy with immunosuppression, dialysis and transplantation and treatment of co-morbidities. However, other studies have suggested that ESRD and associated mortality have not changed over the past two decades [3, 4]. The current prospective, observational study reflects the outcome of LN in a large international multi-racial/ethnic disease inception cohort of SLE patients receiving standard of care for up to 12 years. Although the outcomes are generally favourable, the findings indicate room for further improvement.

The SLICC inception cohort, the largest of its kind, is well placed to address the objectives of the current study. The frequency of the initial manifestations of SLE, as reflected by individual ACR classification criteria [18], is comparable with that of another large cohort [34] and indicates a general lupus population without major selection bias. At presentation, patients had moderate global SLE disease activity and mild organ damage. The cumulative frequency of nephritis of 38.3% in our cohort is very similar to the overall incidence of 37.8% in 2290 SLE patients enrolled in studies from North America, Europe and the Middle East [1]. The predilection for nephritis to present around the time of diagnosis of SLE has also been noted in another previous large observation study [35]. Other features such as a higher frequency of nephritis at a younger age [36, 37], in men [35, 38] and in patients of non-Caucasian race/ethnicity [35–37, 39], and a higher frequency of co-morbidities such as hypertension [40, 41] provide further evidence for the validity of the cohort and generalizability of the findings. More frequent use of corticosteroids and immunosuppressive agents with nephritis is to be expected and is in line with current treatment guidelines [15, 16].

The outcome of LN has frequently been determined by total and renal survival, changes in renal function and achievement of partial or complete remission, albeit variably defined. In the current study, we also selected the

TABLE 3 Univariate and multivariate regression analysis for SF-36 summary scores over time following the diagnosis of LN

Parameter	MCS Estimate (95% CI)	*P*-value	PCS Estimate (95% CI)	*P*-value
Univariate regression for eGFR states				
Intercept	47.84 (47.06 to 48.62)		43.24 (42.47 to 44.01)	
eGFR state 3	−0.91 (−3.76 to 1.93)	0.019	−4.19 (−7.09 to −1.28)	0.010
eGFR state 2	−2.53 (−4.17 to −0.89)		−1.58 (−2.99 to −0.16)	
eGFR state 1	0		0	
Univariate regression for ePrU states				
Intercept	48.21 (47.37 to 49.05)		43.51 (42.63 to 44.38)	
ePrU state 3	−2.56 (−4.25 to −0.86)	0.004	−3.12 (−4.69 to −1.56)	0.004
ePrU state 2	−1.10 (−1.99 to −0.22)		−0.90 (−1.74 to −0.06)	
ePrU state 1	0		0	
Multiple regression for eGFR and ePrU states				
Intercept	47.70 (44.68 to 50.73)		49.21 (46.01 to 52.40)	
Gender	2.47 (0.46 to 4.47)	0.020	2.78 (0.75 to 4.81)	0.010
Age at Dx for SLE	−0.01 (−0.07 to 0.05)	0.724	−0.17 (−0.24 to −0.10)	<.001
Race/ethnicity		0.011		<.001
Other	0.94 (−2.67 to 4.55)		0.04 (−3.87 to 3.95)	
African	0.41 (−1.88 to 2.70)		−1.48 (−3.79 to 0.82)	
Asian	2.76 (0.55 to 4.96)		3.53 (1.43 to 5.63)	
Hispanic	3.42 (1.27 to 5.57)		4.95 (2.92 to 6.98)	
Caucasian	0		0	
SLEDAI w/o renal	−0.19 (−0.36 to −0.02)	0.036	−0.34 (−0.51 to −0.17)	<.001
SDI w/o renal		0.911		<.001
⩾4	−0.78 (−4.62 to 3.07)		−4.90 (−7.84 to −1.96)	
3	−0.32 (−2.91 to 2.28)		−3.97 (−6.47 to −1.47)	
2	0.66 (−1.10 to 2.43)		−3.00 (−4.60 to −1.41)	
1	0.24 (−1.33 to 1.82)		−1.59 (−3.08 to −0.10)	
0	0		0	
Antimalarials	−0.82 (−1.97 to 0.33)	0.165	0.20 (−0.82 to 1.22)	0.703
Immunosuppressants	−0.19 (−1.37 to 0.99)	0.750	0.19 (−0.81 to 1.19)	0.713
Corticosteroids	−0.72 (−1.97 to 0.54)	0.266	−1.97 (−3.18 to −0.75)	0.002
Years since LN	0.30 (0.09 to 0.51)	0.006	0.33 (0.14 to 0.51)	<.001
eGFR state 3	−1.74 (−4.75 to 1.27)	0.008	−3.70 (−6.58 to −0.83)	0.060
eGFR state 2	−2.88 (−4.55 to −1.21)		−0.71 (−2.31 to 0.89)	
eGFR state 1	0		0	
ePrU state 3	−2.65 (−4.54 to −0.76)	0.020	−1.33 (−3.02 to 0.36)	0.302
ePrU state 2	−0.56 (−1.50 to 0.38)		−0.21 (−1.01 to 0.60)	
ePrU state 1	0		0	

MCS: mental component summary score of SF-36; PCS: physical component summary score of SF-36; eGFR: estimated glomerular filtration rate; ePrU: estimated proteinuria; Dx: diagnosis; w/o: without.

hard end-points of total and renal survival, the more frequent and more sensitive outcome of clinically meaningful defined states for renal function and ePrU, and the association with the less tangible but quantifiable outcome of HRQoL.

In a European multicentre study of 1000 prevalent SLE patients [34], 97.1% of whom were white and followed between 1990 and 2000, the overall 10-year survival was 92%. In the 279 (27.9%) patients who presented with nephritis at onset of the study, the 10-year survival was 88%, compared with 94% in patients without nephropathy. In the current study the estimated 10-year survival in the entire cohort and in patients with and without nephritis was 95.7, 94.5 and 96%, respectively. Although this may represent improvement in the outcome of LN, a more likely explanation is the inherent difference between a prevalent and an inception cohort. For example, the mean disease duration at enrolment into the European [42] and SLICC cohorts was 6 years and 6 months, respectively, and longer disease duration is an independent risk for mortality. In both studies, death was attributed to multiple causes and followed ESRD in only 1/40 (2.5%) patients in our study.

The frequency of ESRD, as defined by haemodialysis or renal transplantation, in the European multicentre study [34] between 1990 and 2000 was 37/1000 (3.7%). Two recent registry and population health studies in the USA [36, 37], involving 1156 and 2278 prevalent SLE patients over 3 years (2002–04), reported an overall frequency of ESRD of 6.7–13.3%, depending upon the case definition

for ESRD. In both studies, there was a strikingly higher frequency of LN and ESRD in African Americans, who were also the major racial/ethnic group. In the current study, the cumulative incidence of ESRD (as defined by stage 5 of the NKF classification of CKD) at 5 years was 3.3% and at 10 years following enrolment was 4.3% (as defined in the SDI). Despite methodological differences in study design, it is clear that ESRD and increased mortality persist with current treatment modalities for LN.

The changes in the transition of ePrU states over 3 and 5 years indicate responsiveness to therapy for ePrU over this time frame. Renal function, reflected by different eGFR states and the CKD classification, did not change appreciably. Small changes over time in the eGFR state distribution cannot be excluded, due to the limited duration of follow-up, but these findings do suggest that some patients with LN do not respond, in terms of a marked improvement in renal function, to current treatment modalities, either due to inefficacy, non-adherence or toxicity necessitating discontinuation of medication.

Relatively few studies have examined HRQoL as a primary outcome in patients with LN. Three studies [43–45] have found that those undergoing treatment for severe LN have clinically relevant changes in HRQoL up to 1 year after the commencement of treatment, as quantified by SF-36 scores. In the current study, HRQoL summary scores were not lower for patients with nephritis at enrolment when compared with patients who never developed nephritis. However, patients with the most severe nephritis, as indicated by higher eGFR and ePrU states, had lower SF-36 subscale and summary scores. This association with lower HRQoL was found in both cross-sectional and longitudinal analyses, even after adjusting for multiple potential confounders. Thus, stratification of patients by severity of LN reveals significant associations with HRQoL.

There are a number of limitations to the current study. First treatment decisions were made on the basis of the physician's recommendation and patient preference rather than study protocol. However, this reflects what occurs in clinical practice and is a strength of the study. Second, the SLICC network is based within academic medical centres with a special interest in lupus, and our data may not fully reflect community clinical practice. Third, the frequency of renal biopsy was lower than expected. Recent guidelines [15, 16] encourage performing renal biopsy in all SLE patients with possible renal disease. This permits confirmation of the diagnosis, characterization of glomerular disease and a determination of overall disease activity and renal scaring, all of which inform treatment. Despite these advantages, previous observational cohort studies have indicated a highly variable biopsy rate in 36.8% of 266 [46], 55% of 438 [47], 77% of 26 [48] and 96% of 127 [49] patients with a clinical diagnosis of LN. The reasons for not doing a renal biopsy on patients in our cohort were multiple and included medical contraindication, lack of access due to under-insurance in a fee-for-service system, patient refusal and a low likelihood of influencing the treatment plan, due to other major organ involvement. Finally, our study was based upon a disease inception cohort, and thus the disease duration was shorter and age at enrolment younger than what is seen in prevalent cohorts of lupus cases. As both factors are associated with chronic kidney disease, further follow-up is necessary to determine the long-term outcome of LN in this cohort.

Despite these limitations, the study provides useful information on the frequency, characteristics and expectations for outcome in patients with LN receiving current standard of care. Most of the findings are applicable to SLE patients in general and set the benchmark for planning future clinical trials of novel therapeutic agents and protocols.

Acknowledgements

The Hopkins Lupus Cohort is supported by the National Institutes of Health (grant AR43727).

Funding: The SLICC research network received funding for this study from Bristol-Myers Squibb.

Disclosure statement: I.N.B. holds grants from UCB, Sanofi/Genzyme, Roche and Glaxo Smith Kline and honoraria/speakers bureaus from UCB, Glaxo Smith Kline, Roche, Pfizer and Medimmune outside of the submitted work. R.F.vV. has received research support and grants from AbbVie, BMS, GSK, Pfizer, Roche, UCB; and has received consultancy honoraria from AbbVie, Biotest, BMS, Crescendo, GSK, Janssen, Lilly, Merck, Pfizer, Roche, UCB and Vertex. P.F. has participated on Lupus Advisory Boards for Eli Lilly, AbbVie and GSK. E.M.G. has received clinical trial grant support from GlaxoSmithKline and Aurinia Pharmaceuticals. All other authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

References

1 Rovin BH, Stillman I. Kidney. In: Lahita R, ed. Systemic Lupus Erythematosus, 5th ed. San Diego, CA, USA: Academic Press, 2011: 769–814.

2 Dooley MA. Clinical and epidemiologic features of lupus nephritis. In: Wallace DJ, Hahn BH, eds. Dubois' Lupus Erythematosus and related syndromes. Philadelphia, PA, USA: Elsevier Saunders, 2013: 438–54.

3 Costenbader KH, Desai A, Alarcon GS *et al*. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. Arthritis Rheum 2011;63:1681–8.

4 Croca SC, Rodrigues T, Isenberg DA. Assessment of a lupus nephritis cohort over a 30-year period. Rheumatology 2011;50:1424–30.

5 Houssiau F, Vasconcelos C, D'Cruz D *et al*. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose

versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.

6 Houssiau FA, Vasconcelos C, D'Cruz D *et al*. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2010;69:61–4.

7 Appel GB, Contreras G, Dooley MA *et al*. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103–12.

8 Chan TM, Li FK, Tang CS *et al*. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156–62.

9 Ginzler EM, Dooley MA, Aranow C *et al*. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005;353:2219–28.

10 Chan TM, Tse KC, Tang CS, Mok MY, Li FK, Hong Kong Nephrology Study Group. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005;16:1076–84.

11 Dooley MA, Jayne D, Ginzler EM *et al*. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886–95.

12 Jonsdottir T, Gunnarsson I, Mourao AF *et al*. Clinical improvements in proliferative vs membranous lupus nephritis following B-cell depletion: pooled data from two cohorts. Rheumatology 2010;49:1502–4.

13 Terrier B, Amoura Z, Ravaud P *et al*. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum 2010;62:2458–66.

14 Rovin BH, Furie R, Latinis K *et al*. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum 2012;64:1215–26.

15 Hahn BH, McMahon MA, Wilkinson A *et al*. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res 2012;64:797–808.

16 Bertsias GK, Tektonidou M, Amoura Z *et al*. Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771–82.

17 Isenberg D, Ramsey-Goldman R. Systemic Lupus International Collaborating Group—onwards and upwards? Lupus 2006;15:606–7.

18 Tan E, Cohen A, Fries J *et al*. The 1982 Revised Criteria for the Classification of Systemic Lupus Erythematosus. Arthritis Rheum 1982;25:1271–7.

19 Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992;35:630–40.

20 Gladman D, Ginzler E, Goldsmith C *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.

21 Hanly JG. Disease activity, cumulative damage and quality of life in systematic lupus erythematosus: results of a cross-sectional study. Lupus 1997;6:243–7.

22 Hochberg MC. Updating the American College of Rheumatology criteria for the classification of Systemic Lupus Erythematosus. Arthritis Rheum 1997;40:1725.

23 Weening J, D'Agati V, Schwartz M *et al*. The classification of glomerulonephritis in systemic lupus nephritis erythematosus revisited. J Am Soc Nephrol 2004;15:241–50.

24 Austin HA III, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney Int 1984;25:689–95.

25 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1–266.

26 Patel SB, Korbet SM, Lewis EJ. The prognosis of severe lupus nephritis based on the Modification of Diet in Renal Disease (MDRD) study estimated glomerular filtration rate. Lupus 2011;20:256–64.

27 Christopher-Stine L, Petri M, Astor BC, Fine D. Urine protein-to-creatinine ratio is a reliable measure of proteinuria in lupus nephritis. J Rheumatol 2004;31:1557–9.

28 Matar HE, Peterson P, Sangle S, D'Cruz DP. Correlation of 24-hour urinary protein quantification with spot urine protein:creatinine ratio in lupus nephritis. Lupus 2012;21:836–9.

29 Gladman D, Ginzler E, Goldsmith C *et al*. The development and initial validation of the Systemic Lupus Eythematosus Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.

30 Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data, 2nd edn. New York: Wiley, 2002.

31 Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. J Chronic Dis 1955;1:12–32.

32 Urowitz MB, Gladman DD, Tom BD, Ibanez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. J Rheumatol 2008;35:2152–8.

33 Bernatsky S, Boivin JF, Joseph L *et al*. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54:2550–7.

34 Cervera R, Khamashta MA, Font J *et al*. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine 2003;82:299–308.

35 Cooper GS, Parks CG, Treadwell EL *et al*. Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. Lupus 2002;11:161–7.

36 Lim SS, Bayakly AR, Helmick CG *et al*. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: the Georgia Lupus Registry. Arthritis Rheumatol 2014;66:357–68.

37 Somers EC, Marder W, Cagnoli P *et al*. Population-based incidence and prevalence of systemic lupus

erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol 2014;66:369–78.

38 Jacobsen S, Petersen J, Ullman S *et al*. A multicentre study of 513 Danish patients with systemic lupus erythematosus. I. Disease manifestations and analyses of clinical subsets. Clin Rheumatol 1998;17:468–77.

39 Alarcon GS, McGwin G Jr, Petri M *et al*. Baseline characteristics of a multiethnic lupus cohort: PROFILE. Lupus 2002;11:95–101.

40 Naiker IP, Chrystal V, Randeree IG, Seedat YK. The significance of arterial hypertension at the onset of clinical lupus nephritis. Postgrad Med J 1997;73:230–3.

41 Ward MM, Studenski S. Clinical prognostic factors in lupus nephritis. The importance of hypertension and smoking. Arch Intern Med 1992;152:2082–8.

42 Cervera R, Khamashta MA, Font J *et al*. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine 1993;72:113–24.

43 Daleboudt GM, Berger SP, Broadbent E, Kaptein AA. Health-related quality of life in patients with systemic lupus erythematosus and proliferative lupus nephritis. Psychol Health Med 2011;16:393–404.

44 Grootscholten C, Snoek FJ, Bijl M *et al*. Health-related quality of life and treatment burden in patients with proliferative lupus nephritis treated with cyclophosphamide or azathioprine/ methylprednisolone in a randomized controlled trial. J Rheumatol 2007;34:1699–707.

45 Tse KC, Tang CS, Lio WI, Lam MF, Chan TM. Quality of life comparison between corticosteroid- and-mycofenolate mofetil and corticosteroid- and-oral cyclophosphamide in the treatment of severe lupus nephritis. Lupus 2006;15:371–9.

46 Reich HN, Gladman DD, Urowitz MB *et al*. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. Kidney Int 2011;79:914–20.

47 Alarcon GS, McGwin G Jr, Petri M *et al*. Time to renal disease and end-stage renal disease in PROFILE: a multiethnic lupus cohort. PLoS Med 2006;3:e396.

48 Nossent HC, Koldingsnes W. Long-term efficacy of azathioprine treatment for proliferative lupus nephritis. Rheumatology 2000;39:969–74.

49 Adler M, Chambers S, Edwards C, Neild G, Isenberg D. An assessment of renal failure in an SLE cohort with special reference to ethnicity, over a 25-year period. Rheumatology 2006;45:1144–7.