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The Frequency and Outcome of Lupus Nephritis
Results from an international, inception, cohort study

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Abstract *(word count: 250)*

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 (ePrU) and end stage renal disease (ESRD). Health related quality of life (HRQoL) was measured by SF-36 subscale, mental (MCS) and physical (PCS) component summary scores.

Results: There were 1,827 patients, 89% females, mean±SD age 35.1±13.3 years. The mean±SD SLE duration at enrollment was 0.5±0.3 years and follow-up 4.6±3.4 years. Lupus nephritis occurred in 700 (38.3%) patients: 566/700 (80.9%) at enrollment 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 PCS scores ($p<0.01$) and lower Physical function, Physical role and Bodily pain scores. Over time, patients with abnormal eGFR and ePrU had lower SF-36 MCS ($p \leq 0.02$) scores compared to patients with normal values.

Conclusions: Lupus nephritis 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 HRQoL. Further advances are required for the optimal treatment of lupus nephritis.

Renal disease affects 38% of patients with systemic lupus erythematosus (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 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. Intravenous cyclophosphamide (8, 9) and oral mycophenolate mofetil are effective for induction (10-12) or maintenance therapy (13, 14). Open label studies of targeted B cell depletion therapies have been positive (15, 16), although unconfirmed in controlled studies (17). These immunomodulatory strategies and treatment of co-morbidities have been incorporated into recent treatment guidelines (18, 19). 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), end stage renal disease (ESRD) and death in patients with lupus nephritis 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 (20). Data were collected per protocol at enrollment and annually (± 6 months) thereafter, and entered into a centralized database. Each of the participating center's institutional research ethics review boards approved the study.

Patients: Patients fulfilled the American College of Rheumatology (ACR) classification criteria for SLE (21) and provided written informed consent. Enrollment occurred up to 15 months following the diagnosis. Demographic variables included age, gender, ethnicity and education. Medication history and lupus-related variables, such as the SLE Disease Activity Index-2000 (SLEDAI-2K) (22) and SLICC/ACR damage index (SDI), were also recorded (23). Laboratory testing included hematology, chemistry and immunology required for SLEDAI-2K and SDI scores. Patient self-report HRQoL was measured by the subscale and summary scores of the SF-36 (24).

Lupus nephritis: Nephritis was identified by the "renal disorder" variable of the ACR classification criteria (21) (25) and/or biopsy evidence of nephritis as per the International Society of Nephrology and Renal Pathology Society (ISN/RPS) criteria (26).

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 (26) and activity/chronicity scores of Austin (27) were derived from renal biopsy reports. The National Kidney Foundation (NKF) classification of chronic kidney disease (CKD) (28) and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation (29) were determined at each assessment. Estimated proteinuria (ePrU) was measured by either 24 hour urine collection or spot urine total protein to creatinine ratio (30, 31). ESRD was determined from the SDI renal variable (32).

At each assessment, patients were assigned to one of three GFR and Proteinuria (PrU) 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 gr/day); state 2 (ePrU: 0.25 – 3.0 gr/day); and state 3 (ePrU: > 3.0 gr/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 (33). A Cox regression with a time-varying covariate was also used to examine the effect of lupus nephritis diagnosis on the competing risks of ESRD and death. Analyses of HRQoL outcomes at enrollment or at LN diagnosis 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% confidence intervals were calculated.

Results

Patients: 1,827 patients were recruited between October 1999 and December 2012, from SLICC centers in the United States (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%)). Eighty-nine percent were female and at enrollment the mean±SD age of the cohort was 35.1±13.3 years with a varied ethnic/racial mix although predominantly Caucasian (Table 1).

At enrollment the mean±SD disease duration was 0.5±0.3 years and patients had low SLEDAI-2K and SDI scores whilst 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 followup 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 lupus nephritis: Lupus nephritis occurred in 700 (38.3%) patients: 566/700 (80.9%) at the enrollment visit and 134/700 (19.1%) during follow-up (Figure 1). Renal biopsies were performed on 395/700 (56.4%) patients, the majority (86.6%) when nephritis was first suspected and in 377/395 (95.4%) were of sufficient quality to identify ISN 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), 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 the 377 biopsies, the mean ± SD activity index was 4.3±3.3 and the mean ± SD 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 by renal biopsy only had the following ISN/RSP 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 2 and 1 biopsies with class III/V and IV/V respectively. Of the 134 patients who were diagnosed with lupus nephritis subsequent to the enrollment visit there were 128/134 (94.8%) who had renal disorder. The 6 patients diagnosed by renal biopsy only had the following ISN/RSP classes: I: 1 II: 1 III: 1, IV: 3, V: 0 and VI: 0.

Patients with lupus nephritis at enrollment 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 (21) for serositis, neurological, 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 lupus nephritis. Corticosteroids and immunosuppressive drugs were used more frequently and antimalarials less frequently (49.1%) in the nephritis group at enrollment although antimalarial use increased to 72% over the study. Hypertension was more frequent in patients with nephritis.

Nine-six (5.3%) of 1,827 patients at the enrollment visit were ANA negative. There were no statistically significant differences in ACR classification criteria between ANA positive and 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 enrollment became ANA positive during the study.

Outcome of lupus nephritis: Adjusting for gender, age at enrollment 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 lupus nephritis, 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 enrollment was 4.3% (95%CI: 2.8%, 5.8%) (Figure 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%) (Figure 2b). Excluding patients who ever developed LN, the estimated cumulative incidence of ESRD was 0.5% (95%CI: 0%, 1.4%) (Figure 2c), albeit that this is an ad-hoc analysis because some patients are excluded on the basis of developing LN following the enrollment visit.

The estimated cumulative incidence of death from all causes for the entire cohort at 10 years after enrollment was 4.4% (95%CI: 2.7%, 6.1%) (Figure 2a). Patients with LN at enrollment and those who never developed LN had a cumulative incidence of death at 10 years of 5.0% (95%CI:2.3%,7.6%) (Figure 2d) and 3.6% (95%CI:0.9%,6.2%) (Figure 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 for curves in Figure 2 are provided in a supplementary file (#1). 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%) (Figure 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 file (#2)]. Controlling for gender, age at enrollment, race/ethnicity and the diagnosis of LN, antimalarial use at enrollment 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 enrollment had longer survival (HR(for death)=0.34, 95%CI=[0.15,0.63], p=0.001). Controlling for gender, age at enrollment, 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 class on ESRD (n=16) and death (n=8). The global tests on the impact of all ISN 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 Class IV LN (vs. other ISN 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 6 stages of CKD.

Lupus nephritis and HRQoL at enrollment and followup: SF-36 subscale and summary scores were not significantly lower in patients with lupus nephritis at enrollment compared to the enrollment 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 lupus nephritis and eGFR state 3 at diagnosis had significantly lower scores

in three subscales (Physical function, Role physical and Bodily pain) (Figure 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. SDI scores could not be adjusted for 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 to 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 PCS and MCS values for patients in eGFR or ePrU states 2 and 3 over time (Table 3). After adjustment for gender, age at SLE diagnosis, ethnicity, SLEDAI (without renal variables), medication and SLICC damage score (without renal variables), all but the relationship between PCS and ePrU states remained significant (Table 3). There was no statistical evidence of the dependence of these relationships on time.

Discussion

Since Merrell and Shulman reported a 50% 4-year survival in the 1950's (34) renal and overall survival in patients with lupus nephritis have steadily improved (5, 35, 36). 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 2 decades (3, 4). The current prospective, observational study reflects the outcome of lupus nephritis in a large, multi-ethnic, international, 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 (21) is comparable to another large cohort (37) 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 2,290 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 (38). Other features such as a higher frequency of nephritis at a younger age (39, 40), in men (38, 41) and in patients of non-Caucasian race/ethnicity (38-40, 42) and a higher frequency of co-morbidities such as hypertension (43, 44) 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 (18, 19).

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

In a European multi-center study of 1,000 prevalent SLE patients (37), 97.1% of whom were white and followed between 1990-2000, 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 to 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 lupus nephritis, a more likely explanation is the inherent difference between a prevalent and inception cohort. For example, the mean disease duration at enrollment into the European (45) 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 hemodialysis or renal transplantation, in the European multi-center study (37) between 1990 and 2000 was 37/1,000 (3.7%). Two recent registry and population health studies in the US (39, 40) involving 1,156 and 2,278 prevalent SLE patients over 3 years (2002-2004) reported an overall frequency of ESRD of 6.7% to 13.3% depending upon the case definition for ESRD. In both studies, there was a strikingly higher frequency of lupus nephritis and ESRD in African Americans who were also the major ethnic/racial 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 enrollment 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 lupus nephritis.

The changes in the transition of ePrU states over 3 and 5 years indicate responsiveness to therapy for proteinuria 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 lupus nephritis 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 lupus nephritis. Three studies (46-48) have found that those undergoing treatment for severe lupus nephritis have clinically relevant changes in HRQoL up to one 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 enrollment when compared to 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 lupus nephritis 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, which is a strength of the study. Second, the SLICC network is based within academic medical centers 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 (18, 19) 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 (49), 55% of 438 (50), 77% of 26 (51), and 96% of 127 (52) patients with a clinical diagnosis of lupus

nephritis**.** 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 enrollment younger than what is seen in cohorts of prevalent lupus cases. As both factors are associated with chronic kidney disease, further follow-up is necessary to determine the long-term outcome of lupus nephritis in this cohort.

Despite these limitations the study provides useful information on the frequency, characteristics, and expectations for outcome in patients with lupus nephritis 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.

Word count (Introduction to end of Discussion): 3,422

Key Messages:

- Despite current standard of care and advances over the past decade, lupus nephritis is still associated with a substantial risk of end-stage renal disease (ESRD) and death.
- Additional strategies are required to achieve better outcomes for this common and serious manifestation of SLE

Conflict of interest:

The authors declare no conflicts of interest.

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Table 1: Demographic and clinical manifestations of SLE patients at enrollment

	LN Patients	Non-LN Patients	P value	All Patients
No .of patients:	566	1261		1827
Age (years): (Mean ± SD)	31.3± 11.9	36.9 ±13.6	<0.001	35.1±13.3
Gender (%): Female	477(84.3)	1149(91.1)	<0.001	1626(89.0)
Male	89(15.7)	112(8.9)		201(11.0)
Race/Ethnicity (%): 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 (years)				
(Mean ± SD)	0.5±0.3	0.5±0.4	0.353	0.5±0.3
ACR Classification Criteria (%)				
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)
Hematologic 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)
Antinuclear Antibody	526(92.9)	1205(95.6)	0.027	1731(94.7)
SLEDAI (Mean ± SD)	8.5±6.7	4.0±4.0	<0.001	5.4±5.4
SLEDAI (without renal)	3.6±3.8	3.8±3.7	0.393	3.7±3.7
SDI score (Mean ± SD)	0.5±0.9	0.2±0.6	<0.001	0.3±0.7
SDI score (without renal)	0.4±0.7	0.2±0.6	0.008	0.3±0.7
Medications (%):				
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)
Comorbidities/Lifestyle				
Diabetes (%)	27(4.8)	37(3.0)	0.070	64(3.5)
Hypertension (%)	330(58.3)	205(16.3)	<0.001	535(29.3)
Current Smoker (%)	63(11.2)	210(16.7)	0.003	273(15.0)
Alcohol (Mean ± SD)	0.6±1.9	1.2±3.4	<0.001	1.0±3.0
BMI (Mean ± SD)	25.0±5.9	25.4±5.9	0.129	25.3±5.9
Duration of Follow-up				

(years: Mean ±SD)	5.0±3.6	4.5±3.3	0.008	4.6±3.4

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 lupus nephritis, 3 and 5 years later

	Diagnosis	3 years after diagnosis	5 years after diagnosis	P value
GFR				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	
PrU				<0.001
State 1 (ePrU**: < 0.25 gr/day)	252(39.5)	252(62.2)	173(62.2)	
State 2 (ePrU: 0.25 – 3.0 gr/day)	286(44.8)	134(33.1)	93(33.5)	
State 3 (ePrU: > 3.0 gr/day)	100(15.7)	19(4.7)	12(4.3)	
Total	638	405	278	
NKF classification of CKD* **				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	

***eGFR:** estimated glomerular filtration rate ****ePrU:** estimated protein excretion

***** **NKF classification of CKD:** National Kidney Foundation of chronic kidney disease
Stage 0: no CKD;
Stage 1: kidney damage with normal or increased GFR (≥90 ml/min/1.73m^2)
Stage 2: kidney damage with mild decrease in GFR (60-89 ml/min/1.73m^2)
Stage 3: moderate decrease in GFR (30-59 ml/min/1.73m^2)
Stage 4: severe decrease in GFR (15-29 ml/min/1.73m^2)
Stage 5: kidney failure (<15 ml/min/1.73m^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 ≥ 3 months and sometimes requires a determination of proteinuria or renal imaging.

Table 3: Univariate (A and B) and multivariate (C) regression analysis for SF-36 summary scores over time following the diagnosis of lupus nephritis

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

Legends for figures:

Figure 1: Onset of lupus nephritis following enrollment into the SLICC cohort

Figure 2: Estimated cumulative incidence of end-stage renal disease (ESRD) and death (all causes) in the total SLICC cohort (2a) and in those with (2b) and without (2c) lupus nephritis; estimated cumulative incidence of death (all causes) for those with lupus nephritis at enrollment and those who never developed nephritis (2d).

Figure 3: Spidergram illustrating the difference in eight SF-36 subscale scores in patients at the time of 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)

Figure 1

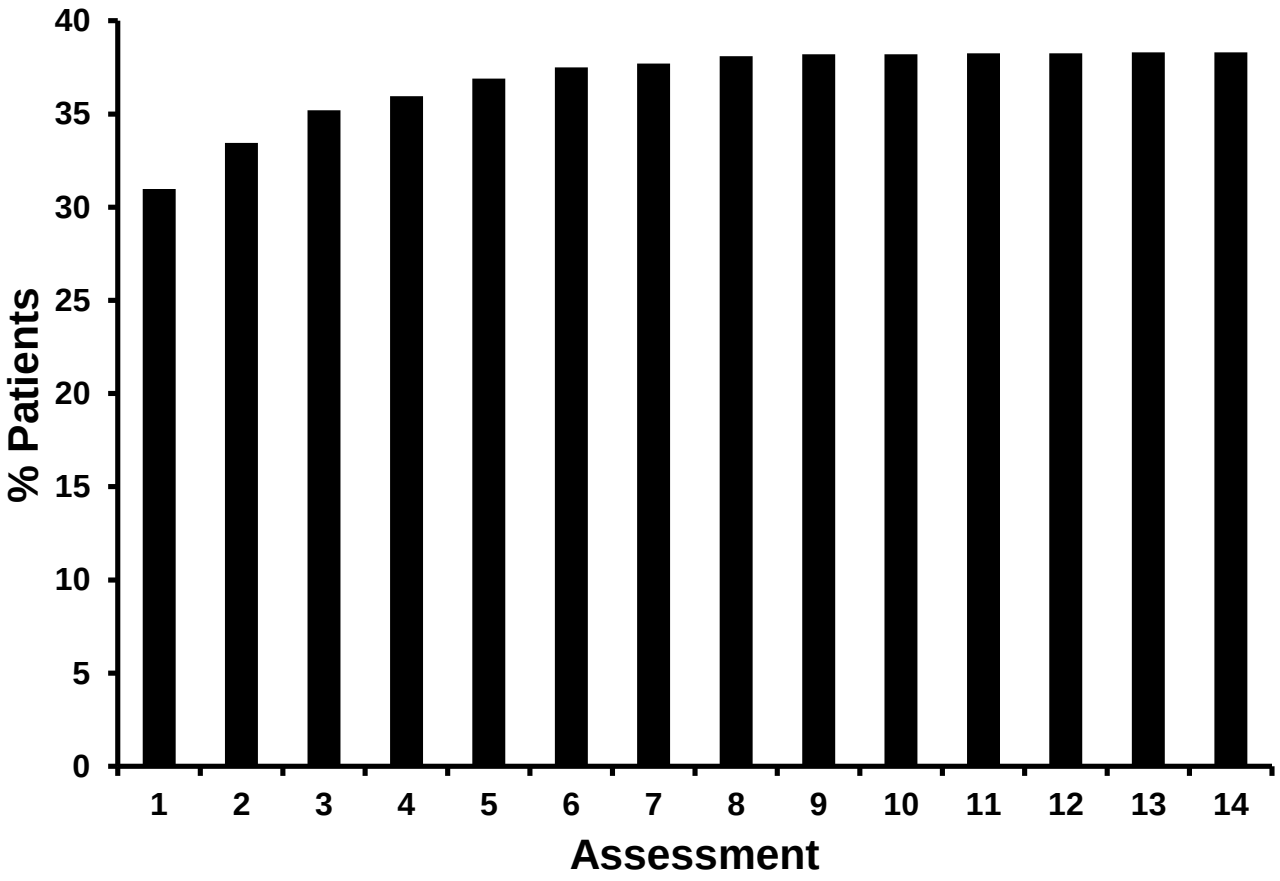


Figure 2:

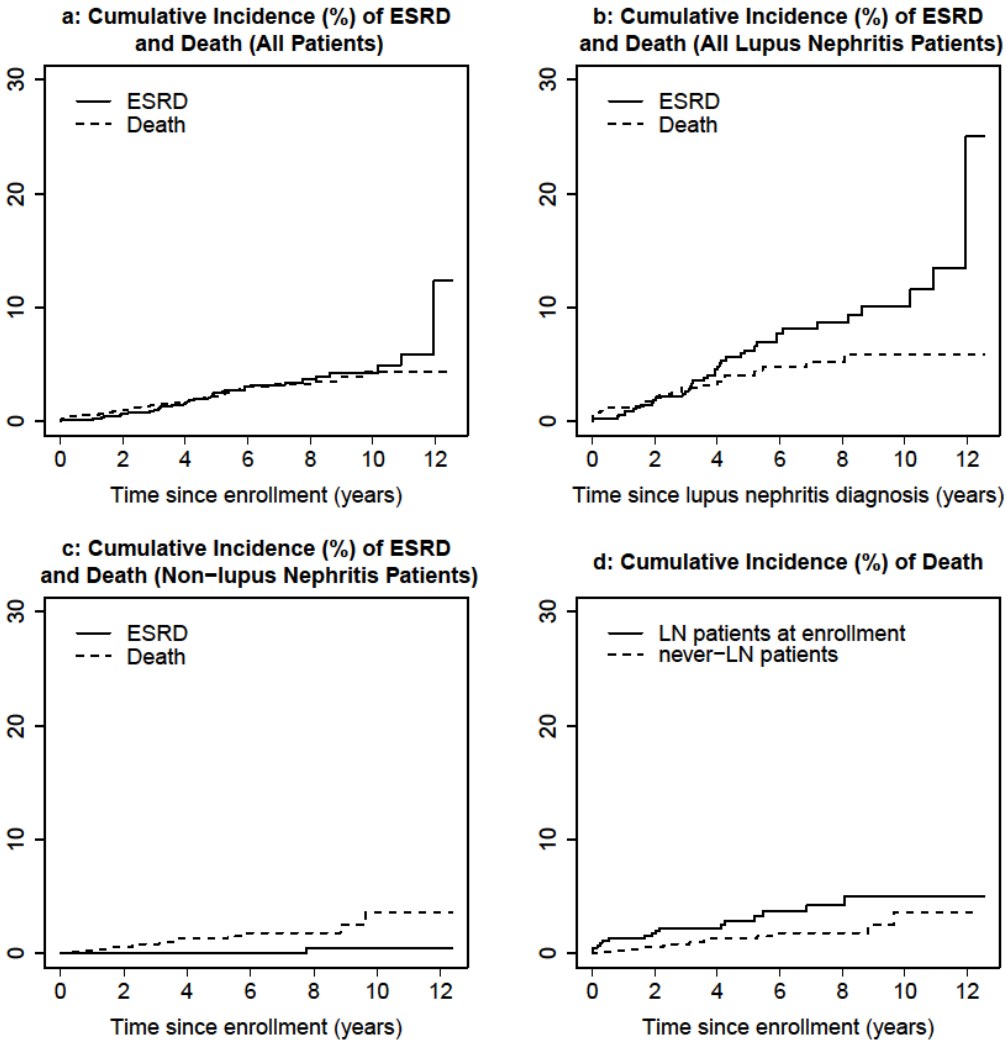
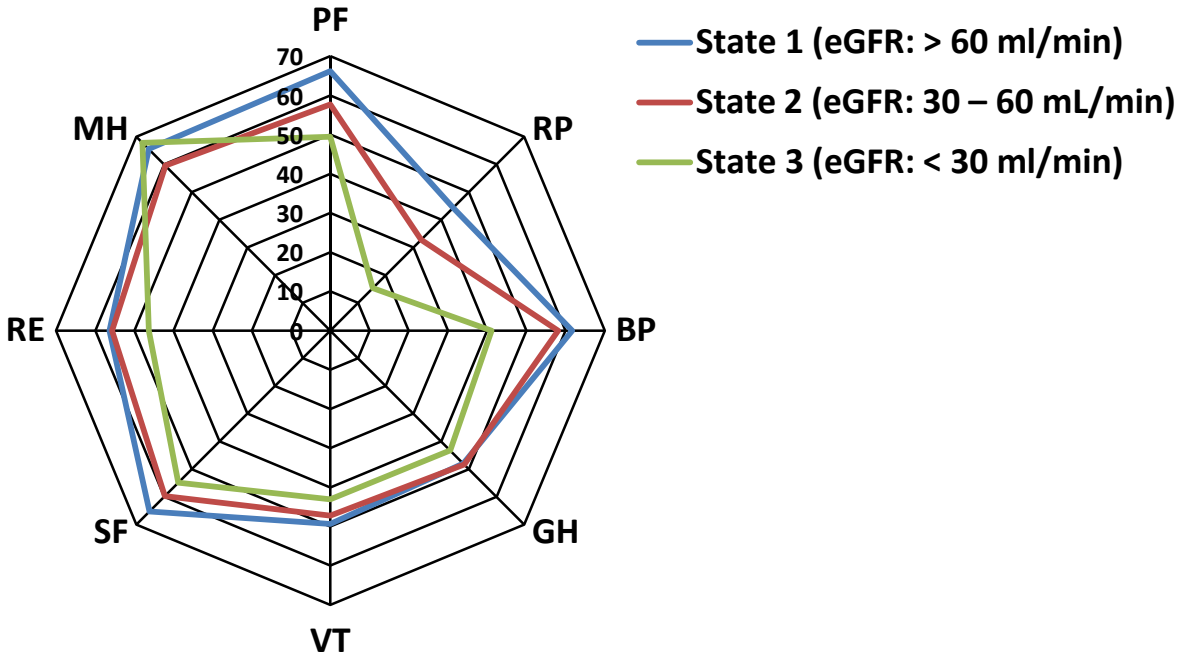

a: Cumulative Incidence (%) of ESRD and Death (All Patients)
ESRD
Death
Time since enrollment (years)
b: Cumulative Incidence (%) of ESRD and Death (All Lupus Nephritis Patients)
ESRD
Death
Time since lupus nephritis diagnosis (years)
c: Cumulative Incidence (%) of ESRD and Death (Non−lupus Nephritis Patients)
ESRD
Death
Time since enrollment (years)
d: Cumulative Incidence (%) of Death
LN patients at enrollment
never−LN patients
Time since enrollment (years)

Figure 3:


PF
RP
BP
GH
VT
SF
RE
MH
70
60
50
40
30
20
10
0
State 1 (eGFR: > 60 ml/min)
State 2 (eGFR: 30 – 60 mL/min)
State 3 (eGFR: < 30 ml/min)

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