Renal Flare as a Predictor of Incident and Progressive CKD in Patients with Lupus Nephritis

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Summary

Background and objectives Renal flares are common in lupus nephritis. The impact of flares on the development of CKD in lupus nephritis was examined.

Design, setting, participants, & measurements A retrospective analysis of prospectively collected data from the Ohio Systemic Lupus Erythematosus (SLE) Study was conducted to determine if renal flares predispose to new CKD or progression of preexisting CKD. Patients in the Ohio SLE Study were followed from 2001 to 2009, with a median follow-up of 6 years. For this analysis, patients with biopsy-proven lupus nephritis and at least 3 years of follow-up were included (*n*=56). Frequency and duration of renal flares were compared between patients who never developed CKD (*n*=29) and patients who developed new CKD (*n*=12) and between patients with preexisting but stable CKD (*n*=7) and patients who progressed (*n*=8). Groups were also combined into good (no CKD and stable CKD) or poor (new CKD and progressive CKD) for analysis.

Results The new CKD group had more renal flares per year compared with the no CKD group (median=0.56 flares/yr [range=0–2] versus median=0 flares/yr [range=0–1.4]; *P*<0.001). Additionally, the poor outcome group had more renal flares per year compared with the good outcome group (median=0.50 flares/yr [range=0–2] versus median=0 flares/yr [range=0–1.4]; *P*<0.001). New or progressive CKD was not preferentially associated with nephritic compared with proteinuric renal flares. Logistic regression showed that spending more than 30% of time in renal flare (odds ratio, 20; 95% confidence interval, 4.6 to 91.3; *P*<0.001) and age>35 years (odds ratio, 69; 95% confidence interval, 6.3 to 753.6; *P*<0.001) were independent predictors of the combined end point of developing new or progressive CKD. All four subjects over 35 years of age that spent over 30% of time in renal flare had a poor outcome.

Conclusion In patients with lupus nephritis, the relative duration of renal flare is an independent predictor of incident and progressive CKD.

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Introduction

There is a prevailing belief among those individuals who provide health care for patients with lupus nephritis (LN) that flares of LN are associated with poor long-term kidney outcomes. This belief is based on only a handful of published studies. Furthermore, the flare-associated risk of CKD or ESRD is thought to be mainly due to those flares that cause an increase in serum creatinine (SCr) and hematuria (so-called nephritic flares) (1,2). In contrast, proteinuric flares, in which SCr does not increase but proteinuria increases above predesignated target levels, have been considered to confer less long-term risk to the kidneys. This conclusion is based on limited evidence (1–4).

Recently, the Joint European League Against Rheumatism (EULAR) and the European Renal Association—European Dialysis and Transplant Association published updated guidelines on the management of LN and proposed specific definitions for LN flares (5). Flares were again divided into nephritic and proteinuric categories. Aggressive induction therapy was recommended for

nephritic flares, whereas the recommendations for proteinuric renal flares were less clear. This distinction was not made in the new LN guidelines provided by the American College of Rheumatology or the Kidney Disease Improving Global Outcomes group (6,7).

If LN flares are considered to be AKI events, the notion that LN flares predispose to CKD and ESRD is consistent with the emerging concept that AKI of other etiologies is a risk factor for future CKD (8–10). It is reasonable to classify LN flares as AKI events. Nephritic flares meet the definition of AKI given the increase in SCr and the decrease in GFR. Furthermore, proteinuria in LN develops because of inflammatory injury to the glomerular basement membrane, and thus, a proteinuric flare may also be considered an AKI equivalent.

In a busy lupus clinic, it has been our impression that most LN flares would be considered proteinuric based on the published definitions but that CKD occurs in patients without regard to the nephritic or

proteinuric designations. We, therefore, consider all LN flares to be potentially detrimental to long-term renal health. To test this theory, we examined the association of LN flares with new or progressive CKD in the Ohio Systemic Lupus Erythematosus Study (OSS), a prospectively followed observational cohort that has been clinically and phenotypically well characterized (11).

Materials and Methods

We conducted an analysis of prospectively collected data from the OSS to determine the impact of renal flares on development or progression of CKD in patients with biopsy-proven LN. The OSS has been described previously (11,12). Patients in the OSS were followed from 2001 to 2009, with a median duration of follow-up of 6 years. For this analysis, patients with World Health Organization classes III–V who had at least 3 years of follow-up were included (n=56). Patients were treated with cyclophosphamide or mycophenolate mofetil for induction of remission after a flare diagnosis and mycophenolate mofetil or azathioprine for maintenance. Medication use was examined and found to be comparable in patients who had good and poor outcomes (defined below).

Four groups were examined: patients who did not develop CKD over the follow-up period (no CKD), patients who developed new CKD over the follow-up period (new CKD), patients who had established CKD when they entered the OSS but did not have progression over the follow-up period (stable CKD), and patients with established CKD at study entry who progressed over the follow-up period (progressive CKD). New CKD was defined as a sustained increase in SCr of 25% or more above a previously normal baseline. Progressive CKD was defined as a sustained increase in SCr of 25% or more above a previously elevated baseline. Increases in SCr were considered sustained when they remained at least 25% above baseline for the entire period of observation.

The OSS database was then reviewed to determine the association of renal flare with CKD. Duration of renal flare episodes, frequency of flare, and mean starting and ending SCr values were compared. The patients who developed new CKD were compared with patients who did not develop CKD, and patients with progressive CKD were compared with nonprogressors. The patients considered to have a poor renal outcome (new and progressive CKD groups) were compared with patients with a good outcome (no and stable CKD groups).

Definition of Renal Flare

In the OSS, LN flares were defined as an increase in disease activity requiring alternative or more intensive treatment. The specific changes of disease activity (proteinuria, SCr, and urine sediment) required to diagnose a flare have been previously published (11). In the OSS, flares were divided into mild, moderate, and severe, and specific treatment guidelines were applied to each level of flare (11,12). Flares were not divided into nephritic and proteinuric, and treatment was not based on the nephritic/proteinuric designation. For the present analysis, nephritic flare was defined as an increase in SCr of 25% or more alone without regard to the level or change in level of proteinuria. The level of hematuria was highly variable among patients, and in many cases, it did not meet the criteria of an increase of more than 10 red blood cells per high-power field, despite increased SCr and proteinuria that were clearly caused by increased LN activity. To avoid excluding LN flares that did not easily fit into the standard definition of nephritic flares, an arbitrary level of hematuria was not included in the definition of a nephritic flare (2–4,13). A proteinuric flare was defined as an increase in proteinuria to greater than 1 g/d if patients were previously in complete renal remission or a doubling to greater than 2 g/d if patients had previously been in partial renal remission.

The duration of each renal flare for each patient was the length of time between declaration of a new flare and resolution of the clinical parameters that defined that flare. Time in renal health was defined for each patient as the number of months of follow-up minus the cumulative duration of renal flares for that patient during the follow-up period.

Statistical Analyses

Continuous data are expressed as mean±SD if normally distributed or median (range) if not normally distributed. Groups with normally distributed data were compared using the t test, and groups were compared using the Wilcoxon test if not normally distributed. Proportions were analyzed using Fisher's exact test. Associations between continuous variables were measured by the Spearman rank correlation coefficient, and odds ratios (ORs) were calculated using contingency tables. Logistic predictive models were created with kidney outcome (good or poor) as the response, and a receiver operating characteristic curve was generated. Clinical predictors included age, race, renal flare rate, and relative duration of renal flare before a change in outcome status (good or poor) was adjudicated. Using the backward selection approach, a model was then constructed that contained only clinical variables that were significantly associated with poor outcomes (development of new or progressive CKD). Statistical analyses were done with SAS JMP 9 (SAS Institute, Cary, NC); a two-tailed P value=0.05 was used as the threshold for significance.

Results

Patient Clinical and Demographic Characteristics

The demographic and clinical characteristics of the OSS patients are shown in Table 1. After an overall follow-up of 9 years, 20 of 56 (35.7%) patients developed significant and sustained increases in SCr and were classified as having new or progressive CKD or collectively, a poor kidney outcome. The patient data are presented according to their outcome group (Table 1). African Americans were overrepresented in the new and progressive CKD groups, but within groups, given the small numbers, this result was not significant. However, if new and progressive CKD groups were considered together and compared with patients with good kidney outcome (no CKD and nonprogressive CKD), African Americans were significantly overrepresented (P=0.04, Fisher's exact test). There was no association between the proliferative histologic classes and poor renal outcome.

Table 1. Patient characteristics

Clinical Data	No CKD	New CKD	P Value	Nonprogressive CKD	Progressive CKD	P Value
N	29	12	—	7	8	—
Age ± SD (yr)	31.3±9.0	34.3±11.7	0.38	39.1±14.1	40.5±10.8	0.83
Mean follow-up (yr)	5.8±1.2	6±1.8	0.68	5.3±0.95	5.6±1.6	0.42
Men (%)	14	0	—	0	0	—
African American (%)	28	50	0.28	14	62.5	0.12
Class III or IV LN (%)	45	67	0.31	43	50	1.00
Initial SCr (mg/dl)	0.85±0.15	0.75±0.15	0.06	1.94±0.83	2.15±0.81	0.63
Final SCr (mg/dl)	0.83±0.12	1.78±1.95[a]	<0.001	1.56±0.87	4.0±2.45[b]	0.009
Median time in flare (mo; range)[c]	0 (0–28)	20 (0–48)	<0.001	0 (0–22)	15.5 (0–48)	0.16
Median new RFs/yr[c]	0 (0–1.4)	0.56 (0–2)	<0.001	0 (0–0.5)	0.33 (0–1)	0.13
Median time in renal health (mo)[c]	52 [(6–74)	30.4 (0–50)	0.004	48 (14–75)	25 (0–48)	0.06

LN, lupus nephritis; SCr, serum creatinine; RFs, renal flares.
[a]$P<0.005$ for final versus initial SCr (new CKD group).
[b]$P=0.02$ for final versus initial SCr (progressive CKD group).
[c]Comparison by Wilcoxon test.

Renal Flare and New CKD

The new CKD group had more renal flares per year compared with the no CKD group (median=0.56 flares/yr [range=0–2] versus median=0 flares/yr [range=0–1.4], respectively; $P<0.001$) (Table 1). During the follow-up period, 59% of the no CKD patients never had a renal flare compared with only 8% of new CKD patients. The no CKD group spent a median of 52 months (6–74 months) in renal health, whereas the new CKD group spent a median of 30.4 months (0–50 months) in renal health (Table 1). The median duration of renal flare was 20 months (0–48 months) in new CKD patients compared with 0 months (0–28 months) for those patients without CKD ($P<0.001$).

Renal Flare and Progressive CKD

There was a tendency to a higher frequency of renal flares in the progressive CKD group compared with the stable CKD group, but this result did not reach statistical significance (median=0.33 flares/yr [range=0–1] versus median=0 flares/yr [range=0–0.5], respectively; $P=0.13$), likely because of small sample size. During follow-up, 71% of stable CKD patients never had a renal flare, whereas only 37.5% of the progressive group did not have a flare. The stable CKD group spent more time in

renal health compared with the progressive CKD group, and this result approached statistical significance (Table 1).

Renal Flare and Combined CKD Outcomes

To increase the sample size for statistical modeling, data were reanalyzed using the poor and good kidney outcome end points. The poor kidney outcome group experienced a significantly higher renal flare rate compared with the good outcome group (median=0.50 flares/yr [range=0–2] versus median=0 flares/yr [range=0–1.4], respectively; $P<0.001$). African Americans were found to be at higher risk for a poor outcome compared with Caucasians (OR, 3.82; 95% confidence interval [95% CI], 1.19 to 13.06; $P=0.03$). Although about one half of each race did not have any renal flares, among those patients with flares, African Americans spent a higher percent of time in flare (62%±26% versus 27%±22%; $P<0.001$) and had a threefold higher median annual rate of renal flare compared with Caucasians (0.75 flares/yr [range=0.19–2] versus median=0.23 flares/yr [range=0.15–1.31], respectively; $P=0.01$).

Proteinuric and Nephritic Flares and CKD

The flares in each CKD group were classified as nephritic or proteinuric (Table 2). Most (72%) of the renal flares

Table 2. Distribution of proteinuric and nephritic flares by kidney outcome

Flare Type	No CKD	New CKD	Nonprogressive CKD	Progressive CKD
Nephritic[a]	7	3	1	4
Proteinuric[b]	8	19	1	10

[a]Increase in serum creatinine of ≥25%, regardless of the level or change in level of proteinuria.
[b]Increase in proteinuria to >1 g/d if previously in complete remission; doubling of proteinuria to >2 g/d if previously in partial remission.
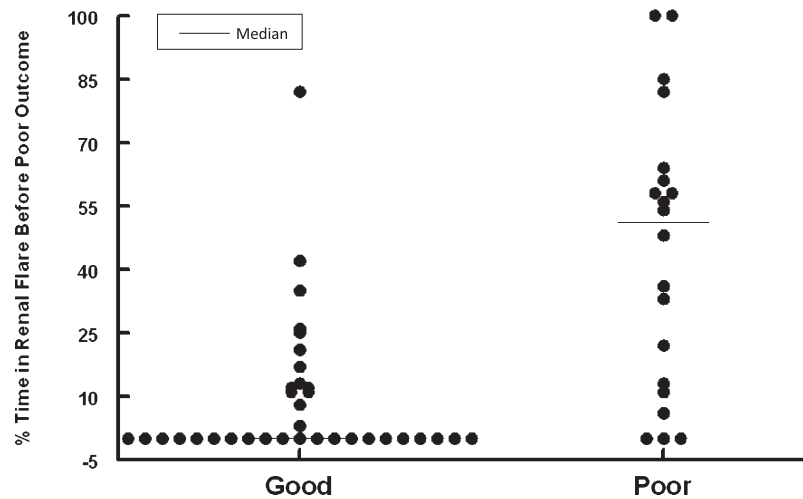
Figure 1. | Time in renal flare and kidney outcome. Percent time in renal flare before development of poor outcome was calculated. The good outcome group spent a median of 0% (0%–82%) time in renal flare compared with a median of 51% (0%–100%) time in renal flare for the poor outcome group (*P*<0.001 by Wilcoxon test). Spending more than 30% of time in renal flare was the threshold for predicting poor kidney disease outcome (*P*<0.001).

experienced by this cohort were proteinuric, and in any of the CKD groups, the majority of the flares was proteinuric. Poor kidney outcomes were not associated with the type of renal flare (Fisher's exact test; that is, both nephritic and proteinuric flares led to poor outcomes, and neither was favored).

Predictors of Poor Outcomes

To define risk factors of a poor kidney outcome, time-dependent flare variables were re-examined in the period before new or progressive CKD developed as opposed to during the entire follow-up period for each patient. The median length of time before new or progressive CKD was diagnosed for the cohort was 30.9 months, with a range of 11.9–103 months. The data for percent of time spent in flare before a poor renal outcome for individual patients are shown in Figure 1. A cutoff of 30% of time in renal flare was determined to be associated with a poor outcome (*P*<0.001). This cutoff value also produced the maximum sum of sensitivity and specificity. The associated receiver operating characteristic curve is shown in Figure 2, and the area under the curve is 0.83. Renal flare rate was highly correlated to percent of time in flare (Spearman *r*=0.95) and therefore, was not an independent predictor. When controlled for percent of time in renal flare, age greater than 35 years was associated with a poor kidney outcome (*P*<0.001) and independent of percent time in flare (Spearman *r*=−0.2; *P*=0.12). Interestingly, race was not an independent predictor of renal outcome.

Contingency table analysis using percent time in renal flare and age was done to calculate the ORs for a poor kidney outcome. The OR for a poor outcome was 20 for percent time in renal flare greater than 30% (95% CI, 4.6 to 91.3; *P*<0.001), and there was an interaction effect between age and percent time in renal flare. Among patients who were less than 35 years old, those patients who spent greater than 30% of time in renal flare had an OR of 69 (95% CI, 6.3 to 753.6; *P*<0.001) for a poor outcome.

Patients with age greater than 35 years and greater than 30% of time spent in renal flare were at higher risk for a poor outcome. All such patients (*n*=4) had a poor outcome, resulting in an unbounded OR.

Each flare resolved as a complete or partial remission. Because individual patients often had multiple flares and each flare could have resolved differently, we could not incorporate type of remission into the prediction model. However, all patients who had a good outcome had either no flare (*n*=22) or flares that resolved in complete remission (*n*=14).

Discussion

This study shows a significant association between renal flare and new-onset CKD as well as a trend between renal flare and progressive CKD in patients with proliferative or membranous LN followed for a minimum of 3 years. The latter association was likely affected by the small number of
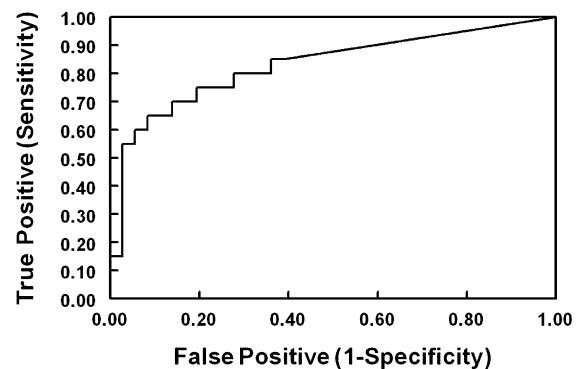
Figure 2. | Receiver operating characteristic curve for poor kidney outcome. A receiver operating characteristic curve was generated to evaluate percent time in renal flare as a single predictor of poor kidney outcomes. The area under the curve is 0.83.

patients with preexisting chronic CKD. However, when new and progressive CKD groups are considered together as a poor kidney outcome, renal flare was significantly associated. The number of new renal flares per year and the time spent in renal flare were significantly higher in patients who had poor long-term kidney outcomes. Patients who spent more than 30% of time in renal flare had a 20-fold higher risk of achieving the combined outcome of developing new or progressive CKD. Age added to this risk, and the combination of age greater than 35 years and greater than 30% of time spent in renal flare showed very high risk. Furthermore, the association of renal flare and adverse kidney outcome was not restricted to nephritic LN flares but was seen mainly in proteinuric LN flares.

To exemplify how these findings could be used clinically, consider a patient with proliferative LN followed in a practice. Calculating the percent time spent in renal flare could provide insight into the patient's overall renal prognosis. Patients who have spent more than 30% of time in renal flare during clinical follow-up would be considered high risk for poor renal outcome. The minimum follow-up time in this study was 3 years; thus, a cumulative time in flare of greater than 0.9 years (30%) is associated with a poor renal outcome. If our data can be generalized to other LN populations, patients approaching a cumulative time in flare of 1 year could be followed more closely to prevent new flares and treated more aggressively to limit duration of new flares.

There are limitations to this report. The study was a single-center retrospective analysis of a prospectively followed cohort with a sample size of 56. Several of the trends that we observed (*e.g.*, over-representation of African Americans in the new and progressive CKD groups and renal flare rate in progressive versus nonprogressive CKD groups) may have reached statistical significance in a larger cohort. Additionally, with more outcomes, the new and progressive CKD groups could have been analyzed separately instead of combined.

Despite these limitations, these data confirm and extend previous observations that renal flare in LN is a risk factor for long-term renal impairment. The first investigation that described this association was done in a Caucasian-European population of 70 patients (2). In the present study, 36% of the patients were African American, suggesting that, as expected, renal flare is an important risk factor for all patients with LN. Although the study by Moroni *et al.* (1) found only nephritic flares to be significantly associated with poor renal outcomes, a more recent study of 91 Caucasian Systemic Lupus Erythematosus patients with proliferative LN found both nephritic and proteinuric flares to be associated with poor kidney outcomes (14), similar to our data. The recent EULAR guidelines emphasized nephritic flares. We suggest that proteinuric flares are common, also lead to poor outcomes, and should be considered together with nephritic flares in determining renal prognosis.

In conclusion, our data suggest that LN flare is a predictor of poor long-term kidney outcome, and the duration of renal flare is an especially robust marker of incident and progressive CKD. Classifying flares as proteinuric or nephritic may not be as clinically useful. These data indicate that, for all LN therapies (including novel drugs that are being brought to clinical trial), flare prevention and

shortening flare duration may be considered important therapeutic goals.

Disclosures
None.

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