

# Effect of Sustained Clinical Remission on the Risk of Lupus Flares and Impaired Kidney Function in Patients With Lupus Nephritis



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**Introduction:** This retrospective study on patients with biopsy-proven lupus nephritis (LN) aimed to assess the probability of sustained clinical remission (sCR) and to investigate sCR effects on disease flares and impaired kidney function (IKF).

**Methods:** sCR was defined as clinical-Systemic Lupus Erythematosus Disease Activity Index 2000 (SLE-DAI-2K) = 0 and estimated glomerular filtration rate (eGFR) >60 ml/min per 1.73 m<sup>2</sup> lasting ≥1 year; IKF: eGFR <60 ml/min per 1.73 m<sup>2</sup> for >3 months. We analyzed the probability of achieving and maintaining sCR, and the yearly risk of flare. Cox models were used to identify predictors of sCR and IKF with variables analyzed as time-dependent covariates when appropriate.

**Results:** Of 303 patients followed-up with for 14.8 (interquartile range: 9.8–22) years, 257 (84.8%) achieved sCR. The probability of achieving sCR progressively increased over time reaching 90% at 15 years. Baseline age (hazard ratio [HR]: 1.017; 95% confidence interval [CI]: 0.005–1.029; *P* = 0.004), hydroxychloroquine intake (HR: 1.385; 95% CI: 1.051–1.825; *P* = 0.021), and absence of arterial hypertension (HR: 0.699; 95% CI: 0.532–0.921; *P* = 0.011) were independent predictors of sCR. Among patients who achieved sCR, 142 (55.3%) developed a lupus flare after a median time of 3.6 (2.3–5.9) years. In the remaining 115 patients, sCR persisted for 9.5 (5.8–14.5) years. The probability of sCR to persist at 15 years was 38%. SLE flare risk decreased to 10%, 5%, and 2% in patients with sCR lasting <5, 5 to 10, and >10 years, respectively. At the last observation, 57 patients (18.81%) had IKF. sCR achievement (HR: 0.18, *P* < 0.001) and its duration (HR: 0.83, *P* < 0.001) were protective against IKF.

**Conclusion:** sCR is an achievable target in LN management and protects against IKF. The longer the sCR, the higher the chance of its persistence and the lower the risk of SLE flares.

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**KEYWORDS:** impaired kidney function; lupus flares; lupus nephritis; remission; sustained clinical remission

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Lupus Nephritis (LN) is a frequent manifestation of systemic lupus erythematosus (SLE)<sup>1</sup> occurring in up to 50% to 70% of patients with SLE during disease course.<sup>2,3</sup> Despite improvement in overall and renal survival in the past few decades,<sup>4–6</sup> LN remains a severe manifestation, leading to kidney failure in 5% to 10% of patients at 10 years.<sup>5,7</sup> Renal flares are the strongest predictors of poor prognosis<sup>8–13</sup> because they are linked to an increased

kidney damage, either due to disease activity or the need for prolonged immunosuppression. Therefore, timely diagnosis and achievement of stable renal remission are required to preserve kidney function.<sup>14-19</sup>

The duration of remission influences the long-term outcome in SLE. It has been reported that spending at least 25% of the follow-up in remission improves patient prognosis<sup>20</sup> and a remission duration over 2 years was associated with a significantly reduced mortality.<sup>21,22</sup> In an Italian SLE cohort of 224 Caucasian patients diagnosed after 1990, a remission of 2 consecutive years was the minimum effective duration of remission associated with a significant decrease in damage progression.<sup>7,23,24</sup> However, most observations concern extrarenal SLE whereas data on LN are limited.<sup>25</sup>

In LN, the achievement of renal remission has been shown to be protective on kidney function.<sup>15,19,26,27</sup> However, few data assessed the effect of the duration of clinical remission on the development of disease flares and IKF in patients with LN. Moreover, solid data about the predictors of sCR are lacking.

In this study, we assessed the probability, duration, and predictors of sCR in a large multicenter cohort of patients with SLE with LN followed-up with for a long period of time, and the effects of sCR on renal and extra-renal flares and IKF.

## METHODS

### Study Cohort

Patients older than 18 years with a biopsy-proven LN were included in this retrospective cohort study.

Criteria for inclusion were as follows: (i) SLE classified according to American College of Rheumatology criteria,<sup>28</sup> (ii) biopsy-proven LN performed between January 1980 and December 2016, (iii) a follow-up of at least 5 years after the initiation of treatment for LN, and (iv) at least 2 evaluations per year. Patients younger than 18 years, those without kidney biopsy and those requiring renal replacement therapy upon admission were excluded from this study.

The study was approved by the Ethics Committee of Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico di Milano, Italy (protocol number 505\_2019bis) and by the Ethics Committee of IRCCS Humanitas Rozzano, Milano, Italy (protocol code NEF0032023). All patients signed an informed consent for the scientific use of their data that was anonymized. Patients or the public were not involved in our research.

### Patient Assessment

We considered as baseline the initiation of induction therapy after kidney biopsy. By histologic examination, LN was classified according to the recent revision

of International Society of Nephrology/Renal Pathology Society criteria.<sup>29,30</sup>

An electronic database was shared across the participating centers to record the type of induction and maintenance therapy, demographics, as well as clinical and laboratory features at baseline, at each clinical evaluation, and at last observation. All compiled data were systematically and regularly evaluated. In cases of inconsistencies or missing information, the centers were required to amend the data. Disease activity was assessed by SLEDAI-2K.<sup>31</sup>

### Definition of Kidney Variables or Events

sCR was defined as clinical-SLEDAI-2K = 0 (which includes proteinuria <0.5 g/24h and is irrespective of serology) and eGFR >60 ml/min per 1.73 m<sup>2</sup>, persisting for at least 1 year with or without glucocorticoids and/or immunosuppressive therapy. eGFR was evaluated by the Modification of Diet in Renal Disease formula and proteinuria was measured by benzethonium chloride on the urine collected over 24 hours expressed as g/24 hours.

SLEDAI-2K,<sup>31</sup> an updated version of the original SLEDAI,<sup>32</sup> is the most popular global disease activity index in SLE, both in clinical practice and research. It measures disease activity within the last 30 days and consists of 24 weighted clinical and serologic variables. Disease activity can range from 0 to 105. Clinical SLEDAI-2K considers only clinical activity without serologic variables. SLEDAI and SLEDAI-2K have been incorporated in SLE responder indexes as well as in the definitions of remission and low disease activity.<sup>33</sup> Acute kidney damage: eGFR <60 ml/min per 1.73 m<sup>2</sup> for <3 months, hematuria (urinary red blood cells >20/high power field), and/or erythrocyte casts, proteinuria ≥0.5 g/d<sup>34</sup>; nephrotic syndrome: proteinuria ≥3.5 g/d, serum albumin ≤3 g/dl; isolated urinary abnormalities: normal renal function, proteinuria <3.5 g/d and ≥0.5 g/d and/or microscopic hematuria; IKF: eGFR <60 ml/min per 1.73 m<sup>2</sup> <sup>34</sup> for at least 3 months; kidney failure: need of chronic dialysis or eGFR <15 ml/min per 1.73 m<sup>2</sup>; arterial hypertension: the mean of 3 consecutive measurements of systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg in sitting position; nephritic flares: increase in serum creatinine of at least 30% over the last value, associated with nephritic urinary sediment, with or without increased proteinuria<sup>8</sup>; proteinuric flares: increase in proteinuria without modification of serum creatinine of at least 2 g/24h if the previous proteinuria was <3.5 g/24h, or doubling if previous proteinuria was ≥3.5 g/24h;<sup>8</sup> extrarenal flares were defined according to revised Safety of Estrogens in Lupus Erythematosus National Assessment-SLEDAI criteria.<sup>35,36</sup>

Damage was assessed by the Systemic Lupus International Collaborating Clinics damage index (SDI) at baseline and at the last observation. The SDI at the last observation was calculated as the annual increase rate.<sup>37</sup>

### Statistical Analysis

Continuous variables were expressed as median and interquartile range, due to nonnormal distribution. Comparison of continuous variables between groups was carried out using nonparametric Mann-Whitney or Kruskal Wallis H test for 2 or more independent samples, respectively. Chi-square test was used to compare categorical or dichotomized variables among groups of patients.

Time to sCR and probability of sCR were estimated using Kaplan-Meier curves. From the Kaplan-Meier estimate of sCR, the yearly risk of flare was also derived. The difference between curves was evaluated using the log-rank test.

To assess baseline predictors of sCR, baseline demographic, clinical, histological, and therapeutic variables were tested using the Cox proportional hazard model. Both univariable and multivariable analyses were performed. Stepwise regression was used to assess the variables that retained significance at multivariable analysis.

Five Cox proportional hazard models were used to assess the effect of sCR, its duration (in number of years) and the type of flare, as time-dependent covariates, on IKF occurrence. The models were controlled both for sex and age at the baseline. Model 1 assessed the effect of sCR, model 2 its duration (in years), and model 3 both sCR and its duration. Model 4 investigated more accurately, the effect of the duration of the remission, by using a categorization of sCR duration in 4 intervals of years through quartiles: (min = 0,  $Q_1 = 0$ ), [1,  $Q_2 = 2.72$ ), (2.73,  $Q_3 = 7.42$ ), and (7.43, max = 33.53) years. The significance of the covariates was overall tested through a likelihood ratio test. The first interval (degenerate in 0) represents the reference category in the models and corresponds to the absence of sCR. The second interval starts at 1 because the shorter duration for an sCR corresponds to 1. Model 5 assessed the effect of the type of flare (proteinuric and nephritic flare) on IKF occurrence. Extrarenal flares were excluded from the analysis because only 1 patient out of 37 with extrarenal flare developed IKF. *P*-values were calculated with (jackknife-corrected) robust standard errors. Proportional hazards assumption was tested globally for each model, through tests based on the scaled Schoenfeld residuals. The R statistical package has been used for all the analyses.<sup>38</sup>

## RESULTS

### Patient Cohort at Baseline and Treatment

Three-hundred three patients were included in this study; 83.2% were females and 91.1% were Caucasian. Baseline demographics and clinical features are reported in Table 1.

At LN onset, 21.2% of patients had acute kidney damage, 41.2% had nephrotic syndrome, 37.6% had isolated urinary abnormalities, and 41.9% had arterial hypertension; notably, none of them had IKF.

At kidney biopsy, 241 patients (79.5%) had a proliferative LN: 51 class III, 23 class III+V, 138 class IV, 29 class IV+V, 52 had pure membranous LN (class V), and 10 class II LN.

At baseline, 267 patients (88.2%) had no chronic damage (SDI = 0), whereas 33 (11.8%) had a median SDI of 1 (interquartile range: 1–1).

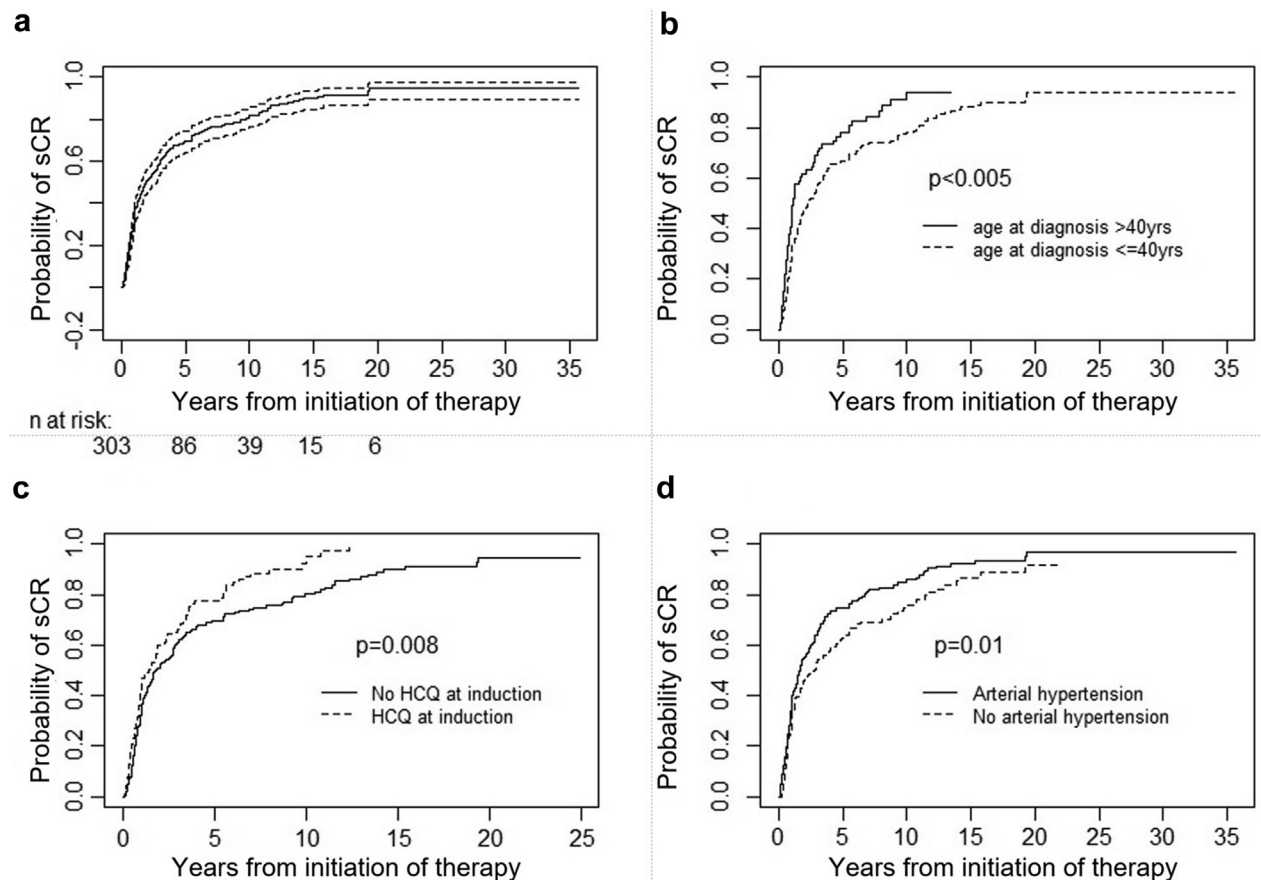
Initial treatment consisted of intravenous methylprednisolone pulses for 3 subsequent days, followed by prednisone 0.5 mg/kg/d for 4 weeks and then tapered to 7.5 to 5 mg/d in 78% of patients. The remaining 22% of patients were treated with oral prednisone 1 mg/kg/d for 4 weeks and then the dosage was progressively tapered. In addition to prednisone, immunosuppressive drugs were used in 85% of patients as

**Table 1.** Demographic, clinical, histologic, and therapeutic variables in our cohort at baseline

Variable	All patients N = 303
Females, n (%)	252 (83.2)
Caucasians, n (%)	276 (91.1)
Age at SLE diagnosis, yr	25.1 (19.7–33.7)
Age at LN diagnosis, yr	28.5 (23.3–39.3)
Serum Creatinine, mg/dl	0.9 (0.7–1.2)
eGFR ml/min per 1.73 m <sup>2</sup>	82.2 (56–100.4)
Acute kidney damage, n (%)	64 (21.1)
Proteinuria, g/d	3.4 (1.9–5.4)
Proteinuria <3.5g/d, n (%)	155 (51.1)
Arterial hypertension, n (%)	127 (41.9)
C3, mg/dl	60 (45–75)
C4, mg/dl	9 (6–14)
Class II or V/III, IV or mixed, n (%)	62 (20.5) / 241 (79.5)
Activity index	6 (3–9)
Chronicity index	1 (0–3)
Methylprednisolone pulses induction, n (%)	237 (78.2)
Immunosuppressive therapy induction, n (%)	258 (85.1)
CYC/AZA/MMF/others <sup>a</sup> , n (%)	156 (51.5) / 23 (7.6) / 67 (22.1) / 12 (3.9)
IS maintenance, n (%)	218 (71.9)
Hydroxychloroquine, n (%)	92 (30.4)
SDI	0 (0–0)

AZA, azathioprine; CYC, cyclophosphamide; IQR, interquartile range; IS, immunosuppressive therapy; LN, lupus nephritis; MMF, mycophenolate mofetil; n, number; sCR, sustained clinical remission; SDI, SLICC-Damage Index; SLE, systemic lupus erythematosus.

<sup>a</sup>Other immunosuppressors 5 Csa: Cyclosporine; 2 MTX: Methotrexate; 5 RTX: Rituximab. Unless otherwise specified data are expressed as median and interquartile ranges.



**Figure 1.** Probability of achieving sustained clinical remission (sCR) during the follow-up (a) in all patients (curve with 95% CI), (b) in patients aged  $\leq 40$  or  $> 40$  years, (c) in patients who were or were not taking hydroxychloroquine at baseline, and (d) in patients with or without arterial hypertension. Kaplan-Meier curves with log-rank test. Dashed lines represent 95% confidence interval. HCQ, hydroxychloroquine; sCR, sustained clinical remission.

induction therapy, and in 71.9% as maintenance therapy.

Hydroxychloroquine was taken by one-third of patients at baseline. In [Supplementary Table S1](#), the initial treatment according to the different histological classes are reported.

### Achievement, Persistence, and Predictors of sCR

Among the 303 patients included in the study, 257 (84.8%) achieved sCR after a median follow-up of 1.44 (0.69–3.58) years after the initiation of LN treatment and 46 (15.2%) did not achieve sCR during a median follow-up of 11.1 (8.4–17.4) years.

The probability of achieving sCR progressively increased during the follow-up. The probabilities of being in sCR at 1, 3, 5, 10, and 15 years were 40%, 60%, 70%, 80%, and 90%, respectively ([Figure 1a](#)).

Among the clinical and demographic features at the time of kidney biopsy, age (HR: 1.017; 95% CI: 1.005–1.029;  $P = 0.004$ ), hydroxychloroquine use (HR: 1.385; 95% CI: 1.051–1.825;  $P = 0.021$ ), and arterial hypertension (HR: 0.699; 95% CI: 0.532–0.921;

$P = 0.011$ ) emerged as independent predictors of sCR at Cox multivariable analysis ([Figure 1b–d](#)) and [Table 2](#). In [figure 1b](#), we considered the threshold of 40 years, corresponding to the 75th percentile of the age distribution, because it well depicts the difference between the 2 curves in the graph. We tested the effect of different medications as predictors of sCR, including methylprednisolone pulses, cyclophosphamide, azathioprine, and mycophenolate mofetil ([Supplementary Table S2](#)). Mycophenolate mofetil was associated with sCR in a univariable analysis (HR: 1.396; 95% CI: 1.039–1.874;  $P = 0.027$ ); however, none of the drugs independently predicted sCR in a multivariable analysis.

Among 257 patients who achieved sCR, 115 (44.7%) maintained it until the end of follow-up of 9.5 (5.8–14.5) years. In this group, glucocorticoids and immunosuppressants were withdrawn in 71 (61.7%) and in 49 (42.6%) patients, respectively. The median time spent on glucocorticoid-free or immunosuppressant-free sCR were 36.5 (0–59) months and 43.5 (0–75.3) months, respectively. These data are summarized in [Supplementary Table S3](#).

**Table 2.** Demographic, clinical, and histological features at time of kidney biopsy which predicted sCR by Cox proportional hazard model

Variable	Univariable analysis			Multivariable analysis		
	HR	CI	P	HR	CI	P
Age (yr)	1.015	1.004–1.026	0.006	1.017	1.005–1.029	0.004
Arterial hypertension	0.694	0.566–0.824	0.005	0.699	0.532–0.921	0.011
Hydroxychloroquine	2.776	2.306–3.250	0.030	1.385	1.051–1.825	0.021
Proteinuria >5 g/d	0.776	0.561–0.989	0.049	-	-	-
Proliferative LN	1.314	0.918–1.709	0.071	-	-	-
Mycophenolate ind.	1.396	1.039–1.874	0.027	-	-	-

CI, confidence interval; HR, hazard ratio; LN, lupus nephritis; mycophenolate ind., induction therapy; sCR, sustained clinical remission.

The probabilities of sCR to persist at 5, 10, and 15 years were 63%, 47%, and 38%, respectively. After the 15th year of remission, the curve of probability of maintaining sCR reached a plateau (Figure 2a).

### SLE Flares

In the other 142 of 257 (55.2%) patients, sCR was interrupted after a median of 3.6 (2.3–5.9) years due to the onset of SLE flares, as calculated by the Kaplan-Meier estimate. One-hundred seventy-four flares occurred over a median follow-up of 17.8 (13.3–24.2) years, corresponding to an annual flare rate of 0.067 flare/patient/yr. Among these patients, 37 (26.1%) developed extra-renal flares, whereas 105 (73.9%) experienced renal flares (16 nephritic and 89 proteinuric).

After treatment of SLE flares, 52 of 142 (36.6%) patients no longer achieved sCR (Figure 3). The other 90 patients (63.4%) achieved sCR again: 58 patients maintained sCR until the end of follow-up, the other 32 developed SLE flares again (Figure 3).

The risk of flare was 10% when the sCR lasted less than 5 years, it decreased to 5% between 5 and 10 years of sCR, and to 2% between 10 and 15 years of sCR (Figure 2b), suggesting that the longer the sCR, the lower the flare risk.

Withdrawal of glucocorticoids and immunosuppressive drugs was less frequent in patients who

experienced flares compared to those who maintained sCR (37/142 [26.1%] vs. 71/115 [61.7%], and 27/142 [19.0%] vs. 49/115 [42.6%];  $P < 0.0001$  for both).

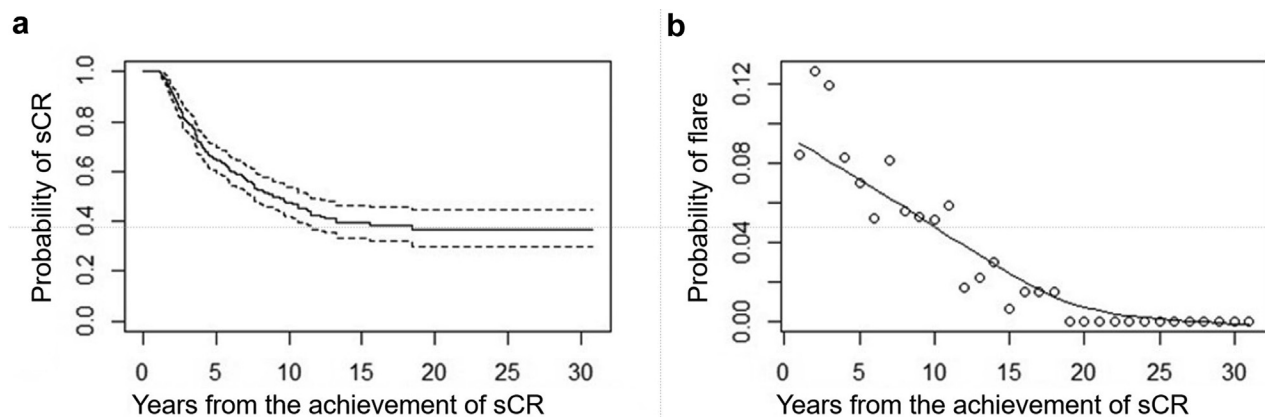
The percentage of follow-up spent on treatment-free sCR was significantly shorter in patients who developed flares compared to those who did not develop flares: (0 [0–37.4] vs. 49.2 [0–79.7]) for glucocorticoids and (19.9 [0–100] vs 61.9 [0–100]) for immunosuppressants. Data are shown in Supplementary Table S3.

Overall, SLE flares occurred in 37 out of 108 patients (34.2%) who stopped glucocorticoids and in 105 out of 139 patients (75.5%) who never stopped glucocorticoids.

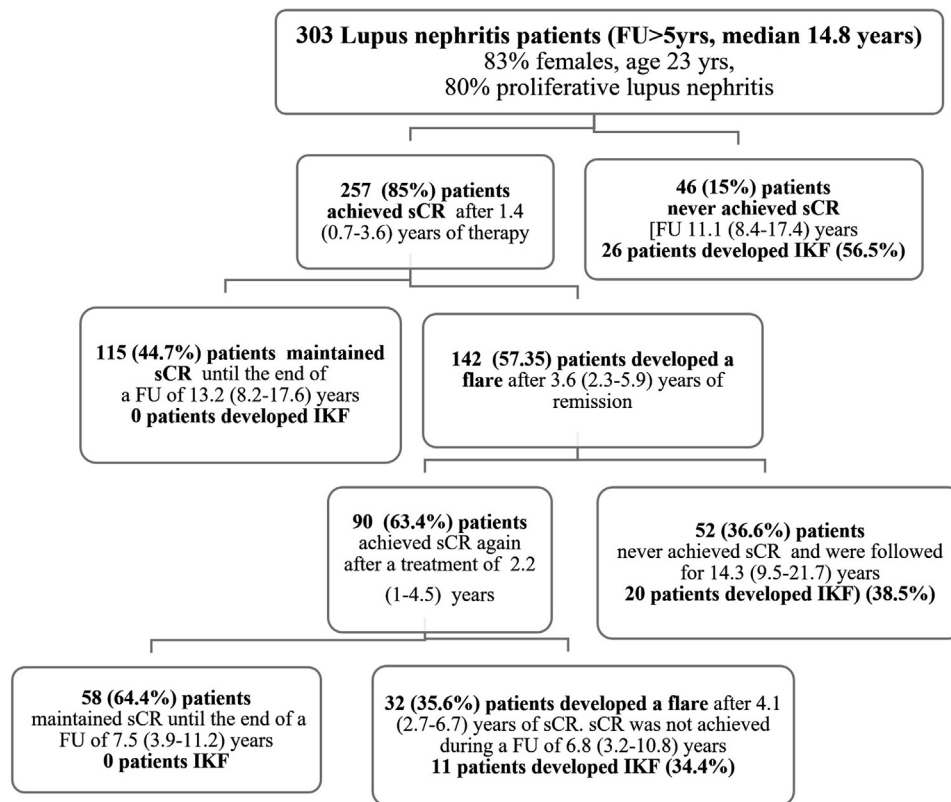
### IKF and Chronic Damage

At the last observation, 57 patients (18.81%) had IKF, 16 of them (28.1%) progressed to kidney failure and 2 other patients died after IKF development.

Patients who achieved sCR (model 1) were 82% less likely (HR: 0.18; [HR-1]<sub>100</sub> = -82;  $P < 0.001$ ) to develop IKF compared with patients who did not (Table 3). The duration of sCR was a significantly protective factor as well (HR: 0.830;  $P < 0.001$ ): the probability of IKF was 17% lower in patients with an additional year of sCR (model 2). In model 3, where both sCR and its duration were included, the duration maintained the protective effect (HR: 0.837;  $P < 0.001$ ),



**Figure 2.** (a) Probability of maintaining sCR, (b) Annual flare rate from the initiation of sCR (every dot depicts flare number in exposed patients). Kaplan Meier curves. Dashed lines represent 95%CI. sCR, sustained clinical remission.



**Figure 3.** Diagram of the whole patient cohort. FU, follow-up; IKF, impaired kidney function; LN, lupus nephritis; sCR, sustained clinical remission.

whereas sCR did not (HR: 0.875;  $P > 0.10$ ). In model 4, the duration of sCR was also confirmed to have a protective effect on IKF (overall significance level:  $P < 0.001$ ); indeed, as the duration increased the probability of IKF decreased (HR: 0.631, 0.300, 0.091). Notably,

the probability of IKF decreased by 36.9%, 70%, and 90.9% in patients with a sCR duration between 1 and 2.72, between 2.73 and 7.42, and between 7.43 and 39.53 years, respectively, as compared to patients who never achieved a remission.

**Table 3.** Results of the Cox proportional hazard models for IKF (controlled for sex and age at the baseline) with sCR, duration of the remission and type of flare as time-dependent covariates

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
Covariate	HR	HR	HR	HR	HR
sCR	0.180 <sup>c</sup> (0.087–0.375)		0.875 <sup>a</sup> (0.412–1.856)		
Duration (yr)		0.830 <sup>c</sup> (0.780–0.882)	0.837 <sup>c</sup> (0.792–0.884)		
Duration (intervals)					
(1–2.72) vs. 0 yr				0.631 <sup>a</sup> (0.270–1.476)	
(2.73–7.42) vs. 0 yr				0.300 <sup>b</sup> (0.128–0.683)	
(7.43–33.53) vs. 0 yr				0.091 <sup>c</sup> (0.039–0.215)	
Type of Flare					
proteinuric vs. nephritic					0.299 <sup>c</sup> (0.137–0.649)

HR, hazard ratio; sCR, sustained clinical remission.  
 Significance level:  
<sup>a</sup> $P > 0.1$ .  
<sup>b</sup> $P < 0.01$ .  
<sup>c</sup> $P < 0.001$ .  
 95% confidence intervals of the HR are in parentheses.  
 Proportional hazard assumption was globally met ( $P > 0.05$ ) in each model.

In model 5, the type of flare was a significant predictor (HR: 0.299, [HR-1]100 = -70.1;  $P < 0.001$ ) of IKF. Patients who developed a proteinuric flare were 70.1% less likely to develop IKF than patients who developed a nephritic flare (Table 3). On the other hand, patients who developed a nephritic flare were 235% more likely to develop IKF than patients who developed a proteinuric flare (1/HR: 3.35: [1/HR-1]100 = 235).

At the last observation, patients who did not achieve sCR had the highest SDI increase per year in comparison to those who achieved sCR (0.14 [0.05–0.27] vs. 0.04 [0–0.11];  $P = 0.0001$ ).

The annual SDI increase was similar in patients experiencing renal or extrarenal flares (median annual SDI increase: +0.1 [0–0.1] vs. +0.1 [0–0.1];  $P = 0.6$ ). Among renal flares, nephritic flares were associated with a higher increase in SDI/yr in comparison to proteinuric flares (+0.10 [0.07–0.19] vs +0.09 [0.06–0.07];  $P = 0.00007$ ).

## DISCUSSION

In this large Italian LN cohort study, we explored the probability of achieving and maintaining sCR, and its effect on the risk of SLE flares and IKF. Over 80% of patients with LN achieved at least 1 year of sCR and the median duration of sCR was >5 years. The probability of achieving sCR progressively increased during follow-up, reaching 90% at 15 years. Older age, treatment with hydroxychloroquine, and absence of arterial hypertension increased the probability of sCR. In keeping with our results, previous studies<sup>22,39</sup> outlined that older age and use of hydroxychloroquine were independent predictors of remission in SLE. It is well known that LN has a more severe course in young patients, and our data show that for them it is more difficult to achieve sCR, suggesting the need for a closer monitoring of young patients from the beginning of the disease.<sup>40</sup> According to the European League Against Rheumatism/European Dialysis and Transplant Association recommendations,<sup>5</sup> hydroxychloroquine should be used in any patients with SLE unless contraindicated, and our results reinforce this statement. The deleterious effect of elevated blood pressure is not unexpected, because arterial hypertension is a well-known predictor of poor renal survival,<sup>41</sup> damage accrual,<sup>42,43</sup> and mortality<sup>44</sup> among patients with SLE. Accordingly, it is crucial to achieve and maintain normal values of blood pressure during the follow-up.

Among the different medications used for LN, none emerged as independent predictor of sCR in our cohort. However, medications and treatment strategies underwent significant changes since initial inclusion of

patients in this cohort, dating back to 1980, which may have blurred the effect of single drugs on the achievement of sCR.

The median time to achieve sCR in our cohort was about 1.5 years; however, the probability of reaching sCR progressively increased along the follow-up, suggesting that a long-term treatment is necessary to achieve remission in LN.<sup>45</sup> The longer the duration of sCR, the lower the risk of SLE flares, flattening to 2% after 10 years of sCR. On the other hand, the failure to achieve sCR was associated with an increase in IKF development.

The achievement of sCR, used as a time-dependent covariate, was observed to be highly protective in preventing IKF. Patients who achieved sCR were 82% less likely to develop IKF than those who never achieved sCR. The higher the number of years spent in sCR, the lower the probability of IKF development.

Of the 257 patients who achieved sCR, 115 patients (37.9%) maintained sCR during the whole follow-up period. After the induction therapy, these patients rapidly achieved sCR, which persisted up to 13.2 years. Thanks to such a prolonged sCR, glucocorticoids and immunosuppressive agents could be withdrawn in up to 60% of patients. The remaining 142 patients (46.9%) had their sCR interrupted after about 3 years due to SLE flare and only a minority of them were able to withdraw glucocorticoids and immunosuppressive agents.

Notably, using flare as a time-dependent variable, we found that a patient who developed a nephritic flare was 3.35 as likely to develop IKF than a patient who had a proteinuric flare. This is in keeping with previous observations.<sup>46,47</sup> Moreover, patients who developed nephritic flares had a higher increase in chronic damage compared to those who developed proteinuric flares. Conversely, extrarenal flares had virtually no effect on kidney function; however, the SDI increase was similar in patients who developed renal and extrarenal flares.

Our results highlight the value not only of achieving<sup>16,48</sup> but also of maintaining longer sCR to avoid kidney damage.<sup>49</sup> Indeed, in an Italian cohort of 187 patients with LN, a remission lasting at least 40% of the follow-up period protected against chronic damage accrual, in particular kidney damage.<sup>44</sup> Similarly, Pakchotanon *et al.*<sup>25</sup> evaluated sustained renal remission in a large cohort of patients with LN, defined as proteinuria <0.5 g/d and inactive urinary sediment, without considering serum creatinine or eGFR and the duration of remission. The diagnosis of LN was performed with kidney biopsy in only 70% of patients and one-third of them had class II LN. Renal remission was achieved by 78.6% of patients and 38% of them

had a remission duration of at least 5 years. In comparison to patients with a remission shorter than 5 years, those with longer remission developed significantly less frequently kidney failure and IKF, which parallels our results. To the best of our knowledge, no other studies evaluated the relationship between persistence of remission and preservation of kidney function in patients with LN,<sup>50,51</sup> and no data on the relationship between the duration of sCR and the risk of disease flares are available to date.

Our data document for the first time that the risk of flares decreased over time along with the increased probability of maintaining a sCR, and that the achievement and the number of years spent in sCR were protective against IKF. After the 15th year, the curve of the probability of maintaining remission reached a plateau, suggesting that after that timepoint, remission might persist.

Our paper has some limitations. Because data were collected from a real-world LN cohort, treatment, time to data collection, and duration of follow-up were not standardized and the indication to discontinuation of glucocorticoids and immunosuppressants was based on clinical judgement. Most of our patients are Caucasians, thus limiting the generalizability of our results. Finally, because the follow-up of patients who achieved sCR was longer than that of those who never achieved sCR, we cannot exclude a later achievement of sCR in this group of patients. However, the remarkably long follow-up of our cohort can mitigate the bias due to the censored nature of the data.

In summary, sCR is an achievable goal and should be pursued as the main target in the management of LN. The failure to achieve sCR or the development of renal flares, and in particular nephritic flares, are strongly associated with the risk of IKF development.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Initial therapy of the different histological classes.

**Table S2.** Univariable Cox regression analysis testing the therapy variables at time of kidney biopsy as sCR predictors.

**Table S3.** Therapy at the initiation and during sCR in 257 patients who achieved sCR.

## REFERENCES

1. Yap DYH, Tang CSO, Ma MKM, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transplant*. 2012;27:3248–3254. <https://doi.org/10.1093/ndt/gfs073>
2. Hanly JG, O’Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatol (Oxf Engl)*. 2016;55:252–262. <https://doi.org/10.1093/rheumatology/kev311>
3. Gasparotto M, Gatto M, Binda V, Doria A, Moroni G. Lupus nephritis: clinical presentations and outcomes in the 21st century. *Rheumatol (Oxf Engl)*. 2020;59:39–51. <https://doi.org/10.1093/rheumatology/keaa381>
4. Gatto M, Zen M, Iaccarino L, Doria A. New therapeutic strategies in systemic lupus erythematosus management. *Nat Rev Rheumatol*. 2019;15:30–48. <https://doi.org/10.1038/s41584-018-0133-2>
5. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis*. 2020;79:713–723. <https://doi.org/10.1136/annrheumdis-2020-216924>
6. Moroni G, Vercelloni PG, Quaglini S, et al. Changing patterns in clinical-histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis. *Ann Rheum Dis*. 2018;77:1318–1325. <https://doi.org/10.1136/annrheumdis-2017-212732>
7. Saccon F, Zen M, Gatto M, et al. Remission in systemic lupus erythematosus: testing different definitions in a large multi-centre cohort. *Ann Rheum Dis*. 2020;79:943–950. <https://doi.org/10.1136/annrheumdis-2020-217070>
8. Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. “Nephritic flares” are predictors of bad long-term renal outcome in lupus nephritis. *Kidney Int*. 1996;50:2047–2053. <https://doi.org/10.1038/ki.1996.528>
9. Mosca M, Bencivelli W, Neri R, et al. Renal flares in 91 SLE patients with diffuse proliferative glomerulonephritis. *Kidney Int*. 2002;61:1502–1509. <https://doi.org/10.1046/j.1523-1755.2002.00280.x>
10. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and bayesian meta-analysis. *Arthritis Rheumatol*. 2016;68:1432–1441. <https://doi.org/10.1002/art.39594>
11. Parikh SV, Nagaraja HN, Hebert L, Rovin BH. Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. *Clin J Am Soc Nephrol*. 2014;9:279–284. <https://doi.org/10.2215/CJN.05040513>
12. Sidiropoulos PI, Kritikos HD, Boumpas DT. Lupus nephritis flares. *Lupus*. 2005;14:49–52. <https://doi.org/10.1191/0961203305lu2059oa>
13. Illei GG, Takada K, Parkin D, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled



- studies. *Arthritis Rheum.* 2002;46:995–1002. <https://doi.org/10.1002/art.10142>
14. Larosa M, Iaccarino L, Gatto M, Punzi L, Doria A. Advances in the diagnosis and classification of systemic lupus erythematosus. *Expert Rev Clin Immunol.* 2016;12:1309–1320. <https://doi.org/10.1080/1744666X.2016.1206470>
  15. Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant.* 2007;22:2531–2539. <https://doi.org/10.1093/ndt/gfm245>
  16. Moroni G, Gatto M, Tamborini F, et al. Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. *Ann Rheum Dis.* 2020;79:1077–1083. <https://doi.org/10.1136/annrheumdis-2020-216965>
  17. Gatto M, Saccon F, Andreoli L, et al. Durable renal response and safety with add-on Belimumab in patients with lupus nephritis in real-life setting (BeRLiSS-LN). Results from a large, nationwide, multicentric cohort. *J Autoimmun.* 2021;124:102729. <https://doi.org/10.1016/j.jaut.2021.102729>
  18. 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;79:914–920. <https://doi.org/10.1038/ki.2010.525>
  19. Davidson JE, Fu Q, Ji B, et al. Renal remission status and longterm renal survival in patients with lupus nephritis: a retrospective cohort analysis. *J Rheumatol.* 2018;45:671–677. <https://doi.org/10.3899/jrheum.161554>
  20. Petri M, Magder LS. Comparison of remission and lupus low disease activity state in damage prevention in a United States systemic lupus erythematosus cohort. *Arthritis Rheumatol.* 2018;70:1790–1795. <https://doi.org/10.1002/art.40571>
  21. Steiman AJ, Gladman DD, Ibañez D, Urowitz MB. Prolonged serologically active clinically quiescent systemic lupus erythematosus: frequency and outcome. *J Rheumatol.* 2010;37:1822–1827. <https://doi.org/10.3899/jrheum.100007>
  22. Medina-Quiñones CV, Ramos-Merino L, Ruiz-Sada P, Isenberg D. Analysis of complete remission in systemic lupus erythematosus patients over a 32-year period. *Arthritis Care Res (Hoboken).* 2016;68:981–987. <https://doi.org/10.1002/acr.22774>
  23. Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis.* 2015;74:2117–2122. <https://doi.org/10.1136/annrheumdis-2015-207347>
  24. Zen M, Iaccarino L, Gatto M, et al. The effect of different durations of remission on damage accrual: results from a prospective monocentric cohort of Caucasian patients. *Ann Rheum Dis.* 2017;76:562–565. <https://doi.org/10.1136/annrheumdis-2016-210154>
  25. Pakhotanon R, Gladman DD, Su J, Urowitz MB. Sustained complete renal remission is a predictor of reduced mortality, chronic kidney disease and end-stage renal disease in lupus nephritis. *Lupus.* 2018;27:468–474. <https://doi.org/10.1177/0961203317726376>
  26. Mok CC, Ying KY, Ng WL, et al. Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. *Am J Med.* 2006;119:355. <https://doi.org/10.1016/j.amjmed.2005.08.045>
  27. Chen YE, Korbet SM, Katz RS, Schwartz MM, Lewis EJ, Collaborative Study Group. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol.* 2008;3:46–53. <https://doi.org/10.2215/CJN.03280807>
  28. Hochberg M. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 1997;40:1725. <https://doi.org/10.1002/art.1780400928>
  29. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *Kidney Int.* 2004;65:521–530. <https://doi.org/10.1111/j.1523-1755.2004.00443.x>
  30. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int.* 2018;93:789–796. <https://doi.org/10.1016/j.kint.2017.11.023>
  31. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol.* 2002;29:288–291.
  32. Petri M, Kim MY, Kalunian KC, et al. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med.* 2005;353:2550–2558. <https://doi.org/10.1056/NEJMoa051135>
  33. Cruciani C, Zen M, Gatto M, Morand E, Doria A. Assessment of disease activity and damage in SLE: are we there yet? *Best Pract Res Clin Rheumatol.* Forthcoming. 2023. <https://doi.org/10.1016/j.berh.2023.101896>
  34. Levey AS, Eckardt KU, Dorman NM, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int.* 2020;97:1117–1129. <https://doi.org/10.1016/j.kint.2020.02.010>
  35. Petri MA, Merrill JT, Davis JC, Kennedy W. FRI029 Validation of the revised SELENA flare index in systemic lupus erythematosus. *Ann Rheum Dis.* 2013;72(suppl 3):A473–A474.
  36. Zen M, Bassi N, Nalotto L, et al. Disease activity patterns in a monocentric cohort of SLE patients: a seven-year follow-up study. *Clin Exp Rheumatol.* 2012;30:856–863.
  37. Gladman DD, Urowitz MB. The SLICC/ACR damage index: progress report and experience in the field. *Lupus.* 1999;8:632–637. <https://doi.org/10.1191/096120399680411335>
  38. R Development Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Accessed February 2, 2024. <http://www.R-project.org>
  39. Urowitz MB, Feletar M, Bruce IN, Ibañez D, Gladman DD. Prolonged remission in systemic lupus erythematosus. *J Rheumatol.* 2005;32:1467–1472.
  40. Arnaud L, Tektonidou MG. Long-term outcomes in systemic lupus erythematosus: trends over time and major contributors. *Rheumatol (Oxf Engl).* 2020;59(suppl 5):v29–v38. <https://doi.org/10.1093/rheumatology/keaa382>
  41. Moroni G, Porata G, Raffiotta F, et al. Beyond ISN/RPS lupus nephritis classification: adding chronicity index to clinical variables predicts kidney survival. *Kidney360.* 2021;3:122–132. <https://doi.org/10.34067/KID.0005512021>

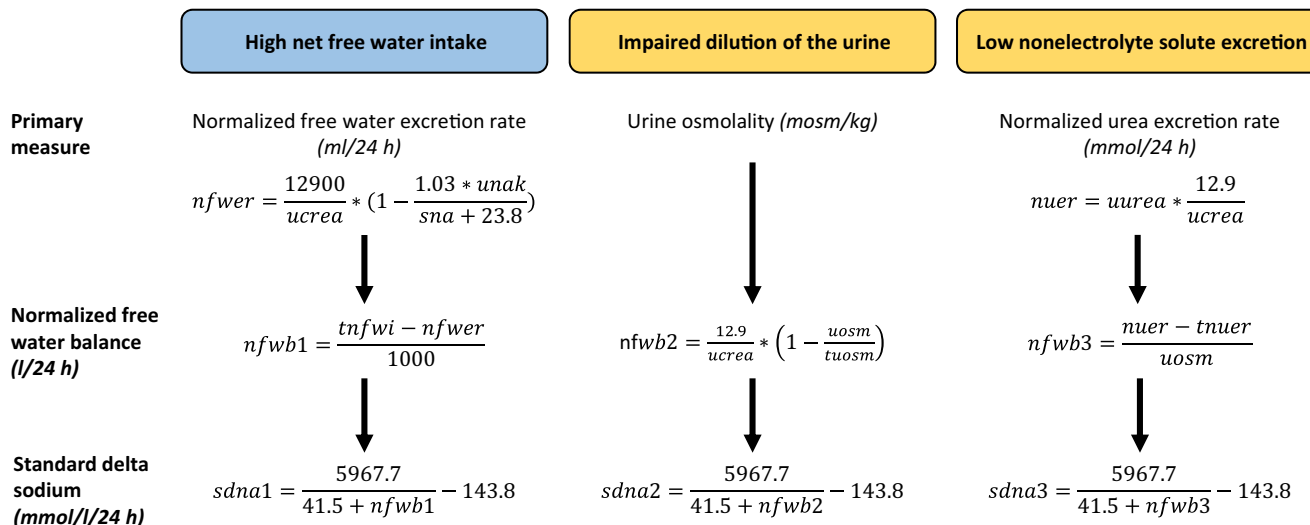
42. Legge A, Doucette S, Hanly JG. Predictors of organ damage progression and effect on health-related quality of life in systemic lupus erythematosus. *J Rheumatol*. 2016;43:1050–1056. <https://doi.org/10.3899/jrheum.150985>
43. Bruce IN, O’Keeffe AG, Farewell V, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. *Ann Rheum Dis*. 2015;73:1706–1713. <https://doi.org/10.1136/annrheumdis-2013-205171>
44. Frontini G, Tamborini F, Porata G, Regalia A, Binda V, Moroni G. Rate and predictors of chronic organ damage accrual in active lupus nephritis: a single centre experience over 18 years of observation. *Clin Exp Rheumatol*. 2022;40:872–881. <https://doi.org/10.55563/clinexp Rheumatol/ig0lu0>
45. Zen M, Fuzzi E, Loredo Martinez M, et al. Immunosuppressive therapy withdrawal after remission achievement in patients with lupus nephritis. *Rheumatol (Oxf Engl)*. 2022;61:688–695. <https://doi.org/10.1093/rheumatology/keab373>
46. Gatto M, Radice F, Saccon F, et al. Clinical and histological findings at second but not at first kidney biopsy predict end-stage kidney disease in a large multicentric cohort of patients with active lupus nephritis. *Lupus Sci Med*. 2022;9:e000689. <https://doi.org/10.1136/lupus-2022-000689>
47. Moroni G, Porata G, Raffiotta F, et al. Predictors of increase in chronicity index and of kidney function impairment at repeat biopsy in lupus nephritis. *Lupus Sci Med*. 2022;9:e000721. <https://doi.org/10.1136/lupus-2022-000721>
48. Pirson V, Enfrein A, Houssiau FA, Tamirou F. Absence of renal remission portends poor long-term kidney outcome in lupus nephritis. *Lupus Sci Med*. 2021;8:e000533. <https://doi.org/10.1136/lupus-2021-000533>
49. Moroni G, Frontini G, Ponticelli C. When and how is it possible to stop therapy in patients with lupus nephritis: a narrative review. *Clin J Am Soc Nephrol*. 2021;16:1909–1917. <https://doi.org/10.2215/CJN.04830421>
50. Korbet SM, Lewis EJ, Collaborative Study Group. Severe lupus nephritis: the predictive value of a  $\geq 50\%$  reduction in proteinuria at 6 months. *Nephrol Dial Transplant*. 2013;28:2313–2318. <https://doi.org/10.1093/ndt/gft201>
51. Tamirou F, Lauwerys BR, Dall’Era M, et al. A proteinuria cut-off level of 0.7 g/d after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. MAINTAIN nephritis trial investigators. *Lupus Sci Med*. 2015;2:e000123. <https://doi.org/10.1136/lupus-2015-000123>

## Update

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**Corrigendum to “Effect of Sustained Clinical Remission on the Risk of Lupus Flares and Impaired Kidney Function in Patients With Lupus Nephritis” [Kidney International Reports Volume 9, Issue 4, April 2024, Pages 1047–1056]**



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The authors regret that the footnote for Table 3 was published with errors in the *P* values. This has since been updated in the online version of the article in this issue.

The authors would like to apologize for any inconvenience caused.

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