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Response to therapy at 6 months predicts long-term renal outcome in lupus nephritis with poor kidney function

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ABSTRACT

Objective It is unclear whether aggressive treatment would benefit lupus nephritis (LN) with poor renal function, which has been excluded from most clinical trials. We aimed at demonstrating their clinicopathological features and prognosis.

Methods From August 2012 to December 2018, patients with active LN with poor renal function (estimated glomerular filtration rate (eGFR) between 15 and 59 mL/min/1.73 m^2) receiving induction therapy were included. Complete response (CR) was defined as proteinuria <0.5 g/24 hours, while partial response (PR) was defined as ≥50% proteinuria reduction to subnephrotic levels (<3.5 g/24 hours), with (near) normal eGFR. The primary outcome was end-stage renal disease (ESRD). The significant variables were selected via the least absolute shrinkage and selection operator method to construct prediction models for ESRD and treatment response.

Results A total of 107 patients were included. At 6 months, 18.7%, 38.3% and 43.0% of patients achieved CR, PR and no response (NR), respectively. During a median follow-up of 60 months, 40.2% ended up with reduced renal function (eGFR <60 mL/min/1.73 m^2) and 14.0% progressed to ESRD. The proportions of NR at 6 months were significantly higher in these patients compared with those with recovered renal function (p<0.001). In multivariable analysis, baseline eGFR ≤33 mL/min/1.73 m^2 (HR 3.499, 95% CI 1.044 to 11.730), fibrous crescent (HR 3.439, 95% CI 1.029 to 11.490) and NR at 6 months (HR 17.070, 95% CI 2.155 to 135.240) independently predicted ESRD (C-index 0.911, 95% CI 0.866 to 0.956). Further, baseline hypertension (HR 2.517, 95% CI 0.820 to 8.580), SLE duration>3 months (2.517, 1.012–7.226) and chronicity index (HR 1.757, 95% CI 1.371 to 2.414) predicted NR at 6 months (C-index 0.833, 95% CI 0.756 to 0.910).

Conclusions In patients with LN with poor renal function, no response at 6 months predicts a poor long-term renal outcome.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with lupus nephritis (LN) with poor renal function are at high risk of progression to end-stage renal disease (ESRD) or chronic kidney disease (CKD), but their response to induction therapy and long-term renal outcomes are unclear.

WHAT THIS STUDY ADDS

⇒ In patients with LN with baseline estimated glomerular filtration rate (eGFR) between 15 and 59 mL/min/1.73 m^2, 40.2% ended up with reduced renal function (eGFR <60 mL/min/1.73 m^2) and 14.0% progressed to ESRD during 5 years of follow-up, despite of induction therapy.

⇒ Also, no response at 6 months was a strong predictor of poor long-term prognosis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Achievement of early treatment response at 6 months could be an important goal in the management of patients with LN with poor renal function.

INTRODUCTION

Lupus nephritis (LN) is one of the most common organ-threatening manifestations of SLE and resulted to the development of chronic kidney disease (CKD) and increased morbidity.[1] With the induction therapy of corticosteroid (CS) and cyclophosphamide (CYC) or mycophenolate mofetil (MMF) as first-line treatment, the renal prognosis of LN improved significantly in the past 50 years.[2] Despite the introduction of new therapies in the last 20 years, the proportion of patients progressing to end-stage renal disease (ESRD) has not decreased, which is reported to be 10%–30% within 15 years.[2 3] Accordingly, it is critical to save patients with LN at high risk of renal deterioration to improve overall prognosis. According to previous studies, baseline serum creatinine or renal function has been a traditional stratifying factor for renal prognosis,[4 5] and so patients with poor baseline renal function are among the above-mentioned high-risk groups.

However, the characteristics of patients with active LN with poor renal function were largely unknown. Most of clinical trials in the past decade failed to include those with estimated glomerular filtration rate (eGFR) <30 or 45 mL/min/1.73 m^2.[6–11] Published data from a post hoc subgroup analysis study included 32 patients (eGFR <30 mL/min/1.73 m^2) from the ALMS trial, showing treatment response in 6 patients (18.8%) and serious adverse events (AEs) in 16 patients (50%) within 24 weeks.[12] But these results were limited by the small sample size and post hoc design. Moreover, a recent retrospective cohort showed that 62% of the LN-related advanced CKD did not progress over 10 years of follow-up, especially in those without active serology.[13] Satisfying management of LN activity might benefit these patients. However, the long-term renal prognosis of these patients is still unclear due to the lack of relevant studies on treatment.

Recent studies have emphasised the predictive value of serum creatinine after induction therapy at 6 months or 1 year.[14 15] The treat to target concept has been applied in several rheumatic disease, as achieving accurate therapeutic targets could optimise the outcomes and facilitate routine follow-ups. The 2019 European League Against Rheumatism/ European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) joint recommendation pointed that complete response (CR) should be targeted by 12 months following induction therapy in LN.[16] Particularly in clinical practice, short-term endpoints are of critical importance in guiding clinical decision and improving treatment efficacy. For patients with severe renal insufficiency, the efficacy of aggressive induction therapy has not been validated. And reliable predictors of long-term renal prognosis are needed.

Above all, we performed this retrospective study in a large cohort of Chinese patient with LN with poor renal function in order to examine (1) long-term prognosis after induction therapy; (2) the potential predictive value of short-term treatment response; and (3) the safety of induction therapy in these patients.

MATERIALS AND METHODS

Patients

We conducted a retrospective cohort study enrolling consecutive patients with a biopsy-proven LN at Peking Union Medical College Hospital (PUMCH) from August 2012 to December 2018. Written informed consents were obtained whenever needed.

A total of 467 patients with LN were screened (online supplemental figure S1). Inclusion criteria were (1) baseline eGFR <60 mL/min/1.73 m^2 and ≥15 mL/min/1.73 m^2, calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; (2) renal pathology defined as class III/IV±V or V, according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria;[17] (3) induction therapies were given. Exclusion criteria were (1) renal biopsy with <5 scorable glomeruli; (2) loss of follow-up within 6 months after renal biopsy; (3) not meeting the follow-up endpoint due to death within 6 months of induction therapy.

Variables

In this study, we defined the status at the time of renal biopsy as baseline. The following baseline clinical variables were collected, including demographics, clinical and laboratory assessments, pathological characteristics based on the 2003 ISN/RPS classification and scored in terms of activity index (AI) and chronicity index (CI).[18] The induction therapies were recorded, as well as the AEs occurring within 6 months after induction therapy according to the Common Terminology Criteria for Adverse Events, version 5.0. The SLE duration was defined as the time interval between SLE diagnosis and renal biopsy. The LN duration was defined as the time interval between the time from the onset of symptoms or abnormal laboratory indicators associated with kidney disease and renal biopsy. CKD was defined as an eGFR <60 mL/min/1.73 m^2 for at least three months. ESRD was defined as an eGFR <15 mL/min/1.73 m^2, dialysis or kidney transplantation. Therapeutic responses were monitored via the level of serum creatinine and proteinuria during the follow-up.

According to the 2019 EULAR/ERA-EDTA recommendations for categorising renal response, CR was defined as proteinuria <0.5 g/24 hours, normal or near normal eGFR (within 10% of normal eGFR if previously abnormal); partial response (PR) was defined as ≥50% proteinuria reduction to subnephrotic levels (<3.5 g/24 hours), normal or near normal eGFR; and no response (NR) was defined as all the other cases. The primary outcome was ESRD during the follow-up, which ended on 31 December 2021.

Statistical analysis

Descriptive data with normal distributions were presented as mean±SD and compared using independent samples t-tests. Data without normal distributions were presented as median with IQR and compared using Wilcoxon test. Normality was explored with the Shapiro-Wilk test. χ^2 test or Fisher's exact test was used for comparison of categorical data, which were expressed as count and percentage. Survival curves were drawn by Kaplan-Meier estimate and compared with log-rank test.

All 32 clinical factors and 13 pathological features were collected and screened for the construction of ESRD or CKD prediction models (online supplemental figure S3). The above clinical variables excluding NR were screened for NR prediction models. Missing antibody profile data were filled in by multiple imputation. The least absolute shrinkage and selection operator (LASSO) method including 10-fold cross-validation via minimum criteria and the 1 SE of the minimum criteria was used to select the most predictive features. The identified statistically significant variables were used in the construction of Cox regression model for ESRD or CKD and logistic

regression model for NR. To extend to patients without renal biopsy, we constructed models based on both clinical and clinicopathological variables, respectively. The optimal cut-offs were chosen based on the highest Youden Index. Nomograms were used for model presentation, while C-index and calibration curves were used for model evaluation. For the ESRD prediction model, 5-year renal survival probability was evaluated by calibration curve and nomograms. This timepoint was chosen on the basis of the median follow-up.

P values <0.05 were considered statistically significant. All statistical analyses were performed using R software (V.4.1.3).

RESULTS

Baseline characteristics and outcome

A total of 107 patients with LN were included in this study, with their clinical and histological characteristics shown in table 1. The median age was 33 years (IQR 23–46) at recruitment, and 84.1% of these patients were female. Of those patients, 72.9% had hypertension. The level of proteinuria was 6.2 g/24 hours (IQR 3.7–10.3) and the median eGFR was 36.6 mL/min/1.73 m^2 (IQR 27.0–49.4). The distributions of baseline eGFR were as follows: 35 patients with eGFR between 15 and 29 mL/min/1.73 m^2, 34 patients between 30 and 44 mL/min/1.73 m^2, and 38 patients between 45 and 59 mL/min/1.73 m^2.

As for the induction schemes, 71.0% of patients received methylprednisolone pulses, 76.6% were treated with large doses of CS combined with CYC (CS-CYC) and 11.2% combined with MMF (CS-MMF). After 6 months, 20 (18.7%) of them reached CR and 41 (38.3%) reached PR. In contrast, the rest of the 46 patients (43.0%) were defined NR at the same time. After a median follow-up of 60 months (IQR 36–84), 64 patients (59.8%) ended up with an eGFR higher than 60 mL/min/1.73m^2, among whom 45 patients achieved complete remission of proteinuria, and 18 achieved partial remission of proteinuria. Notably, 40.2% ended up with reduced renal function (eGFR <60 mL/min/1.73 m^2) and 15 patients (14.0%) progressed to ESRD. A total of four patients (3.7%) died, among whom one died of cardiovascular event, one died of catastrophic antiphospholipid antibody syndrome and two died of unknown causes.

The baseline features of patients who developed ESRD were shown in table 1. The ESRD group presented with higher levels of proteinuria, worse renal function, higher CI, less ACEI/ARB usage and renal response, compared with those in the non-ESRD group (p<0.05). All chronic pathology scores and interstitial inflammation were more severe in the ESRD group, as shown in online supplemental table S1. The treatment response and renal prognosis for patients with different baseline renal functions were shown in online supplemental figure S2.

Feature selection and nomogram models for ESRD

By LASSO regression method, two candidate variables (NR, eGFR) were selected for model 1 from 32 clinical features, and four candidate variables (eGFR, fibrous crescent, CI, NR) were selected to construct model 2 from 45 clinicopathological variables (online supplemental figure S3). The optimal cut-off of eGFR was 33.42 mL/min/1.73 m^2 (online supplemental figure S6A) and the ESRD-free survival rate of patients with eGFR ≤33 mL/min/1.73 m^2 was significantly lower (p=0.002) (figure 1A). By Cox regression, eGFR ≤33 mL/min/1.73 m^2, fibrous crescent and NR were independent predictors for ESRD. The proposed model (model 1), including eGFR ≤33 mL/min/1.73 m^2 (HR 5.149, 95% CI 1.628 to 16.290) and NR (HR 23.828, 95% CI 3.118 to 182.110), was presented with a C-index of 0.884 (95% CI 0.835 to 0.933). Model 2 with renal pathological features included eGFR ≤33 mL/min/1.73 m^2 (HR 3.499, 95% CI 1.044 to 11.730), fibrous crescent (HR 3.439, 95% CI 1.029 to 11.490) and NR (HR 17.070, 95% CI 2.155 to 135.240) showing a C-index of 0.911 (95% CI 0.866 to 0.956) (table 2). The nomograms and calibration curves predicting 5-year renal survival were shown in figure 2 and online supplemental figure S7A,B.

In multivariable analyses, the predictors of CKD were age, SLE duration, CI and NR at 6 months, which were similar to the predictors of ESRD (online supplemental table S2).

Baseline predictors and nomogram models of NR

As shown in the Kaplan-Meier curve, the ESRD-free survival rate of NR group was significantly lower than those of CR and PR (p=0.014, p<0.001, respectively), and ESRD-free survival rates did not differ between the latter two (p=0.355) (figure 1B). Moreover, the renal prognosis was worst for patients with baseline eGFR ≤33 mL/min/1.73 m^2 and NR at 6 months, with no difference in prognosis for the remaining patients (p<0.001) (online supplemental figure S4).

By LASSO regression method, three candidate variables (age, hypertension, SLE duration) were selected from 31 clinical features for model 3 and four candidate variables (hypertension, SLE duration, CI, interstitial fibrosis) were selected from 44 clinicopathological variables for model 4 (online supplemental figure S5). The optimal cut-off of SLE duration was 3.4 months (online supplemental figure S6B). By logistics regression (table 3), model 3 was presented with C-index of 0.746 (95% CI 0.658 to 0.833), including hypertension (HR 3.068, 95% CI 1.097 to 9.555) and SLE duration >3 months (HR 5.036, 95% CI 2.156 to 12.350). Model 4 was composed of hypertension (HR 2.517, 95% CI 0.820 to 8.580), SLE duration >3 months (HR 2.517, 95% CI 1.012 to 7.226) and CI (HR 1.757, 95% CI 1.371 to 2.414), showing a C-index of 0.833 (95% CI 0.756 to 0.910) (vs model 1, p=0.011). The nomograms and calibration curves predicting NR were shown in figure 3 and online supplemental figure S7C,D.

Table 1 Baseline characteristics and outcomes of 107 patients with lupus nephritis

Baseline characteristics	Overall (n=107)	Non-ESRD (n=92)	ESRD (n=15)	P value
Demographics				
Female, n (%)	90 (84.1%)	78 (84.8%)	12 (80.0%)	0.704
Age, years	33 (23–46)	34 (24–46)	30 (21–50)	0.953
SLE duration, months	3.9 (1.2–83.0)	2.3 (1.2–82.5)	54.2 (8.6–94.5)	0.221
LN duration, months	5.2 (1.2–39.8)	3.2 (1.2–39.0)	23.6 (3.6–53.5)	0.134
Hypertension, n (%)	78 (72.9%)	65 (70.7%)	13 (86.7%)	0.346
Diabetes mellitus, n (%)	15 (14.0%)	13 (14.1%)	2 (13.3%)	0.934
Laboratory examinations				
Haemoglobin, g/L	92±17	93±17	85±14	0.101
White cell count, $\times10^9$/L	7.14 (5.06–9.78)	7.12 (5.02–9.53)	7.15 (5.64–9.88)	0.654
Platelets, $\times10^9$/L	169 (131–236)	166 (130–218)	205 (132–274)	0.092
C3, g/L	0.444 (0.336–0.645)	0.435 (0.334–0.639)	0.525 (0.362–0.715)	0.217
C4, g/L	0.091 (0.053–0.154)	0.091 (0.052–0.154)	0.117 (0.060–0.205)	0.296
Anti-dsDNA, n (%)	69 (64.5%)	61 (66.3%)	8 (53.3%)	0.330
Anti-SSA, n (%)	57 (53.3%)	49 (53.3%)	8 (53.3%)	0.996
Anti-SSB, n (%)	14 (13.1%)	13 (14.1%)	1 (6.7%)	0.687
Anti-RNP, n (%)	42 (39.3%)	33 (35.9%)	9 (60.0%)	0.076
Anti-rRNP, n (%)	27 (25.2%)	24 (26.1%)	3 (20.0%)	0.756
Anti-Smith, n (%)	29 (27.1%)	23 (25.0%)	6 (40.0%)	0.228
Coombs' test, n (%)	34 (31.8%)	33 (35.9%)	1 (6.7%)	0.034
aPL antibodies, n (%)	22 (20.6%)	20 (21.7%)	2 (13.3%)	0.731
Serum albumin, g/L	26.1±5.9	26.2±6.0	25.6±5.7	0.720
Proteinuria, g/24 hours	6.2 (3.7–10.3)	5.9 (3.4–9.8)	9.0 (4.9–12.7)	0.039
Microscopic haematuria, /uL	162.2 (52.7–526.7)	180.4 (60.1–561.9)	73.0 (30.0–381.8)	0.087
Serum creatinine, µmol/L	163 (126–202)	152 (123–191)	195 (171–265)	0.012
eGFR, mL/min/1.73 m^2	36.6 (27.0–49.4)	39.3 (28.1–49.7)	27.3 (24.3–33.4)	0.008
Disease evaluation				
SLEDAI	14 (12–18)	14 (12–18)	12 (10–16)	0.074
Extrarenal SLEDAI	5 (2-7)	5 (4-7)	4 (2-6)	0.141
Extrarenal organ involvement	1 (0–1)	1 (0–2)	0 (0–1)	0.388
Histological class, ISN/RPS				0.965
Class III, n (%)	8 (7.5%)	7 (7.6%)	1 (6.7%)	
Class IV, n (%)	69 (64.5%)	59 (64.1%)	10 (66.7%)	
Class V, n (%)	2 (1.9%)	2 (2.2%)	0	
Class III+V, n (%)	5 (4.7%)	4 (4.3%)	1 (6.6%)	
Class IV+V, n (%)	23 (21.4%)	20 (21.8%)	3 (20.0%)	
Activity index	14 (12–17)	14 (11–17)	14 (12–15)	0.815
Chronicity index	4 (3-5)	3 (3-5)	6 (5-8)	0.000
Treatment				
Induction therapy, n (%)				
Methylprednisolone pulses	76 (71.0%)	64 (69.6%)	12 (80.0%)	0.546
CS+CYC	82 (76.6%)	68 (73.9%)	14 (93.3%)	0.184
CS+MMF	12 (11.2%)	12 (13.0%)	0	0.210
CS+others	13 (12.2%)	12 (13.1%)	1 (6.7%)	
Hydroxychloroquine, n (%)	75 (70.1%)	65 (70.7%)	10 (66.7%)	0.766

Continued

Table 1 Continued

Baseline characteristics	Overall (n=107)	Non-ESRD (n=92)	ESRD (n=15)	P value
ACEI/ARB, n (%)	54 (50.5%)	50 (54.3%)	4 (26.7%)	0.047
Haemodialysis, n (%)	7 (6.5%)	6 (6.5%)	1 (6.7%)	0.983
Plasma exchange, n (%)	4 (3.7%)	4 (4.3%)	0	0.410
Outcome				
Follow-up, months	60 (36–84)	64 (39–86)	27 (14–36)	0.000
Proteinuria after 6 months, g/24 hours	1.4 (0.4–3.0)	1.3 (0.4–2.6)	3.0 (2.0–4.7)	0.002
CR after 6 months, n (%)	20 (18.7%)	19 (20.7%)	1 (6.7%)	0.294
PR after 6 months, n (%)	41 (38.3%)	41 (44.6%)	0	0.001
NR after 6 months, n (%)	46 (43.0%)	32 (34.7%)	14 (93.3%)	0.000
Stage 1 CKD, n (%)	32 (29.9%)	32 (34.8%)	/	/
Stage 2 CKD, n (%)	32 (29.9%)	32 (34.8%)	/	/
Stage 3 CKD, n (%)	16 (15.0%)	16 (17.4%)	/	/
Stage 4 CKD, n (%)	8 (7.5%)	8 (8.7%)	/	/
Death, n (%)	4 (3.7%)	4 (4.3%)	0 (0.0%)	0.410

CS+others of induction therapy included CS+CYC+ MMF, CS+MMF+calcineurin inhibitor (CNI), CS+CNI, CS+MMF+Leflunomide.
ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; aPL, antiphospholipid antibodies; CKD, chronic kidney disease; CR, complete response; CS, corticosteroids; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; INS/RPS, International Society of Nephrology/Renal Pathology Society; MMF, mycophenolate mofetil; NR, no response; PR, partial response; SLEDAI, SLE Disease Activity Index.

Adverse events

A total of 111 patients received induction therapy, of whom 4 (3.6%) died (2 died of severe pneumonia and 2 died of cardiovascular events) and 65 (58.6%) suffered AEs during 6 months post treatment (online supplemental table S3). The most common AE was infection (51.4%), including cytomegalovirus (CMV) infections (23.4%) and pneumonia (18.2%). There was no significant difference in adverse events between responders and non-responders (all p>0.05).

DISCUSSION

The long-term prognosis of patients with LN presented with poor renal functions was unknown, as they were mostly excluded from most clinical trials.[6–11] On the other hand, these patients were considered with high risks of progression into ESRD, thus proper management strategies are needed.[4 5] Data are lacking in guiding risk stratifications among these specific group of patients with LN. We retrospectively reviewed 107 consecutive patients with LN with impaired renal function (eGFR 15–59 mL/

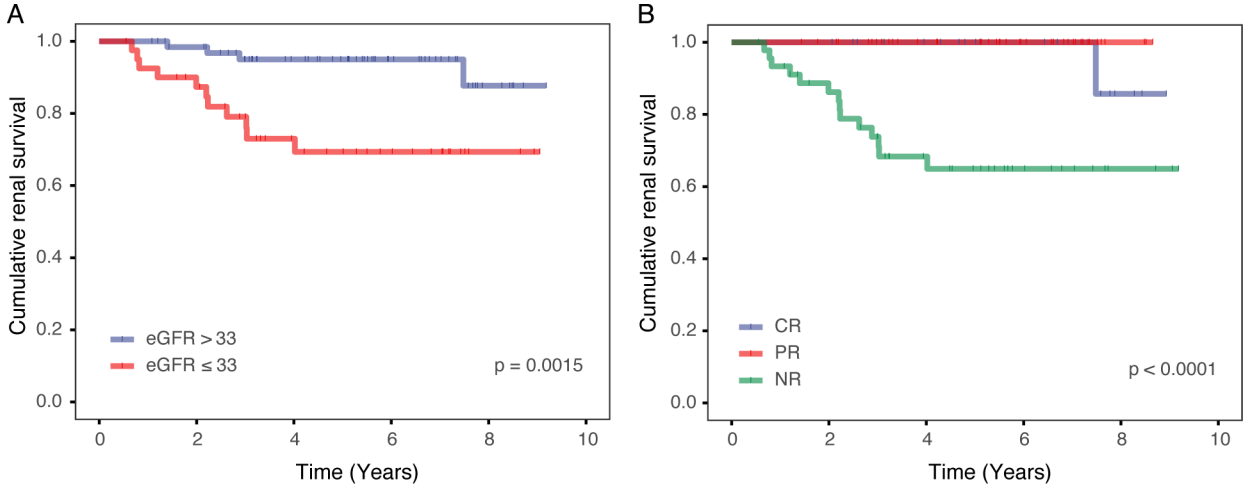

Figure 1 Kaplan-Meier ESRD-free survival curves of 107 patients grouped by baseline eGFR (A) and renal response to induction therapy at 6 months (B). CR, complete response; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NR: no response; PR, partial response.

Table 2 Multivariable Cox regression analyses: predictors of ESRD with baseline clinicopathological characteristics and renal response at 6 months

	Model 1: without pathology			Model 2: with pathology		
	HR	95% CI	P value	HR	95% CI	P value
eGFR ≤33 mL/min/1.73 m^2	5.149	1.628 to 16.290	0.005	3.499	1.044 to 11.730	0.042
Fibrous crescent				3.439	1.029 to 11.490	0.045
NR at 6 months	23.828	3.118 to 182.110	0.002	17.070	2.155 to 135.240	0.007
C-index	0.884 (0.835 to 0.933)			0.911 (0.866 to 0.956)		

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; NR, no response.

min/1.73 m^2). Totally, 14.0% of them progressed to ESRD after a median follow-up of 60 months. This is slightly higher than the 5-year ESRD risk estimates (11%, 95% CI 10% to 12%) provided by a previous meta-analysis.[2] Considering renal histological classes, 5-year ESRD risks have been estimated to be highest in patients with class IV LN (19%, 95% CI 12 to 29%).[2] The general progression risk in our cohort could be partly explained by the popularity of class IV renal histology (class IV 64.5%, class IV+V 21.4%, table 1).

The two models we constructed for ESRD prediction underscored the importance of baseline renal function and treatment response at 6 months. The formal one has been traditionally introduced as a critical prediction component in multiple studies.[4 5] In this specific cohort, the optimal cut-off for eGFR was 33 mL/min/1.73 m^2 in the nomogram. When applied to patients with milder renal function impairment, proper adjustment of this cut-off is needed. Many recent studies have shown that treatment response (combination of eGFR and proteinuria) at 12 month predicts the long-term renal prognosis and renal flares.[14 19 20] The treatment goal derived from the 2019 EULAR/ERA-EDTA is a notable decrease in proteinuria (with GFR normalisation/stabilisation) by 3 months, at least 50% reduction in proteinuria by 6 months, and ultimately proteinuria <0.5–0.7 g/24 hours by 12 months since the start of treatment.[16] In our study, we did not observe a significant difference among the proportions of NR at 6, 12 and 24 months (43.0% vs 34.0% vs 35.9%, Kendall's W test, p=0.459), thus NR at 6 months was chosen for early prediction (online supplemental figure S8). Also, we found that treatment response at 6 months was a better predictor than most baseline features. As shown in the nomogram (figure 2) and Kaplan-Meier curves (online supplemental figure S4), the impact of NR at 6 months was larger than eGFR ≤33 mL/min/1.73 m^2 and fibrous crescent.

During follow-up, 40.2% of patients with LN ended up with reduced renal function despite standard induction therapy. Among these patients, 84.6% presented NR at 6 months (online supplemental table S2). Patients with CKD were at higher risk of progression to ESRD during a longer follow-up, and further observations were needed for these patients.

Specifically, proteinuria after 12 months of treatment has been recognised as a better predictor than the baseline proteinuria in multiple studies of patients with LN.[21–24] In our study, the medium proteinuria levels at baseline and 6 months were significantly higher in the ESRD group (table 1). However, proteinuria level at 6 months was not selected by the LASSO regression model, which was also validated by receiver operating characteristic (ROC) curves. As shown in online supplemental figure S9, the area under curve of proteinuria at 6 months was 0.754

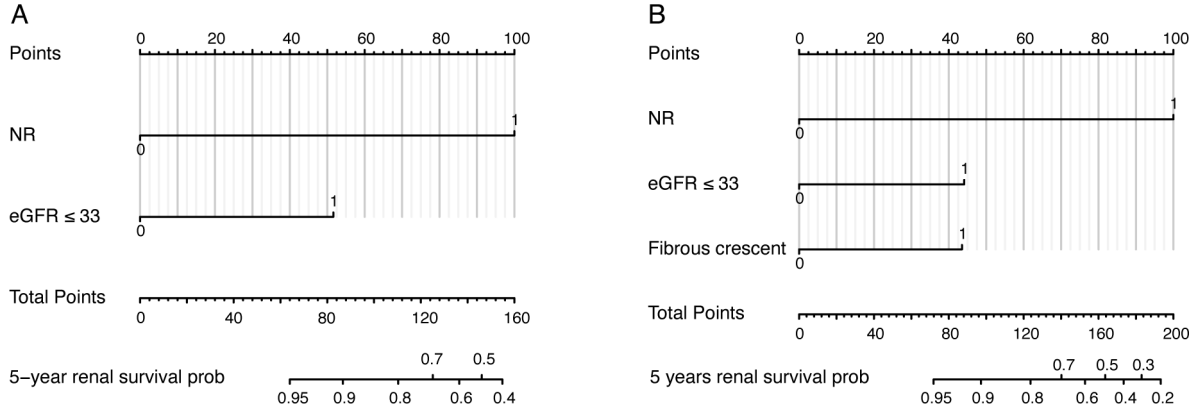

Figure 2 Nomograms of prediction models for 5-year renal survival without and with pathology. (A) The prognostic nomogram with two clinical features for LN patients with ESRD (model 1). (B) The prognostic nomogram with two clinical features and one histological feature for LN patients with ESRD (model 2). eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; LN, lupus nephritis.

Table 3 Univariable and multivariable logistic regression analyses: baseline predictors of no response at 6 months

	Univariable analysis			Model 3: without pathology			Model 4: with pathology		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Female	0.467	0.163 to 1.339	0.156						
Age, years	1.044	1.013 to 1.075	0.004						
SLE duration >3 months	5.808	2.547 to 13.996	0.000	5.036	2.156 to 12.350	0.000	2.517	1.012 to 7.226	0.048
Hypertension	4.035	1.481 to 10.993	0.006	3.068	1.097 to 9.555	0.039	2.517	0.820 to 8.580	0.118
SLEDAI	0.927	0.854 to 1.005	0.066						
Low C3	0.279	0.114 to 0.683	0.005						
Low C4	0.384	0.173 to 0.853	0.019						
Coombs' test	0.314	0.118 to 0.841	0.021						
Proteinuria, g/24 hours	1.014	0.948 to 1.083	0.691						
Microscopic haematuria, /uL	0.999	0.999 to 1.000	0.042						
Serum creatinine, µmol/L	1.003	0.997 to 1.009	0.393						
eGFR, mL/min/1.73 m^2	0.987	0.957 to 1.017	0.386						
Activity index	0.924	0.840 to 1.016	0.103						
Chronicity index	1.949	1.477 to 2.572	0.000				1.757	1.371 to 2.414	0.000
Methylprednisolone pulses	0.421	0.180 to 0.988	0.047						
C-index					0.746 (0.658 to 0.833)		0.833 (0.756 to 0.910)		0.011

eGFR, estimated glomerular filtration rate; SLEDAI, SLE Disease Activity Index.

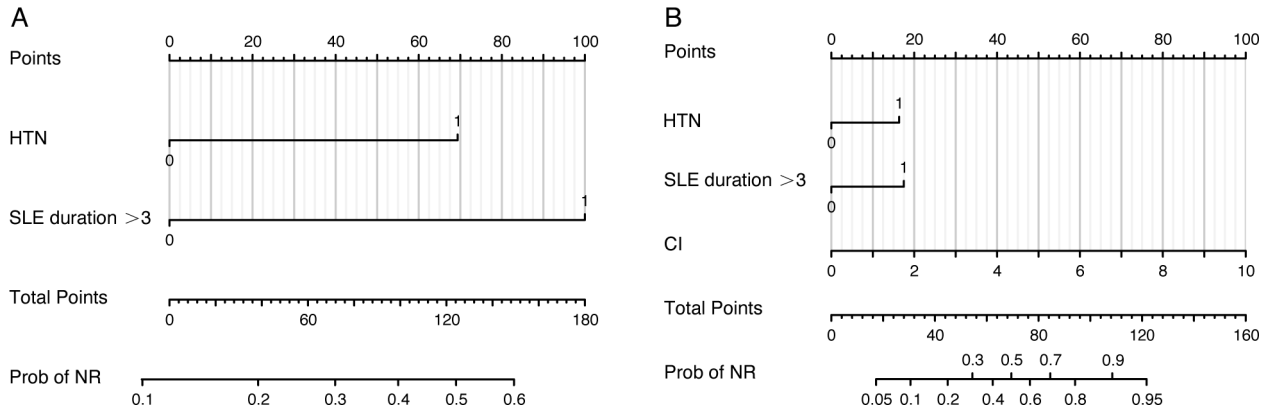

Figure 3 Nomograms of prediction models for NR without and with pathology. (A) The prognostic nomogram with two clinical features for patients with LN with NR (model 3). (B) The prognostic nomogram with two clinical features and one histological feature for patients with LN with NR (model 4). LN, lupus nephritis; NR, no response; HTN, hypertension.

and the optimal cut-off value was 2.5 g/24 hours, with a sensitivity of 73.3% and a specificity of 75%. The discrepancy between our analysis and the literature might arouse from the differences in patients' characteristics. For example, analyses of two important LN trials, the MAINTAIN Nephritis Trial and the Euro-Lupus Nephritis Trial, proposed proteinuria <0.7–0.8 g/24 hours at 12 months after induction therapy was the single best predictor of long-term renal prognosis.[21 22] However, the baseline serum creatinine and proteinuria of patients with LN in this trial was lower than those of our patients.

The use of hydroxychloroquine (HCQ) was not found to be a protective factor for ESRD in our study (HR 0.971, 95% CI 0.327 to 2.883, p=0.957). Although HCQ is an important background therapy among patients with SLE, as recommended by the EULAR/ERA-EDTA.[16] However, most supporting data originated from retrospective observational studies, and the benefit of HCQ in patients with LN was relatively controversial. A recent large retrospective population-based cohort study showed that HCQ use in patient with SLE is neutral in reducing subsequent risk of CKD.[25] Moreover, the serum concentrations of HCQ and adherence of HCQ usage may also affect its therapeutic efficacy.[26–28] The renal protective role of HCQ in patients with LN still needs to be further investigated.

Further analysis revealed that clinical indicators of SLE duration and hypertension, as well as the pathology variable of CI, were independent risk factors for NR at 6 months, in keeping with previous studies.[14 19] Notably, the proportion of hypertension and renal CI scores were higher in our patients compared with those in other studies.[4 8]

We proposed two sets of nomograms, with or without renal pathology features, as convenient tools for prognosis prediction in real-world practice. This was based on the practical notion that not all patients with LN were appropriate for renal biopsy, especially for those with contraindications. Renal pathology features, especially chronic indicators, significantly improved the C-indexes of these models, for both ESRD prediction and NR prediction. CI score was an independent risk for predicting treatment response and renal outcome. Fibrous crescent was strongly associated with CI (r=0.532, p<0.001) and has been validated as an independent risk factor for ESRD in other studies.[29–31] The renal vascular pathology was not evaluated in our text because previous studies indicated that it was not associated with renal outcomes and lacked the good assessment parameters.[32 33]

In terms of AEs, 4 patients from a total of 111 receiving induction therapy died, and the leading causes of death were pulmonary infections and cardiovascular events, in keeping with previous data.[34 35] Since the majority of AEs were observed at the start of treatment and for comparison with published randomized controlled trial (RCT) studies, we summarised the AEs during the 6-month induction treatment period. Notably, 23.4% of patients experienced CMV infections and 3.6% with invasive fungal infections, which were rarely mentioned in RCT studies. A retrospective study of a Chinese population showed that 5.3% of hospitalised patients with LN had CMV infection, which may mimic lupus flares leading to difficulties in diagnosis and subsequent treatment management.[36 37] Our analysis found that CMV was not a predictor of treatment response or ESRD, although it was more common in responders. It suggested that we need to be vigilant about CMV infection and that its effect on lupus needs to be verified in a larger sample of studies.

There were some limitations in our study. First, this was a single-centre retrospective study and the sample size was relatively limited. Second, due to the limitations of the retrospective study itself, detailed data on therapy adjustment after NR were not available in the context, resulting in a lack of in-depth interpretation of the treatment of patients with NR, as well as lack of data related to maintenance regimens, the renal flares and withdrawal of immunosuppressive therapy. Third, our model is based on patients with renal biopsy and needs further validation if it can be fully replicated to patients without renal biopsy. Further prospective studies with multiple centres and more therapeutic information are needed.

CONCLUSION

In summary, patients with LN with poor renal function commonly presented with more proteinuria and proliferative and chronic lesions in renal pathology. But after induction therapy, 57% of them reached CR or PR after 6 months and 14% progressed into ESRD after 5 years. Infections were common in these patients, but could be managed with satisfying results. Apart from baseline renal function, NR at 6 months was an important predictor of long-term prognosis in these patients.

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Patient consent for publication Not applicable.

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