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Long-Term Kidney Outcome of Lupus Nephritis by Renal Response Status

Desmond Yat Hin Yap[1,5], Xiaomeng Xu[2,5], Patricia C. Juliao[3], Colin S.O. Tang[1], Laura Ng[4], Dominique Milea[2] and Tak Mao Chan[1]

[1]School of Clinical Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong, China; [2]GCI VEO, GSK, Singapore; [3]Immunology and Opportunistic Epidemiology, VEO, GSK, Collegeville, Pennsylvania, USA; and [4]GSK HK, Hong Kong

Introduction: Limited evidence exists that clinical trial treatment response criteria predict long-term outcomes in Asian patients with lupus nephritis (LN).

Methods: This retrospective analysis of prospectively collected data from the Hong Kong Queen Mary Hospital Cohort categorized adults with biopsy-proven LN (Class III, IV, V, or mixed [III ± V, IV ± V]) after standard treatment for 2 years postbiopsy and immunosuppression induction according to modified primary efficacy renal response (mPERR: estimated glomerular filtration rate [eGFR] ≥ 60 ml/min per 1.73 m^2 or ≤ 20% below biopsy value AND urine protein-to-creatinine ratio [uPCR] ≤ 0.7) and modified complete renal response (mCRR; eGFR ≥ 90 ml/min per 1.73 m^2 or ≤ 10% below biopsy value AND uPCR ≤ 0.5). Associations between 2-year mPERR/mCRR status and long-term kidney survival and mild chronic kidney disease (CKD) or worse (stage ≥ 3) were assessed.

Results: Of the 176 Chinese patients, 64.2% achieved mPERR and 43.8% achieved mCRR at 2 years postbiopsy. After mean follow-up of 15.3 years, significantly higher proportions of mPERR and mCRR responders versus nonresponders achieved long-term kidney survival (mPERR: 85.8% vs. 71.4%; $P = 0.029$; mCRR: 92.2% vs. 71.7%; $P < 0.001$). mPERR and mCRR achievement was associated with adjusted risk reductions for kidney nonsurvival of 60% ($P = 0.034$) and 86% ($P < 0.001$), respectively. Adjusted risk for mild CKD or worse (stage ≥ 3) was 82% ($P = 0.013$) and 87% ($P = 0.012$) lower for mPERR and mCRR responders, respectively, versus nonresponders.

Conclusion: In Chinese patients with LN, mPERR and mCRR at 2 years postbiopsy predict superior long-term kidney outcomes and lower CKD progression risk.

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The most common severe manifestation of systemic lupus erythematosus (SLE) is LN, which develops in approximately 40% of patients with SLE and varies by patient demographics.[1] If left untreated, the continued inflammation due to immune intolerance and B-cell abnormalities results in kidney damage.[2,3] LN is associated with significantly increased risks of CKD, kidney failure, and death.[1,4,5] In an international cohort study of patients with SLE, LN was associated with a cumulative incidence of kidney failure of 10.1% and a cumulative incidence of death of 5.9% at 10 years after LN diagnosis.[1] Therefore, it is important to be able to identify predictors of improved renal response to optimize patient outcomes.

Glucocorticoids and immunosuppressants are the mainstay of treatment for LN.[6–8] In Asia, glucocorticoids in combination with mycophenolate mofetil or cyclophosphamide are the most commonly used initial therapies for class III/IV LN.[9,10] Latest Kidney Disease Improving Global Outcomes and European guidelines also recommend belimumab (a recombinant human IgG-1λ monoclonal antibody that binds to B lymphocyte stimulator antagonizing its activity), or calcineurin inhibitors, as add-on treatments for active Class III/IV ± Class V LN, or all classes, respectively.[7,8]

Renal response in LN clinical trials is typically defined by an improvement in proteinuria, no worsening in kidney function, and no use of rescue treatment.[7,11] However, there is a lack of consensus on the

Correspondence: Tak Mao Chan, PB408, 4 Fl. Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. E-mail: dtmchan@hku.hk

[5]DYHY and XX are co-first authors.

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optimal threshold levels.[7,12,13] Analyses of long-term follow-up data for the Euro-Lupus Nephritis trial and MAINTAIN Nephritis trial cohorts showed that a reduction in the level of proteinuria to < 0.7 to 0.8 g/d predicted a favorable long-term kidney outcome, and this was supported by real-world studies.[13-15] In addition, an eGFR < 60 ml/min per 1.73 m^2 at biopsy has been demonstrated to be a predictor of poor long-term prognosis.[16,17] In the phase 3 BLISS-LN belimumab trial, the primary end point was a composite primary efficacy renal response, defined as a ratio of uPCR ≤ 0.7, an eGFR $\leq 20\%$ below preflare level or ≥ 60 ml/min per 1.73 m^2, and no use of rescue therapy for treatment failure (e.g., glucocorticoids had to be tapered to ≤ 10 mg/d and this dose could not be exceeded through week 104).[11]

Real-world studies using data from the Hopkins Lupus Cohort and the University of Toronto Lupus Cohort have shown a modified version of the primary efficacy renal response (mPERR [excluding the treatment failure component]) applied in BLISS-LN, assessed at 2 years postbiopsy, can predict long-term outcomes over a median follow-up of approximately 6 years in the Hopkins Lupus Cohort and a mean follow-up of 7 to 11 years in the University of Toronto Lupus Cohort.[18-20] Patients who achieved mPERR at 2 years were significantly less likely to experience kidney failure or death or CKD compared with those without mPERR.[18-20]

Real-world evidence on the prognostic value of mPERR in Asian populations is lacking. Considering that the prevalence and severity of LN have been reported to be higher among Asian patients with SLE compared with Caucasians,[21,22] it is important to examine the clinical utility of mPERR and its prognostic significance in Asian populations. The primary objective of this analysis using data from the Queen Mary Hospital Lupus Nephritis Cohort (QMHLNC) in Hong Kong was to assess the association between mPERR at 2 years postbiopsy and long-term kidney survival in Chinese patients with LN, and hence the predictive value of mPERR in an Asian population with LN.

METHODS

Study Design

In this retrospective, single-center, cohort study (GSK Study 216940), data prospectively collected from the QMHLNC in Hong Kong were analyzed. The QMHLNC database includes inpatient and outpatient records of all patients attending the SLE clinic of Queen Mary Hospital since 1968.[23-25] Data in the QMHLNC were continually updated and included medical history, comorbidities, SLE complications, laboratory measures, treatments, and outcomes. In the early stages of disease, data were recorded every 2 to 4 weeks; in patients with stable disease, data were recorded every 12 to 16 weeks. The daily dose of prednisolone and immunosuppressive medications was recorded at each visit.

Eligible patients with biopsy-confirmed LN from the start of the cohort history up to 2019 were identified and retrospectively categorized into responder or nonresponder categories according to their kidney status determined at 2 years postbiopsy (730 days assuming an average month length of 30.43 days). The time gap between kidney biopsy and the start of induction immunosuppression was generally less than 48 hours. Kidney status assessments were based on laboratory data in the cohort records. Long-term kidney outcomes were assessed from 2 years postbiopsy (time of categorization) until censoring because of an outcome event, loss to follow-up, or the end of the study dataset (Figure 1). Baseline (day 0) was defined as the date of biopsy that confirmed active LN. The QMHLNC dataset included results of laboratory tests performed at routine and unscheduled clinic visits at the Queen Mary Hospital; these tests included measures of serum creatinine and 24-hour urinary protein. Because this was an observational study, the timings of kidney function assessments varied, so a 3-month window for inclusion of laboratory data was allowed for each interval date (baseline, 6 months, 2 years, 3 years, 4 years, and 5 years).

This study complied with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred, and results omitted subject identification. The study protocol was eligible for expedited review by the local institutional review board and was approved (UW 21-199).

Study Population

Patients were included if they were aged ≥ 18 years at LN diagnosis (biopsy date); had a diagnosis of SLE according to revised American College of Rheumatology (1997 or 2019) or European Alliance of Associations for Rheumatology (2019) criteria with biopsy-proven LN (International Society Nephrology Class III, IV, V, or mixed [III + V, IV + V]); and had sufficient available data for assessing renal response 2 years postbiopsy.[26,27] Patients with incident and prevalent LN were included in the analysis. Patients with evidence of kidney nonsurvival prior to year 2 were excluded because the outcome measured was development of severe and end-stage CKD, so patients who had this prior to year 2 were excluded to avoid biased results. Standard immunosuppressive regimen

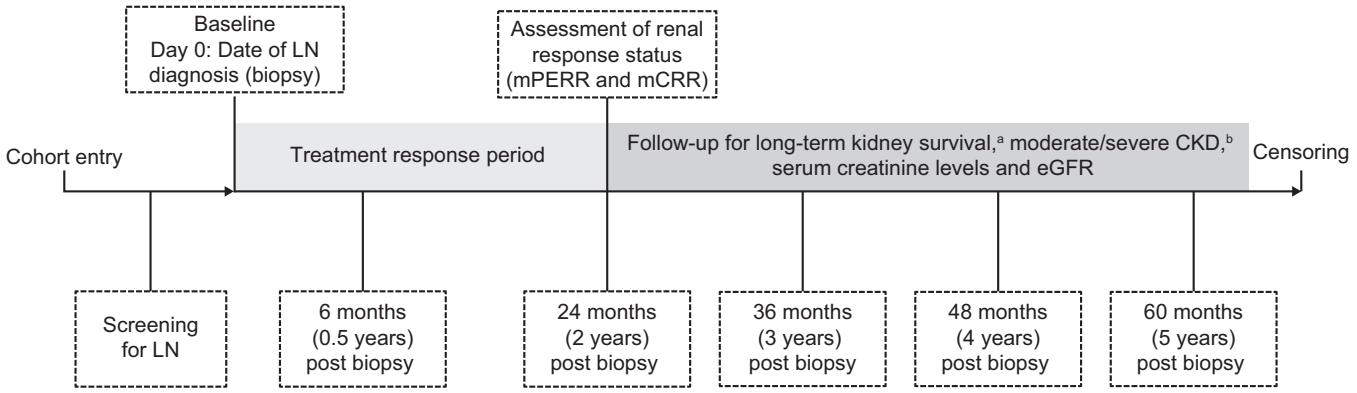

Figure 1. Study design. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; mCRR, modified complete renal response; mPERR, modified primary efficacy renal response. [a]Defined as survival without progression to severe and end-stage CKD (eGFR $<$ 30 ml/min per 1.73 m^2 [CKD stage 4 or 5]) or dialysis or transplant or death; [b]defined as new occurrence of eGFR $<$ 60 ml/min per 1.73 m^2 on at least 2 consecutive measurement occasions $\geq$3 months apart (GFR level equivalent to CKD stage 3a [GFR: 45–59 ml/min per 1.73 m^2], 3b [GFR: 30–44 ml/min per 1.73 m^2], 4 [GFR: 15–29 ml/min per 1.73 m^2], or 5 [GFR: $<$ 15 ml/min per 1.73 m^2]).

for active severe LN was methylprednisolone 0.5 g i.v. for 2 to 3 days followed by oral prednisolone 0.6 to 0.7 mg/kg/d tapered to $\leq$ 5 mg/d by 6 months, then maintained with gradual tapering for $\geq$3 years, in combination with mycophenolate mofetil 1 g twice daily for 12 months, followed by gradual tapering and maintained for $\geq$3 years. Patients were also prescribed angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers as standard treatment for CKD unless contraindicated. Patients with proteinuria $\geq$ 2 g/d after 4 to 6 months of standard treatment were considered for add-on tacrolimus depending on kidney function and blood pressure control. Belimumab and rituximab were used if a patient had $\geq$3 nephritis flares.

Renal Response Status

Renal response status at year 2 by mPERR and mCRR was determined retrospectively. Laboratory records for eGFR and proteinuria with nonmissing uPCR on the date closest to year 2 (day 730) were assessed (if uPCR was missing, 24-hour urinary protein measurement was used if the date of this measurement was within 3 months prior to or 3 months after day 730). If multiple measures were available, the closest uPCR was used, and if missing, the closest 24-hour urinary protein measurement. mPERR responders were defined as having eGFR $\leq$ 20% below the biopsy value or $\geq$ 60 ml/min per 1.73 m^2 and either a uPCR $\leq$ 0.7 g/g or, if missing, 24-hour protein $\leq$ 0.7 g/24 hours; patients who did not meet these criteria were classified as nonresponders. mCRR responders were defined as having eGFR within 10% below the biopsy value or $\geq$ 90 ml/min per 1.73 m^2 and either a uPCR $<$ 0.5 g/g or, if missing, 24-hour proteinuria $<$ 0.5 g/24 hours, whereas patients who did not meet these criteria were categorized as nonresponders.

Study Objectives and Outcomes

All outcomes were screened and recorded prospectively in the QMHLNC database. The primary objective of this analysis was to determine the association between mPERR status at year 2 and long-term kidney survival, defined as no progression to severe and end-stage CKD (eGFR $<$ 30 ml/min per 1.73 m^2 [CKD stage 4 or 5]) or dialysis or transplant and no death from year 2 until censoring. Secondary objectives included evaluating the following: (i) the association between mCRR achievement at year 2 and long-term kidney survival; (ii) the proportion of patients achieving mCRR at 3, 4, and 5 years postbiopsy and among the subgroup of patients who achieved mPERR at year 2; and (iii) the association between mPERR/mCRR at year 2 and the incidence of mild CKD or worse (stage $\geq$ 3) in a subset of patients who did not have mild CKD or worse prior to year 2. Mild CKD or worse (stage $\geq$ 3) is defined as a new occurrence of eGFR $<$ 60 ml/min per 1.73 m^2 on at least 2 consecutive measurements taken $\geq$3 months apart (GFR level is equivalent to CKD stage 3a [GFR: 45–59 ml/min per 1.73 m^2], 3b [GFR: 30–44 ml/min per 1.73 m^2], stage 4 [GFR: 15–29 ml/min per 1.73 m^2], or stage 5 [GFR: $<$ 15 ml/min per 1.73 m^2]). In addition, serum creatinine levels and eGFR, calculated using the Modification of Diet in Renal Disease equation in earlier years of data collection and later switched to the CKD-EPI creatinine equation,[28] were determined at each year of follow-up, defined as day 730 plus 365 days (if more than 1 measurement was available in this window, the value closest to day 365 of the interval was used) and were assessed overall and by mPERR and mCRR status at year 2. Kidney relapse and death were also recorded

during follow-up. Kidney flare was defined as an increase in urine protein to > 1 g/d in patients who had achieved proteinuria < 0.5 g/d after initial immunosuppressive treatments for active LN, and/or increase in serum creatinine by 15% or more compared with stable level during remission, with or without serological activity.

Analysis

Sample size parameters were set for a 1-sided log rank test with 80% power, an alpha of 0.05, 10% dropouts, and a total survival time of 5 years; to detect a difference of 20% in survival, a minimal sample size of 47 and 31 patients for the mPERR responder and nonresponder groups, respectively, was required.

For descriptive analyses, mean and SD values were reported for continuous variables and the proportions of patients were presented for categorical variables. Patient demographic and clinical characteristics were assessed at the time of the biopsy.

Kaplan–Meier plots and log-rank tests were used to compare the proportions of patients with long-term kidney survival or who showed development of mild CKD or worse (stage ≥ 3) from year 2 to censoring, by renal response status at year 2. Associations between the renal response status (mPERR and mCRR) and outcomes were explored with Cox proportional hazards models, including univariate models and covariate-adjusted models. Covariates assessed included International Society Nephrology class, age at biopsy, sex, body mass index, diabetes (before year 2), hypertension (before year 2), proteinuria at day 30, disease activity, eGFR, hydroxychloroquine use (between day 0 and year 2) and other treatments (immunosuppressants, steroids, rituximab, belimumab, angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers). A variable was included in the model as a confounder or covariate if it changed the hazard ratio (HR) by ≥ 10%; if more than 2 confounders or covariates were identified, only the top 2 (ranked by the percentage change in HR) were included. For patients with complete data at 5-year follow-up, an additional chi-square analysis was performed to compare the frequency of long-term outcomes by renal response status; and logistic regression models, including relevant covariates, were used to evaluate associations between renal response at year 2 and long-term outcomes. For analysis of mCRR overall and among patients who were mPERR responders, the proportion of mCRR responders was determined, at 2, 3, 4, and 5 years postbiopsy.

Mean serum creatinine levels and eGFR over time, and the proportions of patients achieving eGFR ≥ 60 ml/min per 1.73 m^2 and serum creatinine ≥ 1.0 mg/dl, were reported in 1-year intervals by renal response category over the follow-up period (from year 2).

RESULTS

Patient Population

Of the 255 patients with LN identified in the QMHLNC, 176 patients met all the eligibility criteria and were included in the analysis (Figure 2). The mean (SD) age was 38.8 (12.9) years; 87.5% of patients were female (Table 1). All the patients were Chinese. At the time of biopsy, the proportions of patients with LN Class III, IV, V, or mixed (III + V or IV + V) were 5.1%, 46.0%, 27.8%, and 21.0%, respectively. A total of 52 patients (29.5%) had a history of previous LN flare.

At 2 years postbiopsy, 113 patients (64.2%) were categorized as mPERR responders and 63 (35.8%) as mPERR nonresponders (Table 1). The median (interquartile range) follow-up was 14.4 (6.8–23.4) years in the overall cohort (15.0 [7.5–22.9] and 13.8 [5.9–23.4] years in the mPERR responder and nonresponder groups, respectively).

Long-Term Kidney Survival by mPERR Status at Year 2

During follow-up, 97 of 113 patients (85.8%) in the mPERR responder group and 45 of 63 patients (71.4%) in the mPERR nonresponder group had kidney survival. There was a statistically significant increased likelihood of long-term kidney survival among mPERR responders compared with nonresponders ($P = 0.029$) (Figure 3a). Body mass index prior to day 0 was included in the Cox proportional hazard model as a confounder as it changed the HR by 16.2%. In this adjusted model, there was a 59.8% lower risk of kidney nonsurvival in the mPERR responder group compared with the nonresponder group (HR: 0.402 [95% CI: 0.173–0.932]; $P = 0.034$; Supplementary Table S1).

Long-Term Kidney Survival by mCRR Status at Year 2

At year 2, 77 of 176 patients (43.8%) were categorized as mCRR responders and 99 of 176 (56.3%) as mCRR nonresponders. Long-term kidney survival was achieved by 71 of 77 patients (92.2%) in the mCRR responder group and 71 of 99 patients (71.7%) in the mCRR nonresponder group. mCRR at year 2 was associated with a statistically significant increased likelihood of long-term kidney survival ($P < 0.001$; Figure 3b). In the Cox proportional hazard model, adjusted for the confounders eGFR > 60 ml/min per 1.73 m^2 at day 0 and SLE Disease Activity Index score at day 0 (that changed the HR by 18.3% and 12.2%, respectively), there was a 85.8% lower risk of kidney nonsurvival in the mCRR responder group compared

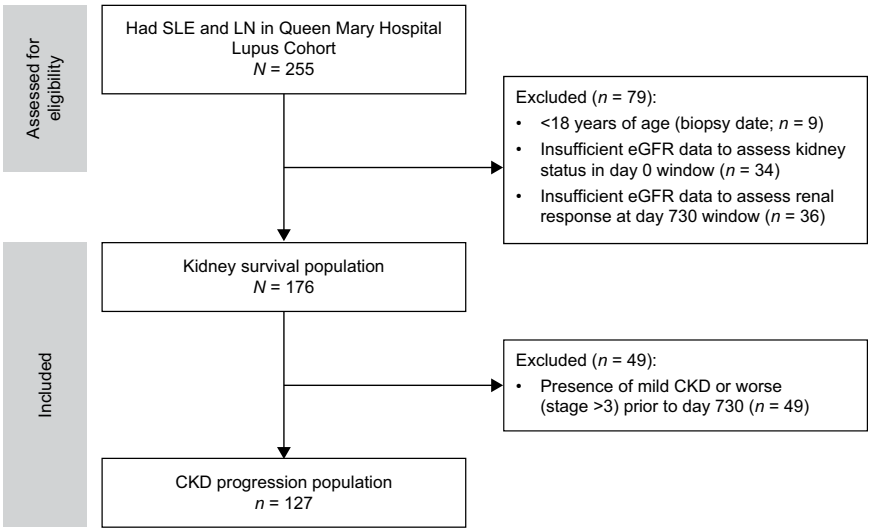

Figure 2. Flow diagram of patient populations. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SLE, systemic lupus erythematosus.

Table 1. Baseline demographic and clinical characteristics of patients in the overall cohort and in the mPERR responder and nonresponder categories

Characteristics	Overall cohort (*N* = 176)	mPERR responders (*n* = 113)	mPERR nonresponders (*n* = 63)
Age at kidney biopsy, yrs, mean (SD)	38.8 (12.9)	38.8 (13.2)	38.8 (12.4)
Female, *n* (%)	154 (87.5)	101 (89.4)	53 (84.1)
Race/ethnicity, %			
Chinese	100	100	100
LN ISN category, n (%)			
III	9 (5.1)	5 (4.4)	4 (6.3)
IV	81 (46.0)	55 (48.7)	26 (41.3)
V	49 (27.8)	28 (24.8)	21 (33.3)
Mixed (III + V or IV + V)	37 (21.0)	25 (22.1)	12 (19.0)
Serum creatinine, mg/dl, mean (SD)	1.1 (0.5)	1.1 (0.5)	1.2 (0.5)
MDRD eGFR, ml/min per 1.73 m^2			
Mean (SD)	68.5 (21.7)	70.4 (21.4)	65.2 (22.1)
<60 at biopsy, *n* (%)	62 (35.2)	36 (31.9)	26 (41.3)
≥60 at biopsy, *n* (%)	114 (64.8)	77 (68.1)	37 (58.7)
Urine protein levels, g/24 h			
Median (IQR)	3.6 (2.1–6.2)	3.4 (2.0–4.9)	4.2 (2.3–6.8)
<0.5 at biopsy, *n* (%)	1 (0.6)	1 (0.9)	0 (0.0)
uPCR			
Median (IQR)	3.5 (1.7–6.2)	3.2 (1.7–6.3)	3.9 (2.4–5.2)
<0.5 at biopsy, *n* (%)	0 (0)	0 (0)	0 (0)
SLEDAI score			
Mean (SD)	8.7 (1.9)	8.8 (1.8)	8.3 (1.9)
Medications[a], *n* (%)			
Immunosuppressants[b]	87 (49.4)	51 (45.1)	36 (57.1)
Glucocorticoids	173 (98.3)	111 (98.2)	62 (98.4)
Rituximab	1 (0.5)	1 (0.8)	0 (0)
Belimumab	0 (0)	0 (0)	0 (0)
ACE or ARB for proteinuria	71 (40.3)	48 (42.5)	23 (36.5)
Hydroxychloroquine	18 (10.2)	13 (11.5)	5 (7.9)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; eGFR, estimated glomerular filtration rate; ISN, International Society of Nephrology; LN, lupus nephritis; MDRD, Modification of Diet in Renal Disease; mPERR, modified primary efficacy renal response; SD, standard deviation; SLEDAI, SLE Disease Activity Index; uPCR, urinary protein to creatinine ratio.
[a]Data on medication use were collected within a 3-month period before day 0.
[b]Relapsed patients receiving low-dose immunosuppressants prior to flare of active nephritis.

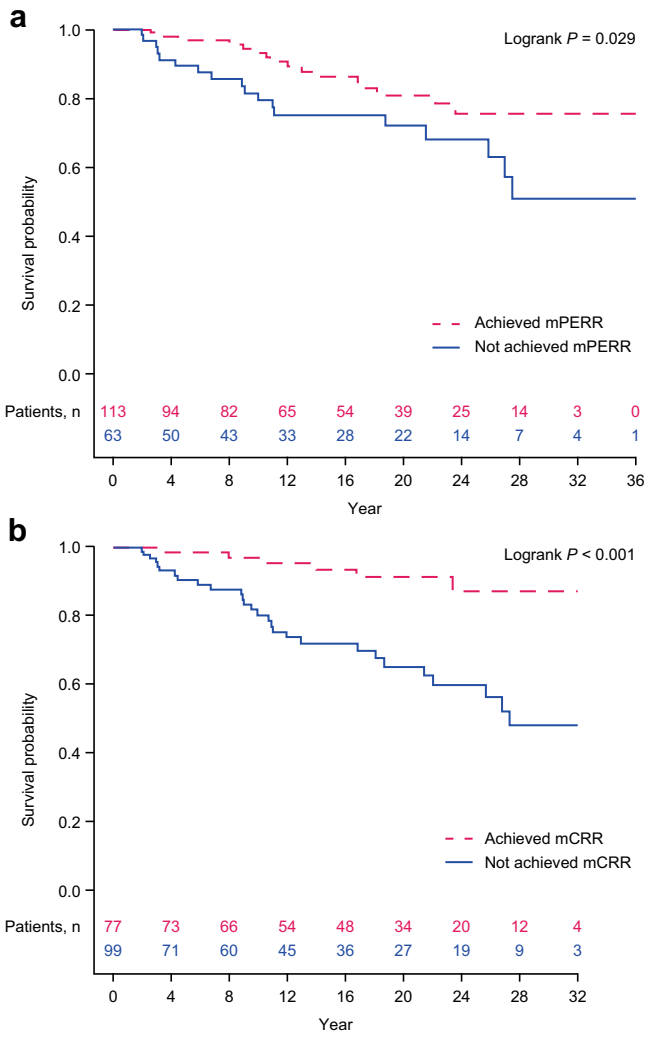

Figure 3. Kaplan–Meier plots comparing the proportion of patients with long-term kidney survival by (a) mPERR status and (b) mCRR status at 2 years postbiopsy. mCRR, modified complete renal response; mPERR, modified primary efficacy renal response.

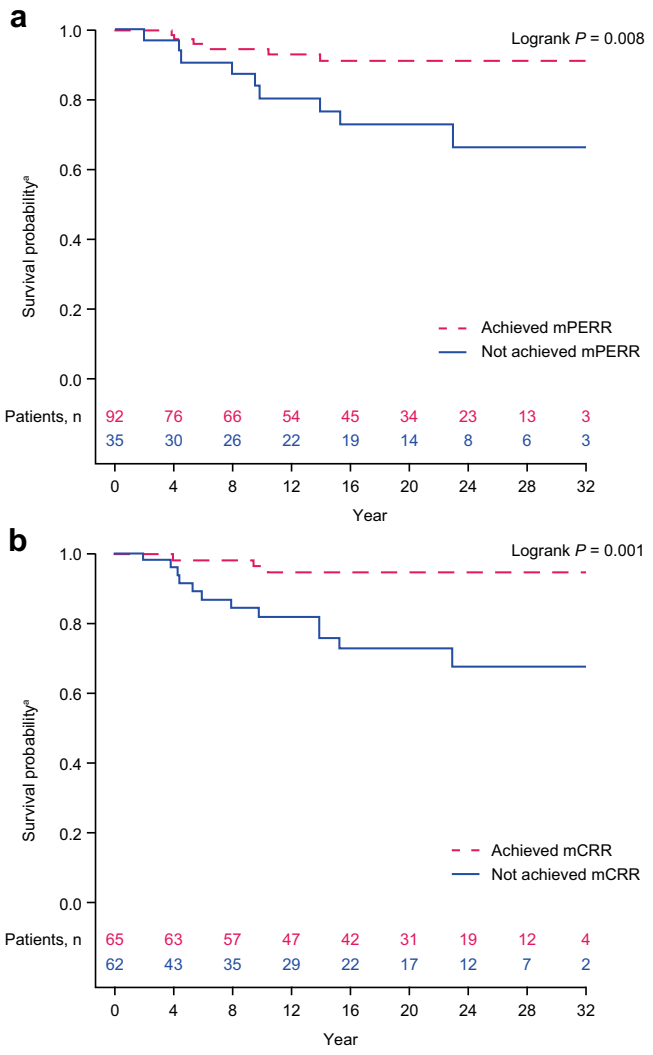

Figure 4. Kaplan–Meier plot comparing the incidence of mild CKD or worse (stage ≥ 3) by (a) mPERR status and (b) mCRR status at 2 years postbiopsy. CKD, chronic kidney disease; mCRR, modified complete renal response; mPERR, modified primary efficacy renal response. [a]Proportion of patients without CKD progression.

with the nonresponder group (HR: 0.142 [95% CI: 0.054–0.372]; $P < 0.001$, Supplementary Table S2).

Proportion of mPERR Responders who Achieve mCRR

Among the patients who attained mPERR 24 months after biopsy, there were 102, 94, and 91 patients still under follow-up at the 3-, 4-, and 5-year time points. Among patients who attained mPERR in year 2, the proportion who achieved mCRR was 66.7% (68/102) at 3 years, 72.3% (68/94) at 4 years, and 72.5% (66/91) at 5 years.

Development of Mild CKD or Worse (Stage ≥ 3) Over Time by mPERR and mCRR Status at Year 2

Out of the 127 patients with no mild CKD or worse (stage ≥ 3) at year 2 (Figure 2), mild CKD or worse (stage ≥ 3) developed in 6 of 92 patients (6.5%) in the mPERR responder group and 9 of 35 patients (25.7%) in the mPERR nonresponder group. mPERR responders at year 2 were associated with a significantly lower likelihood of developing mild CKD or worse (stage ≥ 3) compared with nonresponders ($P = 0.008$; Figure 4a). After adjustment for the confounders, body mass index prior to day 0 and SLE Disease Activity Index score on day 0, there remained a significant 82.4% lower risk of developing mild CKD or worse (stage ≥ 3) in the mPERR responder group versus nonresponders (HR: 0.176 [95% CI: 0.044–0.696]; $P = 0.013$, Supplementary Table S3).

In the mCRR year 2 responder and nonresponder groups, respectively, mild CKD or worse (stage ≥ 3) developed in 3 of 65 (4.6%) and 12 of 62 (19.4%) patients, with patients in the mCRR responder group having a significantly lower likelihood of developing

Table 2. eGFR and serum creatinine levels over follow-up by mPERR and mCRR status at 2 years postbiopsy

Outcome	Year 2 postbiopsy (N = 176)	Follow-up year 1 (n = 154)	Follow-up year 2 (n = 120)	Follow-up year 3 (n = 112)	Follow-up year 4 (n = 104)	Follow-up year 5 (n = 85)
eGFR, ml/min per 1.73 m^2						
mPERR responders	113	103	84	77	71	62
Mean (SD)	75.3 (17.8)	74.4 (17.6)	74.9 (18)	74.4 (18.8)	72.2 (20.3)	73.2 (19.6)
eGFR ≥ 60 ml/min per 1.73 m^2, n (%)	73 (64.6)	83 (80.6)	67 (79.8)	60 (77.9)	55 (77.5)	47 (75.8)
mPERR nonresponders	63	51	36	35	33	23
Mean (SD)	60.3 (23.9)	63 (22.6)	66.5 (19.4)	61.2 (21.7)	59.3 (21.3)	60.5 (23.3)
eGFR ≥ 60 ml/min per 1.73 m^2, n (%)	32 (50.8)	31 (60.8)	23 (63.9)	21 (60.0)	18 (54.5)	15 (65.2)
mCRR responders	77	73	66	62	59	50
Mean (SD)	76.1 (17.2)	74.8 (16.4)	76.1 (16.2)	74.5 (17.6)	72.4 (18.4)	74.8 (17.9)
eGFR ≥ 60 ml/min per 1.73 m^2, n (%)	48 (62.3)	61 (83.6)	54 (81.8)	50 (80.6)	47 (79.7)	39 (78.0)
mCRR nonresponders	99	81	54	50	45	35
Mean (SD)	65.2 (23.1)	66.8 (22.3)	67.9 (20.7)	65 (22.8)	62.5 (23.9)	62.5 (23.8)
eGFR ≥ 60 ml/min per 1.73 m^2, n (%)	57 (57.6)	53 (65.4)	36 (66.7)	31 (62.0)	26 (57.8)	23 (65.7)
Serum creatinine, mg/dl						
mPERR responders	113	103	84	77	71	62
Mean (SD)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	0.9 (0.4)	0.9 (0.4)	0.9 (0.4)
< 1.0 mg/dl, n (%)	77 (68.1)	59 (57.3)	58 (69.0)	51 (66.2)	46 (64.8)	43 (69.4)
mPERR nonresponders	63	51	36	35	33	23
Mean (SD)	1.3 (0.8)	1.2 (0.8)	1.1 (0.4)	1.2 (0.6)	1.2 (0.6)	1.3 (0.8)
< 1.0 mg/dl, n (%)	25 (40.3)	20 (39.2)	18 (50.0)	13 (37.1)	12 (36.4)	14 (60.9)
mCRR responders	77	73	66	62	59	50
Mean (SD)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)	0.9 (0.3)
< 1.0 mg/dl, n (%)	50 (64.9)	45 (61.6)	45 (68.2)	40 (64.5)	36 (61.0)	36 (72.0)
mCRR nonresponders	99	81	54	50	45	35
Mean (SD)	1.2 (0.7)	1.1 (0.7)	1.0 (0.5)	1.1 (0.6)	1.2 (0.7)	1.2 (0.7)
< 1.0 mg/dl, n (%)	52 (52.5)	34 (42.0)	31 (57.4)	24 (48.0)	22 (48.9)	21 (60.0)

eGFR, estimated glomerular filtration rate; mCRR, modified complete renal response; mPERR, modified primary efficacy renal response; SD, standard deviation.

mild CKD or worse (stage ≥ 3) compared with the nonresponders (P = 0.001) (Figure 4b). After adjustment for the confounders, body mass index prior to day 0 and SLE Disease Activity Index score at day 0, there remained a significant 86.6% lower risk of developing mild CKD or worse (stage ≥ 3) in mCRR responders compared with nonresponders (HR: 0.134 [95% CI: 0.028–0.639]; P = 0.012; Supplementary Table S4).

eGFR and Serum Creatinine Levels Over Time by mPERR and mCRR Status at Year 2

During the 5-year follow-up period, mean eGFR and the proportions of patients with eGFR ≥ 60 ml/min per 1.73 m^2 were consistently higher in the mPERR and mCRR responder groups compared with the mPERR and mCRR nonresponder groups, respectively (Table 2). Among mPERR and mCRR responders, the mean eGFR values remained relatively constant (72.2–75.3 and 72.4–76.1 ml/min per 1.73 m^2, respectively). This was also observed in the mPERR and mCRR nonresponders (59.3–66.5 and 62.5–67.9 ml/min per 1.73 m^2, respectively).

Achievement of both mPERR and mCRR at year 2 was associated with lower mean serum creatinine levels and higher proportions of patients with serum creatinine levels < 1 mg/dl over the 5 years of follow-up. In mPERR and mCRR responders, the mean serum creatinine levels remained relatively constant at approximately 0.9 mg/dl.

Kidney Relapse and Death Outcomes

Overall, 32 of 176 patients (18.2%) experienced kidney relapse. The kidney relapse rates were 18 of 133 (15.9%) and 14 of 63 (22.2%), respectively, in patients who had or had not achieved mPERR; and 9 of 77 (11.7%) and 23 of 99 (23.2%), respectively, in patients who had or had not attained mCRR. Overall, 17 of 176 patients (9.7%) died during follow-up. The mortality rates were 11 of 113 (9.7%) and 6 of 63 (9.5%), respectively, in patients who had or had not achieved mPERR; and 3 of 77 (3.9%) and 14 of 99 (14.1%), respectively, in patients who had or had not attained mCRR.

DISCUSSION

This retrospective analysis of real-world data from the QMHLNC demonstrates that a modified version of the primary end point used in the BLISS-LN trial, mPERR, as well as mCRR, are important and clinically significant prognostic factors for long-term kidney outcomes and for the prediction of CKD progression in Chinese

patients with LN over a mean follow-up of approximately 15 years. In adjusted models, the risk of kidney nonsurvival was 60% lower in mPERR responders compared with mPERR nonresponders and 86% lower in mCRR responders versus mCRR nonresponders. The risk of developing mild CKD or worse (stage $\geq$ 3) was 82% and 87% lower in mPERR responders and mCRR responders, respectively, compared with the nonresponder groups.

The present results provide a valuable addition to previously published data that focused on Western ethnicities and have limited data on Chinese populations[19,20] by demonstrating that achievement of mPERR or mCRR was a strong prognostic indicator for long-term kidney benefits in Chinese patients and thereby supporting measures of renal response being a universal prognostic marker regardless of ethnicity. However, it is important to note that these results are reflective of a single-center study in Hong Kong and additional research in Asian communities may help to support these findings. Compared with the Hopkins and Toronto real-world cohorts, the QMHLNC population had some differences in baseline clinical characteristics and medication use. Although the studies cannot be directly compared because of differences in patient populations and timings of biopsies, the proportion of patients achieving mPERR at 2 years postbiopsy was similar to that reported for the Hopkins and Toronto cohorts.[19,29]

Among patients who achieved mPERR in year 2, the proportion who achieved mCRR was approximately 67% at 3 years and then approximately 72% at 4 and 5 years, highlighting that the improvement in proteinuria after treatment can slowly continue over time. The prognostic value of both mPERR and mCRR response at 2 years postbiopsy, related to long-term kidney function, was further demonstrated by the higher eGFR levels and lower serum creatinine levels in mPERR and mCRR responders, compared with nonresponders, during the follow-up period. The serum creatinine results showing a higher proportion of mPERR/mCRR responders with levels below 1 mg/dl corroborate previous studies demonstrating that levels below 1 mg/dl suggest better long-term renal outcomes.[30]

Limitations of this study include that data were collected and analyzed retrospectively; therefore, assessments may not have been as comprehensive as in prospective clinical trials. The observational setting also meant kidney function assessments were not conducted at strictly regular intervals, necessitating the use of a window of dates for data collection. In prospective clinical trials, multiple measures are included to assure the persistence of outcomes. However, the clinical data in this study were retrieved from a real-world setting, so repeated testing at the 2-year time point was not performed. Nevertheless, it has always been our practice to measure uPCR at every follow-up visit, and we have reviewed the records to confirm that the proteinuria level at the study time point was consistent with levels at the preceding and subsequent visits. This study was based on data from a single health care institution, the Nephrology Unit at Queen Mary Hospital in Hong Kong. The center is a dedicated unit for management of patients with LN in Hong Kong that provides care for both straightforward and difficult-to-treat LN, thereby minimizing the potential limitation of reduced generalizability of results due to a center effect on patient outcomes. Due to the study objective and design, patients with significant CKD prior to the time point for responder categorization were excluded. Therefore, the results are not applicable to patients who already have significant CKD at presentation when presenting with active nephritis flare. The strengths of this study are that it allowed assessment of the prognostic value of mPERR and mCRR in a relatively large sample of Chinese patients with LN in real-life clinical practice and with a long mean follow-up duration of 15.3 years. Although the patients of this cohort had kidney biopsy data, histological variables had not been included in the analysis, in order to retain the generalizability of the results to populations that do not have readily available histological data.

In conclusion, mPERR and mCRR at 2 years postbiopsy (date of active LN diagnosis) are significant predictors of long-term kidney outcomes and the risk of CKD progression in Chinese patients with LN, which is consistent with results from other populations. This highlights the value of mPERR and mCRR both as end points in clinical trials and as clinical management targets for clinicians treating LN in real-world practice.

DISCLOSURE

DYHY received consulting fees from GSK, AstraZeneca, Otsuka, and Boehringer Ingelheim. TMC received grant/research support from Astellas and AstraZeneca, consulting fees from GSK and Novartis, and was an advisor/review panel member for GSK, Kezar, Novartis, and Visterra. XX, LN and DM are employees of GSK. PCJ was an employee of GSK at the time of the study. PCJ and DM hold financial equities in GSK. CSOT declared no competing interests.

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The sponsor (GSK) was involved in study design and implementation, as well as data retrieval, analysis, interpretation, drafting the study report and reviewing this manuscript. All authors had full access to the data upon request and had final responsibility for the decision to submit for publication.

DATA AVAILABILITY STATEMENT

Requests for access to the data can be made by contacting the corresponding author.

AUTHOR CONTRIBUTIONS

DYHY was involved in data acquisition and interpretation; CSOT was involved in data analysis; TMC was involved in data acquisition, interpretation, and overall direction of study and manuscript oversight; XX, PCJ, LN, and DM were involved in the study concept or design and data interpretation. All the authors drafted or revised the manuscript and approved the final version.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Cox proportional hazards models for the association between mPERR variables and long-term kidney survival.

Table S2. Cox proportional hazards models for the association between mCRR variables and long-term kidney survival.

Table S3. Cox proportional hazards models for the association between mPERR variables and incidence of mild CKD or worse (stage $\geq$ 3).

Table S4. Cox proportional hazards models for the association between mCRR variables and incidence of mild CKD or worse (stage $\geq$ 3).

STROBE statement.

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