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Revised ISN/RPS 2018 classification of lupus renal pathology predict clinical remission

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Abstract

Background A precise description of renal histological lesions and an appropriate classification of lupus nephritis are both essential for nephrologists to guide treatment and predict prognosis among patients. The prognostic value of ISN/RPS 2003 classification is controversial. A new classification for lupus nephritis was recently proposed, namely, the revised ISN/RPS 2018 classification.

Objective The study aimed to evaluate the predictive value of the clinical and pathological factors according to ISN/RPS 2018 classification on renal remission among patients with proliferative lupus nephritis.

Methods A total number of 41 patients with proliferative lupus nephritis on adequate renal biopsy specimen between 2017 and 2018 were included. Clinical and histological variables were tested for their association with renal remission. Univariate and multivariate logistic regression analysis were performed to identify independent predictors of renal remission after 24 weeks of induction therapy.

Results After induction therapy, 56.1% of patients reached complete and partial remission and 43.9% reached no remission. In univariate analyses, baseline glomerular filtration rate (GFR), presence of anti-DNA titer, cellular crescents, interstitial inflammation, glomerulosclerosis, interstitial fibrosis, tubular atrophy and total chronicity index strongly impacted renal response. After multivariate logistic regression analysis, we identified aging, presence of cellular crescents, and high total renal chronicity index as independent predictors of renal remission. Receiver operating characteristic (ROC) analysis revealed that baseline estimated GFR (AUC = 0.708; 95% CI 0.527–0.888), anti-DNA titer (AUC = 0.674; 95% CI 0.491–0.858), cellular crescent (AUC = 0.750; 95% CI 0.585–0.915) and renal chronicity index (AUC = 0.765; 95% CI 0.585–0.915) predicted renal remission. Combining all factors achieved a perfect score predicting renal response (AUC 0.924; 95% CI 0.840–1.000).

Conclusion The study identified baseline GFR, anti-DNA titer, cellular crescent, and high chronicity index according to revised ISN/RPS 2018 classification as important predictors of renal response after induction therapy in proliferative lupus nephritis.

Keywords Lupus nephritis · Pathological classification · Renal remission · Lupus classification

Background

Lupus nephritis is common among patients with systemic lupus erythematosus (SLE), resulting in increased morbidity and mortality [1]. The manifestations and outcomes among patients with lupus nephritis are heterogenous and remission after intensive induction therapy is achieved in only 50–70% of patients [2]. Clinical and laboratory findings at renal biopsy correlated well with high activity index and chronicity index of lupus pathology [3]. Histologic overlap is relatively common in the lupus nephritis pathologic classes especially mixed proliferative lupus nephritis (Class III/IV + V). The histopathologic categorization among

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patients with mixed proliferative lupus nephritis provides information relevant to their long-term outcome [4]. A precise description of renal histological lesions and an appropriate classification of lupus nephritis are both essential for nephrologist to guide treatment and predict prognosis among patients.

The International Society of Nephrology/Renal Pathology Society (ISN/RPS 2003) classification represents the standard for the histological evaluation of SLE glomerulonephritis. ISN/RPS 2003 classification used to predict clinical remission, renal remission, renal failure, end stage renal disease and patient survival in lupus nephritis [5–7]. Variation is found regarding the methods and time to measure outcomes of treatment among these patients. Moreover, dealing with the lack of adequate definitions of renal histological lesions in the classification is challenging [8, 9]. Recently, a working group for lupus nephritis classification met definitions of lupus nephritis lesion and advanced a revised ISN/RPS 2018 classification [10]. The revision classification aimed to improve problematic definitions that form the basis of lupus nephritis classification and thereby increase the interobserver agreement between nephropathologists worldwide to apply the definitions to classify lupus nephritis.

In this study, we aimed to identify evidence-based clinical and histopathologic predictors according to revised ISN/RPS 2018 classification on renal remission among patients with proliferative lupus nephritis after standard immunosuppressive therapy.

Methods

We collected a cohort of patients with biopsy-confirmed lupus nephritis from December 2017 to August 2018 at Phramongkutklao Hospital. Patients with SLE as defined by the American College of Rheumatology (ACR) criteria and documented proliferative lupus nephritis (Class III, IV, and III/IV + V) were enrolled in the study. Exclusion criteria included other glomerular diseases and inadequate tissue biopsy with less than 8 glomeruli. The sample size was calculated at 61 patients in each group to reach statistical power of 80% with a type I error of 5% [11]. The study was conducted under the provisions of the Declaration of Helsinki and the protocol was approved by the local ethics committee. Informed consent was obtained at the time of registry enrollment.

Baseline clinical and laboratory data were collected at the time of biopsy and at 24 weeks after induction therapy to determine renal remission. The renal outcomes were divided in two groups: remission group (complete remission and partial remission) and nonremission. Complete remission was defined as return of serum creatinine to previous baseline, plus a decline in the UPCR < 500 mg/g and partial remission was defined as stabilized (± 25%), or improved serum creatinine plus a ≥ 50% decrease in UPCR when nephrotic-range proteinuria (UPCR ≥ 3000 mg/g), improvement required a ≥ 50% reduction in UPCR, and a UPCR < 3000 mg/g by the definition of KDIGO 2012 [12].

Clinical data were recorded for each patient at the time of biopsy including age, sex, weight, body mass index, duration of disease, systolic and diastolic blood pressure, clinical and organ involvement, antihypertensive medications and immunosuppressive agents. Laboratory variables including urine exam, serum creatinine, estimated glomerular filtration rate (GFR, calculated by the Chronic Kidney Disease Epidemiology Collaboration equation), urine protein creatinine ratio, serum complement levels (C3 and C4), the presence of antinuclear antibodies and anti-double-stranded (ds) DNA antibodies were measured at baseline and 24 weeks after induction therapy.

All histological diagnoses were sent to a single renal pathologist, unaware of patients' clinical data, to evaluate the biopsies according to the ISN/RPS classification 2018. The scoring system for activity and chronicity was also calculated. For every case, the histological slides included hematoxylin and eosin (H&E), periodic acid–Schiff (PAS), Masson trichrome and periodic acid methenamine silver stains for light microscopy. The study exclusively analyzed morphological data; however, immunofluorescence (IgG, IgA, IgM, C3, C1q, fibrinogen, kappa and lambda light chains) was always performed to confirm central diagnosis.

Statistical analysis

Descriptive analyses were performed on the histological and clinical data collected at the time of biopsy. The Wilcoxon–Mann–Whitney and Fisher's exact test were used for continuous and categorical variables comparing clinical and histological data in remission and nonremission groups. Univariate and multivariate logistic regression analysis were performed to identify independent predictors of renal remission. Receiver operating characteristic (ROC) analysis and calculated area under the curve (AUC) were employed to determine the best cut-off value to identify clinical remission. Statistical analysis was performed using the SPSS Software (SPSS, Version 20, Chicago, IL, USA). All tests were two-sided with a significance level of 0.05.

Results

A total of 41 patients with biopsy-proven lupus nephritis were enrolled in this. On all, 56.1% patients experienced complete and partial renal remission, and 43.9% patients developed nonremission after induction therapy. All patients

received oral prednisone therapy (100%). The patients completed treatment with mycophenolate mofetil (total = 20, 4 patients in class III, 5 patients in class IV and 11 patients in class III/IV + V), high dose intravenous cyclophosphamide (total = 15, 2 patients in class III, 3 patients in class IV and 10 patients in class III/IV + V), and low dose intravenous cyclophosphamide (total = 6, 2 patients in class III, 2 patients in class IV sand 2 patients in class III/IV + V).

The majority of patients were female ($N = 34$, 82.9%), mean age at kidney biopsy was 29.5 ± 9.5 years, the median onset of SLE preceding the time of kidney biopsy was 3.5 with interquartile range (IQR) 0.25 to 10 years. The baseline renal involvement included UPCR of 2.8 with IQR 1.8–4.4 g/gCr, estimated GFR of 79.9 ± 39.9 mL/min/1.73 m^2, serum albumin of 2.8 ± 0.6 g/dL, low C3 complement of 82.9%, low C4 complement of 68.3% and positive anti-dsDNA antibody of 85.4%. The remission group had a higher estimated GFR (remission: 90.9 ± 37.4 vs. nonremission: 65.9 ± 39.7 mL/min/1.73 m^2, $P = 0.046$) and lower serum creatinine levels (remission: 0.9 ± 0.4 vs. nonremission: 1.4 ± 0.6 mg/dL, $P = 0.030$) at baseline than the remission group. Immunosuppressive agents, as induction therapy, did not show significant differences between the two groups. The baseline demographic and clinical characteristics of the two groups are summarized in Table 1.

Table 1 Baseline characteristics

	Remission group ($N = 23$)	Non remission group ($N = 18$)	*P* value
Female (%)	18 (78.3%)	16 (88.9%)	0.369
Age (year)	27.7 ± 9.4	31.8 ± 9.7	0.178
Body weight (kg)	61.5 ± 11.3	61.1 ± 14.2	0.911
Body mass index (%)	23.7 ± 3.9	23.2 ± 4.9	0.727
Systolic blood pressure (mmHg)	133.2 ± 21.5	138.5 ± 18.6	0.416
Diastolic blood pressure (mmHg)	82.2 ± 16.6	90.4 ± 16.7	0.125
Organ involvements			
Arthritis (%)	18 (78.3%)	16 (88.9%)	0.369
Cutaneous (%)	18 (78.3%)	16 (88.9%)	0.369
Hematologic (%)	11 (47.8%)	11 (61.1%)	0.397
Serositis (%)	2 (8.7%)	1 (5.6%)	0.702
Neurological (%)	3 (13%)	1 (5.6%)	0.423
Duration of SLE (year)	2 (0.1, 7)	6 (1.5, 10)	0.120
Underlying diseases			
Hypertension (%)	11 (47.8%)	13 (76.5%)	0.119
Type 2 diabetes (%)	0 (0%)	1 (5.9%)	0.234
Induction therapy			
NIH regimen (%)	9 (39.1%)	6 (33.3%)	0.684
Euro-lupus regimen (%)	4 (17.4%)	2 (11.8%)	
MMF regimen (%)	10 (43.5%)	10 (58.8%)	
Hydroxychloroquine (%)	22 (95.7%)	16 (88.9%)	0.409
RAAS blockade (%)	8 (34.8%)	3 (16.7%)	0.094
CCB (%)	5 (21.7%)	4 (22.2%)	0.431
Low C3 complement (%)	18 (78.3%)	16 (88.9%)	0.338
Low C4 complement (%)	17 (73.9%)	11 (61.1%)	0.382
Positive ANA titer (%)	21 (91.3%)	15 (83.3%)	0.494
Positive anti-dsDNA (%)	21 (91.3%)	14 (77.8%)	0.224
Serum creatinine (mg/dL)	0.9 ± 0.4	1.4 ± 0.6	0.030
Estimated GFR (mL/min/1.73 m^2)	90.9 ± 37.4	65.9 ± 39.7	0.046
Hematocrit (%)	32.6 ± 7.5	32.1 ± 5.5	0.812
Serum albumin (g/dL)	2.9 ± 0.7	2.6 ± 0.6	0.120
Urine protein creatinine ratio (g/gCr)	2.3 (1.1, 4.6)	2.9 (2.0, 4.4)	0.232

Data are *n* (%) or mean ± SD or median (IQR) and *n* (%), Independent t test or Mann–Whitney *U* and Chi-square test

RAAS renin-angiotensin aldosterone system, *CCB* calcium channel blocker, *GFR* glomerular filtration rate

Table 2 shows the histological characteristics in the remission and nonremission groups. In terms of histological findings, 51.2, 31.7, and 17.1% of patients had Class III/IV + V, Class IV, and Class III, respectively. Overall renal activity index did not differ in the remission and nonremission groups. Presence of cellular crescents (2.2 ± 1.9 vs. 0.9 ± 1.0, $P = 0.006$) and interstitial cell infiltration (0.4 ± 0.5 vs. 0.1 ± 0.3, $P = 0.014$) were more often observed in the nonremission group than in the remission group. Additionally, total chronicity index (3.9 ± 2.2 vs. 1.8 ± 1.9, $P = 0.002$), presence of glomerular sclerosis (1.8 ± 0.9 vs. 0.7 ± 0.8, $P = 0.001$), of tubular atrophy (1.1 ± 0.9 vs. 0.5 ± 0.6, $P = 0.016$), and of interstitial fibrosis score (1.1 ± 0.9 vs. 0.5 ± 0.6, $P = 0.016$) were significantly higher in the nonremission than in the remission group (Table 2).

The initial step by univariate analysis for all variables that were associated with the renal remission were analyzed. Estimated GFR (hazard ratio (HR), 1.02; 95% confidence interval (95% CI), 1.01 to 1.04) was positively associated with achieving renal remission. In contrast, presence of anti-dsDNA titer (HR 0.95; 95% CI 0.90–0.99), cellular crescent (HR 0.54; 95% CI 0.32–0.91), interstitial inflammation (HR 0.15; 95% CI 0.03–0.85), total renal chronicity index (HR 0.61; 95% CI 0.43–0.88), glomerulosclerosis (HR 0.24; 95% CI 0.09–0.63), tubular atrophy (HR 0.33; 95% CI 0.12–0.87) and interstitial fibrosis (HR 0.33; 95% CI 0.12–0.87) were negatively associated with achieving renal remission following immunosuppressive treatment (Table 3). However, in multivariate analysis, only aging (HR 0.62; 95% CI 0.39–0.99), presence of cellular crescent (HR 0.01; 95% CI 0.01–0.88) and high total renal chronicity index (HR 0.11; 95% CI 0.01–0.88) were confirmed as independent

Table 3 Univariate logistic regression analysis of the predictors of renal remission in patients with lupus nephritis

Variables	Remission vs. non remission	
	HR (95% CI)	*P*
Male	2.22 (0.38, 13.08)	0.377
Age (year)	0.95 (0.89, 1.02)	0.180
Body weight (kg)	1.00 (0.95, 1.05)	0.908
Body mass index (kg/m^2)	1.03 (0.89, 1.19)	0.719
Systolic blood pressure (mmHg)	0.99 (0.96, 1.02)	0.408
Diastolic blood pressure (mmHg)	0.95 (0.90, 1.02)	0.330
Duration of SLE (year)	0.93 (0.83, 1.04)	0.198
C3 complement	0.67 (0.09, 4.95)	0.694
Anti-dsDNA titer	0.95 (0.90, 0.99)	0.030
Hematocrit (%)	1.01 (0.92, 1.11)	0.807
Estimated GFR (mL/min/1.73 m^2)	1.02 (1.01, 1.04)	**0.034**
Serum albumin (g/dL)	2.35 (0.78, 7.07)	0.129
Urine protein creatinine ratio (g/gCr)	0.93 (0.74, 1.17)	0.541
Renal activity index	0.92 (0.79, 1.07)	0.292
Hyaline deposit	0.94 (0.56, 1.6)	0.829
Endocapillary hypercellularity	0.95 (0.53, 1.7)	0.869
Neutrophils/karryorrhexis	1.28 (0.77, 2.12)	0.349
Fibrinoid necrosis	1.10 (0.42, 2.84)	0.851
Cellular crescent	0.54 (0.32, 0.91)	**0.022**
Interstitial infiltration	0.15 (0.03, 0.85)	**0.032**
Renal chronicity index	0.61 (0.43, 0.88)	**0.008**
Glomerulosclerosis	0.24 (0.09, 0.63)	**0.004**
Fibrous crescent	0.36 (0.03, 4.37)	0.425
Tubular atrophy	0.33 (0.12, 0.87)	**0.026**
Interstitial fibrosis	0.33 (0.12, 0.87)	**0.026**

Bold values denote statistical significance at the $P < 0.05$ level

Table 2 Histological finding by ISN/RPS 2018 classification

	Remission group ($n = 23$)	Non-remission group ($n = 18$)	*P* value
ISN/RPS classification			
Class III (%)	6 (26.1%)	1 (5.6%)	0.200
Class IV (%)	6 (26.1%)	7 (38.9%)	
Class III/IV + V (%)	11 (47.8%)	10 (55.6%)	
Total renal activity index (24)	5.8 ± 3.6	7.2 ± 4.9	0.300
Hyaline deposit (3)	1.1 ± 1.3	1.2 ± 1.1	0.834
Endocapillary hypercellularity (3)	2 ± 1.1	2.1 ± 1.1	0.873
Neutrophils/karryorrhexis (3)	1.5 ± 1.2	1.1 ± 1.3	0.359
Fibrinoid necrosis (6)	0.3 ± 0.7	0.2 ± 0.7	0.856
Cellular/fibrocellular crescent (6)	0.9 ± 1.0	2.2 ± 1.9	0.006
Interstitial infiltration (3)	0.1 ± 0.3	0.4 ± 0.5	0.014
Total renal chronicity index (12)	1.8 ± 1.9	3.9 ± 2.2	0.002
Glomerulosclerosis (3)	0.7 ± 0.8	1.8 ± 0.9	0.001
Fibrous crescent (3)	0.1 ± 0.2	0.1 ± 0.3	0.422
Tubular atrophy (3)	0.5 ± 0.6	1.1 ± 0.9	0.016
Interstitial fibrosis (3)	0.5 ± 0.6	1.1 ± 0.9	0.016

Data are *n* (%) or mean ± SD. Independent *t* test and Chi-square test

Table 4 Multivariate logistic regression analysis of the predictors of renal remission in patients with lupus nephritis

Variables	Remission vs. non remission	
	HR (95% CI)	*P* value
Age (year)	0.62 (0.39, 0.99)	**0.044**
Diastolic blood pressure	1.00 (0.90, 1.12)	0.932
Cellular crescent	0.01 (0.01, 0.88)	**0.045**
Interstitial infiltration	1.45 (0.03, 65.44)	0.848
Renal chronicity index	0.11 (0.01, 0.88)	**0.038**
Estimated GFR	0.94 (0.87, 1.01)	0.097
Anti-dsDNA titer	1.02 (0.91, 1.04)	0.342
Urine protein creatinine ratio	0.75 (0.37, 1.50)	0.415

Bold values denote statistical significance at the $P < 0.05$ level

GFR glomerular filtration rate

predictors for renal remission in our cohort of patients with lupus nephritis (Table 4).

Clinical and pathological parameters analyzed by ROC for best predicting renal mission are illustrated in Fig. 1. Estimated GFR (AUC = 0.708; 95% CI 0.527–0.888), anti-dsDNA titer (AUC = 0.674; 95% CI 0.491–0.858), cellular crescent (AUC = 0.750; 95% CI: 0.585 to 0.915) and renal chronicity index (AUC = 0.765; 95% CI 0.585–0.915) constituted predicting factors for renal remission. Best multivariate model from estimated GFR, anti-dsDNA titer, pathological of cellular crescent and renal chronicity index demonstrated good ability to predict renal remission after induction therapy among patients with proliferative lupus nephritis (AUC = 0.924; 95% CI 0.840–1.000) (Table 5 and Fig. 1).

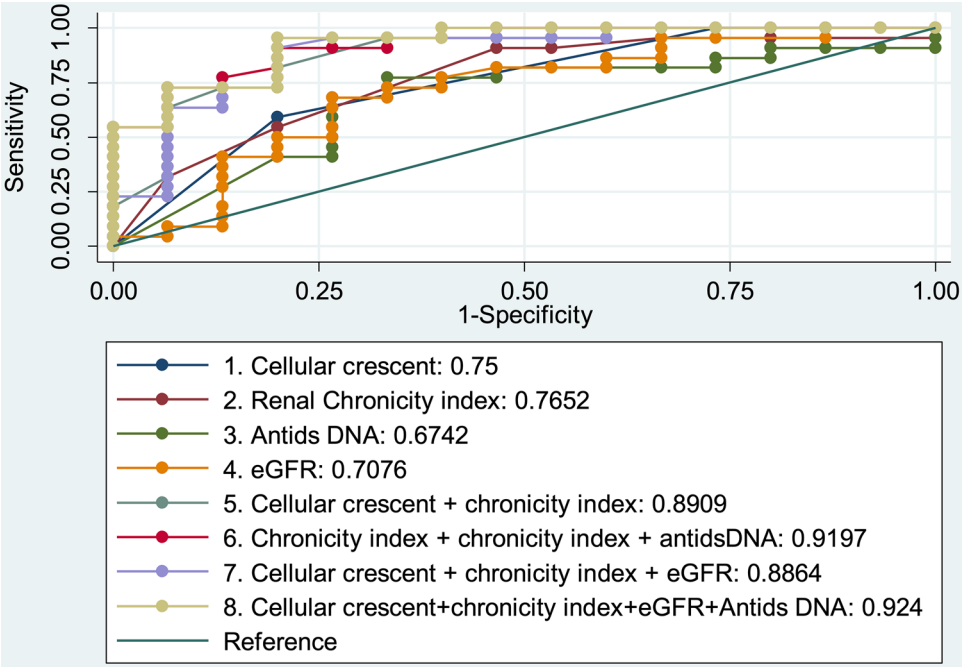

Fig. 1 Graph ROC curves shows area under the curve of variable factors to predict renal response after induction therapy

Table 5 Area under the curve of predictor factors of renal remission

Variables	AUC	95% CI		*P* value
1. Anti-dsDNA titer	0.674	0.491	0.858	0.075
2. Estimated GFR	0.708	0.527	0.888	0.034
3. Cellular crescent	0.750	0.585	0.915	0.011
4. Renal chronicity index	0.765	0.605	0.926	0.007
5. Cellular crescent + chronicity index	0.891	0.777	1.000	< 0.001
6. Cellular crescent + chronicity index + anti-dsDNA titer	0.920	0.834	1.000	< 0.001
7. Cellular crescent + chronicity index + estimated GFR	0.886	0.768	1.000	< 0.001
8. Cellular crescent + chronicity index + estimated GFR + anti-dsDNA titer	0.924	0.840	1.000	< 0.001

Discussion

SLE is a prototypic auto-immune disease, comprising a wide range of renal complications. Renal biopsy according to ISN/RPS 2003 classification is considered the standard for histological evaluation and specifying lupus glomerulonephritis class. Renal pathology could provide additional information on patient outcomes. However, predicting renal outcomes and response to treatment remains controversial regarding the definitions of ISN/RPS 2003 classification of pathological lesions and their prognostic significance [13, 14]. Scoring systems using this classification showed poor interpathologist agreement and variations in pathologic reporting, limiting its use in clinical practice [15, 16]. A revised ISN/RPS 2018 score needs to evaluate the correlation regarding histological and clinical remission. Limited studies have been conducted to determine a predictive model based on clinical and pathological parameters to estimate the risk of renal response to standard induction therapy [17, 18]. Our result confirmed good performance of the model using both clinical and histological variables (AUC = 0.924) to predict renal remission after induction therapy among patients with proliferative lupus nephritis.

The impact of renal remission on long-term prognosis in SLE has been described in many studies. A total of 56.1% of our patients reached renal remission. Our results confirmed that the clinical predictors of age, baseline GFR and anti-dsDNA were associated with renal remission and those of renal pathology including presence of cellular crescent and high renal chronicity index were the predictors of renal response in lupus nephritis [9, 19, 20]. These results agree with related studies that identified crescents as an independent predictor of renal outcomes [9] and a higher proportion of chronic lesions as a critical factor for refractoriness to aggressive therapy in diffuse proliferative lupus nephritis [21–23]. Therefore, quantitative scoring of glomeruli with crescents and renal chronicity according to ISN/RPS 2018 classification might prove beneficial in determining renal response. Moreover, we suggest that the combination of histopathological findings especially chronicity index and clinical variables at baseline performed better than clinical findings in predicting a clinical response to treatment of active lupus nephritis. Similar to related studies, renal biomarkers, glomerular and tubulointerstitial lesions in addition to clinical variables showed increased power in predicting renal response and outcomes among patients with SLE [24, 25].

Renal outcomes from ISN/RPS 2003 classification of lupus nephritis focuses on endocapillary proliferation in class III to IV and the power to determine renal prognosis was observed n proliferative lupus nephritis compared with nonproliferative lupus nephritis (classes I, II and V) [4, 26, 27]. All patients included in our study had class III or IV, renal activity findings, such as cellular crescents and interstitial cell infiltration and renal chronicity findings such as glomerulosclerosis, tubular atrophy and interstitial fibrosis score providing additional therapeutic outcome information. This was consistent with related retrospective studies that identified tubulointerstitial lesions, biomarkers of tubulointerstitial injury and glomerular crescents among Asian patients with SLE using renal involvement as predictors of renal outcomes [28–31]. Early identification of patients with active lupus nephritis at high risk of renal progression could prompt more aggressive intervention. A large prospective multicenter cohort of patients with different classes of lupus nephritis should be formed to validate data coming from this relatively small study.

The main limitation encountered was the relatively small size, in a single-center prospective study of clinical and histopathologic predictors of renal progression among patients with lupus nephritis, indicating we may have been underpowered to detect meaningful histopathologic predictors and the population might not be normalized with the whole population of active lupus nephritis in Thailand. Our results for estimation and validation of new lupus nephritis classification on renal remission should be interpreted cautiously in light of the data limitations for these outcomes as well as the small number of study (only 23 patients in renal remission, and 18 patients in nonremission group). Second, the only short-term outcomes were evaluated. A long-term study of renal outcomes is needed including renal survival, dialysis or end-stage renal disease. Third, the limited special renal pathological findings including microthrombi, karyorrhexis and vasculitis in the study could not assess the prognostic value of rarely occurring events. Fourth, the main study population involved class III or IV lupus nephritis, making it impossible to define putative early histopathologic predictors of progression from nonproliferative lupus nephritis to proliferative lupus nephritis. Finally, follow-up was based on estimated GFR and urine protein to define renal remission, instead of renal biopsy, which may have revealed mildly deviated renal outcomes.

Conclusion

In summary, our study validated clinical and pathological variables according to ISN/RPS 2018 classification to evaluate the probability of renal response with standard induction therapy in active lupus nephritis. We identified cellular crescent and total renal chronicity index in addition to clinical variables (aging and renal function) as important predictors of renal response. These findings suggested that intensity induction treatment is required for patients with proliferative

lupus nephritis and histological features to improve the renal remission to the therapy.

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Availability of data and materials Data supporting this study are available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The study was approved by the Ethics Committee of the Institute Review Board at the Royal Thai Army Medical Department and was conducted according to the Declaration of Helsinki.

Informed consent Informed consent was obtained from all participants.

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