Comparison of 2018 and 2003 International Society of Nephrology/Renal Pathology Society classification in terms of renal prognosis in patients of lupus nephritis: a retrospective cohort study.

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Abstract

Background: Although 2018 revised ISN/RPS classification was proposed recently, until now, no reports have been made comparing the association of renal prognosis between 2018 revised ISN/RPS classification and 2003 ISN/RPS classification. The present study aimed to assess the usefulness, especially of activity and chronicity assessment, of the 2018 revised International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification for lupus nephritis (LN) in terms of renal prognosis compared to the classification in 2003.

Methods: We retrospectively collected medical records of 170 LN patients from the database of renal biopsy in Fujita Health University from January 2003 to April 2019. Each renal biopsy specimen was reevaluated according to both the 2003 ISN/RPS classification and the 2018 revised ISN/RPS classification. Renal endpoint was defined as 30% decline of estimated glomerular filtration rate (eGFR).

Results: A total 129 patients were class III/IV±V (class III, 44 patients; class IV, 35 patients; class III/IV+V, 50 patients). Mean age was 42 years, 88% were female, and median observation period was 50.5 months. Renal prognosis was significantly different among the classes, and significantly poor in the patients with higher modified National Institute of Health (mNIH) Chronicity index (C index, ≥4) by a log-rank test (p=0.05, p=0.02 respectively). By Cox proportional hazard models, only C index was significantly associated with renal outcome (Hazard Ratio; 1.32, 95% CI; 1.11-1.56, $p \leq 0.01$), while the classes, the 2003 activity and chronicity subdivision, and mNIH activity index had no significant association with renal outcome. Each component of C index was significantly associated with renal outcome in different models.

Conclusion: This study demonstrates that the 2018 revised ISN/RPS classification was more useful in terms of association with renal prognosis compared to the 2003 ISN/RPS classification

Background

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects many organ systems. Renal involvement is quite common (60–70%) among SLE patients, and it is associated with poor prognosis of the disease and higher mortality (1). Early diagnosis and treatment of lupus nephritis (LN) is essential to preserving kidney function, and renal biopsy is recommended for the correct evaluation of renal pathological findings.

In 2003, in order to make some definitions of pathological findings clear and produce replicable results, the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification was proposed, which has since been widely accepted as the classification of LN (2, 3). It was adopted by the following guidelines for the management of LN such as the American College of Rheumatology (ACR) (2), the Joint European League Against Rheumatism and the European Renal Association (EULAR/ERA-EDTA) (3, 4), the Kidney Disease: Improving Global Outcomes (KDIGO) working group (5), and the Japan College of Rheumatology (6).

However, this classification has several problems. For instance, definitions for some lesions such as endocapillary proliferation or fibrinoid necrosis are unclear. Furthermore, a meta-analysis study shows that there was no difference in renal prognosis between the S subclass and G subclass of class IV introduced in this revision (1, 7). The classification is based only on glomerular lesion, and tubulointerstitial or vascular lesions are merely noted; on the other hand, tubulointerstitial lesions such as interstitial fibrosis and tubular atrophy are reported to be better predictors of estimated glomerular filtration rate (eGFR) decline than some active glomerular lesions (8). Additionally, designation of activity and chronicity through A, A/C, and C can be too broad of a categorization, as details are not reflected.

In 2018, an international working group of leading nephropathologists proposed updates to the ISN/RPS classification system to solve such conflictions found in the classification proposed in 2003. In this new proposal, the definition of pathological findings was much more detailed and precise. Moreover, the subclass of class IV was removed. They also changed the method of evaluation of active and chronic status from shorthand A, A/C, C subdivision to semiquantitative activity/chronicity index based on the National Institute of Health (NIH) index, labeled as modified NIH index (mNIH index) (9, 10).

There are several reports on the relationship between the prognosis of LN and 2003 ISN/RPS classification or the original NIH index. For example, class IV LN (11), mixed proliferative and membranous LN (12), and high original NIH Chronicity index (C index) score (13) are related to poor prognosis. However, until now, there have been few reports that investigate the prognostic value of 2018 revised ISN/RPS classification or the mNIH index. Furthermore, no reports have been made comparing the association of renal prognosis between 2018 revised ISN/RPS classification and 2003 ISN/RPS classification. The present study aimed to confirm whether the classes, especially activity and chronicity subdivision in the 2003 ISN/RPS classification and mNIH index in the 2018 revised ISN/RPS classification are associated to renal prognosis among the histologically proven LN patients.

Materials And Methods

Patients

We used a retrospective cohort design and collected medical records of two hundred adult SLE patients from 1208 patients who underwent kidney biopsy in Fujita Health University from January 2003 to April 2019. From these, 9 cases not documented in the medical records and 3 cases of pathological findings unassociated with LN were excluded. For the 18 cases of patients who repeatedly received renal biopsies, data from the first renal biopsy of each case were used. Thus, a total of 170 cases were included for analysis (Fig. 1). All cases fulfilled ≥ 4 of the SLE classification criteria of the ACR in 1997 (14). This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Board of Fujita Health University (No. HM20-245) and opt-outed on its website.

Histopathological studies

Renal biopsy specimens underwent light microscopy, immunofluorescence study, and electron microscopy study. Renal tissues were fixed in a 10% Formalin Neutral Buffer Solution, paraffin embedded,

and sectioned at 1–3μ thickness. Periodic acid-Schiff stain, periodic acid-methenamine silver stain, hematoxylin-eosin stain, and Masson's trichrome stain were routinely performed. For immunofluorescent examination, parts of the tissues were embedded in Optimal Cutting Temperature compound and quick-frozen in a dry ice-acetone mixture. After, they were sectioned at 3 μm by Tissue Tek POLAR-D (Sakura Seiki Co., Ltd., Japan) and stained with fluorescein isothiocyanate (FITC) conjugated antihuman immunoglobulin (Ig) G, IgA, IgM, C3, C1q goat polyclonal antibodies (F. Hoffmann-La Roche Ltd., Switzerland), and FITC conjugated antihuman C4 rabbit antibodies (DAKO., USA). As the evaluation was performed using an electron microscope, parts of the tissue were fixed in 2.5% glutaraldehyde and osmium tetroxide, embedded in Epon812 (OkenShoji Co., Tokyo, Japan), sectioned at 100 nm, stained with uranyl acetate and lead citrate, and observed with the electron microscope (JEM-1400Flash; JEOL Ltd., Tokyo, Japan).

All specimens contained more than 10 glomeruli and were each reevaluated using the 2003 ISN/RPS classification and the 2018 revised ISN/RPS classification (9, 15, 16). For the activity and chronicity assessment, A, A/C, and C subdivisions were added to class III/IV ± V in the 2003 ISN/RPS classification, and mNIH index was added to all classes in the 2018 revised ISN/RPS classification. A summary of the components of the mNIH index is as follows: endocapillary hypercellularity, neutrophil infiltration or karyorrhexis, fibrinoid necrosis, hyaline deposits, cellular/fibrocellular crescent, and interstitial infiltration as active lesions; glomerulosclerosis, fibrous crescent, tubular atrophy, and interstitial fibrosis as chronic lesions. Scores were assigned accordingly to the following percentages (0%: 0 points; <25%: 1 point; 25 ~ 50%: 2 points; >50%: 3 points): for endocapillary hypercellularity, neutrophil infiltration or karyorrhexis, fibrinoid necrosis, hyaline deposits, cellular/fibrocellular crescent, glomerulosclerosis, and fibrous crescent, the percentage of glomeruli with lesions out of the total number of glomeruli; for interstitial fibrosis and interstitial inflammation, the percentage of the cortex with lesions; for tubular atrophy, the percentage of the cortical tubules with lesions. Scores were doubled for fibrinoid necrosis and cellular/fibrocellular crescent, and each of their total scores became Activity index (A index) and C index. This contrasts with the original NIH activity and chronicity index in that the category including karyorrhexis is different and fibrocellular crescent is newly defined in the mNIH index. Pathological tissues were interpreted by experienced pathologist S.H. and experienced nephrologists R.U. and H.H. with medical records blinded. Readings by S.H. and the consulted results by R.U. and H.H. were compared; if a result differed, a final decision was made upon consultation by the three.

Clinical evaluation

Clinical data at the date of renal biopsy (age, sex, body mass index, baseline eGFR, serum creatinine [sCr], serum albumin, anti-phospholipid antibody, urinary protein to creatinine ratio [UPCR, g/g], duration between SLE diagnosis and renal biopsy), and longitudinal clinical examination data (sCr, eGFR, UPCR [g/g], medication) from the date of renal biopsy to April 2019 were extracted. eGFR was calculated using the equation for the Japanese population (17).

Outcome

The primary outcome was set as the period from the date of renal biopsy to when GFR declined by 30%. When a patient reached to the outcome or underwent renal replacement therapy or died or transferred to another hospital, data collection was terminated at that point. Patients usually took blood test once every a few months and eGFR was calculated.

Statistical Analysis

Baseline characteristics were summarized by mean (standard deviation [SD]) for continuous variables and N (%) for categorical variables. We plotted survival curves for the associations of the pathological features (i.e., classes, activity and chronicity subdivision in 2003, mNIH activity or chronicity index in 2018) with eGFR decline by 30% using Kaplan-Meier curves method and log-rank tests. The cutoff value of A index and C index was set to be its number of 80th percentile.

To investigate associations of pathological features with the primary outcome, we used Cox proportional hazard models. In the models, eGFR decline by 30% was modeled as a dependent variable, and pathological features were modeled as independent variables (i.e. classes, activity and chronicity subdivision in 2003, mNIH activity or chronicity index in 2018). We obtained hazard ratios (HR) and 95% confidence intervals (CI) that were crude in one model (i.e., non-adjusted; Model 1) and adjusted for potential confounders in two models (i.e., Model 2 and Model 3). Model 2 was adjusted for age, sex, eGFR, and UPCR. Model 3 was adjusted for age, sex, eGFR, UPCR, duration of systemic lupus erythematosus, use of cyclophosphamide (CYC) or mycophenolate mofetil (MMF), use of renin angiotensin aldosterone inhibitor, presence of nephrotic syndrome (NS), and presence of rapidly progressive glomerulonephritis (RPGN). Additionally, we investigated associations of each component of chronicity index with the 30% eGFR decline using Cox proportional hazard models in which each component of chronicity index was separately analyzed (i.e., these were analyzed in different models).

The significance tests were two-sided, and the significance level for all analyses was p-value < 0.05. When there were missing values of a potential confounder, they were excluded from the analyses. We used R statistical software (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.).

Results

Clinical characteristics of patients of LN

The baseline data for proliferative LN (class III/IV ± V) patients are shown in Table 1 (class III, 44 patients; class IV, 35 patients; and class III/IV + V, 50 patients). The age of patients ranged between 17 to 78 with a mean (SD) of 42 (14), and 88% were female. Baseline eGFR (mL/min/1.73 m^2) and UPCR (g/g) was 79.5 (24.3), 1.2 (1.3) in class III, 66.7 (27.0), 3.2 (2.4) in class IV, 82.9 (32.6), 3.0 (3.1) in class III/IV + V, respectively. The percentage of patients with NS/RPGN was 18.2/9.1 in class III, 65.7/25.7 in class IV, 50.0/6.0 in class III/IV + V, respectively. All the patients from the 2003 ISN/RPS classification matched with the 2018 revised ISN/RPS classification. Proportion of the subdivision of 2003 ISN/RPS

classification were as follows: A was 25.6%, A/C was 54.3%, and C was 20.1%. The median (Interquartile range, IQR) for A index and C index of the mNIH index from the 2018 revised ISN/RPS classification was 3 (2, 5)/2 (2, 4) in class III, 8 (1, 6)/3 (2, 5) in class IV, 3 (1, 6)/3 (2, 4) in class III/IV + V, respectively. Frequency distribution of A index and C index are shown in Fig. 2, and all the baseline data including patients of class I, II, and V are presented in Table 2.

Table 1
Baseline characteristics of patients of proliferative lupus nephritis.

	III	IV	III/IV + V
Number	44	35	50
Age, years, mean ± SD	45.7 (15.3)	40.0 (14.1)	41.1 (11.6)
Sex, female, n (%)	41 (93.2)	32 (91.4)	40 (80.0)
BMI, mean ± SD	22.0 (3.5)	21.8 (4.0)	21.5 (3.8)
Duration of SLE, years, mean ± SD	10.9 (9.7)	10.5 (7.9)	12.1 (6.6)
Systolic BP, mmHg, mean ± SD	128.0 (18.0)	137.7 (25.7)	128.3 (24.0)
Serum creatinine, mg/dL, mean ± SD	0.8 (0.3)	0.9 (0.5)	1.0 (0.6)
Antiphospholipid antibody, n (%)	18 (40.9)	12 (34.3)	12 (24.0)
eGFR, mL/min/1.73 m^2, mean ± SD	79.5 (24.3)	66.7 (27.0)	82.9 (32.6)
Urinary protein, g/g, mean ± SD	1.2 (1.3)	3.2 (2.4)	3.0 (3.1)
Nephrotic syndrome, n (%)	8 (18.2)	23 (65.7)	25 (50.0)
RPGN, n (%)	4 (9.1)	9 (25.7)	3 (6.0)
Activity and chronicity assessment			
ISN/RPS 2003 classification, n (%)			
A	18 (40.9)	8 (22.9)	7 (14.0)
A/C	20 (45.5)	22 (62.9)	28 (56.0)
C	6 (13.6)	5 (14.3)	15 (30.0)
2018 mNIH index, median (IQR)			
Activity index	3 (2, 5)	8 (1, 6)	3 (1, 6)
Chronicity index	2 (2, 4)	3 (2, 5)	3 (2, 4)
Treatment			
Initial dosage of PSL, mean ± SD	39.3 (15.5)	42.8 (15.5)	38.3 (15.5)
CYC or MMF, n (%)	8 (18.2)	16 (45.7)	8 (16.0)

Abbreviations: SD, standard deviation; BMI, body mass index; BP, blood pressure; SLE, systemic lupus erythematosus; EGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; ISN/RPS, International Society of Nephrology/Renal pathology Society; IQR; interquartile range; mNIH, modified National Institute of Health; PSL, prednisolone; CYC, cyclophosphamide; MMF, mycophenolate mofetil; RAS, renin angiotensin aldosterone system

	III	IV	III/IV + V
RAS inhibitor, n (%)	14 (31.8)	15 (42.9)	16 (32.0)

Abbreviations: SD, standard deviation; BMI, body mass index; BP, blood pressure; SLE, systemic lupus erythematosus; EGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; ISN/RPS, International Society of Nephrology/Renal pathology Society; IQR; interquartile range; mNIH, modified National Institute of Health; PSL, prednisolone; CYC, cyclophosphamide; MMF, mycophenolate mofetil; RAS, renin angiotensin aldosterone system

Table 2
Baseline characteristics of patients of all classes of lupus nephritis.

	I/II	III	III + V	IV	IV + V	pure V
Number	14	46	36	35	16	21
Age, years, mean ± SD	35.4 (15.2)	44.9 (15.4)	41.8 (12.8)	40.0 (14.1)	40.7 (10.6)	39.7 (13.9)
Sex, female, n (%)	9 (64.3)	43 (93.5)	28 (77.8)	32 (91.4)	13 (81.2)	15 (71.4)
BMI, mean ± SD	20.8 (2.8)	21.9 (3.5)	21.5 (3.8)	21.8 (4.0)	21.9 (3.8)	21.3 (3.1)
Duration of SLE, years, mean ± SD	9.4 (8.6)	10.6 (9.6)	11.9 (6.3)	10.5 (7.9)	12.7 (6.7)	8.3 (3.8)
Systolic BP, mmHg, mean ± SD	122.6 (16.7)	126.8 (18.4)	122.0 (20.4)	137.7 (25.7)	130.0 (27.1)	118.7 (17.5)
Serum Cr, mg/dL, mean ± SD	0.66 (0.19)	0.80 (0.30)	0.87 (0.62)	0.90 (0.49)	1.17 (0.62)	0.73 (0.35)
Antiphospholipid antibody, n (%)	1 (7.1)	19 (41.3)	9 (25.0)	12 (34.3)	3 (18.8)	7 (33.3)
eGFR, mL/min/1.73 m^2, mean ± SD	114.9 (35.8)	79.5 (24.3)	91.8 (30.3)	66.7 (27.0)	63.8 (29.7)	98.6 (35.7)
Urinary protein, g/g, mean ± SD	0.83 (0.89)	1.19 (1.28)	2.80 (2.58)	3.22 (2.36)	3.77 (4.03)	1.48 (1.76)
Nephrotic syndrome, n (%)	1 (7.1)	8 (17.4)	17 (47.2)	23 (65.7)	9 (56.2)	4 (19.0)
RPGN, n (%)	0 (0.0)	5 (10.9)	1 (2.8)	9 (25.7)	2 (12.5)	0 (0.0)
Activity and chronicity assessment						
ISN/RPS 2003 classification, n (%)						
A	0 (0.0)	18 (39.1)	6 (16.7)	8 (22.9)	1 (6.2)	0 (0.0)
A/C	0 (0.0)	22 (47.8)	17 (47.2)	22 (62.9)	12 (75.0)	0 (0.0)

Abbreviations: SD, standard deviation; BMI, body mass index; BP, blood pressure; Cr, creatinine; SLE, systemic lupus erythematosus; EGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; ISN/RPS, International Society of Nephrology/Renal pathology Society; IQR; interquartile range; mNIH, modified National Institute of Health; CYC, cyclophosphamide; MMF, mycophenolate mofetil; RAS, renin angiotensin aldosterone system; ref, reference.

	I/II	III	III + V	IV	IV + V	pure V
C	14 (100)	6 (13.0)	13 (36.1)	5 (14.3)	3 (18.8)	21 (100)
2018 mNIH index, median (IQR)						
Activity index	0 (0, 0)	3 (2, 5)	2 (1, 5)	8 (1, 6)	6 (4, 79)	0 (0, 1)
Chronicity index	0 (0, 0.75)	2 (2, 4)	3 (1.5, 4)	3 (2, 5)	4 (3, 5)	2 (0, 3)
Treatment, n (%)						
CYC or MMF	2 (15.4)	8 (17.4)	4 (11.1)	16 (45.7)	4 (25.0)	2 (9.5)
RAS inhibitor	3 (23.1)	14 (30.4)	11 (30.6)	15 (42.9)	7 (43.8)	4 (19.0)

Abbreviations: SD, standard deviation; BMI, body mass index; BP, blood pressure; Cr, creatinine; SLE, systemic lupus erythematosus; EGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; ISN/RPS, International Society of Nephrology/Renal pathology Society; IQR; interquartile range; mNIH, modified National Institute of Health; CYC, cyclophosphamide; MMF, mycophenolate mofetil; RAS, renin angiotensin aldosterone system; ref, reference.

Pathological findings and renal prognosis

Survival curves using Kaplan-Meier curves method and log-rank tests, and a multivariate analysis using Cox proportional hazard models for the associations of eGFR decline by 30% and the pathological features (class, activity and chronicity subdivisions in the 2003 classification, and mNIH index) were shown in Fig. 3 and Table 3, respectively. Renal prognosis was significantly different among the classes by a log-rank test (Fig. 3A), while there was no significant difference by Cox proportional hazard models (Table 3). There was also no significant difference in renal outcome among the activity and chronicity subdivisions of A, A/C, and C by a log-rank test (Fig. 3B). Although subdivision A/C showed significant association to renal outcomes in model 1 (HR; 3.08, 95% CI; 1.12–8.44, $p = 0.03$), the difference was not seen in models 2 and 3 (HR; 2.67, 95% CI; 0.84–8.49, p = 0.10 in Model 2, Table 3). There was no difference among the two A index groups (8 ≥ or 9≤) in log-rank test (Fig. 3C) and no association in outcome by Cox proportional hazard models (Table 3). On the other hand, there was significant different among the two groups of C index (4 ≤ or 5≥) in log-rank test (Fig. 3D) and C index showed significant association with renal prognosis by Cox proportional hazard models (HR; 1.29, 95% CI; 1.14–1.46, $p \leq 0.01$ in Model 1, HR; 1.32, 95% CI; 1.11–1.56, $p \leq 0.01$ in Model 2, HR; 1.29, 95% CI; 1.05–1.58, $p = 0.01$ in Model 3).

Table 3
Associations between pathological features and eGFR decline by 30%; Cox proportional hazard models.

	Model 1 (n = 129)			Model 2 (n = 128)			Model 3 (n = 128)		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
2003 classification model									
class									
III (ref)	1.00			1.00			1.00		
IV	0.46	(0.16–1.27)	0.13	0.76	(0.25–2.33)	0.63	0.83	(0.27–2.62)	0.76
III or IV + V	1.29	(0.60–2.79)	0.52	1.82	(0.67–4.89)	0.24	1.41	(0.49–4.02)	0.52
Activity/chronicity assessment									
A(ref)	1.00		1.00			1.00			
A/C	3.08	(1.12–8.44)	0.03	2.67	(0.84–8.49)	0.10	2.16	(0.64–7.34)	0.22
C	2.19	(0.68-7.00)	0.19	2.59	(0.71–9.47)	0.15	2.52	(0.66–9.61)	0.17
2018 classification model									
class									
III (ref)	1.00			1.00			1.00		
IV	0.39	(0.12–1.21)	0.10	0.62	(0.19-2.00)	0.42	0.61	(0.18–2.09)	0.43
III or IV + V	1.35	(0.63–2.89)	0.44	1.68	(0.65–4.34)	0.28	1.30	(0.46–3.69)	0.62
2018 mNIH index									
Activity index	1.05	(0.93–1.17)	0.43	1.04	(0.92–1.18)	0.53	1.05	(0.92–1.19)	0.49

Abbreviations: HR, Hazard ratio; CI, Confidence Interval; mNIH, modified National Institute of Health; ref, reference.

Model 1, not adjusted; Model 2, adjusted for age, sex, estimated glomerular filtration rate, urinary protein; Model 3, adjusted for age, sex, estimated glomerular filtration rate, urinary protein, duration of systemic lupus erythematosus, use of cyclophosphamide or mycophenolate mofetil, use of renin angiotensin aldosterone inhibitor, nephrotic syndrome or not, rapidly progressive glomerulonephritis or not.

	Model 1 (n = 129)			Model 2 (n = 128)			Model 3 (n = 128)		
Chronicity index	1.29	(1.14–1.46)	< 0.01	1.32	(1.11–1.56)	< 0.01	1.29	(1.05–1.58)	0.01
Activity and Chronicity index	1.02	(0.97–1.07)	0.52	1.01	(0.96–1.07)	0.72	1.02	(0.97–1.08)	0.44
Abbreviations: HR, Hazard ratio; CI, Confidence Interval; mNIH, modified National Institute of Health; ref, reference.									
Model 1, not adjusted; Model 2, adjusted for age, sex, estimated glomerular filtration rate, urinary protein; Model 3, adjusted for age, sex, estimated glomerular filtration rate, urinary protein, duration of systemic lupus erythematosus, use of cyclophosphamide or mycophenolate mofetil, use of renin angiotensin aldosterone inhibitor, nephrotic syndrome or not, rapidly progressive glomerulonephritis or not.									

Survival curves using Kaplan-Meier curves method and a multivariate analysis using Cox proportional hazard models of patients of all classes including class I, II, and V is shown in Fig. 4, Table 4. Although significant difference was not seen among the A index groups (8 ≥ or 9≤), classes (I/II, III, IV, III + V, IV + V, V) and C index (4 ≤ or 5≥) were significantly associated with renal outcome in log-rank test. By Cox proportional hazard models, only C index had significant association with renal outcome (HR; 1.28, 95% CI; 1.09–1.50, $p \leq 0.01$).

Table 4
Associations between pathological features and eGFR decline by 30%; Cox proportional hazard models (n = 162).

	HR	95% CI	*p* value
Class			
I or II (ref)	1.00		
III	1.25	(0.12–12.86)	0.85
IV	0.72	(0.05–9.64)	0.80
III + V	2.07	(0.21–20.34)	0.53
IV + V	3.00	(0.23–38.81)	0.40
V	1.47	(0.16–13.30)	0.73
2018 mNIH index			
Activity index	1.04	(0.91–1.18)	0.55
Chronicity index	1.28	(1.09–1.50)	< 0.01
Activity/Chronicity index	1.00	(0.95–1.05)	0.94

Abbreviations: HR, Hazard ratio; CI, Confidence Interval; mNIH, modified National Institute of Health; ref, reference. Those HRs were adjusted for age, sex, estimated glomerular filtration rate, urinary protein.

Cox proportional hazard models for the association of each component of mNIH C index with renal outcome are shown in Table 5. Glomerular sclerosis, fibrous crescent, tubular atrophy, and interstitial fibrosis all showed significant associations with renal outcomes in Model 2 (HR; 1.94, 95% CI; 1.11–3.39, $p = 0.02$, HR; 2.04, 95% CI; 1.03–4.03, $p = 0.04$, HR; 1.68, 95% CI; 1.04–2.71, $p = 0.03$, HR; 2.01, 95% CI; 1.27–3.20, $p \leq 0.01$, respectively).

Table 5
Association of every component of chronicity index and eGFR decline by 30% (n = 128).

Component of chronicity index	HR	95% CI	*p* value
Glomerulosclerosis	1.94	(1.11–3.39)	0.02
Fibrous crescent	2.04	(1.03–4.03)	0.04
Tubular atrophy	1.68	(1.04–2.71)	0.03
Interstitial fibrosis	2.01	(1.27–3.20)	< 0.01

Abbreviations: HR, Hazard ratio; CI, Confidence Interval.

Hazzard ratio was adjusted for age, sex, estimated glomerular filtration rate, urinary protein, class, activity index. Each component of chronicity index was analyzed in different models.

Discussion

In our study of this proliferative LN cohort, the mNIH C index from the 2018 revised classification showed a significant association of a 30% decrease of eGFR. The renal outcome was significantly associated with all C index components, including tubulointerstitial lesions not only glomerular lesions. On the other hand, there was no significant association between renal outcome and the activity and chronicity subdivisions based on the 2003 ISN/RPS classification. In terms of associations with renal prognosis, the activity and chronicity assessment based on the 2018 revised ISN/RPS classification was more useful compared to that of the 2003 ISN/RPS classification.

Tao et al had already studied the association of 2018 revised ISN/RPS classification with renal prognosis, and reported that fibrous crescent, tubular atrophy/interstitial fibrosis, and the C index were associated with poor renal prognosis (18). Our study also showed significant associations of the C index and its components including fibrous crescent, tubular atrophy, and interstitial fibrosis by a 30% decrease of eGFR, which supported the previous study. In this study, we further investigated the usefulness of 2018 revised ISN/RPS classification in terms of the association with renal prognosis compared to 2003 ISN/RPS classification by reclassifying the patients of LN using both classification criteria. Such reports had not been made until now, making this the first report of its kind.

In this study, the mNIH C index showed significant association by a 30% decrease of eGFR, although it was not shown in the activity and chronicity subdivisions in 2003. The most important difference in activity and chronicity assessment between the 2003 and 2018 ISN/RPS classifications is the inclusion of the evaluation for tubulointerstitial lesions. This is because tubulointerstitial lesions, not only glomerular lesions, has shown to be significantly associated with renal prognosis of LN in previous studies (8, 13, 19, 20). It is known that whatever the causes of Chronic Kidney disease (CKD) are, CKD gradually exacerbates tubulointerstitial hypoxia by multifactorial mechanisms such as loss of peritubular capillaries, decreased oxygen diffusion by fibrosis, or decreasing of blood flow by glomerulosclerosis. As a result of tubulointerstitial hypoxia, CKD progress, and it forms a malignant cycle. It is known as the ‘final common pathway’ (21). We should recognize tubulointerstitial lesions as the important prognostic factors even in a glomerular disease. Actually, in IgA nephropathy, a common form of glomerulonephritis, interstitial fibrosis and tubular atrophy are shown to be significant lesions that strongly associate with renal prognosis (22). In this context, adoption of evaluation of tubulointerstitial lesions in the classification of LN should improve the predictability of renal outcome.

As explanations for why chronicity assessment of the 2003 ISN/RPS classification showed no significant association with renal prognosis, in addition to the absence of the evaluation for tubulointerstitial lesions mentioned above, there is a problem in designation of subdivisions. Chronicity subdivisions in 2003

classification is not quantitative. Patients with a single C lesion and patients with diffuse C lesions are classified into the same C subdivision. In A/C subdivision, whether the active lesion is dominant, or the chronic lesion is dominant is not expressed. Subdivision of A/C occupies a large proportion (54.3% in our cohort), and they are formed as a heterogeneous group. Hiramatsu et al has reported that class IV-G (A/C) patients with diffuse C lesions are more likely to reach to the outcome of the doubling of sCr than class IV-G (A/C) patients with focal C lesions (23). This study showed the importance of quantitatively of chronic lesions in prediction of renal prognosis.

Meanwhile, the A index was not significantly associated with renal outcome in our study. Austin et al showed patients with high A index had a strong association with ESRD (10), but no significant associations have been shown in recent reports (11, 13, 19). In recent years, the treatment regimen of glucocorticoid with other immunosuppressants including CYC or MMF for the remission induction in recent years would sufficiently improve the some components of A index (24). A index may be less important as a renal prognostic factor in this era.

The mNIH index of the 2018 revised classification is proposed to be applied to all classes, unlike the activity and chronicity subdivision of the 2003 ISN/RPS classification which are limited to class III/IV ± V patients. Although many patients in class I, II, V had a low A index and C index, some patients had a relatively high C index. In multivariate analysis using cox proportional hazard models in all classes, C index was also shown to have significant associations with renal prognosis. Even in class II or pure class V, for cases with high C index, careful observation and follow-up on renal function may be desirable. Additionally, we set 30% GFR decline as the primary endpoint. Although arrival of doubling sCr, which is strongly associated with subsequent risk of ESRD, has been widely accepted as the renal outcome, it is a late event. In fact, in this study, a 30% GFR decline was observed in 36 patients, while the doubling of sCr and ESRD was observed only in 13 and 3 patients, respectively. It is shown that 30% eGFR decline, in replacement of sCr doubling, is effective as an early predictive marker of CKD progression (25).

There are several limitations. First, this study is a retrospective observational study. Second, the nationality and race are limited to mostly Japanese. Third, MMF or CYC as the current standard drug for proliferative LN was only used for 25% of patients in our cohort. This is because MMF or CYC was recently approved for the treatment of LN as health insurance treatment in Japan.

The strength of this study is that Compared to SLE patient cohorts of previous reports, there are more patients in this study. In addition, this is the first report that investigates the usefulness of 2018 revised ISN/RPS classification compared to 2003 ISN/RPS classification in terms of the association with renal prognosis.

While the activity and chronicity subdivision of the 2003 ISN/RPS classification showed no association with renal prognosis, the mNIH C index of the 2018 revised classification showed a significant association by a 30% eGFR decrease. Each category of the C index was independently associated with poor renal prognosis. In terms of associations with renal prognosis, the 2018 activity and chronicity assessment was more useful compared to the 2003 activity and chronicity assessment.

Abbreviations

LN: lupus nephritis; ISN/RPS: International Society of Nephrology/Renal Pathology Society; eGFR: estimated glomerular filtration rate; mNIH: modified National Institute of Health; A index: Activity index; C index: Chronicity index; SLE: Systemic lupus erythematosus; ACR: the American College of Rheumatology; EULAR/ERA-EDTA: the Joint European League Against Rheumatism and the European Renal Association; KDIGO: the Kidney Disease: Improving Global Outcomes; FITC; fluorescein isothiocyanate; Ig: immunoglobulin; sCr: serum creatinine; UPCR: urinary protein to creatinine ratio; SD: standard deviation; CI: confidence intervals; CYC: cyclophosphamide; MMF: mycophenolate mofetil; NS: nephrotic syndrome; RPGN: rapidly progressive glomerulonephritis; IQR: Interquartile range; CKD: Chronic Kidney disease.

Declarations

Ethics approval and consent to participate:

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Board of Fujita Health University (No. HM20-245) and opt-outed on its website.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets supporting the conclusions of this article are included within the article.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

All data were collected by RU. Pathological tissues were interpreted RU and HH and SH. SO was in charge of statistics. All the patient’s data was analyzed and interpreted by RU, KT, DI, MH, YY, HH, and NT as a nephrologist, and HY as a rheumatologist. RU was a major contributor in writing the manuscript. All the

authors have read the manuscript and have approved this submission. All authors have required ethical approvals, and all authors have given necessary attention to ensure the integrity of the work.

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Figures

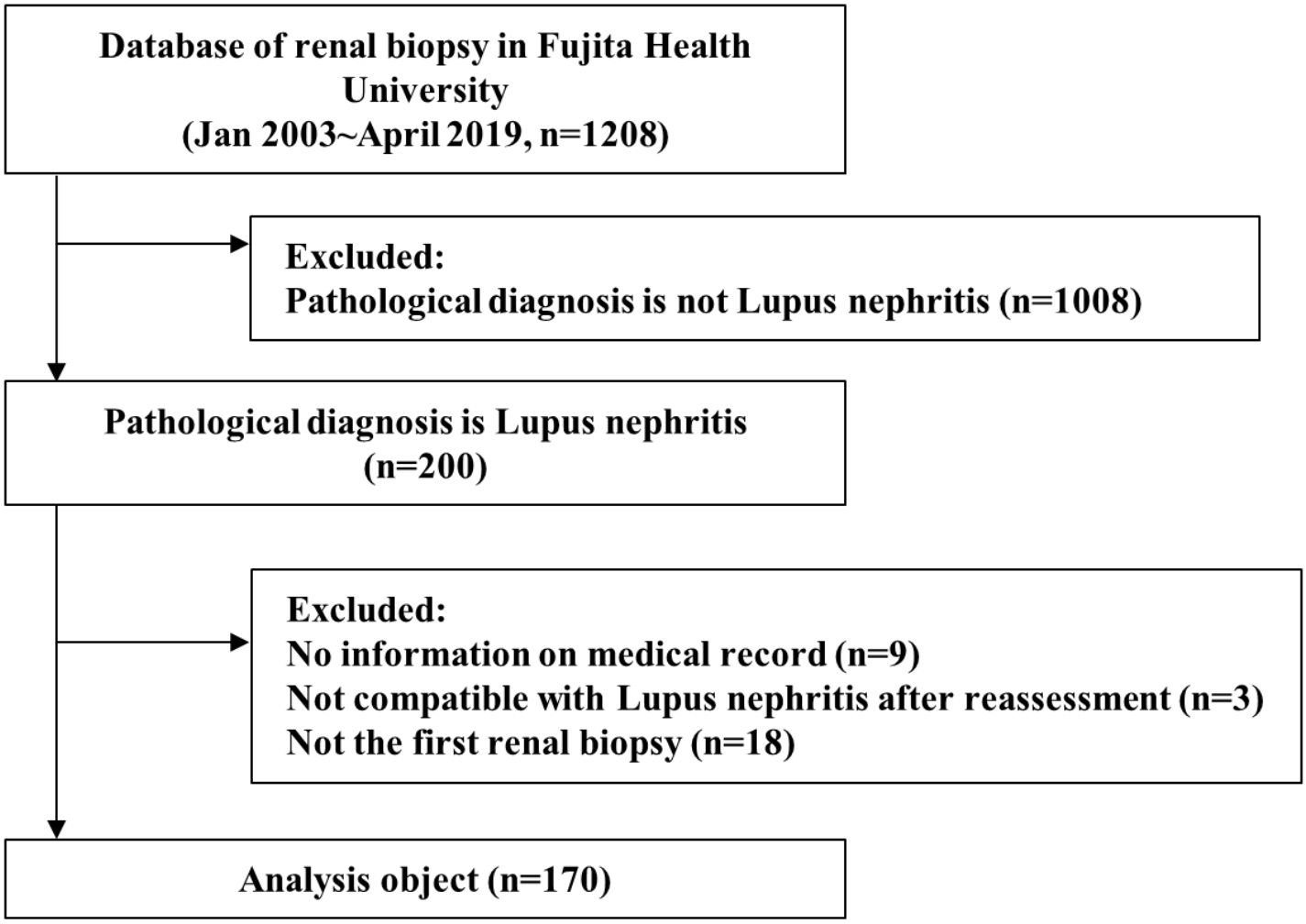

Figure 1

Patients' flow chart.

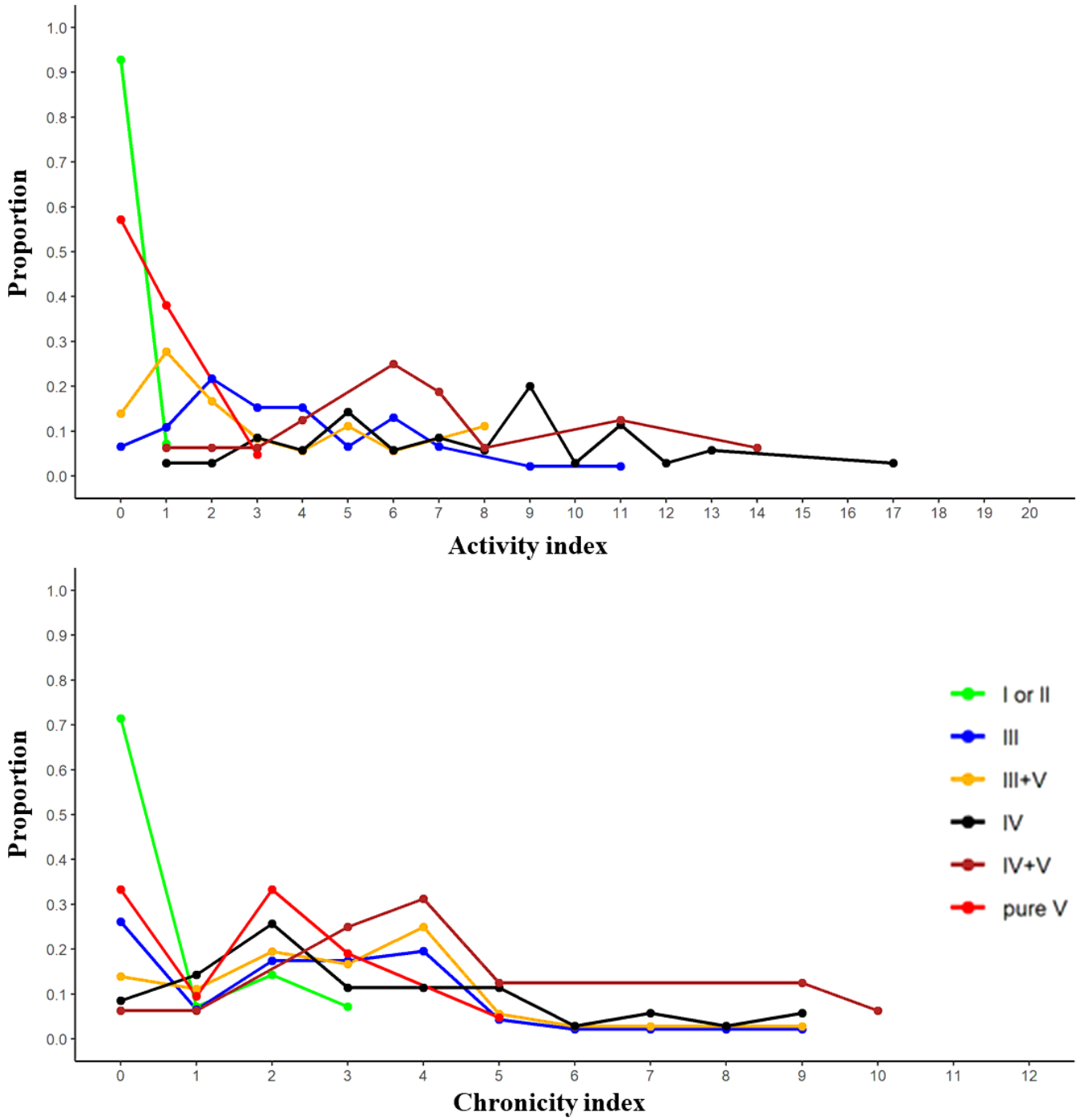

Figure 2

Frequency distribution chart of modified National Institute of Health Activity and Chronicity index.

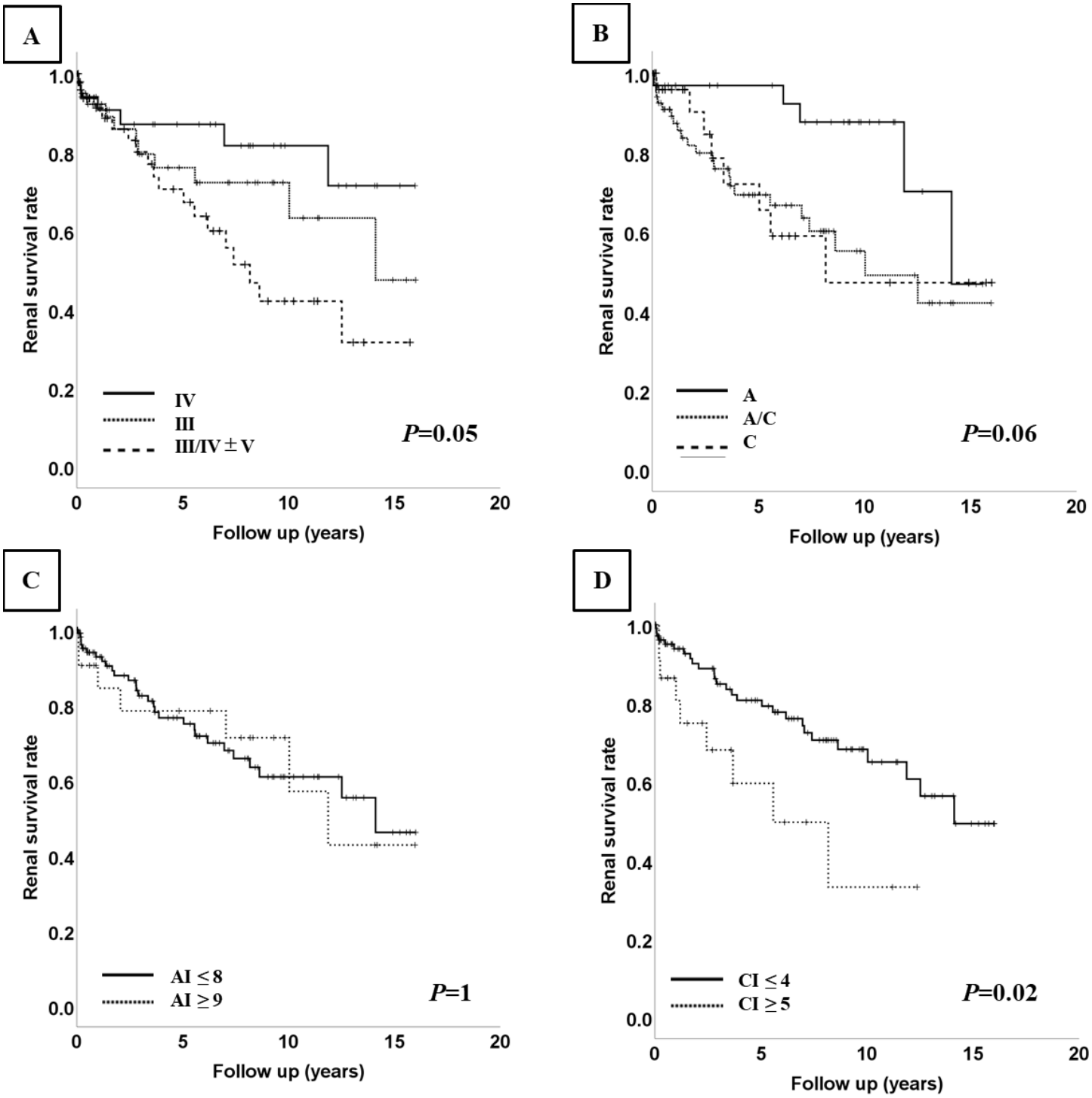

Figure 3

Kaplan–Meier analysis with 30 % decline of eGFR in patients of proliferative lupus nephritis. (A) Class (III, IV, III/IV+V); (B) 2003 activity and chronicity assessment (A, A/C, C); (C) modified National Institute of Health Activity index (AI≤8, 9≤AI); (D) modified National Institute of Health Chronicity index （CI≤4, 5≤CI）. AI, activity index; CI, chronicity index

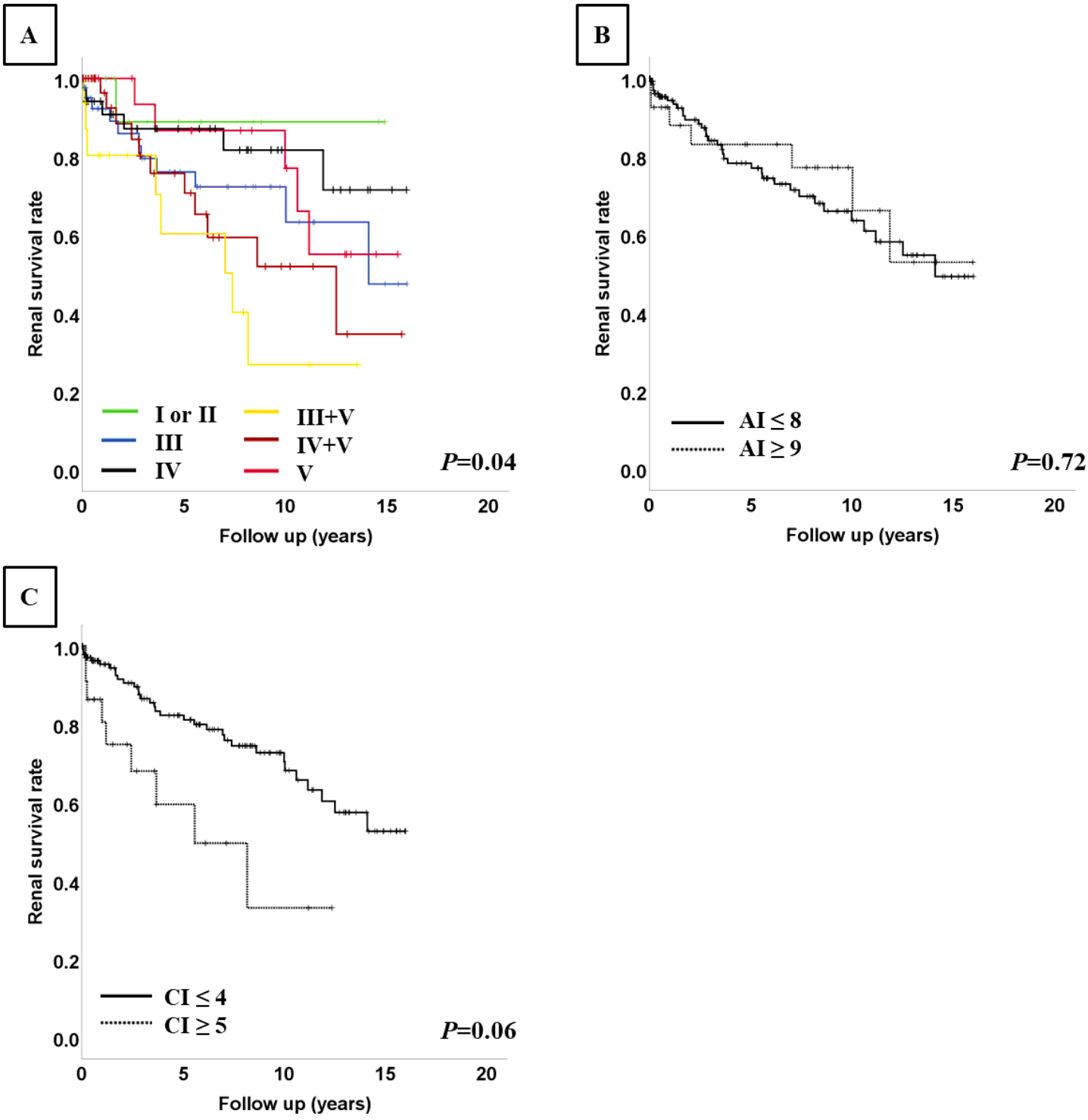

Figure 4

Kaplan–Meier analysis with 30 % decline of eGFR in patients of all classes. (A) Class (I or II, III, IV, III+V, IV+V, V); (B) modified National Institute of Health Activity index (AI≤8, 9≤AI); (C) modified National Institute of Health Chronicity index （CI≤4, 5≤CI）.