Diagnostic Determinants of Proliferative Lupus Nephritis Based on Clinical and Laboratory Parameters: A Diagnostic Study

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ABSTRAK

Latar belakang: *nefritis lupus (NL) proliferatif memiliki prevalensi yang lebih tinggi dan prognosis yang lebih buruk dibandingkan NL non-proliferatif. Pemeriksaan histopatologi memegang peranan penting dalam diagnosis dan terapi NL proliferatif, namun terdapat beberapa kendala dalam pelaksanaannya. Sistem skor NL proliferatif diperlukan untuk membantu diagnosis NL proliferatif terutama pada kondisi biopsi ginjal tidak dapat dilakukan. Tujuan penelitian adalah menetapkan sistem skor diagnosis NL proliferatif berdasarkan determinan hipertensi, proteinuria, hematuria, eGFR, kadar anti-dsDNA, dan C3.* ***Metode:*** *penelitian diagnostik dengan desain potong-lintang terhadap 113 pasien NL yang terbukti dari pemeriksaan Patologi Anatomik di RSCM sejak Januari 2007 hingga Juni 2017 dengan metode total sampling. Data yang digunakan adalah data sekunder. Analisis data dilakukan dengan program statistik SPSS Statistics 20.0 untuk analisis univariat, bivariat, multivariat, Receiving Characteristics Operator, serta analisis bootstrapping pada Kalibrasi Hosmer-Lemeshow.* ***Hasil:*** *sebanyak 191 subjek dianalisis untuk proporsi NL proliferatif, didapatkan proporsi NL proliferatif pada pasien NL yang terbukti dari biopsi ginjal di RSCM sebesar 74,8%. Sebanyak 113 subjek dianalisis untuk mendapatkan determinan NL proliferatif. Pada analisis multivariat, hipertensi (OR= 3,39; 95%IK 1,30-8,84), eGFR <60ml/min/1,73m2 (OR= 9,095; 95%IK 1,11-74,68), dan penurunan kadar C3 (OR= 3,97; 95%IK 1,41-11,17) merupakan determinan NL proliferatif. Hipertensi, eGFR <60ml/min/1,73m2, penurunan kadar C3, dan hematuria, menjadi bagian sistem skor diagnosis NL proliferatif. Pada kurva ROC didapatkan AUC sebesar 80,4% (95% IK 71,9-89), dengan titik potong skor 3.* ***Kesimpulan:*** *proporsi NL proliferatif pada pasien NL yang terbukti dari biopsi ginjal di RSCM adalah 74,8%. Komponen sistem skor diagnosis NL proliferatif terdiri dari hipertensi, eGFR <60ml/menit/1.73m2, penurunan kadar C3, dan hematuria.*

Kata kunci: *determinan, nefritis lupus proliferatif, sistem skor, LES, klinikopatologi.*

ABSTRACT

Background: *proliferative lupus nephritis (LN) has higher prevalence and worse prognosis than non-proliferative LN. Renal biopsy plays an important role in diagnosis and therapy of LN, but there are some obstacles in its implementation. A diagnostic scoring system for proliferative LN is necessary, especially for cases in which renal biopsy cannot be performed. This study aimed to develop a diagnostic scoring system of proliferative LN based on its diagnostic determinants including hypertension, proteinuria, hematuria, eGFR, anti-dsDNA antibody, and*

C3 levels. ***Methods:*** *a cross-sectional study with total sampling method was conducted. Our subjects were adult LN patients who underwent renal biopsy in Cipto Mangunkusumo Hospital between January 2007 and June 2017.* ***Results:*** *from a total of 191 subjects with biopsy-proven LN in this study, we found a proportion of proliferative LN of 74.8%. There were 113 subjects included for analysis of proliferative LN determinants. The multivariate analysis demonstrated that determinants for proliferative LN were hypertension (OR 3.39; 95% CI 1.30-8.84), eGFR <60ml/min/1.73m^2 (OR 9.095; 95% CI 1.11-74.68), and low C3 levels (OR 3.97; 95% CI 1.41-11.17). After further analysis, we found that hypertension, eGFR <60ml/min/1.73m^2, low C3 levels, and hematuria were essential components of the diagnostic scoring system on proliferative LN. The scoring system was tested with ROC curve and an AUC of 80.4% was obtained (95% CI 71.9-89).* ***Conclusion:*** *the proportion of proliferative LN in biopsy-proven LN patients of Cipto Mangunkusumo Hospital is 74.8%. Components of scoring system for proliferative LN consist of hypertension, eGFR <60ml/min/1.73m^2, low C3 levels, and hematuria.*

Keywords: *determinants, proliferative lupus nephritis, scoring system, SLE, clinicopathology.*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is one of systemic autoimmune diseases commonly found in women at reproductive age. One of the clinical manifestations in SLE is renal damage, which is known as lupus nephritis (LN). In the natural course of the disease, LN occurs in 40-60% patients.[1,2] The cumulative incidence of LN is the highest among Asian with higher prevalence of proliferative compared to non-proliferative LN.[2-8] Proliferative lupus nephritis (LN) has worse prognosis than non-proliferative LN, either regarding morbidity or mortality.[5,9-11] However, with appropriate management, the prognosis may improve significantly in patients who have achieve remission.[12]

To achieve remission, earlier diagnosis of LN and appropriate treatment play an essential roles. However, it is not easy to establish early diagnosis of proliferative LN based on clinical and laboratory features since there are various clinical manifestations of LN. Until now, the histopathological examination (renal biopsy) is still the gold standard for diagnosing LN as well as for principles of LN treatment.[1,4,5,11]

Challenges in Indonesia include uneven distribution of facilities for renal biopsy. Moreover, there are also some conditions, which are the contraindications for performing renal biopsy. Therefore, it is necessary to have a tool that can be used practically both in clinical and laboratory setting to diagnose proliferative LN. Some parameters have been previously estimated to have some capacity in predicting histological class of LN and can differentiate proliferative from non-proliferative LN. Those parameters are hypertension, degree of proteinuria, hematuria, eGFR, anti-dsDNA and low C3 levels.

There have been extensive studies discussing clinicopathology of LN, however, no study has been specifically designed to develop a scoring system for proliferative LN based on clinical and laboratory parameters.[1,5-8] In our study, we attempted to develop a scoring system to assist the diagnosis of proliferative LN based on clinical and laboratory parameters, particularly when the renal biopsy cannot be performed.

METHODS

The present study was a diagnostic study with a cross-sectional design in LN subjects who underwent renal biopsy in Cipto Mangunkusumo Hospital between January 2007 and June 2017. The data used were secondary data obtained from patient medical records, data from the Division of Nephrology and Hypertension and data of Pathology Anatomy Department at Cipto Mangunkusumo National Central General Hospital. The inclusion criteria in our study were patients with biopsy-proven LN and aged over 18 years (adult patients); while the exclusion criteria of the present study were incomplete medical records. Samples were obtained by total sampling. This study has been approved by the ethics committee of Faculty of Medicine Universitas Indonesia on May 29th, 2017, with a reference number 493/UN2.F1/ETIK/2017.

When the study criteria were fulfilled,

Anatomical Pathology slides would be re-read by a Pathology Anatomy specialist and data were documented regarding hypertension, proteinuria, hematuria, creatinine level and eGFR as well as anti-dsDNA and C3 levels. Hypertension was defined as a systolic blood pressure (SBP) of ≥140 mm Hg and diastolic blood pressure (DBP) of (TDD) ≥90 mmHg according to JNC 7 classification or the patient had been diagnosed with hypertension previously. Proteinuria was measured by calculating the level of protein in urine quantitatively within 24 hours (mg/24 hours). Hematuria was defined by the presence of >5 red blood cells per high power field (HPF) in urine sediment and by excluding the presence of urinary stone, infection and other causes.

Estimated Glomerular Filtration Rate (eGFR) was calculated based on the CKD-EPI formula. The level of anti-dsDNA was measured by using ELISA method. C3 was defined as low when it was <90 mg/dL. Data analysis was performed using a SPSS statistic software program version 20.0 for univariate, bivariate and multivariate analysis, Receiving Characteristics Operator, as well as bootstrapping analysis in Hosmer-Lemeshow calibration.

RESULTS

There were 191 subjects aged >18 years with biopsy-proven LN who had undergone renal biopsy at Cipto Mangunkusumo National Central General Hospital within the period of January 2007 to June 2017. The proportion of proliferative LN in those 191 subjects who had been confirmed with LN on their renal biopsies was 74.8% (95%CI= 68.6-80.96%). There were 78 subjects that had been excluded from the study due to incomplete data. As many as 113 patients were included in data analysis. Basic characteristics of all study subjects can be seen in **Table 1**.

Table 1. Basic characteristics of study subjects

Subject characteristics	Total
Sex, n (%)	
- Male	7 (6.2)
- Female	106 (93.8)
Age, median (range, years)	27 (18-56)
Duration of SLE, median (range, months)	9 (0-216)

Table 1. Basic characteristics of study subjects

Subject characteristics	Total
Organ involvement, n (%)	
- Neurologic	10 (10.8)
- Mucocutaneous	61 (66.3)
- Hematological	48 (50)
- Musculoskeletal	68 (73.9)
- Serositis	25 (26.9)
Therapy, n (%)	
- Not available	7 (6.2)
- Only steroids	24 (21.2)
- Steroids and immunosuppresants	82 (72.6)
Hypertension, n (%)	
- No hypertension	43 (38.05)
- Hypertension	70 (61.95)
Pyuria (n=112), n (%)	
- No pyuria	60 (53.6)
- Pyuria	52 (46.4)
Hematuria, n (%)	
- No hematuria	32 (28.3)
- Hematuria	81 (71.7)
Cellular cylinders (n=111), n (%)	
- No cellular cylinders	70 (61.9)
- Cellular cylinders	41 (36.3)
Quantitative urine protein, median (range, mg/24 hours)	2812.5 (276.25-22140)
Creatinine level, median (mg/dL)	0.7 (0.3-7.3)
eGFR, n (%)	
- >60 ml/minute/1.73 m^2	85 (75.2)
- <60 ml/minute/1.73 m^2	28 (24.8)
- Median (range, ml/minute/1.73m^2)	108.95 (7.2-172)
Albumin level, median (range, g/dL)	2.54 (0.8-4.69)
Anti-dsDNA level, median (range, U/ml)	397.25 (1.5-5510.4)
C3 level, n (%)	
- Normal	25 (22.1)
- Low	88 (77.9)
- Median (range, mg/dL)	55.6 (0.9-154)
C4 level, n (%)	
- Normal	60 (53.1)
- Low	51 (45.1)
- Median (range, mg/dL)	11 (0-51)
Lupus Nephritis Classification (n=113)	
- LN class I	3 (2.7)
- LN class II	15 (13.3)
- LN class III	21 (18.6)
- LN class IV	50 (44.2)
- LN class V	13 (11.5)
- LN class V+III	1 (0.9)
- LN class V+IV	10 (8.8)

On bivariate analysis, we found that the determinants, which had significant correlation with proliferative LN were hypertension (p=0.002), hematuria (p=0.004), eGFR <60 ml/minute/1.73 m2 (p=0.001), anti-dsDNA (p=0.027) and C3 level (p=0.002). Those five variables together with the quantitative urine protein which had p<0.25 (p=0.181) were included in the multivariate analysis as shown in **Table 2**.

The development of scoring system for diagnosing proliferative a LN was carried out by calculating B coefficient and standard error, which resulted in a diagnostic scoring for proliferative LN based on clinical and laboratory parameters (**Table 3**). The scoring system was tested on ROC curve (**Figure 1**) and an AUC of 0.804 (95%CI 0.709-0.89) was found.

From the curve, we obtained the intersection of sensitivity and specificity curve as well as the cut-off point for diagnosis (**Figure 2**).

Based on tables and cut-off point curves of sensitivity, specificity with total score of diagnosis, we found that the best cut-off point to estimate the diagnosis of proliferative LN was

Table 2. Multivariate analysis on determinants associated with proliferative LN

	Variables	P value	Odd Ratio (OR)	95% CI
Stage 1	C3 level	0.061	2.910	0.95-8.88
	eGFR	0.074	7.011	0.83-59.18
	Hypertension	0.016	3.308	1.25-8.88
	Hematuria	0.150	2.086	0.7-3.00
	Quantitative urine protein	0.699	1.000	0.86-3.59
	anti-dsDNA	0.420	1.000	0.99-1.00
Stage 2	C3 level	0.058	2.942	0.96-8.98
	eGFR	0.074	6.990	0.83-58.85
	Hypertension	0.016	3.318	1.25-8.80
	Hematuria	0.139	2.125	0.78-5.77
	anti-dsDNA	0.430	1	0.99-1.00
Stage 3	C3 level	0.021	3.481	1.20-10.031
	eGFR	0.068	7.221	0.87-60.2
	Hypertension	0.015	3.337	1.26-8.82
	Hematuria	0.137	2.117	0.79-5.69
Stage 4	C3 level	0.009	3.972	1.41-11.17
	eGFR	0.040	9.095	1.108-74.68
	Hypertension	0.013	3.389	1.3-8.84

Table 3. Diagnostic scoring for proliferative LN

No	Variables	Category	Score
1	Hypertension	Yes	2
		No	0
2	eGFR	< 60 ml/minute/1.73 m^2	1
		> 60 ml/minute/1.73 m^2	0
3	C3 level	Low C3 level (<90)	2
		Normal C3 level (90-180)	0
4	Hematuria	Yes	1
		No	0
	Maximum Total Score		6
	Minumum Total Score		0

eGFR, estimated Glomerular Filtration Rate

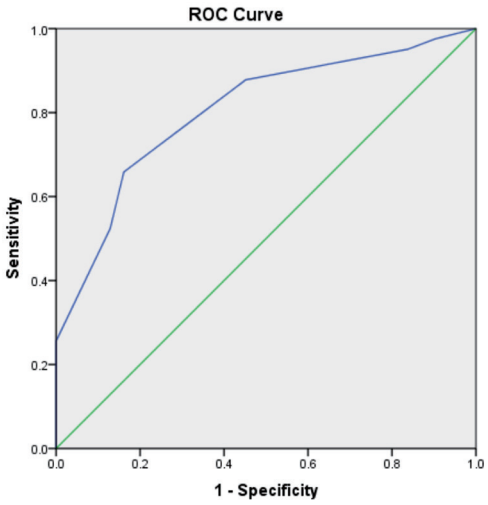

Figure 1. ROC curve

3 (three). The score of >3 had a sensitivity of 65.9%, specificity of 83.8%, positive predictive value of 91.5%, and negative predictive value of 48.14%. The scoring system had a good calibration based on statistical significance using Hosmer-Lemeshow test (p>0.05), in which the p value =0.157. Following 1000 times bootstrappings, the calibration stays good based on the statistical significance using Hosmer-Lemeshow test with p=0.157.

DISCUSSION

In our study, there were 106 female subjects out of 113 total subjects (93.8%). The result is similar to the results in Himawan study[13] in Indonesia and Wakasugi et al.[5] in Japan. In those studies, the proportion of female to male subjects was 93% and 93.7%, respectively. The median age of study subjects was 27 years (with a range of 18-56 years). Moreover, the median duration of time since the subjects had their first diagnosis of SLE to the moment they underwent renal biopsy was 9 months (with a range of time of 0 – 216 months) and a mean duration of 21.16 months (SD 33.91 months). The medians and mean for duration of illness in our study are almost similar to those in Wakasugi et al.[5] and LUMINA[14] studies. There were various organ involvement of SLE patients with LN and in our study the most common one was musculoskeletal involvement, which is consistent to the findings in Mavragani et al.[6] and Kalim et al.[15] studies. The wide range of age and duration of illness as well as various organ involvement implicates that the outcomes of our study can be implemented in LN population with wide range of age and duration of SLE as well as a varied manifestations of organ involvement in SLE.

The proportion of proliferative LN based on ISN/RPS 2003 in our study was 74.8% (95%CI of 68.6-80.96). The proportion of proliferative LN, which was higher than other classes, had also been found in other studies as presented in **Table 4**.

In our study, there were six determinant variables that had been studied, i.e. hypertension, quantitative urine protein, hematuria, eGFR, anti-dsDNA and C3 levels. Among the six determinants, there are four variables that become the component of proliferative LN score, which are hypertension, hematuria, eGFR and C3 level. Hypertension occurred in 82.9% patients with proliferative LN. In the final model of multivariate analysis, we found that hypertension was correlated with proliferative LN. It is consistent with the results of Mavragani et al. study.[6] In LN, particularly

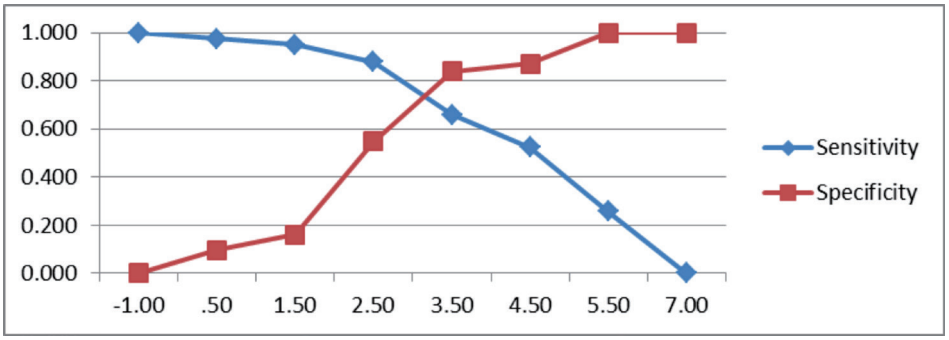

Figure 2. The intersection of sensitivity and specificity curve and total score of diagnosis

Table 4. Frequency of lupus nephritis class (%)

	Our study (n=191)	Mavragani[6] (n=297)	Okpechi[8] (n=251)	Guo[4] (n=82)
I	3.67		0.4	
II	12.04	15.83	13.5	9.76
III	21.47	63.29 (Class III/IV)	20.7	12
IV	43.46		20.7	52.4
V	9.42	20.88	14.7	8.53
V+III	0.52		11.2	7.31
V+IV	9.42		8.4	9.76
VI			8.4	

the proliferative LN, there were loss of nephrons and progressive glomerular damage. It can exacerbate hemodynamic changes of the kidney and increases renal vascular resistance as well as reduces renal blood supply, which leads to hypertension.[16]

In our study, there was no significant correlation between proteinuria and proliferative LN, which is consistent with Hsieh et al.[14] However, it is different from the results of Wakasugi et al.[5] and Okpechi et al.[8] studies. There is a significant difference regarding the median of proteinuria between our study and the Wakasugi et al.[5] study; while there is also a difference in method of measuring proteinuria between our study and the Okpechi et al.[8] study. Proteinuria in SLE patient is generally associated with deposition of immune complex in subepithelial (particularly in LN class V) and subendothelial tissues (particularly in LN class IV); therefore, nephrotic-range proteinuria is also commonly found in LN class V, which is included in the non-proliferative LN. In addition to the mechanism of immune complex deposition, neprhotic-range proteinuria may also occur due to podocyte injuries; therefore, it can also be found in LN class II. The findings support the hypothesis that the degree of severity of LN histopathological findings does not always correlate with the degree of proteinuria.[17]

Hematuria is one of components in proliferative LN score. The addition of hematuria variable in the scoring system increases the discrimination capacity of the system, which was evaluated based on AUC in ROC curve. In addition to the better score discrimination capacity, the pathophysiological (biological plausibility) has also become our consideration when adding hematuria variable into the proliferative LN scoring system. Hematuria in LN occurs due to extravasation of red blood cells into urine, which is caused by damage on glomerular basement membrane (GBM).[18] Several studies have demonstrated that hematuria is associated with proliferative LN including the Martinez et al.[19] and Okpechi et al.[8] studies. Hematuria is associated with high LN activity index and most commonly found in LN class III and IV.[11,20,21]

In LN, inflammation occurs in the kidney simultaneously with cytokines and chemokines production, which subsequently will stimulate leukocyte migration to glomerulus, amplify local inflammatory reaction that result in greater loss of nephrons and atrophy. It causes reduced glomerular filtration rate (GFR).[22,23] In addition to inflammatory conditions, reduced GFR can also be affected by hypertension, which is consistent with the presence of renal vasoconstriction and the phenomenon of shift to the right of pressure-natriuresis correlation. GFR and renal plasma flow will be reduced.[16] In our study eGFR of <60 ml/minute/1.73 m^2 is a determinant in diagnosing proliferative LN, which is consistent with the study by Wakasugi et al.[5] Another study by Vozmediano et al.[24] has also found that eGFR of <60 ml/minute/1.73m^2 was more commonly found in patients with LN class III and IV.

In our study, there was no correlation between anti-dsDNA level and proliferative LN, which is consistent with the Alba et al.[25] study, which showed that the anti-dsDNA was

not associated with histological class of NL. The Wakasugi et al[5] study showed that anti-dsDNA was a determinant for diagnosing proliferative LN. There are differences in the method of evaluating anti-dsDNA between our study and the Wakasugi et al.[5] study. In SLE patients, the titer of their anti-dsDNA did not follow the existing pattern, in which was higher when there was a flare and was lower without flare. The condition is known as serologically-active clinically quiescent (SACQ) and clinically-active serologically quiescent (CASQ).[26] Other studies also could not demonstrate the correlation between anti-dsDNA and the degree of LN severity. Anti-dsDNA in serum shows lower cross reaction compared to anti-dsDNA found in the kidney of LN patients.[27] Another study suggests that in patients with active severe LN, the anti-dsDNA serum levels can be low and is assumed to be due to the adsorption of anti-dsDNA from blood circulation into the kidney; therefore, the anti-dsDNA is deposited in the kidney. Another explanation would be that in LN, there is proteinuria and in such condition anti-dsDNA is found, which is excreted in the urine. Several animal experimental studies have also found that there is a disassociation between anti-dsDNA level and renal disorders.[28-30] Low C3 level is a determinant for diagnosing proliferative LN, which is supported by Okpechi et al. and Wakasugi et al. studies. Low C3 level is caused by increased catabolic rate due to complement activation and reduced C3 synthesis, which is consistent with the role of complement in the pathophysiology of LN. Products of complement activation in the circulation will stimulate inflammatory cascades that consequently will cause tissue damage.[26]

Our study has developed a scoring system as a tool for diagnosing proliferative LN based on clinical and laboratory parameters. The advantage of developing the scoring system is to select LN patients that have high estimation value (which are characterized by higher score than the cut-off point limit) to experience proliferative LN, particularly when renal biopsy is not possible.

To our knowledge, there have been many studies discussing the clinicopathology of LN; however only three studies had demonstrated determinant results to estimate LN with components of class III/IV with different results among those studies. There are some differences between our study and previous studies, which are: (1) no study has been conducted which develop a scoring system for proliferative LN; (2) previous study was performed for different ethnical background, i.e. the study by Wakasugi et al.[5] in Japan (Asia), which also involved children population; (3) in the study by Wakasugi et al.[5] the estimation of proliferative LN was divided into silent and overt LN and there was no score model for overall estimation of proliferative LN; (4) Mavragani et al.[6] did not differentiate specifically the estimation for diagnosing proliferative LN and excluded the LN mixed class V; (5) in Okpechi et al.[8] study, LN mixed class V (V+II) was included in proliferative LN and the proteinuria parameter was measured by dipstick test; while the gold standard of evaluating proteinuria should be performed by measuring 24-hour proteinuria.

Our scoring system is labeled as the Diagnostic Score for Proliferative LN. The score system has good calibration and discrimination. When an analysis was performed on probability of total score in study subjects against the proliferative LN, we could see that the higher the total score, the greater the probability to have proliferative LN. In patients with total score of >3, e.g. those with total score of 4 had 80.77% probability; those with total score of 5 had 89.75% probability and those with score of 6 had 94.81% probability. Following the analysis for probability, sensitivity and specificity tests was performed for score of >3 against proliferative LN. We found that the sensitivity for the score was 65.9%, the specificity was 83.9%, the positive predictive value (PPV) was 91.5% and negative predictive value (NPV) was 48.2%. It indicates that score of >3 are specific to determine that the subject should be included in proliferative LN. It is also supported by the high PPV, although the score may not exclude the proliferative LN (65.9% sensitivity and 48.2% NPV).

Our study has collected samples in a relatively long period, i.e. 10 years and it is the first study demonstrating the proportion

of proliferative LN in adult LN patients in Indonesia with classification of NL class based on ISN/RPS 2003. The development of diagnostic scoring system for proliferative LN is the first attempt that has ever been done. The limitation of our study is that many patients had received corticosteroid treatment and/or immunosuppressant when the renal biopsy was performed. However, it was inevitable and had also been found in previous studies. Our study also used secondary data; therefore, incomplete medical records made subjects became excluded. However, in the overall analysis, which is accompanied with missing data, there was no difference in basic subject characteristics.

CONCLUSION

The proportion of proliferative LN in patients who have undergone renal biopsy is 74.8%. Components of scoring system for proliferative LN consist of hypertension, eGFR <60ml/min/1.73m^2, low C3 levels, and hematuria

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